
*Official Journal of the*
*Malaysian Medical Association*

# *The Medical Journal of Malaysia*

**Volume: 81**

**Issue No: 4**

**July 2026**

ISSN 0300-5283 PP 2121/01/2013 (031329) MITA(P) 124/1/91

# MJM

*Official Journal of the Malaysian Medical Association*

*Volume 81 Number 4 July 2026*


## EDITORIAL BOARD




PP 2121/01/2013 (031329) MCI (P) 124/1/91 ISSN 0300-5283

The Medical Journal of Malaysia is published six times a year.
MJM is published bimonthly ie. January, March, May, July, September and November.





**Advertisement Rates:**
Enquiries to be directed to the Secretariat.

**Subscription Rates:**
Price per copy is RM100.00 or RM360.00 per annum, for all subscribers.

**Secretariat Address:**
Malaysian Medical Association
4th Floor, MMA House, 124, Jalan Pahang, 53000 Kuala Lumpur.
Tel: (03) 4042 0617, 4041 8972, 4041 1375 Fax: (03) 4041 8187
E-mail: info@mma.org.my / mjm@mma.org.my
Website: www.mma.org.my

Printed by: Digital Perspective Sdn. Bhd.
42-1, Level 1, Plaza Sinar, Taman Sri Sinar, 51200 Kuala Lumpur. Tel: 03-6272 3767
Email: dpsbkl@gmail.com

*The Medical Journal of Malaysia*

MJM

# INSTRUCTION TO AUTHORS

The *Medical Journal of Malaysia* ***(MJM)*** welcomes articles of interest on all aspects of medicine in the form of original papers, review articles, short communications, continuing medical education, case reports, commentaries and letter to Editor. Articles are accepted for publication on condition that they are contributed solely to *The Medical Journal of Malaysia*.

**NOTE: MJM is published bimonthly ie. January, March, May, July, September and November.**

**REQUIREMENTS FOR ALL MANUSCRIPTS**
Please ensure that your submission to MJM conforms to the International Committee of Medical Journal Editors Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals.

Neither the Editorial Board nor the Publishers accept responsibility for the views and statements of authors expressed in their contributions.

The Editorial Board further reserves the right to reject papers read before a society. To avoid delays in publication, authors are advised to adhere closely to the instructions given below.

**MANUSCRIPTS**
Manuscripts should be submitted in English (British English). Manuscripts should be submitted online through *MJM Editorial Manager*, http://www.editorialmanager.com/mjm.

Instructions for registration and submission are found on the website. Authors will be able to monitor the progress of their manuscript at all times via the *MJM Editorial Manager*. For authors and reviewers encountering problems with the system, an online Users' Guide and FAQs can be accessed via the "Help" option on the taskbar of the login screen.

MJM charges a one-time, non-refundable Article Processing Charge (APC) upon submission. Waiver of the APC applies only to members of the editorial board, and authors whose articles are invited by the editor. In addition, recipients of the MJM Reviewer Recognition Award from the previous year may enjoy a waiver of the APC for the next calendar year (e.g. recipients of MJM Reviewer Recognition Award 2022 will enjoy waiver of APC for articles submitted between January and December 2023).

**MJM**
Member: RM500
Non Member: RM800
Overseas: USD200

**MJM Case Report**
Member: RM400
Non Member: RM500

**Preparing your manuscript**

The MJM Article Processing Charge is a non-refundable administrative fee. Payment of the APC does not guarantee acceptance of the manuscript. Submitted articles will only be sent for reviews once the MJM APC has been successful completed.

All submissions must be accompanied by a completed **Copyright Assignment Form**, **Copyright Transfer Form and Conflict of Interest Form** duly signed by all authors. Forms can be download from MJM website at https://www.e-mjm.org/

Manuscript text should be submitted as **Microsoft Word** documents. Tables and flow-charts should be submitted as **Microsoft Word** documents. Images should be submitted as separate **JPEG files** (minimum resolution of 300 dpi).

**PEER REVIEW PROCESS**
All submissions must include at least two (2) names of individuals who are especially qualified to review the work. All manuscripts submitted will be reviewed by the Editor in-charge before they are send for peer review. Manuscripts that are submitted to MJM undergo a double-blinded peer review and are managed online. Proposed reviewers must not be involved in the work presented, nor affiliated with the same institution(s) as any of the authors or have any potential conflicts of interests in reviewing the manuscript. The selection of reviewers is the prerogative of the Editors of MJM.

**ELIGIBILITY AS AN AUTHOR**
MJM follows the recommendation of the International Committee of Medical Journal Editors (ICMJE) for eligibility to be consider as an author for submitted papers. The ICMJE recommends that authorship be based on the following four (4) criteria:

1 Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2 Drafting the work or revising it critically for important intellectual content; AND
3 Final approval of the version to be published; AND
4 Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**TYPES OF PAPERS**
**Original Articles:**
Original Articles are reports on findings from original unpublished research. Preference for publications will be given to high quality original research that make significant contribution to medicine. Original articles shall consist of a structured Abstract and the Main Text. The word count for the structured abstract should not exceed 500 words. The main text of the articles should not exceed 4000 words, tables/illustrations/figures/images up to five (5) and references up to 40. Manuscript describing original research should conform to the IMRAD format, more details are given below.

Original articles of cross-sectional and cohort design should follow the corresponding STROBE check-lists; clinical trials should follow the CONSORT check-list.

**Review Articles:**
Review Articles are solicited articles or systematic reviews. ***MJM*** solicits review articles from Malaysian experts to provide a clear, up-to-date account of a topic of interest to medical practice in Malaysia or on topics related to their area of expertise. Unsolicited reviews will also be considered, however, authors are encouraged to submit systematic reviews rather than narrative reviews. Review articles shall consist of a structured Abstract and the Main Text. The word count for the structured abstract should not exceed 500 words. Systematic Review are papers that presents exhaustive, critical assessments of the published literature on relevant topics in medicine. Systematic reviews should be prepared in strict compliance with MOOSE or PRISMA guidelines, or other relevant guidelines for systematic reviews.

**Short Communications:**
Shorts communication are short research articles of important preliminary observations, findings that extends previously published research, data that does not warrant publication as a full paper, small-scale clinical studies, and clinical audits. Short communications should not exceed 1,500 words and shall consist of a Summary and the Main Text. The summary should be limited to 100 words and provided immediately after the title page. The number of tables/illustrations/figures/images should be limited to three (3) and the number of references to ten (10).

**Continuing Medical Education (CME) Articles:**
A CME article is a critical analysis of a topic of current medical interest. The article should include the clinical question or issue and its importance for general medical practice, specialty practice, or public health. It shall consist of a Summary and the Main Text. The summary should be limited to 500 words and provided immediately after the title page Upon acceptance of selected articles, the authors will be requested to provide five multiple-choice questions, each with five true/false responses, based on the article. For guideline, please refer to: Sivalingam N, Rampal L. Writing Articles on Continuing Medical Education for Medical Journals. Med J Malaysia. 2021 Mar;76(2):119-124.

**Case Reports:**
Papers on case reports (one to five cases) must follow these rules: Case reports should not exceed 2,000 words; with a maximum of two (2) tables; three (3) photographs; and up to ten (10) references. It shall consist of a Summary and the Main Text. The summary should be limited to 250 words and provided immediately after the title page. Having a unique lesson in the diagnosis, pathology or management of the case is more valuable than mere finding of a rare entity. Being able to report the outcome and length of survival of a rare problem is more valuable than merely describing what treatment was rendered at the time of diagnosis. There should be no more than seven (7) authors.

Please note that all Case Reports will be published in the new MJM Case Reports Journal (www.mjmcasereports.org).

**Commentaries:**
Commentaries will usually be invited articles that comment on articles published in the same issue of the ***MJM***. However, unsolicited commentaries on issues relevant to medicine in Malaysia are welcomed. They should not exceed 2,000 words. They maybe unstructured but should be concise. When presenting a point of view, it should be supported with the relevant references where necessary.

**Letters to Editor:**
Letters to Editors are responses to items published in ***MJM*** or to communicate a very important message that is time sensitive and cannot wait for the full process of peer review. Letters that include statements of statistics, facts, research, or theories should include only up to three (3) references. Letters that are personal attacks on an author will not be considered for publication. Such correspondence must not exceed 1,500 words.

**Editorials:**
These are articles written by the editor or editorial team concerning the ***MJM*** or about issues relevant to the journal.

**STRUCTURE OF PAPERS**
**Title Page:**
The title page should state the brief title of the paper, full name(s) of the author(s) (with the surname or last name bolded), degrees (limited to one degree or diploma), affiliation(s), and corresponding author's address. All the authors' affiliations shall be provided after the authors' names. Indicate the affiliations with a superscript number at the end of the author's degrees and at the start of the name of the affiliation. If the author is affiliated to more than one (1) institution, a comma should be used to separate the number for the said affiliation.

Do provide preferred abbreviated author names for indexing purpose, e.g. L Rampal (for Lekhraj Rampal), BS Liew (for Liew Boon Seng), B Abdullah (for Baharudin Abdullah), Hoe VC (for Victor Hoe Chee Wai).
Please indicate the corresponding author and provide the affiliation, full postal address and email.

Articles describing Original Research should consist of the following sections (IMRAD format): Abstract, Introduction, Materials and Methods, Results, Discussion, Acknowledgment and References. Each section should begin on a fresh page.
Scientific names, foreign words and Greek symbols should be in italic.

**Abstract and Key Words:**
A structured abstract is required for Original and Review Articles. It should be limited to 500 words and provided immediately after the title page. Below the abstract provide and identify three (3) to 10 key words or short phrases that will assist indexers in cross-indexing your article. Use terms from the medical subject headings (MeSH) list from Index Medicus for the key words where possible. Key words are not required for Short Communications, CME articles, Case Reports, Commentaries and Letter to Editors.

**Introduction:**
Clearly state the purpose of the article. Summarise the rationale for the study or observation. Give only strictly pertinent references, and do not review the subject extensively.

**Materials and Methods:**
Describe your selection of the observational or experimental subjects (patients or experimental animals, including controls) clearly, identify the methods, apparatus (manufacturer's name and address in parenthesis), and procedures in sufficient detail to allow other workers to reproduce the results. Give references to established methods, including statistical methods; provide references and brief descriptions of methods that have been published but are not well-known; describe new or substantially modified methods, give reasons for using them and evaluate their limitations.

Identify precisely all drugs and chemicals used, including generic name(s), dosage(s) and route(s) of administration. Do not use patients' names, initials or hospital numbers. Include numbers of observation and the statistical significance of the findings when appropriate.

When appropriate, particularly in the case of clinical trials, state clearly that the experimental design has received the approval of the relevant ethical committee.

**Results:**
Present your results in logical sequence in the text, tables and illustrations. Do not repeat in the text all the data in the tables or illustrations, or both: emphasise or summarise only important observations in the text.

**Discussion:**
Emphasise the new and important aspects of the study and conclusions that follow from them. Do not repeat in detail data given in the Results section. Include in the Discussion the implications of the findings and their limitations and relate the observations to other relevant studies.

**Conclusion:**
Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not completely supported by your data. Avoid claiming priority and alluding to work that has not been completed. State new hypotheses when warranted, but clearly label them as such. Recommendations, when appropriate, may be included.

**Acknowledgements:**
Acknowledgements of general support, grants, technical assistance, etc., should be indicated. Authors are responsible for obtaining the consent of those being acknowledged.

**Referencing guide:**
The Medical Journal of Malaysia, follows the Vancouver numbered referencing style. Citations to someone else's work in the text, should be indicated by the use of a number. In citing more than one article in the same sentence, you will need to include the citation number for each article. A hyphen should be used to link numbers which are inclusive, and a comma used where numbers are not consecutive. The following is an example where works 1.3,4,5.have been cited in the same place in the text.

Several effective drugs are available at fairly low cost for treating patients with hypertension and reducing the risk of its sequelae.[1,3-5]

The list of all of the references that are cited in the article should be presented in a list labelled as 'References'. This reference list appears at the end of the paper. Authors are responsible for the accuracy of cited references and these should be verified by the author(s) against the original documents before the manuscript is submitted. It is important that the author should never place in the list of references a document that he or she has not seen. The Journals names should be abbreviated according to the style used in the Index Medicus. All authors when six or less should be listed; when seven or more list only the first six and add et al.

If you are citingthe author's name in your text, you must insert the citation number as well. Jewell BL (8) underlined that as focus in the SARS-CoV-2 pandemic shifts to the emergence of new variants of concern (VOC), characterising the differences between new variants and non-VOC lineages will become increasingly important for surveillance and maintaining the effectiveness of both public health and vaccination programme. If you are citing more than one author's name in your text and you want to cite author names in your text, use 'et al.' after the first author. Example: Rampal et al. (9) highlighted that the. disregard of the manuscript guidelines and instruction to authors of the journal you submit, is one of the common reasons for 'Rejection' of the article.

**Example references Journals:**
**Standard Journal Article**
Rampal L and Liew BS. Coronavirus disease (COVID-19) pandemic. Med J Malaysia 2020; 75(2): 95-7.
Rampal L, Liew BS, Choolani M, Ganasegeran K, Pramanick A, Vallibhakara SA, et al. Battling COVID-19 pandemic waves in six South-East Asian countries: A real-time consensus review. Med J Malaysia 2020; 75(6): 613-25.
NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. Lancet 2021; 11; 398(10304): 957-80.

**Books and Other Monographs:**
**Personal Author(s)**
Goodman NW, Edwards MB. 2014. Medical Writing: A Prescription for Clarity. 4 th Edition. Cambridge University Press.

**Chapter in Book**
McFarland D, Holland JC. Distress, adjustments, and anxiety disorders. In: Watson M, Kissane D, Editors. Management of clinical depression and anxiety. Oxford University Press; 2017: 1-22.

**Corporate Author**
World Health Organization, Geneva. 2019. WHO Study Group on Tobacco Product Regulation. Report on the scientific basis of tobacco product regulation: seventh report of a WHO study group. WHO Technical Report Series, No. 1015.

NCD Risk Factor Collaboration (NCD-RisC). Rising rural body-mass index is the main driver of the global obesity epidemic in adults. Nature 2019; 569: 260–64.

World Health Organization. Novel Coronavirus (2019-nCoV) Situation Report 85, April 14, 2020. [cited April 2020] Accessed from: https://www.who.int/docs/defaultsource/coronaviruse/situationreports/20200414-sitrep-85-covid-19.

**Online articles**
**Webpage:** Webpage are referenced with their URL and access date, and as much other information as is available. Cited date is important as webpage can be updated and URLs change. The "cited" should contain the month and year accessed.

Ministry of Health Malaysia. Press Release: Status of preparedness and response by the ministry of health in and event of outbreak of Ebola in Malaysia 2014 [cited Dec 2014]. Available from: http://www.moh.gov.my/english.php/database_stores/store_view_page/21/437.

**Other Articles:**
**Newspaper Article**
Panirchellvum V. 'No outdoor activities if weather too hot'. the Sun. 2016; March 18: 9(col. 1-3).

**Magazine Article**
Rampal L.World No Tobacco Day 2021 -Tobacco Control in Malaysia. Berita MMA. 2021; May: 21-22.

**Tables:**
All tables and figures should have a concise title and should not occupy more than one printed page. The title should concisely and clearly explain the content of the table or figure. They should be numbered consecutively with Roman numerals (e.g Table I) and figures with Arabic numerals (e.g. Figure 1), and placed after the sections of the manuscript which they reflect, particularly the results which they describe on separate pages. Cite tables in the text in consecutive order. Indicate table footnotes with lower-case letters in superscript font. Place the information for the footnote beneath the body of the table. If a table will be submitted as a separate document, the filename should contain the surname of the first author and match its label in the manuscript (e.g., SMITH Table I).Vertical lines should not be used when constructing the tables. All tables and figures should also be sent in electronic format on submission of the manuscript as supplementary files through the journal management platform. Clinical Photographs should conceal the subject's identity. Tables and flow-charts should be submitted as Microsoft Word documents. Images should be submitted as separate JPEG files (minimum resolution of 300 dpi).

**Photographs of Patients:**
Proof of permission and/or consent from the patient or legal guardian must be submitted with the manuscript. A statement on this must be included as a footnote to the relevant photograph.

**Colour reproduction:**
Illustrations and diagrams are normally reproduced in black and white only. Colour reproductions can be included if so required and upon request by the authors. However, a nominal charge must be paid by the authors for this additional service; the charges to be determined as and when on a per article basis.

**Abbreviations:**
Use only standard abbreviations. The full-term for which an abbreviation stands should precede its first use in the abstract, article text, tables, and figures, unless it is a standard unit of measurement. Abbreviations shall not be used in the Title. Abbreviations should be kept to a minimum.

**Formatting of text:**
Numbers one to ten in the text are written out in words unless they are used as a unit of measurement, except in tables and figures. Use single hard-returns to separate paragraphs. Do not use tabs or indents to start a paragraph. Do not use the automated formatting of your software, such as hyphenation, endnotes, headers, or footers (especially for references). Submit the Manuscript in plain text only, removed all 'field codes' before submission. Do not include line numbers. Include only page number.

**BEST PAPER AWARD**
All original papers which are accepted for publication by the MJM, will be considered for the 'Best Paper Award' for the year of publication. No award will be made for any particular year if none of the submitted papers are judged to be of suitable quality.

**CONTENTS** **Page**

## Editorial



## Original Articles

## CONTENTS Page

**CONTENTS** **Page**

## Systematic / Narrative Review Article

# Beyond the treatment episode: Closing gaps across the continuum of care

**Keng Sheng Chew, PhD[1], Boon Seng Liew, MS (Neurosurgery) USM[2]**

[1]Faculty of Medicine and Health Sciences, Universiti Malaysia Sarawak, Kota Samarahan, Sarawak, Malaysia, [2]Department of Neurosurgery, Hospital Sungai Buloh, Sungai Buloh, Selangor, Malaysia

Tuberculosis (TB) remains endemic disease in tropical countries, such as in Malaysia. According to the global report on Tuberculosis 2025 by the World health Organisation (WHO), estimated TB incidence per 100,000 population was 99.6% in the year 2010, with slight reduction in the incident rate of 96% in 2024. In term of number of deaths, it was estimated of 2569 deaths due to TB in 2010 (9.1 deaths per 100,000 population, 28 million population) with reduction in death per population in 2024 with 2963 deaths (8.7 deaths per 100,000 population of 34.1 million population).[1] Ho et al.[2] who studied the mortality rate among TB patients in Lubok Antu Health Clinic, in a rural area of Sarawak state in Malaysia in 2020, and found that patients compliant with treatment were more likely to survive with odd ratio, OR of 12.5 (95% CI: 1.61, 97.34), p=0.028.[2]

There were also high estimated percentage of TB patients who had multidrug resistant among previously treated pulmonary TB cases when compared with new Pulmonary TB cases. The level of multidrug resistant was 7.3% and 1.5% in 2015 compared with 11.7% and 0.8% in 2024.[1] The increasing trend of multidrug resistant cases among previously treated patients should be our concern. Sidek MY, et al (3) reported that 66.7% drug-resistant TB patients in the cohort of his study received supervised treatment from healthcare providers, with 37.4% had more than one anti-TB resistance. Favourable treatment outcomes were observed in 56.7% of cases, while 42.1% had unfavourable outcomes, mainly due to loss to follow-up (49.7%), death (42.6%) and treatment failure (7.7%).[3] The estimate funding for TB prevention, diagnostic and treatment in Malaysia was USD 15.6 million in 2020 with just slight increment with USD 17.6 million in 2024 (12.8%).[1] This infectious disease is also predominately affecting those living in a crowded living condition, and poor health conditions due to poverty.

In this issue, Ganesan et al (4) found the adherent rate to TB treatment was only 84%.[4] He found that stigma, knowledge on TB, direct observed treatment short course modality and clinic waiting time were the independent association with poor treatment adherence. Another study published in this issue by Jastin et al (5) found that failure to perform screening among TB contacts was the main issue in the eradication and control of the disease, in locality of high-burden of such as in Kudat district, Sabah state of Malaysia.[5] The authors found that factors associated with a lower odd of non-attendance were contacts of male TB index patients, contacts of extrapulmonary TB index patients and higher altitude scores.

A third paper published in this issue is a systematic review of TB recurrence in Asia by Isa. The author found that recurrence was highest within the first two years after treatment and was associated with clinical, behavioural, socioeconomic and environmental determinants.[6]

In a way, these three papers highlight the critical points representing the vulnerabilities where patients can be "lost" across the continuum of care: (1) non-attendance at initial contact screening[5], (2) adherence during treatment[4], and (3) recurrence even after treatment completion.[6] One should remember that healthcare is often rendered in discrete episodic manner, e.g., a screening appointment, a diagnosis, a course of treatment, a discharge. But from the patient's perspective, illness is experienced as a continuous journey with vulnerable transitions along the way. Hence, as hard as it may be, these episodes of care must be monitored and integrated into a coherent whole; failure of which, care risks becoming fragmented across its various stages. At each transition, some never enter the designated clinical pathway, some disengage, and some return with recurrence, with complications or with unresolved morbidity even after apparent completion.

In this regard, a helpful framework that may be adapted is the Haddon matrix. Originally developed for injury prevention, this matrix examines factors operating before, during and after an event across the broad categories of "host", "agent" and "environment".[7] In the context of TB, the "host" represents the TB patient, the "agent" represents the pathogen or the disease progression and the "environment" represents the physical environment, as well as the social support and health-system environment that the patient is in. Horizontally, the "pre-event" phase concerns the entry, i.e., recognition of risk, contact tracing, screening and linkage to care. The "event" phase concerns engagement: diagnosis, treatment initiation, adherence and completion. The "post-event" phase concerns endurance: surveillance, recurrence, residual morbidity and re-entry into care. The matrix then asks two questions: When did the continuity of care break, and where are their contributing factors?

Having this kind of big picture mapped out in a matrix is believed to be important because we often tend to gravitate our explanations toward patient column. Yes, poor knowledge, weak motivation or individual non-compliance matters, but so are the infrastructure support, family support,

*Corresponding Author: Keng Sheng Chew*
*Email: kschew@unimas.my*

clinic organisation and destigmatization. The matrix restores causation to context.

In conclusion, closing the gaps across the continuum of care requires more than improving the acute treatment for those already under our follow-up. It requires us as healthcare providers to reach out to those who have not yet entered the care journey, retaining those at risk of disengagement and remain attentive even after treatment formally ends. After all, our measure of success should not be myopic. It should not be just when the patient has completed the treatment that we render to them but to journey alongside with the patient across the continuum of care.

## REFERENCES


1. World Health Organisation. The global tuberculosis report 2025. [cited July 2026] Available from : https://www.who.int/teams/global-programme-on-tuberculosis-and-lung-health/data
2. Ho YH, Lim CT, Albart SA, Schee JP, Yong MC, Looi I. Characteristics of patients with tuberculosis and the associated factors with TB-related mortality in a rural setting in Sarawak, Malaysia: A single-centre study. Med J Malaysia 2023; 78(1): 1-6.
3. Sidek MY, Kamarul Zaman MF, Nik Rosmawati NH, Zamzurina AB. Drug-resistant tuberculosis in Malaysia: Prevalence, characteristics, and treatment outcomes. Med J Malaysia 2024; 79(6): 661-8.
4. Ganesan V, Jastin H.G, Jayaraman S, Gangatharan S, Avol R. Psychosocial and health system factors associated with tuberculosis treatment adherence in Kota Kinabalu, Sabah. Med J Malaysia 2026; 81(4): 413-20.
5. Jastin HG, Ganesan V, Abdul Hamid MH, Avol R. Factors associated with non-attendance at initial tuberculosis screening among contacts in Kudat, Sabah. Med J Malaysia 2026; 81(4): 504-12.
6. Isa MR. Quantifying the risk of tuberculosis recurrence in Asia: A systematic review of hazard estimates. Med J Malaysia 2026; 81(4): 601-11.
7. Haddon W Jr. A logical framework for categorizing highway safety phenomena and activity. J Trauma 1972; 12(3): 193-207.

# Precision medicine in Malaysia: Aligning genomics research, policy and translation

**Wan Nazatul Shima Shahidan, PhD[1], Mohd Nor Azim Ab Patar, PhD[2], Sarina Sulong, PhD[3], Mohd Nazri Hassan, MPath (Haematology)[4], Irfan Mohamad, MMed (ORL-HNS)[5], Bin Alwi Zilfalil, PhD[3]**

[1]Department of Pharmacology, [2]Department of Neurosciences, [3]Human Genome Centre, [4]Department of Haematology, [5]Department of Otorhinolaryngology-Head & Neck Surgery, School of Medical Sciences, Universiti Sains Malaysia, Health Campus, Kubang Kerian, Kelantan, Malaysia

**The Integration of Genomics into Malaysian Healthcare**

The transition of clinical medicine toward precision medicine represents a fundamental shift in how we conceptualize patient care, moving from empirical, population-level protocols to strategies tailored to individual genetic, clinical and environmental profiles. Following the completion of the Human Genome Project, the clinical focus has shifted from the basic generation of raw sequence data to the practical application of this molecular information at the bedside.[1] Today, genomics is no longer a peripheral research interest, as it is increasingly integrated into routine diagnostics, disease risk stratification and targeted therapeutic selection.

In Malaysia, incorporating genomic medicine into public healthcare is supported by key national strategies, including the 12th Malaysia Plan and the Ministry of Health's Health White Paper.[2] These national policy frameworks are actively translated into clinical action through major nationwide initiatives, including the Academy of Sciences Malaysia Position Paper on the Precision Medicine Initiative published in 2020,[3] the National Policy for Rare Diseases and the MyGenom Project.[4]

The formal development of the National Precision Medicine Implementation Plan commenced in 2025, establishing the essential clinical, laboratory and ethical guidelines required for the clinical application of genomic medicine. This clinical blueprint was recently reinforced by national consultation workshops involving genomic experts and stakeholders across key academic centres, which were jointly organised and co-chaired by the Ministry of Health, the Ministry of Science, Technology and Innovation and the Ministry of Higher Education. Alongside this administrative effort, the MyGenom Project serves as the critical sequencing vehicle focused on mapping local genomes to build a comprehensive, high-resolution national reference database. The completion of Phase 1 of the MyGenom Project from 2024 to 2025 has laid a solid foundation, with Phase 2 planned to run from 2026 to 2028. Engaging with all relevant stakeholders remains essential for the successful execution of the Precision Medicine Action Plan in Malaysia, ensuring a unified direction for genomics-driven healthcare.

**The Genomics and Life Sciences (GLS) Research Cluster**

The GLS Research Cluster at the School of Medical Sciences, USM, was established in 2023 to support this clinical translation. Although still relatively new, the cluster has developed a clear strategic direction to strengthen genomics and life sciences research within the institution. Based at the Health Campus in Kubang Kerian, Kelantan, this cluster brings together researchers and clinicians from various basic science and clinical departments, such as pharmacology, neurosciences, haematology and paediatrics, alongside the Human Genome Centre and other allied medical and life science disciplines, to study the genetic factors of diseases common in Malaysia.[5]

Since its establishment, the cluster has focused on building a structured research ecosystem through strategic planning, subcluster development, research profiling, enhanced research visibility and interdisciplinary project matching. Through digital platforms like ThinkLab (www.thinklab.my), the cluster provides an interactive portal to highlight research expertise and promote collaboration opportunities, hosting major events such as the Science, Technology, Engineering and Mathematics Next Generation (STEMNEXT) webinar, the Fakultas Kedokteran Universitas Padjadjaran (FK-UNPAD) and GLS-USM Joint Webinar Series and collaborative webinars with the Human Genome Centre and the Malaysian Society of Human Genetics. This early strategic planning ensures that genomic and life sciences research within USM is coordinated, visible and aligned with both institutional priorities and Malaysia's national precision medicine agenda.

By working closely with Hospital Pakar USM (HPUSM), the cluster uses a translational research model that allows laboratory findings to be evaluated in clinical settings, which helps to develop local diagnostic services and support targeted clinical research. In alignment with Malaysia's broader national health agenda, this integrated ecosystem of clinicians, scientists and genomic researchers is well positioned to contribute strategically to national initiatives such as the National Precision Medicine Project and the MyGenom Project. Through its research initiatives, the cluster supports the generation of locally relevant genomic data, facilitates translational and implementation research and strengthens national capacity. This close linkage between academic research, clinical services and patient cohorts enables the development of evidence-based approaches

*Corresponding Author: Irfan Mohamad*
*Email: irfankb@usm.my*

tailored to Malaysia's multi-ethnic population, positioning the cluster as an important academic and clinical partner in advancing a sustainable national genomic healthcare framework.

**Addressing Rare Diseases, Oncology, Thalassaemia and Neurodevelopmental Disorders**

A major clinical objective of this collaborative work is reducing the diagnostic delay for patients with rare genetic conditions. Using whole exome sequencing and whole genome sequencing, USM researchers identify molecular causes for these conditions, which helps clinicians manage patients and advise families on risk.[6]

In oncology, precision medicine has progressed through the clinical application of molecular profiling alongside standard histopathology, which allows clinicians to match specific genetic alterations within a tumour to regulatory-approved targeted therapies.[7] Research within the cluster focuses on identifying and analysing these actionable mutations within the local population, ensuring that treatment decisions are guided by data that accurately represent Malaysian patients. Similarly, in the neurosciences, genomic research is closely aligned with established institutional expertise in molecular genetics, neurogenetics, neuro-oncology and cellular and molecular neuroscience. This includes active research directions involving clinically relevant genes and molecular markers such as SCN1A in epilepsy-related neurogenetic disorders, *IDH1, MGMT, BAX* and *CCND1* (cyclin D1) in glioma and other central nervous system tumours, as well as mitochondrial DNA alterations in brain tumour biology.[8] By linking these molecular findings with clinical phenotypes, neuroimaging features and disease progression, genomic research in neuroscience strengthens its contribution to precision medicine and supports more targeted diagnostic and translational approaches for Malaysian patients.

Thalassaemia remains one of the most important inherited disorders in Malaysia and continues to represent a major public health challenge. Research within the cluster has focused on improving molecular characterisation, carrier detection and genotype–phenotype correlation studies among the local population. These efforts not only strengthen early diagnosis and genetic counselling services but also support the development of more personalised approaches to disease monitoring and management for affected patients and families.[5]

Collectively, the multidisciplinary expertise within the USM GLS Research Cluster places it in a strong position to support Malaysia's broader national precision medicine agenda. By integrating genomic research, clinical data and translational implementation strategies, the cluster contributes to national initiatives aimed at expanding genomic databases, strengthening local diagnostic capabilities and improving equitable access to precision medicine services. Such efforts are essential for ensuring that future national genomic policies and healthcare strategies are informed by evidence that reflects the diversity of the Malaysian population.

**Pharmacogenomics and Patient Safety**

Pharmacogenomics, which studies how genetic variations influence drug efficacy and adverse reactions, represents one of the most clinically impactful applications of genomic medicine because it provides a clear pathway for translating genetic discovery into daily patient care. Identifying patients at high risk of severe drug reactions or treatment failure is critical for improving therapeutic outcomes across various medical fields. For instance, incorporating pharmacogenomic testing in clinical settings helps predict individual drug responses, which optimises dosing regimens, minimises adverse effects and significantly improves drug safety profiles.[9]

Implementing pre-emptive genetic screening allows clinicians to choose alternative drugs for high-risk patients. This clinical practice protects patients from preventable harm and reduces the hospital costs associated with treating severe drug reactions, which contributes to a more efficient healthcare system.

As one of the emerging centres advancing translational genomic research in Malaysia, the USM GLS Research Cluster is well positioned to support patients within the Ministry of Health Malaysia healthcare system. Through collaborative precision medicine initiatives, the cluster aims to expand access to pharmacogenomic-guided therapies and genomic-informed clinical decision-making in line with ongoing global developments in personalised healthcare.

**Bioinformatics, Diagnostics and Data Sovereignty**

Managing large-scale genomic data requires secure computing systems and specialised analysis. The bioinformatics resources at USM support the storage, quality control and interpretation of clinical sequencing data.

Integrating next-generation sequencing technologies into clinical workflows is essential for advancing precision medicine across Asia, as demonstrated by regional frameworks that highlight the clinical transition toward genomic-based diagnostics.[10] Through initiatives like the Malaysian Node of the Human Variome Project, USM researchers help build a representative national reference database.[11] This leadership in genetic research is further highlighted by international appointments, such as the designation of local experts to lead global research on diseases like thalassaemia.[5] This database helps clinicians distinguish actual disease-causing variants from harmless genetic variations unique to our population.

Additionally, combining genomic data with routine pathology, haematology and biochemistry improves diagnostic precision. For example, in blood cancers, combining genetic profiling with flow cytometry and cytogenetics provides a clearer prognosis and helps monitor treatment response.

Taken together, these capabilities position the USM GLS Research Cluster as an important contributor to Malaysia's evolving national precision medicine ecosystem. The cluster's strengths in genomic sequencing, bioinformatics infrastructure, clinical data integration and translational research provide a strong platform for supporting nationwide efforts in genomic-based diagnostics and personalised

healthcare implementation. Through collaborations involving clinical institutions, research networks and national genomic initiatives, the cluster contributes towards developing harmonised genomic databases, strengthening local analytical capacity and establishing evidence-based frameworks that facilitate the integration of precision medicine into routine healthcare practice across the country.

**Cultivating Genomic Literacy in Medical Education**

As genomic tools become part of clinical workflows, medical training must adapt to prepare future clinicians for the demands of personalised medicine. To address existing curricular gaps and the divide between laboratory technology and clinical application, there is a clear need to bridge pharmacogenomics with core medical genetics education. At the School of Medical Sciences in USM, this integration focuses on establishing competency-based frameworks and interprofessional, case-based learning to equip students with practical skills in interpreting genetic variation and navigating genomic technologies.[12]

Specialised programmes such as the Master of Pathology (Medical Genetics) offered by the Human Genome Centre, case-based clinical discussions and DNA Day celebrations further support genomic literacy in medical education. These activities expose medical students and young clinicians to real-world examples of how genomic data are generated, interpreted and applied in clinical decision-making, thereby strengthening their understanding of personalised medicine beyond the formal curriculum.

The goal is to ensure that future doctors can interpret molecular test results, understand their limitations and explain them clearly to patients. Communicating genetic risk requires both scientific understanding and cultural sensitivity. These educational initiatives are directly aligned with Malaysia's national precision medicine agenda, helping to ensure a sustainable pipeline of clinicians who are competent in applying genomic information in routine care. By embedding genomics and pharmacogenomics training within competency-based medical education, the USM GLS Research Cluster contributes directly to build a workforce capable of supporting the implementation of the National Precision Medicine Project, accelerating the transition toward precision medicine at scale.

**Ethical, Legal and Social Implications (ELSI)**

We must also address the ethical, legal and social challenges associated with genomic data, particularly concerning the practicalities of conducting and reviewing human genomics research within the country. In Malaysia's multi-ethnic society, these ethical oversight processes are crucial for managing data privacy, preventing genetic discrimination and establishing robust institutional frameworks that protect participant autonomy while supporting scientific progress.[13] It is important that these diagnostic advances are accessible to all patient groups, regardless of socioeconomic background, to avoid widening existing health disparities.

At present, the Malaysian Personal Data Protection Act (PDPA) does not explicitly recognise genetic data as sensitive personal data. This regulatory gap leaves the public vulnerable to potential discriminatory misuse, such as employer coercion for genetic testing or the exploitation of genetic results by the insurance industry. As national genomic databases expand, it is critical for Malaysia to establish a comprehensive legislative blueprint. This framework must introduce explicit prohibitions against genetic discrimination, expand statutory definitions to protect genomic data and establish strong supervisory mechanisms to govern research, insurance underwriting, employment and the commercialisation of genetic information.

Furthermore, given that individual institutions often operate under their own research ethics committees and governance structures, greater harmonisation of ethical review processes and genomic consent frameworks is needed among centres actively involved in genomic and precision medicine research. Establishing more standardised approaches to genomic consent, data sharing, and secondary data use would facilitate multicentre collaboration while ensuring consistency in participant protection and regulatory oversight across institutions. It is essential that these diagnostic advances are accessible to all patient groups, regardless of socioeconomic background, to avoid widening existing health disparities.

## CONCLUSION

The integration of genomics into Malaysian healthcare represents a fundamental shift toward precision medicine, where clinical care is increasingly guided by molecular and patient-specific data rather than population-based approaches. Supported by national initiatives such as the National Precision Medicine Project and the MyGenom programme, Malaysia is progressively building the infrastructure, policy framework and clinical capacity required for genomics-driven healthcare.

Within this context, the USM GLS Research Cluster serves as a key translational platform, linking genomic research, bioinformatics and clinical practice to generate locally relevant evidence that supports improved diagnosis, risk stratification and therapeutic decision-making across diseases including rare disorders, cancer, thalassaemia and pharmacogenomics. Strengthened by integrated medical education, strategic institutional frameworks like ThinkLab and evolving ethical governance, these efforts collectively reinforce Malaysia's trajectory toward an equitable and sustainable precision medicine ecosystem that is responsive to its diverse population.

## REFERENCES

1. Green ED, Gunter C, Biesecker LG, et al. Strategic vision for improving human health at the forefront of genomics. Nature 2020; 586(7827): 1-16.
2. Ministry of Health Malaysia. Health White Paper: A Future-Proof Healthcare System. Putrajaya: MOH; 2023.
3. Academy of Sciences Malaysia. Position Paper on Precision Medicine Initiative in Malaysia. Kuala Lumpur: Academy of Sciences Malaysia; 2020. Available from: https://issuu.com/asmpub/docs/precision_medicine_report.

4. Malaysian Genome and Vaccine Institute. MyGenom Project: National Human Genome Sequencing Initiative. Kajang: National Institutes of Biotechnology Malaysia (NIBM), MOSTI; 2023.
5. The Petri Dish. UNESCO appoints local expert to lead in genetic research on thalassaemia. The Petri Dish. 2023. Available from: https://thepetridish.my/2023/02/06/unesco-appoints-local-expert-to-lead-in-genetic-research-on-thalassaemia/.
6. Shafie AA, Supian A, Ahmad Hassali MA, et al. Rare disease in Malaysia: Challenges and solutions. PLoS One 2020; 15(4): e0230850.
7. Brlek P, Škaro V, Hrvatin N, et al. Advances in Precision Oncology: From Molecular Profiling to Regulatory-Approved Targeted Therapies. Cancers (Basel) 2025; 17(21): 3500.
8. Aziz A, Farizan NH, Patar MNAA, et al. Molecular genetics and neurogenetics in central nervous system tumours: clinical implications for precision medicine in Malaysia. Malays J Med Sci 2024; 31(2): 45-58.
9. Principi N, Petropulacos K, Esposito S. Impact of pharmacogenomics in clinical practice. Pharmaceuticals (Basel) 2023; 16(11): 1596.
10. Phanthunane C, Pongcharoen S, Pannarunothai S, et al. Precision medicine in Asia enhanced by next-generation sequencing: Implications for Thailand through a scoping review and interview study. Clin Transl Sci 2024; 17: e13868.
11. Halim-Fikri H, Etemad A, Abdul Latif AZ, et al. The first Malay database toward the ethnic-specific target molecular variation. BMC Res Notes 2015; 8: 176.
12. Azizova M, Ochilova G, Azimova K, et al. Bridging pharmacogenomics and medical genetics education to prepare students for personalized medicine. Genetics and Molecular Research 2026; 25(1): gmr24124.
13. Zee TW, Abdul Aziz MFB, Wei PC. Ethical challenges of conducting and reviewing human genomics research in Malaysia: An exploratory study. Dev World Bioeth 2024; 24(4): 331-41.

# Psychosocial and health system factors associated with tuberculosis treatment adherence in Kota Kinabalu, Sabah

**Veshny Ganesan, MPH[1], Holly Girlchy Jastin, MPH[1], Saravanan Jayaraman, MD[2], Sarveshwarry Gangatharan, MBBS[2], Richard Avoi, MPH(Epidemiology)[1]**

[1]Public Health Medicine Department, Faculty of Medicine and Health Sciences, Universiti Malaysia Sabah, Kota Kinabalu, Sabah, Malaysia, [2]Sabah State Health Department, Kota Kinabalu, Sabah, Malaysia

**ABSTRACT**

**Introduction: Treatment adherence remains a major challenge in tuberculosis (TB) control and may be influenced by psychosocial and health system factors that remain underexplored in many settings. This study aimed to examine the association between psychosocial and health system factors and treatment adherence among TB patients in Kota Kinabalu, Sabah.**

**Materials and Methods: A cross-sectional study was conducted among 351 TB patients registered in the National TB Registry between 2023 and 2024. Data were collected using structured, validated, and translated questionnaires, including the TB Stigma Scale and the Patient Health Questionnaire-9 (PHQ-9). Variables included sociodemographic characteristics, TB knowledge, treatment-related factors, and healthcare system factors. Simple and multivariable logistic regression analyses were performed to identify factors of treatment adherence.**

**Results: Stigma was negatively associated with treatment adherence (AOR=0.90; 95% CI: 0.86–0.95; p<0.001), whereas higher TB knowledge was associated with higher treatment adherence (AOR=1.20; 95% CI: 1.06–1.35; p=0.004). Compared with video directly observed therapy (VDOT), healthcare worker (HCW)-supervised direct observed treatment short-course (DOTS) was associated with lower treatment adherence (AOR=0.23; 95% CI: 0.06–0.90; p=0.030). Longer clinic waiting time was associated with higher treatment adherence (AOR=1.09; 95% CI: 1.05–1.13; p<0.001). Depression was negatively associated with adherence in univariate analysis but was not statistically significant in the multivariable model (AOR=0.58; 95% CI: 0.21–1.58; p=0.285).**

**Conclusion: Stigma, TB knowledge, DOTS modality, and clinic waiting time were independently associated with TB treatment adherence in this setting. These findings highlight the importance of integrated, patient-centered TB care that addresses stigma, strengthens patient education, and incorporates digital approaches such as VDOT. Strengthening multifaceted interventions targeting both psychosocial and health system factors may improve TB treatment outcomes in Malaysia and similar high-burden settings.**

**KEYWORDS:**
*Tuberculosis; stigma; depression; DOTS, knowledge; adherence*

## INTRODUCTION

Tuberculosis (TB) remains a major global public health challenge, particularly in developing countries. Although substantial progress has been made in diagnosis and treatment, TB continues to cause significant morbidity and mortality worldwide. Ensuring consistent treatment adherence remains a critical challenge in achieving effective TB control.

The Global Tuberculosis Report estimated that approximately 10.7 million people developed TB worldwide in 2024. In Malaysia, the incidence of TB in 2022 was 113 cases per 100,000 population, with a treatment success rate of 79% for the 2021 cohort. Effective TB control depends largely on sustained adherence to treatment regimens, which typically extend for six months or longer, as recommended by the Ministry of Health Malaysia (MOH) Clinical Practice Guidelines. Maintaining adherence throughout the treatment is essential for successful therapy completion, preventing relapses, reducing the emergence of drug resistance, limiting disease transmission, and lowering TB-related mortality.

Numerous studies have identified a range of factors associated with medication adherence among TB patients, including sociodemographic characteristics, patient-related factors, treatment-related factors, health system influences, and social support systems.[1-2] However, psychosocial determinants such as stigma and depression remain insufficiently addressed despite growing evidence of their influence on treatment adherence. Evidence suggests that between 42% and 82% of TB patients experience some form of stigma. TB-related stigma may lead to social isolation, fear of disclosure, and reduced motivation to continue treatment.[3] It can affect patients' self-esteem and quality of life. Depression is also common among TB patients and may further compromise adherence by worsening health-seeking behaviour and treatment engagement.[4-5] Previous studies have reported depression prevalence ranging from 40% to 70% among TB patients in high-burden settings.[6] Depression can impair cognitive function, reduce motivation, and limit patients' ability to consistently follow treatment

*This article was accepted: 21 April 2026*
*Corresponding Author: Veshny Ganesan*
*Email: drveshny@gmail.com*

recommendations, thereby increasing the risk of treatment non-adherence.[7]

Despite increasing global attention, evidence on the psychosocial determinants of TB treatment adherence remains limited in Malaysia, particularly in Sabah. Therefore, this study aimed to examine the association between psychosocial and health system factors and treatment adherence among TB patients in Kota Kinabalu, Sabah. Addressing these determinants through integrated, patient-centered care approaches is essential to ensure that patients receive adequate psychological and social support to complete treatment. The findings may inform the development of more effective and context-specific TB control strategies aligned with the WHO End TB Strategy 2035, ultimately contributing to improved treatment outcomes in Sabah and other high-burden settings.

## MATERIALS AND METHODS

### Study Design and Study Setting

This cross-sectional study was conducted in Kota Kinabalu, the capital and largest district of Sabah, Malaysia, with an estimated population of 500,421 according to the Department of Statistics of Malaysia (DOSM 2020). The district has a high TB burden, with approximately 1,400 cases reported in 2023, according to the National Tuberculosis Registry (NTBR). In Kota Kinabalu, TB treatment services are provided through four government primary care facilities, namely Luyang, Manggatal, Inanam, and Telipok, all operated under the supervision of the Kota Kinabalu District Health Office. These four health centers were chosen as study sites for data collection. The data collection period lasted three months, from May 2024 to July 2024, spanning twelve weeks.

### National Tuberculosis Registry (NTBR)

In Malaysia, TB is a legally notifiable disease. All newly diagnosed TB cases, including those identified in both public and private healthcare facilities, are mandatorily notified to the district health office and recorded in the NTBR system. The Ministry of Health Malaysia coordinates the NTBR and functions as the national surveillance and monitoring system for TB.

### Study Population and Sampling Criteria

All adult TB patients registered at the selected TB treatment center in Kota Kinabalu were considered the study population. Patients aged 18 years or older, registered in the NTBR during the 2023–2024 cohort year, and who had completed at least 1 month of TB treatment were included. TB patients with pre-existing (documented) mental health conditions, pregnant or postpartum TB patients within six weeks of delivery, and those who declined to give written informed consent were all excluded.

### Sample Size Calculation

The sample size was calculated using G*Power with a 95% confidence level to estimate the prevalence of stigma and depression among adult TB patients in Kota Kinabalu. Based on a reported depression[8] prevalence of 45% and using the single population proportion formula with a 5% margin of error, the required sample size was determined to be 381. For stigma, a prevalence of 57% was used[9], yielding a sample size of 377. The larger estimate of 381 was adopted as the final target sample size. Participants were consecutively recruited from the NTBR 2023–2024 cohort, based on the most recent notification dates, and all met the study's inclusion and exclusion criteria.

### Operational Definition and Study Variables

The primary outcome variable in this study was TB treatment adherence. According to the World Health Organization, medication adherence refers to the extent to which a patient's behaviour aligns with the prescribed treatment recommendations provided by healthcare professionals.[10] In this study, non-adherence was defined as missing 10% or more of the total prescribed doses during either the intensive or continuation phase of TB treatment.[11] Key independent variables included stigma (measured by the TB Stigma Scale), depression (measured by Patient Health Questionnaire-9), and TB knowledge (measured by the TB Knowledge Questionnaire). Potential confounders included sociodemographic characteristics (age, sex, nationality, education level, employment status, and income), treatment-related factors (side effects, Directly Observed Treatment Short course abbreviated as DOTS, treatment duration), and healthcare access variables (distance to clinic and waiting time).

Healthcare worker (HCW)-supervised DOTS refers to direct observation of medication intake by healthcare personnel at health facilities. Family-supervised DOTS involves treatment observation by a designated household member following counselling by HCWs. Video directly observed therapy (VDOT) allows patients to record or submit videos of medication intake via a mobile application, which are reviewed subsequently by HCWs. Treatment-related side effects were identified based on patient self-report during routine clinic visits and documented in medical records by attending healthcare providers. Distance to the clinic was assessed using the patient's residential location and the estimated travel distance to the treatment facility. Clinic waiting time was defined as the duration from registration to medical consultation and was assessed based on patient self-report during the interview.

### Data Collection Tools

Data were collected using a structured, self-administered questionnaire comprising five sections: sociodemographic information, stigma, depression, TB knowledge, and treatment adherence. The first section comprises semi-structured items on sociodemographic characteristics, TB treatment-related factors, and health system-related factors.

Stigma was assessed using the 12-item TB Stigma Scale (TSS) developed by Zakaria et al.[5], rated on a 4-point Likert scale. Total scores ranged from 0 to 36, with higher scores indicating greater perceived stigma. The scale demonstrated acceptable internal consistency (Cronbach's alpha = 0.78).

Depression was measured using the Patient Health Questionnaire-9 (PHQ-9), a 9-item screening tool rated on a 4-point Likert scale. Scores ranged from 0 to 27 and were categorized into normal, mild, moderate, and severe levels based on validated cut-off points. The tool showed strong

internal consistency (Cronbach's alpha = 0.89) in prior Malaysian validation studies by Sun et al.[12] TB knowledge was assessed using the 25-item TB Knowledge Questionnaire by Zakaria et al.[5], with a maximum score of 25. Higher scores indicated greater knowledge. The instrument showed moderate internal consistency (Cronbach's alpha = 0.62).

Treatment adherence was measured using the Malaysian Medication Adherence Assessment Tool (MyMAAT), developed by Hatah et al.[13] This 12-item scale, rated on a 5-point Likert scale, yields a total score ranging from 0 to 60. Respondents scoring ≥54 were classified as adherent, while those scoring <54 were considered non-adherent. The cut-off points were based on validated scoring systems to ensure interpretability and clinical relevance. The tool demonstrated high internal consistency (Cronbach's alpha=0.91). Self-reported adherence was verified through cross-checking with clinic DOTS records and confirmation by HCWs to enhance data accuracy and reduce reporting bias. All instruments were translated into the Malay language and previously validated for use in the Malaysian context.

**Data Management and Analysis**

Data were entered into Microsoft Excel and analysed using SPSS version 29 and Jamovi version 2.6.26. The dataset was complete with no missing values. Descriptive statistics summarised participant characteristics, with categorical variables presented as frequencies and percentages, and continuous variables as medians with interquartile ranges (IQRs). Simple and multivariable logistic regression were used to examine associations between treatment adherence and independent variables, including sociodemographic characteristics, treatment-related factors, healthcare system factors, stigma, depression, and TB knowledge. Depression was initially categorized into four levels (normal, mild, moderate, and severe) based on established cut-offs. Due to small numbers in the moderate and severe groups, it was dichotomized into "normal" and "depression" to ensure adequate statistical power. Variables with $p<0.05$ and theoretically relevant predictors with $p<0.25$ in the univariable analysis were included in the multivariable model to control potential confounders.[14-15] Adjusted odds ratios (AORs) with 95% confidence intervals were reported. A p-value ≤0.05 was considered statistically significant. Model assumptions, including multicollinearity and model fit, were assessed.

**Ethical Consideration**

This study received ethical approval from the Medical Research Ethics Committee (MREC) of Malaysia (NMRR ID: 24-00556-TXG), the Research Committee of University Malaysia Sabah [JKEtika 1/24 (13)], and the Sabah State Health Department (UMS/FPSK6.9/600-2/1/33). All participants provided written informed consent after being informed of the study objectives and procedures. Confidentiality was maintained, and participants were informed of their right to withdraw at any time without consequences. The study was conducted in accordance with the Declaration of Helsinki and reported in line with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines to ensure transparency and completeness.

## RESULTS

**Sociodemographic Characteristics of Respondents**

The study included 351 respondents, a response rate of 92.0%. The sociodemographic characteristics of the respondents are summarised in Table I. Among the respondents, 59 (16.8%) were 18–24 years old, 236 (67.2%) were 25–59 years old, and 56 (16.0%) were over 60 years old. Age >60 had the highest adherence at 89.3%. A majority of responders were male (n=213, 60.7%), while 39.3% were female (n=138). Adherence was higher among women (85.5%) than men (83.1%). Malaysians (n=199, 56.7%) outnumbered non-Malaysians (n=152, 43.3%). Non-Malaysians (81.6%) had lower adherence than Malaysians (85.9%). The unemployed were the majority (n=194, 55.3%), while employed respondents were 44.7% (n=157). The unemployed had a greater adherence rate (85.1%) than the employed (82.8%). Among the respondents, 27.4% had no formal education, 32.8% had primary education, 29.6% had secondary education, and 9.4% had tertiary education. The highest adherence rate was observed among those with secondary education (87.9%), while the lowest was among those with no formal education (79.2%). In terms of income, 24.5% earned less than RM 1000, 32.8% earned RM 1000–1999, 39.9% earned RM 2000–3999, and 2.9% earned more than RM 4000. Adherence rates increased with income, with the highest adherence in the > RM 4000 group (90.0%) and the lowest in the < RM 1000 group (74.4%).

**Prevalence of Depression and Medication Adherence**

Of the 351 TB patients, 295 (84.0%; 95% CI: 80.2–87.9) were adherent to their medication regimen, while 56 (16.0%; 95% CI: 12.1-19.8) were non-adherent. Depression was reported in 10.9% of respondents, with most cases classified as mild (9.4%; 95% CI: 6.4–12.5), followed by moderate (0.9%; 95% CI: 0.0–1.8) and severe depression (0.6%; 95% CI: 0.0–1.4). Details are represented in Table II.

**Factors associated with medication adherence**

Simple logistic regression identified stigma, depression, TB knowledge, monthly income, clinic waiting time, and distance to the clinic as significant predictors of treatment adherence (Table III). Higher stigma (OR=0.89; 95% CI: 0.85–0.93; $p<0.05$) and depression scores (OR=0.23; 95% CI: 0.11–0.48; $p<0.05$) were associated with lower treatment adherence, whereas higher TB knowledge scores (OR=1.17; 95% CI: 1.09–1.26; $p<0.05$) were associated with better treatment adherence. Patients with higher monthly income (RM 2,000–3,999) also demonstrated better treatment adherence (OR=2.87; 95% CI: 1.39–5.90; $p<0.05$). In addition, longer clinic waiting time (OR=1.10; 95% CI: 1.06–1.13; $p<0.001$) and greater distance to the clinic (OR=1.10; 95% CI: 1.01–1.20; $p<0.05$) were associated with higher treatment adherence.

In the final multivariable logistic regression model (Table IV), stigma, TB knowledge, clinic waiting time, and DOTS modality remained significant predictors of treatment adherence. Stigma was inversely associated with treatment adherence (AOR=0.90; 95% CI: 0.86–0.95; $p<0.001$), while higher TB knowledge (AOR=1.20; 95% CI: 1.06–1.35; $p<0.05$) and longer clinic waiting time (AOR=1.09; 95% CI: 1.05–1.13; $p<0.001$) were associated with higher treatment adherence.

**Table I: Sociodemographic Characteristics of the Participants (n=351)**

| Variables | Characteristics | Total | Adherent (n=295) | | Non-adherent (n=56) | |
|---|---|---|---|---|---|---|
| | | | n | % | n | % |
| Age (years) | 18 - 24 | 59 | 49 | 83.1 | 10 | 16.9 |
| | 25 - 59 | 236 | 196 | 83.1 | 40 | 16.9 |
| | > 60 | 56 | 50 | 89.3 | 6 | 10.7 |
| Gender | Male | 213 | 177 | 83.1 | 36 | 16.9 |
| | Female | 138 | 118 | 85.5 | 20 | 14.5 |
| Nationality | Malaysian | 199 | 171 | 85.9 | 28 | 14.1 |
| | Non-Malaysian | 152 | 124 | 81.6 | 28 | 18.4 |
| Employment status | Employed | 157 | 130 | 82.8 | 27 | 17.2 |
| | Unemployed | 194 | 165 | 85.1 | 29 | 14.9 |
| Education level | Tertiary | 33 | 28 | 84.8 | 5 | 15.2 |
| | Secondary | 107 | 94 | 87.9 | 13 | 12.1 |
| | Primary | 115 | 97 | 84.3 | 18 | 15.7 |
| | No formal education | 96 | 76 | 79.2 | 20 | 20.8 |
| Income (RM) | < 1000 | 86 | 64 | 74.4 | 22 | 25.6 |
| | 1000-1999 | 115 | 97 | 84.3 | 18 | 15.7 |
| | 2000-3999 | 140 | 125 | 89.3 | 15 | 10.7 |
| | >4000 | 10 | 9 | 90.0 | 1 | 10.0 |
| Depression | Normal | 313 | 272 | 86.9 | 41 | 13.1 |
| | Mild | 33 | 20 | 60.6 | 13 | 39.4 |
| | Moderate | 3 | 1 | 33.3 | 2 | 66.7 |
| | Severe | 2 | 2 | 100.0 | 0 | 0.0 |
| DOTS modality | HCW-supervised | 212 | 185 | 87.3 | 27 | 12.7 |
| | Family-supervised | 104 | 82 | 78.8 | 22 | 21.2 |
| | VDOT | 35 | 28 | 80.0 | 7 | 20.0 |
| Duration of treatment (days) | <180 | 288 | 242 | 84.0 | 46 | 16.0 |
| | >180 | 63 | 53 | 84.1 | 10 | 15.9 |
| Side effects | Present | 58 | 47 | 81.0 | 11 | 19.0 |
| | Absent | 293 | 248 | 84.6 | 45 | 15.4 |
| Clinic waiting time (min) | 0-30 | 285 | 229 | 80.4 | 56 | 19.6 |
| | >30 | 66 | 66 | 100.0 | 0 | 0.0 |
| Distance to clinic (km) | 0-10 | 307 | 257 | 83.7 | 50 | 16.3 |
| | >10 | 44 | 38 | 86.4 | 6 | 13.6 |
| Stigma | Median (IQR) | | 0.0(12.0) | | 12.0(6.0) | |
| Knowledge | Median (IQR) | | 22.0(1.0) | | 22.0(2.0) | |

**Table II: Prevalence of Depression and Medication Adherence among the Respondents (n=351)**

| Variable | Characteristics | Frequency, n | Percentage, % | CI (95%) |
|---|---|---|---|---|
| Depression | Normal | 313 | 89.2 | 85.92- 92.42 |
| | Mild | 33 | 9.4 | 6.35- 12.45 |
| | Moderate | 3 | 0.9 | 0.0- 1.82 |
| | Severe | 2 | 0.6 | 0.0- 1.36 |
| Medication adherence | Adherent | 295 | 84.0 | 80.21- 87.88 |
| | Non-adherent | 56 | 16.0 | 12.12- 19.79 |

*CI: confidence interval

Compared with VDOT, HCW-supervised DOTS was associated with lower treatment adherence (AOR=0.23; 95% CI: 0.06–0.90; p<0.05). In the unadjusted analysis, HCW-supervised DOTS showed higher odds of adherence compared with VDOT (p=0.25). However, after adjustment for potential confounders, HCW-supervised DOTS was associated with lower adherence, indicating that the crude association was influenced by underlying differences between patient groups. Depression was not statistically significant in the adjusted model (AOR=0.58; 95% CI: 0.21–1.58; p=0.285). The final model explained 34.2% of the variance in treatment adherence (Nagelkerke $R^2$=0.342). Multicollinearity was not observed, with variance inflation factor (VIF) values ranging from 1.08 to 1.31. The inclusion of depression slightly reduced the model fit (Hosmer–Lemeshow p=0.03); however, this variable was retained due to its theoretical relevance in adherence behaviour.

## DISCUSSION

This study identified stigma, knowledge, DOTS modality, and clinic waiting time as key factors of treatment adherence among TB patients in Kota Kinabalu. The median stigma score was lower among adherent patients compared with non-adherent patients, indicating a negative relationship between stigma and treatment adherence. This finding is

**Table III: Simple Logistic Regression Model for Factors Associated with TB Treatment Adherence**

| Variables | Characteristics | Total | OR | CI (95%) | p-value |
|---|---|---|---|---|---|
| Age (years) | Median (IQR) | 1.01 | 0.99-1.03 | 0.241 | |
| Gender | Male | 213 | 0.83 | 0.46 -1.51 | 0.548 |
| | Female | 138 | Ref | - | - |
| Nationality | Malaysian | 199 | 1.38 | 0.78-2.45 | 0.271 |
| | Non-Malaysian | 152 | Ref | - | - |
| Employment status | Employed | 157 | Ref | - | - |
| | Unemployed | 194 | 1.18 | 0.67-2.09 | 0.568 |
| Education level | Tertiary | 33 | Ref | - | - |
| | Secondary | 107 | 1.29 | 0.42-3.94 | 0.653 |
| | Primary | 115 | 0.96 | 0.33-2.82 | 0.944 |
| | No formal education | 76 | 0.68 | 0.23-1.98 | 0.478 |
| Income (RM) | < 1000 | 86 | Ref | - | - |
| | 1000-1999 | 115 | 1.85 | 0.92-3.72 | 0.084 |
| | 2000-3999 | 140 | 2.87 | 1.39-5.90 | 0.004** |
| | >4000 | 10 | 3.09 | 0.37-25.83 | 0.297 |
| Depression | Normal | 313 | Ref | - | - |
| | Depression | 38 | 0.23 | 0.11-0.48 | <0.001** |
| DOTS modality | HCW-supervised | 212 | 1.71 | 0.68-4.30 | 0.252 |
| | Family-supervised | 104 | 0.93 | 0.36-2.42 | 0.884 |
| | VDOT | 35 | Ref | - | - |
| Side effects | Present | 58 | Ref | - | - |
| | Absent | 293 | 1.29 | 0.62-2.68 | 0.494 |
| Duration of treatment (days) | Median (IQR) | | 1.00 | 1.00-1.01 | 0.539 |
| Clinic waiting time (min) | | | 1.10 | 1.06-1.13 | <0.001** |
| Distance to clinic (km) | | | 1.10 | 1.01-1.20 | 0.034* |
| Stigma | | | 0.89 | 0.85-0.93 | <0.001** |
| Knowledge | | | 1.17 | 1.09-1.26 | <0.001** |

OR: Unadjusted Odds Ratio; CI: Confidence Interval; Ref: Reference
*p<0.05; **p<0.01

**Table IV: Multivariable Logistic Regression Model for Factors Associated with TB Treatment Adherence**

| Variable | AOR | CI (95%) | p-value |
|---|---|---|---|
| Stigma | 0.90 | 0.86-0.95 | <0.001** |
| Knowledge | 1.20 | 1.06-1.35 | 0.004** |
| Depression | 0.58 | 0.21-1.58 | 0.285 |
| Normal | Ref | - | - |
| Clinic waiting time (min) | 1.09 | 1.05-1.13 | <0.001** |
| DOTS modality | | | |
| HCW-supervised | 0.23 | 0.06-0.90 | 0.030* |
| Family supervised | 0.35 | 0.09-1.30 | 0.115 |
| VDOT | Ref | - | - |

AOR: Adjusted Odds Ratio; CI: Confidence Interval; Ref: Reference
*p <0.05; **p<0.01

consistent with studies from Malaysia, China, India, and several African countries, which have demonstrated that both external and internalised stigma can hinder care-seeking behaviours and treatment completion.[1,16-21] A substantial proportion of participants in this study had lower educational attainment, which may contribute to higher levels of stigma and, in turn, adversely affect treatment adherence. In addition, the lack of routine psychological screening for TB patients may intensify the psychological burden associated with stigma. External stigma, including social exclusion and discrimination by peers, family members, or HCWs, may contribute to patient isolation, while internalised stigma can diminish self-worth and foster feelings of hopelessness, further discouraging treatment adherence.[17,22-23] A study from Tanzania reported that 52.6% of HCWs exhibited high levels of TB-related stigma, including negative attitudes, stereotyping, and stigmatising behaviours toward patients.[18] Such stigma may undermine patient trust and compromise the quality of TB services. Collectively, these findings highlight the need for stigma-reduction strategies at both community and healthcare levels. Public health initiatives should prioritise community education to challenge negative perceptions of TB. In parallel, HCWs should be trained to deliver compassionate and non-judgmental care. Integrating routine mental health screening into TB services may further support the identification and management of stigma-related psychosocial challenges, ultimately improving treatment adherence and outcomes.

Consistent with our hypothesis, this study found that higher TB knowledge was significantly associated with better treatment adherence. This is consistent with findings from Nigeria, Eritrea, and China, in which patients with a good understanding of TB aetiology, transmission, and treatment were more likely to adhere to their medication regimens.[24-27] A lack of knowledge may lead to misconceptions, underestimation of disease severity, and treatment discontinuation. However, knowledge alone may not ensure adherence. Beliefs, attitudes, and lived experiences play a critical role in shaping health behaviour. Patients who perceive themselves as cured before completing treatment or who view TB as non-threatening may discontinue medication prematurely. Similarly, perceived barriers such as side effects, long treatment duration, and logistical challenges may discourage adherence when they outweigh perceived benefits.[28] Cultural beliefs and traditional healing practices also influence adherence.[29] A study in Ethiopia reported that belief in traditional remedies led some patients to abandon conventional TB treatment.[28] These findings highlight the importance of integrating culturally sensitive health education that resonates with patients' values and worldviews to drive behaviour change. Patients are more likely to adhere when the information provided is accurate, relevant, and respectful of their culture. Therefore, TB education strategies should be community-based, culturally appropriate, and focused on both increasing awareness and addressing misconceptions to promote sustained adherence.

A notable finding of this study was higher treatment adherence observed among patients monitored via VDOT compared with those supervised by HCWs, challenging the long-standing assumption that HCW-supervised DOTS is the optimal approach. These findings are consistent with studies from Tibet, the United Kingdom, and the United States, which have highlighted the practical challenges of traditional DOTS and the benefits of remote monitoring options, including VDOT, medication reminders, and TB mobile apps.[29-32] VDOT enables patients to complete treatment in the privacy of their homes, thereby reducing social discomfort and stigma associated with daily clinic visits.[2,33] This is particularly relevant in Sabah, where logistical and financial barriers may hinder adherence. Emerging evidence also suggests that VDOT and gamified digital platforms may enhance adherence and patient motivation.[31] However, the observed association between VDOT and higher treatment adherence should be interpreted within the context of routine clinical practice. In this setting, VDOT was primarily offered to patients who faced logistical barriers to daily clinic attendance as part of efforts to strengthen telehealth services. Participation required access to a smartphone, either owned by the patient or available through a family member, which may reflect differences in digital access or social support. These factors suggest that patients enrolled in VDOT may have differed from those under HCW-supervised DOTS in ways not fully captured by measured variables. Although multivariable adjustment was performed, residual confounding related to digital access, family support, or patient engagement may have contributed to the observed association. Nevertheless, these findings highlight the potential of VDOT as a flexible and patient-centered supervision strategy within routine TB care. Integrating digital approaches may strengthen treatment adherence and improve outcomes, particularly when tailored to address logistical, financial, and psychosocial barriers in Malaysia and other high-burden settings.

The association between longer clinic waiting time and higher treatment adherence was unexpected and contrasts with most published evidence, where prolonged waiting time is typically considered a barrier to care.[34-36] In Table I, the subgroup of patients reporting waiting times greater than 30 minutes demonstrated 100% adherence (n = 66). This finding should be interpreted in the context of the relatively small subgroup size, which may reflect a ceiling effect and limited variability rather than a true association. In this study, waiting time may reflect underlying clinic- or patient-level characteristics that were not directly measured. For example, clinics with higher patient volumes may experience longer queues while simultaneously implementing more systematic treatment management practices, such as scheduled follow-up, active tracing of missed appointments, and closer adherence monitoring. Similarly, individuals who are more motivated to complete treatment may be more willing to tolerate longer waiting times. In this context, waiting time may serve as a proxy for broader organisational or behavioural factors rather than a direct determinant of adherence. These findings highlight the complexity of service delivery dynamics in routine practice and warrant further investigation using objective workflow assessments and qualitative approaches to elucidate the underlying mechanisms better.

Numerous studies have reported a significant association between depression and poor TB treatment outcomes, including non-adherence, delayed recovery, and drug resistance.[37-39] In contrast, our study did not find a significant association between depression and treatment adherence. A possible explanation is the low prevalence and severity of depressive symptoms in our sample, where most participants reported only mild symptoms (9.4%), and fewer than 2% had moderate to severe depression. Similar findings have been reported in Sarawak, where depression was observed in only 7.7% of TB patients.[40] These findings suggest that mild psychological distress may not substantially influence adherence behaviour. The relatively low prevalence of depression in this population may reflect a supportive healthcare environment. TB treatment is provided free of charge in public facilities, reducing financial burden. Out-of-pocket transportation costs for DOTS visits may continue to pose challenges for some patients. However, additional support is provided through initiatives by non-governmental organisations (NGOs), such as SABATA in Sabah and MAPTB in Peninsular Malaysia. These NGOs provide transportation subsidies, nutritional support, and psychosocial counseling, which may help alleviate the physical, psychological, and social burdens associated with TB. These findings highlight the importance of integrated care models that incorporate mental health assessment and social support within TB services. While depression has been shown to adversely affect TB outcomes globally, the present findings suggest that its impact may be attenuated in settings with comprehensive, patient-centered support systems.

**Strengths and Limitations of the Study**

This study achieved a good response rate of 92%, with 351 TB patients completing guided questionnaires, ensuring consistency in data collection. Measurement validity was enhanced using validated instruments in the local language. However, several limitations must be acknowledged. Delays in ethical approval shortened the data collection period and may have limited the recruitment of patients with clinic appointments outside the study timeframe. The cross-sectional design allowed estimation of prevalence but precluded causal inferences. Depression was dichotomized for analysis due to the small number of participants with moderate to severe depressive symptoms. While this approach improved statistical stability, it may have reduced sensitivity to detect severity-specific effects. In addition, the relatively low prevalence and severity of depressive symptoms in the study sample may have limited statistical power to identify an independent association with treatment adherence. Future studies with larger samples across varying levels of depression severity may better elucidate potential dose–response relationships. Finally, self-reported adherence may be subject to recall and social desirability bias. Nevertheless, this was mitigated through triangulation with DOTS records and verification with HCWs.

**Implications**

This study's findings align with the End TB Strategy by identifying key areas to strengthen treatment adherence. The observed associations between stigma, knowledge, DOTS modality, and clinic waiting time with treatment adherence highlight the importance of addressing psychosocial and health system factors through patient education, counseling, and integrated support services. These approaches are consistent with Pillar 1: Integrated, patient-centered care and prevention, which emphasises comprehensive care that addresses both clinical and psychosocial needs. In line with Pillar 2: Bold policies and supportive systems, integrating mental health screening within TB services may facilitate early identification and management of stigma and depressive symptoms. In addition, health system improvements such as flexible clinic hours and transportation support may help reduce logistical barriers and enhance treatment adherence. Consistent with Pillar 3: Intensified research and innovation, future research should build upon existing evidence on the effectiveness of VDOT and evaluate the scalability, long-term impact, and cost-effectiveness of digital adherence technologies across diverse settings.

## CONCLUSION

This study found that stigma, TB knowledge, DOTS modality, and clinic waiting time were significantly associated with treatment adherence among TB patients in Kota Kinabalu. Higher stigma and lower TB knowledge were associated with reduced adherence, highlighting the importance of psychosocial and educational support. The associations observed on DOTS modality and clinic waiting time likely reflect complex system- and patient-level dynamics within routine clinical practice. These findings highlight the need for multifaceted strategies that address stigma, strengthen patient education, and optimize context-appropriate service delivery to improve TB treatment outcomes in Malaysia and similar high-burden settings.

## ACKNOWLEDGEMENTS

The authors express their sincere appreciation to the Kota Kinabalu District Health Office and the staff of primary healthcare facilities in Luyang, Manggatal, Inanam, and Telipok for their invaluable support during data collection. The authors also thank all TB patients who participated in this study, as well as the academic staff of the Faculty of Medicine and Health Sciences, Universiti Malaysia Sabah, for their continuous guidance and support.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## FUNDING

This study was self-funded by the authors.

## REFERENCES

1. Yan S, Zhang S, Tong Y, Yin X, Lu Z, Gong Y. Nonadherence to antituberculosis medications: the impact of stigma and depressive symptoms. Am J Trop Med Hyg 2018; 98(1): 262-5.
2. Sazali MF, Rahim SSSA, Mohammad AH, Kadir F, Payus AO, Avoi R, et al. Improving tuberculosis medication adherence: the potential of integrating digital technology and health belief model. Tuberc Respir Dis 2023; 86(2): 82-93.
3. Chen X, Du L, Wu R, Xu J, Ji H, Zhang Y, et al. Tuberculosis-related stigma and its determinants in Dalian, Northeast China: a cross-sectional study. BMC Public Health 2021; 21(1): 6.
4. Medina-Marino A, de Vos L, Daniels J. Social isolation, social exclusion, and access to mental and tangible resources: mapping the gendered impact of tuberculosis-related stigma among men and women living with tuberculosis in Eastern Cape Province, South Africa. BMC Glob Public Health 2025; 3(1): 50.
5. Zakaria R, Amri NS, Mohamad N. Stigma and depression among tuberculosis patients in Kedah, Malaysia. IIUM Med J Malaysia 2022; 21(4): 114-9.
6. Alemi Q, Panter-Brick C, Oriya S, Ahmady M, Alimi AQ, Faiz H, et al. Afghan mental health and psychosocial well-being: thematic review of four decades of research and interventions. BJPsych Open 2023; 9(4): e125.
7. Abdurahman S, Yadeta T, Ayana D, Abdurke M, Ahmed J, Abdurehman A. Magnitude of depression and associated factors among patients on tuberculosis treatment at public health facilities in Harari Regional State, Eastern Ethiopia: multi-center cross-sectional study. Neuropsychiatr Dis Treat 2022; 18: 1405-19.
8. Duko B, Bedaso A, Ayano G. The prevalence of depression among patients with tuberculosis: a systematic review and meta-analysis. Ann Gen Psychiatry 2020; 19(1): 30.
9. Mohammedhussein M, Hajure M, Shifa JE, Hassen TA. Perceived stigma among patient with pulmonary tuberculosis at public health facilities in southwest Ethiopia: a cross-sectional study. PLOS One 2020; 15(12): e0243433.
10. Gudeta DB, Leta K, Alemu B, Kandula UR. Medication adherence and associated factors among psychiatry patients at Asella Referral and Teaching Hospital in Oromia, Ethiopia: institution based cross sectional study. PLOS One 2023; 18(4): e0283829.
11. Mekonnen HS, Azagew AW. Non-adherence to anti-tuberculosis treatment, reasons and associated factors among TB patients attending at Gondar town health centers, Northwest Ethiopia. BMC Res Notes 2018; 11(1): 691.

12. Sun Y, Kong Z, Song Y, Liu J, Wang X. The validity and reliability of the PHQ-9 on screening of depression in neurology: a cross-sectional study. BMC Psychiatry 2022; 22(1): 98.
13. Hatah E, Rahim N, Makmor-Bakry M, Mohamed Shah N, Mohamad N, Ahmad M, et al. Development and validation of Malaysia Medication Adherence Assessment Tool (MyMAAT) for diabetic patients. Mathes T, editor. PLOS One 2020; 15(11): e0241909.
14. Miller BS, Loftus J, Kelkar M, Shrestha S, Parzynski C, Benjumea D, et al. Impact of daily growth hormone adherence on height velocity among children with growth hormone deficiency. Endocr Pract 2024; 30(9): 837-46.
15. Hosmer DW, Lemeshow S, Sturdivant RX. Applied logistic regression. 3rd ed. New York: Wiley; 2013.
16. Dixit K, Rai B, Aryal TP, de Siqueira-Filha NT, Dhital R, Sah MK, et al. Stigma, depression, and quality of life among people with pulmonary tuberculosis diagnosed through active and passive case finding in Nepal: a prospective cohort study. BMC Glob Public Health 2024; 2(1): 20.
17. Suliman Q, Lim PY, Md Said S, Tan KA, Mohd Zulkefli NA. Risk factors for early TB treatment interruption among newly diagnosed patients in Malaysia. Sci Rep 2022; 12(1): 745.
18. Muhandiki WD, Matemba LE, Mabega NG, Kisonga RM, Matechi EH, Kigumi HO, et al. Tuberculosis-related stigma among healthcare workers in Tanzania: level, experience and manifestations. Am J Health Res 2023; 11(1): 14-24.
19. Pradhan A, Koirala P, Bhandari SS, Dutta S, García-Grau P, Sampath H, et al. Internalized and perceived stigma and depression in pulmonary tuberculosis: do they explain the relationship between drug sensitivity status and adherence? Front Psychiatry 2022; 13: 869647.
20. Matakanye H, Tshitangano TG, Mabunda JT, Maluleke TX. Knowledge, beliefs, and perceptions of TB and its treatment amongst TB patients in the Limpopo Province, South Africa. Int J Environ Res Public Health 2021; 18(19): 10404.
21. Yi Y, Sun M, Chen X, Pan Y, Lu J, Yu Y, et al. Prejudice and determinants regarding tuberculosis patients among medical students in Dalian, Northeast China: a cross-sectional study. Front Public Health 2023; 11: 1292333.
22. Vericat-Ferrer M, Ayala A, Ncogo P, Eyene-Acuresila J, García B, Benito A, et al. Knowledge, attitudes, and stigma: the perceptions of tuberculosis in Equatorial Guinea. Int J Environ Res Public Health 2022; 19(14): 8227.
23. Mahbub T, Mathur T, Isaakidis P, Daftary A. "One-by-One, TB took everything away from me": a photovoice exploration of stigma in women with drug-resistant tuberculosis in Mumbai. Affilia 2024; 39(1): 148-69.
24. Iweama CN, Agbaje OS, Umoke PCI, Igbokwe CC, Ozoemena EL, Omaka-Amari NL, et al. Nonadherence to tuberculosis treatment and associated factors among patients using directly observed treatment short-course in north-west Nigeria: a cross-sectional study. SAGE Open Med 2021; 9: 2050312121989497.
25. Gebreweld FH, Kifle MM, Gebremicheal FE, Simel LL, Gezae MM, Ghebreyesus SS, et al. Factors influencing adherence to tuberculosis treatment in Asmara, Eritrea: a qualitative study. J Health Popul Nutr. 2018; 37(1): 1.
26. Lemma Tirore L, Ersido T, Beyene Handiso T, Shiferaw Areba A. Non-adherence to anti-tuberculosis treatment and associated factors among TB patients in public health facilities of Hossana town, Southern Ethiopia. Front Med 2024; 11: 1360351.
27. Fang XH, Shen HH, Hu WQ, Xu QQ, Jun L, Zhang ZP, et al. Prevalence of and factors influencing anti-tuberculosis treatment non-adherence among patients with pulmonary tuberculosis: a cross-sectional study in Anhui Province, Eastern China. Med Sci Monit 2019; 25: 1928-35.
28. Nezenega ZS, Perimal-Lewis L, Maeder AJ. Factors influencing patient adherence to tuberculosis treatment in Ethiopia: a literature review. Int J Environ Res Public Health 2020; 17(15): 5626.
29. Zhang L, Weng TP, Wang HY, Sun F, Liu YY, Lin K, et al. Patient pathway analysis of tuberculosis diagnostic delay: a multicentre retrospective cohort study in China. Clin Microbiol Infect 2021; 27(7): 1000-6.
30. Story A, Aldridge RW, Smith CM, Garber E, Hall J, Ferenando G, et al. Smartphone-enabled video-observed versus directly observed treatment for tuberculosis: a multicentre, analyst-blinded, randomised, controlled superiority trial. Lancet 2019; 393(10177): 1216-24.
31. Abas SA, Ismail N, Zakaria Y, Yasin SM, Ibrahim K, Ismail I, et al. Enhancing tuberculosis treatment adherence and motivation through gamified real-time mobile app utilization: a single-arm intervention study. BMC Public Health 2024; 24(1): 249.
32. Tadesse AW, Mohammed Z, Foster N, Quaife M, McQuaid CF, Levy J, et al. Evaluation of implementation and effectiveness of digital adherence technology with differentiated care to support tuberculosis treatment adherence and improve treatment outcomes in Ethiopia: a study protocol for a cluster randomised trial. BMC Infect Dis 2021; 21(1): 1149.
33. Jerene D, Levy J, Van Kalmthout K, Rest JV, McQuaid CF, Quaife M, et al. Effectiveness of digital adherence technologies in improving tuberculosis treatment outcomes in four countries: a pragmatic cluster randomised trial protocol. BMJ Open 2023; 13(3): e068685.
34. Gebremariam RB, Wolde M, Beyene A. Determinants of adherence to anti-TB treatment and associated factors among adult TB patients in Gondar city administration, Northwest, Ethiopia: based on health belief model perspective. J Health Popul Nutr 2021; 40(1): 49.
35. Workie MG, Aycheh MW, Birhanu MY, Tsegaye TB. Treatment interruption among drug-susceptible pulmonary tuberculosis patients in Southern Ethiopia. Patient Prefer Adherence 2021; 15: 1143-51.
36. Opperman M, Du Preez I. Factors contributing to pulmonary TB treatment lost to follow-up in developing countries: an overview. Afr J Infect Dis 2023; 17(1): 60-73.
37. Anye LC, Agbortabot Bissong ME, Njundah AL, Siewe Fodjo JN. Depression, anxiety and medication adherence among tuberculosis patients attending treatment centres in Fako Division, Cameroon: cross-sectional study. BJPsych Open 2023; 9(3): e65.
38. Agbeko CK, Mallah MA, He B, Liu Q, Song H, Wang J. Mental health status and its impact on TB treatment and its outcomes: a scoping literature review. Front Public Health 2022; 10: 855515.
39. Shringarpure K, Gurumurthy M, Sagili KD, Taylor M, Garner P, Tonsing J, et al. Patient adherence to tuberculosis treatment in the Indian subcontinent: systematic review and meta-synthesis of qualitative research. BMJ Open 2023; 13(5): e063926.
40. Tiong CY, Abd Aziz NA, Kamaluddin R, Hamzah Z. Prevalence of depression and associated factors among tuberculosis patients in primary care in the district of Kuching, Sarawak. Sains Malays 2020; 49(5): 1089-96.

ORIGINAL ARTICLE

# Mortality trends from 2010-2023 and excess mortalities in Perak during the COVID-19 pandemic

**Arvinder-Singh HS, PhD Community Health (Epidemiology & Statistics)[1,2], Ding Lay Ming, MHA[3], Nga Shih Hang, MRCPCH[4], Nur Ashikin Ahmad Razali, MD[3], SK David Raj Sinnapan, MD[3], Raja-Mangeet-Singh Basant Singh, Dip Medical Assistant[5], Siti Fatimah Kamaruddin, BA Organisational Management[3], Philip Rajan Devesahayam, MMed ORL[1,6], Jeyaseelan P Nachiappan, MRPCH[7]**

[1]Clinical Research Centre, Hospital Raja Permaisuri Bainun Ipoh, Ministry of Health, Malaysia, [2]Faculty Research Support Unit, Deputy Dean (International and Research) Office, Faculty of Medicine & Health Sciences, Universiti Putra Malaysia, [3]Perak State Health Department, Perak, Ministry of Health, Malaysia, [4]Clinical Research Centre, Hospital Seri Manjung, Perak, Ministry of Health, Malaysia, [5]Forensic Department, Hospital Raja Permaisuri Bainun Ipoh, Ministry of Health, Malaysia, [6]Otorhinolaryngology Department, Hospital Raja Permaisuri Bainun Ipoh, Ministry of Health, Malaysia, [7]Faculty of Medicine, Universiti Kuala Lumpur, Royal College of Medicine Perak, Malaysia

## ABSTRACT

**Introduction: COVID-19, caused by SARS-CoV-2 virus, is a respiratory infection that led to the 2020 pandemic. During the pandemic, mortality directly related to COVID-19 infection were classified as COVID-19 death based on case definition. However, excess mortality would be a more comprehensive method to look at the true impact of the pandemic rather than focusing only on COVID-19 deaths alone. The objective of this study was to determine the excess mortalities and top 5 causes of mortality that occurred during and after the COVID-19 pandemic in Perak.**

**Materials and Methods: Total and age-specific mortality data tabulated by the Department of Statistics Malaysia (DOSM) for the years 2010-2023 for the state of Perak was obtained. Data for the years 2010–2019 was re-grouped according to clustered age groups. This was used to generate the linear prediction line for mortality in 2020-2023 using Microsoft Excel 2010. Excess mortalities were calculated for 2020-2023 by subtracting the actual deaths from the predicted deaths. The top 5 common causes of mortality and COVID-19 deaths were also re-tabulated for the years 2020-2023 for the clustered age groups. "Positive Excess Mortality" (PEM) meant that the number of actual deaths were higher than predicted and "Negative Excess Mortality" (NEM) meant that the actual deaths were lower than the predicted number. Significant PEM meant that the value of the actual mortality was above the upper limit of the 95% confidence interval of the predicted mortality.**

**Results: All clustered age groups showed NEM for the year 2020. For the years 2021-2022, there was a PEM for all clustered age groups except those in the group "19 and below". The highest excess mortality was in the "65 and above" group with 343.44 and 685.56 per 100,000 age-specific population for 2021 and 2022 respectively. The mortality rate returned to the predicted value in 2023. In 2021 and 2022, there was a PEM for the "20-39" and "40-64" clustered age groups, however they were lower compared to the "65 and above" groups. Significant PEM was seen for all deaths in the "65 and above" in 2021 (237 per 100,000) and in 2022, 596 per 100,000. There was also a significant PEM after the removal of COVID-19 deaths in 2022 for the "65 and above" age groups- 366 per 100,000. Significant PEM was also seen in the "20-39" age groups and "40-64" age groups in 2021- 14 per 100,000 and 36 per 100,000 respectively. The other values that passed the 95%CI were deemed to be negligible. There were a few changes in the top 5 ranking for causes of death in Perak, the only obvious inclusion was deaths due to COVID-19 infections in 2021 in all groups except the "19 and below".**

**Conclusion: There was a PEM in all groups except "19 and below" after the year 2020, with the highest in the "65 and above" group. COVID-19 deaths were included in the top 5 causes of death and contributed only partly to the excess mortality across all groups except "19 and below".**

**KEYWORDS:**
*Excess mortality; COVID-19 deaths; mortality review; positive excess mortalities; negative excess mortalities; Malaysia*

## INTRODUCTION

COVID-19 infection is a respiratory infection caused by the virus SARS-CoV-2, a Coronaviridae family in the Nidovirales order and is known to be a single-stranded RNA virus.[1] It spreads through close contact via droplets and causes upper and lower respiratory tract illness. The severity ranged from being asymptomatic to having severe respiratory failure.[1] COVID-19 caused a pandemic in 2020 and resulted in many deaths globally.[1] The pandemic in Malaysia was officially declared from March 2020 to April 2022 with multiple waves hitting the country- the first being the alpha variant in 2020 followed by the beta, delta and finally the omicron variants.[1-3] Countries were forced into lock-downs and instituted various measures to reduce transmission such as masking, compulsory admission and self-isolation/quarantine.[1] Crowd control was applied to public areas especially in high-risk (ie hospitals and health clinics) to reduce transmission causing altering patient's regular time of follow up according to the standard of care.[4] COVID-19 pandemic impacted the

*This article was accepted: 21 April 2026*
*Corresponding Author: Arvinder-Singh HS*
*Email: arvinder.crc@gmail.com*

management of other communicable and non-communicable diseases including mental health issues and could have contributed to deaths.[5] These were known as collateral damages that occurred with COVID-19 that might have resulted into a compromise of the healthcare system.[6]

A "COVID-19 death" was defined as a death that was caused by COVID-19 (confirmed via a recognized Rapid Test Kits or Reverse-Transcriptase Polymerase Chain Reaction test recognized by the Ministry of Health Malaysia), no period of complete recovery from COVID-19 at the point of death and/or death within 30-days of being COVID-19 positive with the absence of any other known or possible cause.[7] This was the definition of COVID-19 mortality that was used in Malaysia for death reviews. Deaths that occurred with evidence of COVID-19 infection but didn't meet the criteria of a "COVID-19 death", was classified as "deaths with COVID-19". Though the deaths of COVID-19 were recorded accordingly, it was said that world-wide, it might have been severely underestimated due to the potential capacity of testing, reporting mechanisms of cases/deaths, threshold capacities of healthcare systems and inaccessibility due to restrictions.[4] The other issue that contributed to inaccurate reporting at a global stage was the different definitions of "COVID-19 death" in different countries- as communicated in a research by the World Health Organization.[8]

After considering the shortcomings and inaccuracy of looking at COVID-19 deaths alone, measuring the overall effect of the pandemic might not be as accurate- especially when intending to describe the impact of the pandemic on mortality trends in Perak.[4] This is where tracking all-cause mortalities during the pandemic might be a more accurate way to measure the effect of COVID-19 on deaths in total.[4]

The tracking of all-cause mortality has become an acceptable way of measuring disease burden on a particular event especially in the case of infectious diseases.[4] Excess mortalities refers to excess deaths, more than what is anticipated over a period of time and have been used for the surveillance of infectious diseases such as influenza and COVID-19.[2,4]

Excess mortalities can be measured and classified as "Positive Excess Mortality" (PEM) which means that the number of deaths that occurred were higher than what was predicted and a "Negative Excess Mortality" (NEM) refers to the number of deaths lower than what was predicted. When done with predicting deaths based on models, excess mortalities (actual mortalities minus the predicted morality- regardless of yielding PEM or NEM) can be used to see if particular significant events over time have led to an increase in the number of anticipated deaths or reduced it.[4] The mortality burden before, during and after the COVID-19 pandemic can offer a perspective of the mortality rates- if it were higher, the same or reduced.[9-10]

In a mathematical study conducted in Malaysia, the statistical modeling done with mortality data from 1995-2018 predicting potential excess mortalities after COVID-19 reported that Malaysia would see an increase in PEM especially in the elderly groups (age 60 and above).[7] In the initial phase, COVID-19 deaths were low but increased over a period of time especially with the ease of restrictions.[10] However, after vaccine coverage was achieved to a large population, the number of deaths began stabilizing before being reduced to lower numbers.[1,11] The excess mortalities might have differed according to countries (due to definitions, testing availability, acceptable sensitivity of testing and access to healthcare systems), and within a country, the dynamics of the population in each state may have caused difference rates of excess mortalities.[2] Though excess mortalities of Malaysia data was studied, very few studies focusing on state stratified results were done, especially looking at data according to age specific groups.

In Perak, the population dynamics slightly differ especially in the number of elderly people (ageing city potentially by 2030) when compared to average national numbers.[12] Thus, the difference of excess mortalities and reasons of causes of deaths can differ. In the earlier papers of excess mortalities in Malaysia, it showed that, there was no PEM but when fragmenting the data into different age groups, there was a PEM in those aged 60 and above.[4,10]

Perak is a state in northern Peninsula Malaysia and it is the 4th largest state. It has a population of about 2.5 million and it is known to be an ageing population. Perak has a major tertiary referral hospital and 4 other smaller tertiary hospitals.[13]

The primary objective of this study was to determine the excess mortalities in Perak during (2020-2021) and after (2022-2023) the COVID-19 pandemic. Another objective was to determine the top 5 mortality causes during and after the COVID-19 pandemic years.

## MATERIALS AND METHODS

The researchers obtained secondary data from the database managed by the Department of Statistics, Malaysia (DOSM), for Perak. These were age specific population and mortality for the years 2010-2023. We also received data for the total number of COVID-19 deaths (2020-2023) and the causes of mortality based on the ICD-10 coding from 2020-2023. Age-specific data obtained was for the following age groups were separated : ages week (w) 1, w2,w3,w4,w5,w6, 1 year,2,3,4, 5-9 years, 10-14, 15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84 and ≥85. The researchers then re-grouped the data into the following categories: "19 and below", "20-39", "40-64" and "65 and above". We then tabulated the mortality rate results according to "number of deaths", "population" and the "crude mortality rate per 100,000". The crude mortality rate per 100,000 population was calculated as "number of deaths" divided by "number of population" times 100,000 yielding the crude mortality rate per 100,000 population. The researchers then applied a linear regression predictive line for each age standardized group using data from 2010-2019 (pre- COVID-19 era) and this was matched against the actual mortality that occurred in 2020-2023. For the years 2020, 2021, 2022 and 2023- the researchers also tabulated data to generate mortality lines that included and excluded COVID-19 deaths as reported by the Department of Statistics Malaysia (DOSM). The graph and prediction lines were plotted using Microsoft Excel 2010.

The researchers tabulated the results according to the age groups and according to each year from 2010-2023. The deaths and population were tabulated into Table I and the Crude Mortality Rate per 100,000 population including the Crude Mortality Rate per 100,000 population after the removal of COVID-19 related deaths (2020-2023) was tabulated into Table II.

**Deaths and Population numbers according to age standardized groups**
Table I depicts the trends of deaths and population (in 1,000s) of the different age groups

**Population**
From Table I, that the population number for the different age groups. From 2020-2023, the "≤19" population decreased whilst the other age groups ("20-39", "40-64" and "≥65") grew in number.

**Deaths**
From Table I, that the deaths amongst the standardized groups were rather stagnant for the "20- 39" groups and down-going for the age groups of "≤19" through-out the years of 2010-2023. Though the "≤19" increased slightly from 2021-2023, it did not surpass the numbers before 2020. The deaths for the "40-64" and "≥65" were steadily going up and in 2021, there was a noticeable increase in deaths for both age groups.

Full details are shown in Table I. The border was to demarcate the COVID-19 and non-COVID-19 years.

The study was registered with the National Medical Research Register and Medical Research Ethical Committee (NMRR ID-22-00344-S8C (IIR)). Data used in the study/obtained data were anonymised.

## RESULTS

**All-cause mortality (per 100,000 population) by age standardized groups from 2010-2023 in Perak**
The all-cause mortality (per 100,000 population) by age-standardized groups from the year 2010 till 2023 was tabulated (Table II) and included in 2 graphs. We included data of mortality before and after the removal of COVID-19 deaths from 2020-2023 to see if deaths due to COVID-19 had affected the mortality rate. For each age standardized group, we calculated a linear regression predictive line (utilising data from 2010-2019) to predict deaths that were anticipated in 2020-2023. Actual mortality rates from 2020-2023 were then compared with the predicted number of deaths.

The subtraction of the actual deaths from the predicted deaths then yielded the Excess Mortality (either a PEM or NEM) of the specific age-group. A negative yield (NEM) meant that the deaths that occurred were lower than anticipated number and positive (PEM) yields meant that more deaths were seen than the anticipated number.

To determine if the actual deaths were significantly higher than the predicted values, it should be higher than the upper limit of the 95% confidence interval of the predicted value. These values were then reviewed to see if they were negligible or not.

• Ages ≤19
The linear regression predicted line was generated and the trend line gradient was negative in nature (decreasing prediction in deaths).

• 20-39
The liner regression predicted line was generated and the trend line gradient was negative in nature- meaning that from the prediction analysis, we expect deaths in this age group to reduce in the coming years.

• 40-64
The linear regression predicted line was generated and the trend line gradient was positive in nature- meaning to say that it is expected that the number of deaths will increase every year after 2019.

• ≥65
The linear regression predicted line was generated and the trend line gradient was positive in nature- meaning to say that we expect the number of deaths to increase every year.

Figure 1 ("40-64" and "≥65") and Figure 2 ("19 and below" and "20-39") depicts the Crude Mortality Rate per 100,000 that was calculated from the deaths and population according to the age standardized categories. The graphs were first plotted with data from 2010-2019. Data from 2020-2023 were plotted in 3 different ways:
1. The prediction line of deaths (linear regression line) plotted using data from 2010-2029.
2. The actual number of deaths recorded from 2020-2023
3. The number of deaths recorded after the removal of "COVID-19 deaths" from 2020-2023

The "y-axis" represented the mortality in the age specific group per 100,000 population. The "x-axis" represented data used in the formula to calculate the mortality per 100,000 population represented the chronological order of the year (i.e.: 2010 was year 1, so x=1, 2011 was year 2, so x=2 etc.). The excess mortalities that were of interest were from 2020-2023. Special markings to denote data used for the linear regression prediction line (2010-2019) and the occurrence of COVID-19 were made. To accommodate the 2 different age groups into a single graph, Figure 1 had 2 "y-axes" with that on the left demarcating the mortality per 100,00 for the "≥65" age group and that on the right demarcating the mortality per 100,000 for the "40-64" age groups.

For the "20-39" age groups, there was a significant PEM in 2021 (for all deaths- about 14 per 100,000 from the upper predicted limit or 112 excess deaths from the age-specific population) (Table II). For all deaths and deaths excluding COVID-19 in 2022 for the "20-39" age group, the excess was 1 to 3 per 100,000 from the upper predicted limit or 8 to 24 excess deaths from the age-specific population- this was considered negligible. For the "40-64" age groups, there was a significant PEM of 36 per 100,000 or 249 excess deaths from the age -specific group population. For the "≥65 and above: groups, there was significant PEM (for all deaths) in 2021-

**Table I: All-cause mortality numbers and the population numbers (in 1,000s) by age standardized groups in the state of Perak from 2010-2023**

| Age | Status | Years | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 | 2022 | 2023 |
| ≤19 | Deaths | 702 | 635 | 660 | 616 | 592 | 565 | 631 | 584 | 536 | 521 | 400 | 378 | 469 | 464 |
| | Population | 889 | 873.2 | 861.5 | 853.2 | 844.9 | 837.9 | 833.5 | 828.3 | 825.8 | 818.7 | 801.2 | 792.7 | 781.5 | 766.4 |
| 20-39 | Deaths | 1069 | 1026 | 1065 | 996 | 1031 | 1050 | 1053 | 1034 | 1020 | 1017 | 943 | 1151 | 1063 | 1052 |
| | Population | 663.2 | 683.1 | 702.7 | 725 | 736.4 | 746.7 | 754.6 | 763.4 | 762.9 | 764.8 | 789.6 | 799.5 | 800.5 | 826.6 |
| 40-64 | Deaths | 4646 | 4814 | 4915 | 4984 | 5065 | 5234 | 5403 | 5493 | 5520 | 5529 | 5281 | 6446 | 6238 | 5845 |
| | Population | 644.2 | 646 | 648.2 | 651 | 649.7 | 651.8 | 655.9 | 657.5 | 664.9 | 667.2 | 682.1 | 689.3 | 692.7 | 701.1 |
| ≥65 | Deaths | 9023 | 9537 | 9755 | 9790 | 10237 | 10310 | 10733 | 10936 | 11524 | 11673 | 11335 | 13365 | 14588 | 13478 |
| | Population | 182.6 | 186.8 | 191.3 | 195.8 | 200.1 | 205 | 208.7 | 212.2 | 215.6 | 218.2 | 223.3 | 234.2 | 239.7 | 247.2 |

Population in 1,000s

**Table II: All-cause mortality rate (per 100,000 population) of the age standardized groups in the state of Perak from 2010-2023. Data from 2020-2023 included data of All-cause mortality and excluding COVID-19 deaths**

| Age | Years | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | | 2021 | | 2022 | | 2023 | |
| | | | | | | | | | | | All | Exc COVID | All | Exc COVID | All | Exc COVID | All | Exc COVID |
| ≤19 [a] | 78.97 | 72.72 | 76.61 | 72.20 | 70.07 | 67.43 | 75.70 | 70.51 | 64.91 | 63.64 | 49.93 | 49.93 | 47.69 | 47.05 | 60.01 | 59.50 | 60.54 | 60.54 |
| ≤19 [b] | | | | | | | | | | | 64.10 | | 62.79 | | 61.49 | | 60.18 | |
| 95%CI | | | | | | | | | | | 60.0-70.0 | | 60.0-70.0 | | 60.0-70.0 | | 50.0-70.0 | |
| ≤19 [c] | | | | | | | | | | | **-14.17** | | **-15.11** | | **-1.48** | | **+0.36** | |
| 20-39 [a] | 161.19 | 150.20 | 151.56 | 137.38 | 140.01 | 140.62 | 139.54 | 135.45 | 133.70 | 132.98 | 119.43 | 119.43 | 143.96 | 129.21 | 132.79 | 130.42 | 127.27 | 127.15 |
| 20-39 [b] | | | | | | | | | | | 127.50 | | 124.81 | | 122.13 | | 119.45 | |
| 95%CI | | | | | | | | | | | 120-140 | | 120-130 | | 110-130 | | 110-130 | |
| 20-39 [c] | | | | | | | | | | | **-8.07** | | **+19.15** | | **+10.66** | | **+7.82** | |
| 40-64 [a] | 721.20 | 745.20 | 758.25 | 765.59 | 779.59 | 803.01 | 823.75 | 835.44 | 830.20 | 828.69 | 774.23 | 773.35 | **935.15** | 859.42 | 900.53 | 885.81 | 833.69 | 831.69 |
| 40-64 [b] | | | | | | | | | | | 860.63 | | 873.63 | | 886.64 | | 899.65 | |
| 95%CI | | | | | | | | | | | 840-880 | | 850-900 | | 860-910 | | 880-920 | |
| 40-64c | | | | | | | | | | | **-86.40** | | **+61.52** | | **+13.89** | | **-65.96** | |
| ≥65 [a] | 4941.40 | 5105.46 | 5099.32 | 5000.00 | 5115.94 | 5029.27 | 5142.79 | 5153.63 | 5345.08 | 5349.68 | 5076.13 | **5074.34** | 5706.66 | 5349.27 | **6085.94** | **5855.65** | 5452.27 | 5434.06 |
| ≥65 [b] | | | | | | | | | | | 5327.07 | | 5363.22 | | 5399.38 | | 5435.53 | |
| 95%CI | | | | | | | | | | | 5230-5420 | | 5190-5470 | | 5310-5490 | | 5350-5530 | |
| ≥65 [c] | | | | | | | | | | | **-250.94** | | **+343.44** | | **+686.56** | | **+16.74** | |

a= actual, b= predicted value [via linear regression with 95% CI listed below], c=difference [between actual and predicted (a - b)]
Within the 95%CI Below the 95% CI Above the 95%CI [Bolded= Significant PEM- not negligible]
Numbers listed are per 100,000 population

**Table III: The top 5 mortality causes per 100,000 population by the age standardized groups in the state of Perak from 2020-2023**

| Age | Rank | 2020 | | 2021 | | 2022 | | 2023 | |
|---|---|---|---|---|---|---|---|---|---|
| | | Cause of death | Per 100,000 population | Cause of death | Per 100,000 population | Cause of death | Per 100,000 population | Cause of death | Per 100,000 population |
| ≤19 | 1 | Certain conditions originating in the perinatal period | 10.73 | Certain conditions originating in the perinatal period | 11.23 | Certain conditions originating in the perinatal period | 11.00 | Certain conditions originating in the perinatal period | 11.00 |
| | 2 | Congenital malformations, deformations and chromosomal abnormalities | 9.11 | Congenital malformations, deformations and chromosomal abnormalities | 8.83 | Congenital malformations, deformations and chromosomal abnormalities | 8.45 | Congenital malformations, deformations and chromosomal abnormalities | 8.45 |
| | 3 | All other diseases | 5.24 | All other diseases | 5.05 | Transport accidents | 8.19 | Transport accidents | 8.19 |
| | 4 | Transport accidents | 4.12 | Transport accidents | 4.67 | All other diseases | 6.01 | All other diseases | 6.01 |
| | 5 | All other external | 3.37 | All other external | 3.15 | All other external | 5.12 | All other external | 5.12 |
| 20-39 | 1 | Transport accidents | 16.97 | Transport accidents | 15.38 | Transport accidents | 20.49 | Transport accidents | 20.49 |
| | 2 | Ischemic heart diseases | 13.68 | COVID-19 infection (due to) | 14.76 | Uncertified | 14.87 | Uncertified | 14.87 |
| | 3 | All other external | 11.02 | All other diseases | 13.88 | Ischemic heart diseases | 11.12 | Ischemic heart diseases | 11.12 |
| | 4 | All other diseases | 10.76 | Ischemic heart diseases | 10.51 | All other diseases | 10.62 | All other diseases | 10.62 |
| | 5 | Uncertified | 9.75 | Uncertified | 10.38 | All other external | 10.12 | All other external | 10.12 |
| 40-64 | 1 | Ischemic heart diseases | 144.11 | Ischemic heart diseases | 155.38 | Uncertified | 272.85 | Uncertified | 272.85 |
| | 2 | Uncertified | 136.93 | Uncertified | 150.30 | Ischemic heart diseases | 121.26 | Ischemic heart diseases | 121.26 |
| | 3 | All other diseases | 66.71 | COVID-19 infection (due to) | 75.73 | All other diseases | 76.51 | All other diseases | 76.51 |
| | 4 | Pneumonia | 58.35 | All other diseases | 71.96 | Pneumonia | 63.66 | Pneumonia | 63.66 |
| | 5 | Cerebrovascular diseases | 47.65 | Pneumonia | 67.17 | Cerebrovascular diseases | 42.59 | Cerebrovascular diseases | 42.59 |
| ≥65 | 1 | Uncertified | 1924.76 | Uncertified | 2026.47 | Uncertified | 3296.62 | Uncertified | 3296.62 |
| | 2 | Ischemic heart diseases | 717.87 | Ischemic heart diseases | 793.77 | Pneumonia | 526.91 | Pneumonia | 526.91 |
| | 3 | Pneumonia | 437.08 | Pneumonia | 453.89 | Ischemic heart diseases | 373.80 | Ischemic heart diseases | 373.80 |
| | 4 | All other diseases | 367.22 | All other diseases | 358.24 | All other diseases | 336.25 | All other diseases | 336.25 |
| | 5 | Cerebrovascular diseases | 312.14 | COVID-19 infection (due to) | 357.39 | COVID-19 infection (due to) | 230.29 | COVID-19 infection (due to) | 230.29 |

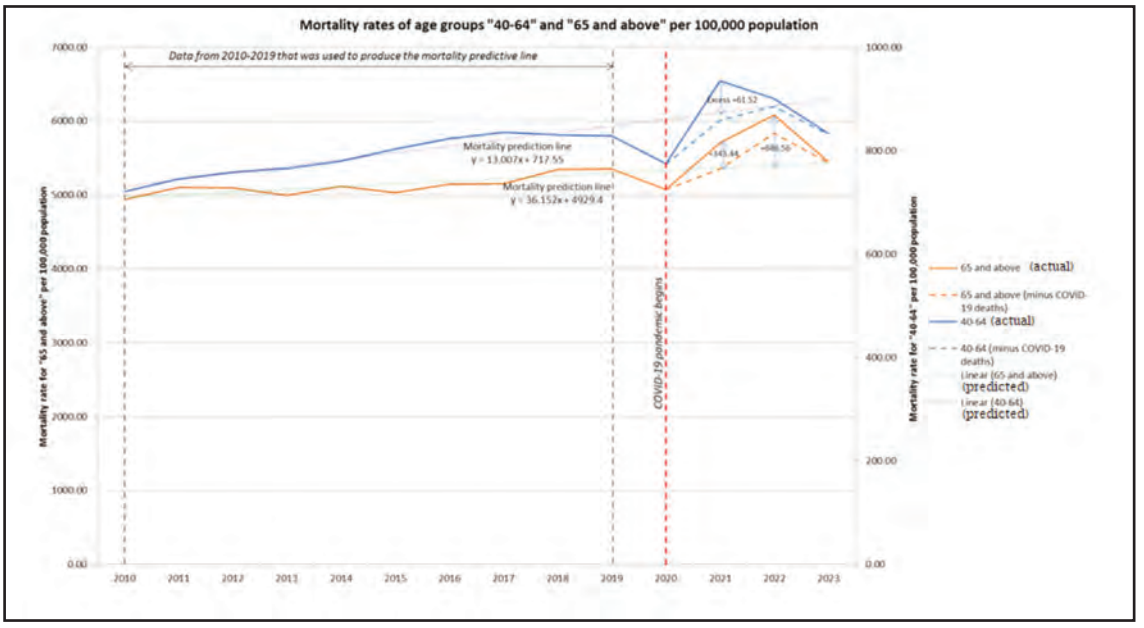



**Fig. 1:** Age standardized All-Cause Mortality Rate and COVID 19 Mortalities in Perak per 100,000 population from 2010-2023 for age groups of "40-64" and "65 and above" with predictive lines plotted utilising data from 2010-2019

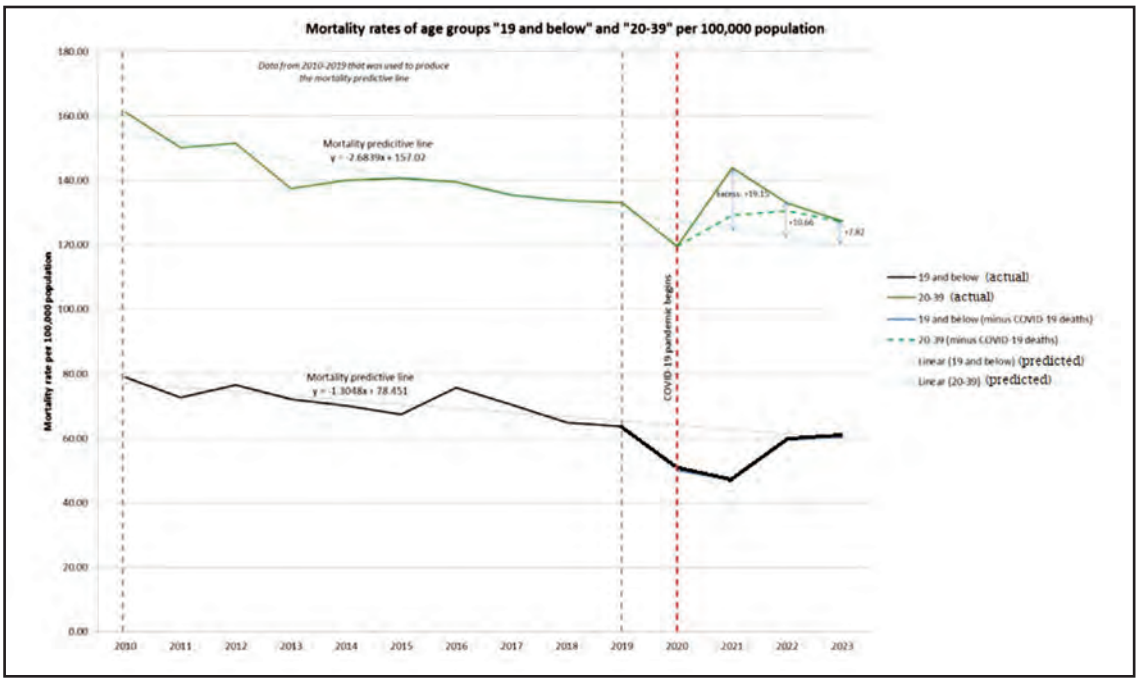



**Fig. 2:** Age standardized All-Cause Mortality Rate and COVID 19 Mortalities in Perak per 100,000 population from 2010-2023 for age groups of "19 and below" and "20-39" with predictive lines plotted utilising data from 2010-2019

237 per 100,000 from the upper predicted limit (555 excess deaths from the age-specific group). There were 596 per 100,000 (for all deaths) or 1430 excess mortalities in the age-specific population and 366 per 100,000 (for deaths after the removal of COVID-19 deaths) or 879 excess mortalities in the age-specific population in 2022.

The prediction line was down-going in trend as shown in Fig 1. It was also found that a PEM was generally seen amongst the "≥65" group for the year 2021 (+343.44) and 2022 (+686.56). The mortality in 2020 was below the predicted number or a NEM. In 2021, the number of deaths recorded after the removal of "COVID-19 deaths" was similar to the value of the predicted deaths. However, in 2022, there was a PEM even after the removal of the COVID-19 deaths. The mortality in 2023 was nearly similar as the predicted number. For the "40-64" group, PEM was seen through-out, however, after removing "COVID-19 deaths", the net yield resulted in NEM. These NEM numbers were however a very small number

Fig 2 depicts the mortality for age groups of "≤19" as well as the "20-39" age groups. The prediction trend-line was generally down-going in nature. Both mortality graphs were depicted on the same y and x-axes. From the graph, the "≤19" had NEM for the 2020-2022 (the COVID-19 related deaths were negligible). In 2023, the mortality became a PEM- a slight excess compared to the predicted (however, this is a very small value that is negligible). Fig 2 also shows the mortality of the age group of "20-39". When plotted for the COVID-19 years (2020-2023), it was found that there were PEM from 2021-2023. After the removal of the deaths due to COVID-19, the PEM remained, but the numbers were relatively small (between about 8-20 people per 100,000 population of the age standardised group).

**Top 5 causes of mortality rate per 100,000 population by age groups in Perak from 2020-2023.**

The researchers also tabulated the top 5 causes of mortality per 100,000 population for the causes of mortality in 2020 to 2023. This is listed in Table III in a descending order.

**≤19 years**

For this age group, we calculated that the 2 general causes of deaths namely "Certain conditions originating in the perinatal period" and "Congenital malformations, deformations and chromosomal abnormalities" for 2020-2023.

**20-39 years**

For this age group, "Transport accidents" were the main cause of death for the years 2020 till 2023. For 2020, "Ischemic Heart Disease" was the number 2 cause before dropping to the 4th (2021), 3rd (2022) and 5th (2023). In 2021, "COVID-19" was the 2nd cause of mortality in this age group causing about 15 deaths per 100,000 age standardised population.

**40-64 years**

For this age group, we can see that "Ischemic Heart Disease" was the common cause of death except in 2022 and 2023 where the common cause of death was "Uncertified". Deaths due to "COVID-19" was only seen in 2021 as the 3rd common cause of deaths where about 76 per 100,000 age standardised population succumbed. "Pneumonia", "Cerebrovascular events" and "All other diseases" were the causes of deaths from number 3 to number 5 changing sequence in between the years of 2020-2023.

**≥65 years**

For this age group, the common causes of deaths were "Uncertified" deaths from 2020-2023. "Ischemic heart disease" and "Pneumonia" related deaths were 2nd and 3rd placing (interchangeable over the years of 2020-2023). "All other diseases" were the 4th common cause of deaths for 2020-2023. However, for 2021 (about 356 people per 100,000 age standardised population) and 2022 (about 231 per 100,000 age standardised population) deaths were due to "COVID-19"- being the 5th common cause of deaths. For 2020 and 2023, "Cerebrovascular accidents" were the 5th common cause of deaths. The full data can be seen in Table III.

## DISCUSSION

**Excess mortalities capture the true burden of the pandemic**

The working definition of a COVID-19 death could have caused an over or underestimation of deaths due to COVID-19 because of the variations in testing strategies used across the pandemic. However, in contexts of all deaths - any death captured regardless of the cause. This will reflect on the direct and indirect impact of the COVID-19 infection on the population. The indirect impact includes the disruption to health care services and restriction of movement caused by mitigation plans to stop transmission.

Generally, many studies conducted had seen that the hardest hit of mortalities during COVID-19 especially in the cases of excess mortalities were seen increase in nature with the age groups.[6,14] In this study, we found similar results- but it must highlighted that "≤19" had experienced lesser deaths than expected, the "20-39" as well as the "40-64" saw a slight increase and finally the "≥65" group showed the biggest number of excess mortalities. The elderly age group were the ones largely affected as co-morbids are common amongst them (especially uncontrolled comorbidities) and susceptibility of the immune system in response to infections are rather slower than the younger age group- that might eventually cause death.[1,2,9,15-16] This reflected on the mortalities seen in Perak as the state has a high number of elderly population in the country. However, after the pandemic, it was found that the mortality rates of the elderly returned to the predicted numbers. This might imply that the COVID-19 pandemic had claimed the lives of the elderly earlier rather than later. The mortality rate for those above 40 has not returned to the normal predicted values implying that perhaps the effects of the pandemic is now over.

Missed appointments, re-scheduled appointments, delayed procedures (especially due to strict precautions) that were in-place to stop the spread, might have been some of the many causes that resulted in many patients presenting after surpassing the critical intervention time-frame.[17] This was where the true burden of the pandemic was as the after-effects of it has resulted in healthcare services dealing with prolonged disease complications especially with non-communicable diseases.[17] Thus it is ever so important that even with mitigation restrictions (for future pandemics), it will not cause an overcrowding of our facilities that might affect the intervention of healthcare.[18]

**Causes of all-cause mortality might have been due to policies during COVID-19**

During the pandemic, there was a disruption of health care services due to system overload, resource diversion and shortages. There were changes in health seeking behaviours especially among patients because of travel restrictions and the fear of contracting COVID-19 from healthcare centers. These factors could have contributed to the death increase-caused by the effects of the COVID-19 pandemic rather than directly from COVID-19. One of the major problems was to identify the areas of spread or hot-spots.[1] This was due to the fact that reporting mechanisms, lockdown policies to different industries and contact tracing methods had drawbacks into identifying actual areas of spread.

Areas/industries that were allowed to operate during the pandemic had a higher spread as they were allowed to function at a restricted capacity, allowing for person-to-person contact if there was a case of COVID-19, especially in the pre-symptomatic phase. This might have made a difference to the counts of COVID-19 cases as well as mortality.[1]

Therefore, looking at all-cause mortality would be a more accurate way to analyse the effect of the pandemic on mortality patterns.[2,6,16] In this paper, we predicted the mortality based on historical death data and compared it with actual mortality during the pandemic to determine positive or negative excess mortality.

According to a paper that reported PEM during the COVID-19 pandemic in Germany, the "COVID-19 deaths" were said to have been highly associated with the response of the government in terms of tight regulations and adherences.[9] However, due to political pressure and difference of opposed views in Germany, the difference in regulated mitigation coupled with poor coordination resulted in poor control as well as deaths.[16]

Though Malaysia did control the first wave well (as depicted by the low number of deaths in 2020), however, due to the change in variants and economically unsustainable methods- just like Germany- policies were revised and spread patterns changed.[16] Due to different preventive methods applied (compared to other leading countries) and perhaps a possible delay in screening/detection/therapeutics for other diseases, it might have resulted to an increase in all-cause mortalities especially in the elderly groups.[1,4] Some of the causes of increase in PEM could be attributed to the delay in diagnosing and treating other conditions especially those relating to non-communicable diseases as well as a change in human-behaviour that refrained from seeking medical care for the fear of being infected with COVID-19.[1,4,15]

**NEM in 2020**

A German study conducted on a weekly analysis of PEM and NEM during the early COVID-19 period (2020), reported that for the groups 30-49 and 50-59 years of age had a minimal increase in excess mortalities (PEM) was observed.[2] However the obvious increase in comparisons of excess mortalities (PEM) were observed in those groups above the age of 60 (except the 70-79 age group).[9] This was slightly different than what was found in our study. In this study, all age groups had a NEM during the year 2020. This might have been due to the stringent lockdown and mitigation mechanisms that were put into place. In some countries of the European Union, UK and US- generally there was an increase by more than 10 in 100,000 population for mortalities during the COVID-19 period for all ages (no age specific data but estimated to be at 1.4 million in excess deaths (PEM) globally in 2020- largely attributed to non- "COVID-19 deaths").[14]

**The main all-cause mortality PEM was seen mainly in the elderly**

A Malaysian study with national data from 1995-2020 had reported that the authors predicted PEM in Malaysia would increase after the COVID-19 pandemic but it was suggested that this would be mainly among those who were above the age of 60 years.[19] Similarly, a study conducted in Iran utilising mortality data from 2019-2022 similarly reported that they saw an increased PEM among those who were above the age of 75.[10] Even after removing "COVID-19 deaths", the PEM seen in the Iranians in multiple studies at different points, were high among those aged 75 and above.[2,10,16] This was similarly found in this current study- that PEM were higher in the "65 and above" (older group) compared to the other groups- though there were minimal increases in the "20-39" and the "40-64" groups.

Obtaining higher numbers of COVID-19 deaths after the declaration of the pandemic was also reported in another paper. A paper published in 2022, utilising data at the peak of COVID-19, a predictivity analysis done in Iran showed that the excess mortality was due to increase 2 years after the height of COVID-19 (2021-2022) with the elderly mainly being affected to suffer from PEM.[16] This was nearly similar to the current study where an increase in PEM were seen after the peak of COVID-19 (2021) but mainly affected the elderly age group (65 and above- 687 per 100,000 population) compared to minimal PEM changes from the predicted mortality numbers in other groups. In another 2021 study conducted in South Korea, it was reported that the majority of PEM were seen as age increased (especially the 65- 79 age groups) and NEM were seen in the younger age groups.[6]

When the World Health Organization conducted an analysis utilising world-wide data, it was reported that the largest PEM occurred in 2021 and that the total PEM were nearly 3 times higher than "COVID-19 deaths" for the same requisite period of time.[8] This was similarly seen in this current study for the years 2021-2022.

In a paper written in Malaysia regarding PEM during the early COVID-19 period, it was reported that the PEM for Malaysians (86.2-100%) in 2021 was attributed solely to COVID-19.[4] Though the same paper reported that Perak matched the predicted mortality rate, the authors of that paper calculated mortality in the state of Perak based on data from 2017- in contrast with this research that calculated the mortality prediction line based on age groups and data ranging from 2010- 2019.[4] However, the 2021 paper looked at mortality from a month-to-month basis during the pandemic whereas this current study looks at the yearly data.

**Causes of death**

From this research, though PEM was high in the older age groups for all the years from 2020-2023. However, it cannot be attributed to direct deaths caused by COVID-19 infections. In a study conducted in Malaysia in 2021 (during the initial phase of COVID-19), it was reported that though age was not a factor that determined the type of deaths during the early days of COVID-19 (2020-2021), from the descriptive data, those who died in hospital were about 65 years old.[8] Amongst the causes of mortality for the non-"COVID-19 deaths" matched the findings of this study, mostly being causes from metabolic conditions and undefined deaths.[6]

Some of the reasons of the causes of PEM could be explained via literature from different papers. Another study conducted in South Korea reported differently- that the deaths from

respiratory linked diseases were reduced, whereas in this current study (especially those of 65 and above), the cause of death from pneumonia rose from the 3rd to 2nd highest cause of deaths.[6] Most countries did not see a PEM during the initial phase of the pandemic (2020) but saw a PEM in 2021.[6]

In a world-wide (140 World Health Organization countries) data study conducted, excess mortalities (PEM) were seen around the world with some being nearly as high as 10%- with many attributing the deaths to non-communicable diseases like diabetes, ischemic heart diseases and cardiovascular related diseases than to COVID-19.[14] The reason for excess deaths (PEM) could be explained that those who had a COVID-19 infection remained at higher risk to develop de novo cardiovascular and metabolic disorders.[14] Amongst some of the reasons stated for such events happening is because of the constriction of services due to the focus on healthcare services towards COVID-19.[14]

This study has several strengths. It used cleaned data from the Department of Statistics Malaysia, which improves the reliability of the analysis. It also focused on the top five causes of death in Perak, allowing the findings to address the main contributors to mortality in the state. Additionally, the researchers applied linear predictive analysis using 10 years of mortality data to estimate deaths from 2020 to 2022.

However, several limitations should be acknowledged. The findings are representative only of Perak and may not be generalisable to other Malaysian states. The prediction period was also limited to three years; a longer prediction period may have provided a more robust model. The study also assumed that deaths remained constant throughout each year from 2010 to 2022, which may not reflect seasonal or temporal variation. Finally, ARIMA analysis was not performed because there were insufficient time points, as ARIMA modelling generally requires approximately 50 to 100 observations.

## CONCLUSION

There was a PEM in all groups except "19 and below" after the year 2020, with the highest in the "65 and above" group. Mortalities returned to normal predicted values in 2023. COVID-19 deaths were included in the top 5 causes of death and contributed only partly to the excess mortality across all groups except "19 and below".

## ACKNOWLEDGEMENTS

We would like to acknowledge the Director General of Health Malaysia for allowing this publication. We would like to acknowledge Premaa Supramaniam of the Clinical Research Centre, HRPB, Ipoh for her contribution towards this project.

## REFERENCES

1. Arvinder-Singh HS. Comparison of the COVID-19 mortality occurring in hospitals and those brought in dead within Malaysia. Med J Malaysia 2022; 77(3): 338-46.
2. Ahmadi Gohari M, Chegeni M, Haghdoost AA, Mirzaee F, White L, Kostoulas P, et al. Excess deaths during the COVID-19 pandemic in Iran. Infect Dis (Lond) 2022; 54(12): 909-17.
3. Salim S. Malaysia to transition to endemic phase of Covid-19 on April 1, says PM. The Edge Malaysia. 2022 Mar 8. Cited on April 2025.[cited April 2025] Accessed from: https://theedgemalaysia.com/article/malaysia-enter-endemic-phase-april-1-says-pm
4. Jayaraj VJ, Chong DWQ, Wan KS, Hairi NN, Bhoo-Pathy N, Rampal S, et al. Estimating excess mortalities due to the COVID-19 pandemic in Malaysia between January 2020 and September 2021. Sci Rep 2023; 13(1): 86.
5. Loo TH, Arvinder-Singh HS, Ang YC, Kong YH, Vikram Suarn S, Rakesh S. Psychological impact amongst patients with COVID-19 in Perak state. Med J Malaysia 2022; 77(6): 643-9.
6. Oh J, Min J, Kang C, Kim E, Lee JP, Kim H, et al. Excess mortality and the COVID-19 pandemic: causes of death and social inequalities. BMC Public Health 2022; 22(1): 2293.
7. Malaysia MoH. Classification of COVID-19 Deaths for National COVID-19 Death Statistics In: Malaysia MoH, editor. Malaysia: Ministry of Health Malaysia; 2024. [cited April 2025] Accessed from: https://covid-19.moh.gov.my/garis-panduan/garis-panduan-kkm/ANNEX-45-CLASSIFICATION-OF-COVID19-DEATH-10JAN2024.pdf
8. Msemburi W, Karlinsky A, Knutson V, Aleshin-Guendel S, Chatterji S, Wakefield J. The WHO estimates of excess mortality associated with the COVID-19 pandemic. Nature 2023; 613(7942): 130-7.
9. Stang A, Standl F, Kowall B, Brune B, Böttcher J, Brinkmann M, et al. Excess mortality due to COVID-19 in Germany. J Infect 2020; 81(5): 797-801.
10. Edrus RA, Siri Z, Haron MA, Safari MAM, Kaabar MKA, Chen M. A Comparative Analysis of the Forecasted Mortality Rate under Normal Conditions and the COVID-19 Excess Mortality Rate in Malaysia. J Mathematics 2022; 2022: 7715078.
11. Omar K, Baha Raja D, Abdul Taib NA, Rajaram N, Ahmed J, Arvinder-Singh HS, et al. Risk stratification and assessment framework for international travel and border measures amidst the COVID-19 pandemic - A Malaysian perspective. Travel Med Infect Dis 2022; 47: 102318.
12. Abdul Taib NA, Baha Raja D, Teo AKJ, Kamarulzaman A, William T, Hs AS, et al. Characterisation of COVID-19 deaths by vaccination types and status in Malaysia between February and September 2021. Lancet Reg Health West Pac 2022; 18: 100354.
13. NST. Perak developing Elderly-Friendly Rating System amid growing ageing population. New Straits Times. 2025 Feb 20; Sect. Business Times. [cited April 2025]. Accessed from: https://www.nst.com.my/news/nation/2025/02/1177877/perak-developing-elderly-friendly-rating-system-amid-growing-ageing
14. Alicandro G, La Vecchia C, Islam N, Pizzato M. A comprehensive analysis of all-cause and cause-specific excess deaths in 30 countries during 2020. Eur J Epidemiol 2023; 38(11): 1153-64.
15. Vasconcelos PFC, Jayaraj VJ, Ng C-W, Bulgiba A, Appannan MR, Rampal S. Estimating the infection burden of COVID-19 in Malaysia. PLOS Negl Trop Dis 2022; 16(11): e0010887.
16. Ebrahimoghli R, Abbasi-Ghahramanloo A, Moradi-Asl E, Adham D. The COVID-19 pandemic's true death toll in Iran after two years: an interrupted time series analysis of weekly all-cause mortality data. BMC Public Health 2023; 23(1): 442.
17. Swarnakar R, Yadav SL. Communicable to Non-communicable Disease Pandemic in the Making: An Urgent Call for Post-COVID-19 Preparedness. Cureus 2022; 14(7): e27453.
18. Pan XF, Yang J, Wen Y, Li N, Chen S, Pan A. Non-Communicable Diseases During the COVID-19 Pandemic and Beyond. Engineering (Beijing) 2021; 7(7): 899-902.
19. Department of Statistic M. Perak State Population: City Population; 2023 [cited April 2025]. Accessed from: http://www.citypopulation.de/en/malaysia/admin/08__perak/

ORIGINAL ARTICLE

# Clinical characteristics and outcomes of myocardial infarction, stroke, and cardiovascular mortality among patients undergoing complex high-risk indicated percutaneous coronary intervention: A one-year review in a single non-surgical centre

**Yee Shen Yew, MRCP[1], Arvinder-Singh HS, PhD (Community health)[2,3], Chai Hui Yi, MD[1], Ang Jian-Gang, MRCP[1], Chen Tai Meng, MRCP[1], Chow Hsin Wei, MRCP[1], Chin Wee Lee, MRCP[1], Lim Chun Liang, MRCP[1], Philip Rajan Devesahayam, MMed (ORL)[2,4], Gurpreet Pal Singh Jugindar Singh, MRCP[1], Ramachandran Sathappan, MRCP[1], Kwan Yew Fung, MRCP[1], Hazleena Mohamed Hasnan, MMed (Internal Medicine)[1], Nor Hanim Mohd Amin, MMed (Internal Medicine)[1]**

[1]Department of Cardiology, Hospital Raja Permaisuri Bainun, Ministry of Health, Ipoh, Perak, Malaysia, [2]Clinical Research Centre, Hospital Raja Permaisuri Bainun, Ministry of Health, Ipoh, Perak, Malaysia, [3]Faculty Research Support Unit (FRSU) and Deputy Dean's Department (International & Research), Faculty of Medicine & Health Sciences, Universiti Putra Malaysia, Serdang, Selangor, Malaysia, [4]Department of ORL, Hospital Raja Permaisuri Bainun, Ministry of Health, Ipoh, Perak, Malaysia.

## ABSTRACT

**Introduction: Complex High-risk Indicated Percutaneous Coronary Intervention (CHIP-PCI) addresses complex coronary artery disease in patients unsuitable for or declining surgery. Performing CHIP-PCI in non-surgical centres presents unique challenges requiring robust risk mitigation. CHIP-PCI was defined as PCI in any patient meeting at least one of the following criteria: PCI to left main stem, chronic total occlusion, severe coronary artery calcification (CAC), bifurcation lesions, left ventricular ejection fraction (LVEF) < 30%, serum creatinine > 200µmol/L, chronic dialysis, intra-aortic balloon pump use, previous coronary artery bypass graft, or age ≥ 80 years. Locally, the outcomes of major adverse cardiovascular events (MACE) - a composite of myocardial infarction, stroke, and cardiovascular mortality - and their associated factors after CHIP-PCI remain poorly understood. This study aims to evaluate 30-day MACE, patient characteristics and variables associated with mortality in CHIP-PCI.**

**Materials and Methods: This single-centre retrospective cohort study with 30-day follow-up utilised anonymous secondary data from CHIP-PCI patients treated at the Department of Cardiology, Hospital Raja Permaisuri Bainun between 1st January and 31st December 2024. Data extracted included demographics, comorbidities, laboratory investigations (low-density lipoprotein [LDL], serum creatinine, echocardiography findings), and intra- and post-procedural findings. Patients with missing data for ≥ 3 variables of interest were excluded. A multivariate binary logistic regression analysis was conducted to identify the variables associated with mortality post CHIP-PCI.**

**Results: Of the 161 total patients, 146 (90.7%) were included in the analysis. Among these, 71.9% were male, and the mean age was 63.03 ± 10.19 years. Common comorbidities included hypertension (83.6%), diabetes mellitus (66.4%), elevated LDL (51.6%), serum creatinine > 200µmol/L (38.4%), prior Acute Coronary Syndrome (37.0%), chronic dialysis (30.1%), and LVEF < 30% (9.6%). Radial access was the most common approach (72.6%), and PCI was most frequently performed for severe CAC (46.6%). Intracoronary imaging was used in 43.8% of cases, and 39.0% required advanced calcium modification technique (atherectomy or intravascular lithotripsy). Most were single-lesion PCI (80.8%), with the left anterior descending artery (80.8%) being the most treated vessel. The 30-day MACE rate was 5.5% (4.8% mortality, 0.7% stroke, and 0% recurrent myocardial infarction). Multivariate analysis demonstrated that LVEF < 30% (AOR: 41.1, 95% CI: 1.1–1563.8, p = 0.04), severe CAC (AOR: 28.2, 95% CI: 1.3–619.3; p = 0.03), elevated LDL (AOR: 28.7, 95% CI: 1.2–701.1; p = 0.04), and re-admission (AOR: 81.7, 95% CI: 4.1–1618.3, p < 0.001) were exploratory variables associated with 30-day mortality.**

**Conclusion: This study demonstrates that the 30-day MACE rate for CHIP-PCI was 5.5%, suggesting the procedure may be feasible with acceptable short-term outcomes in a non-surgical centre. Severely reduced LVEF, severe CAC, elevated LDL levels, and hospital re-admission showed potential associations with 30-day mortality highlighting the need for optimised strategies for patient risk mitigation.**

**KEYWORDS:**
*Percutaneous coronary intervention; complex high-risk indicated percutaneous coronary intervention; major adverse cardiovascular event; non-surgical centre*

## INTRODUCTION

Percutaneous Coronary Intervention (PCI) has become a cornerstone in the management of coronary artery disease,

*This article was accepted: 02 June 2026*
*Corresponding Author: Arvinder-Singh*
*Email: arvinder.crc@gmail.com*

particularly for patients with Acute Coronary Syndrome (ACS).[1] For patients with complex coronary lesions and significant comorbidities, a subset of procedures known as Complex High-risk Indicated Percutaneous Coronary Intervention (CHIP-PCI) presents considerable procedural and clinical challenges. These patients often have multiple high-risk features, including left main stem disease, chronic total occlusions, bifurcation lesions, severe coronary artery calcification, prior coronary artery bypass grafting (CABG), severely reduced left ventricular ejection fraction (LVEF) < 30%, presence of significant comorbidities such as chronic kidney disease (serum creatinine > 200µmol/L or on chronic dialysis), or age ≥ 80 years old.[2-4]

While surgical revascularisation remains the standard of care for many high-risk patients, CHIP-PCI has emerged as a viable alternative for individuals who are poor surgical candidates or those who do not consent for surgical procedure.[5] Advances in PCI techniques, including the use of drug-eluting stents, advanced calcium modification techniques such as atherectomy or intravascular lithotripsy, intravascular imaging, and mechanical circulatory support devices (such as intra-aortic balloon pump), has significantly expanded the scope of PCI for this population.[6] However, the success and safety of CHIP-PCI remain a major concern, especially when performed in centres without on-site surgical backup.

Non-surgical centres performing CHIP-PCI face distinct challenges, including the need for sufficient operator experience, sound clinical judgment, careful case selection, and the implementation of risk-mitigation strategies to reduce major adverse cardiovascular events (MACE), defined as a composite of myocardial infarction, stroke, and cardiovascular mortality.[7-8] While previous studies have examined outcomes of CHIP-PCI in tertiary surgical centres, there is relative paucity of data evaluating the safety and efficacy of these procedures in non-surgical settings.[2] Understanding the clinical characteristics and outcomes of patients undergoing CHIP-PCI in these environments is critical for improving procedural safety, refining risk stratification, and optimising post-procedural management.

The primary objective of this study was to determine the 30-day incidence of MACE following CHIP-PCI. Secondary objectives included a characterisation of baseline patient demographics and the identification of factors associated with MACE. By elucidating factors of adverse outcomes, this study endeavours to contribute to evidence-based advancements in the management of CHIP-PCI patients and to provide guidance for centres performing CHIP-PCI without immediate on-site surgical support.

## MATERIALS AND METHODS

### Study Design and Study Population

This was a single-centre retrospective cohort study with 30-day follow-up conducted at the Department of Cardiology, Hospital Raja Permaisuri Bainun, utilising secondary data from patients who underwent CHIP-PCI between January and December 2024. Data were extracted from electronic medical records, coronary angiography and echocardiography reports from 1 January 2024 to 31 December 2024, with MACE data extracted up to 31 January 2025. Extracted data were then entered into an online spreadsheet by designated study personnel. Parameters extracted included demographics, comorbidities (diabetes mellitus, hypertension, history of ACS, stroke, PCI, CABG, peripheral vascular disease, chronic dialysis), laboratory variables (low-density lipoproteins [LDL] and serum creatinine), coronary angiography and echocardiography findings (LVEF). Only the most recent laboratory values documented within the preceding six months before PCI were included for analysis. Data on re-admission and major bleeding events were also extracted. A major bleeding event was defined according to the standardised bleeding definition of the Bleeding Academic Research Consortium.[9] From the extracted data, only patients who underwent PCI with at least one of the following characteristics were included: PCI to left main stem, chronic total occlusion, severe coronary artery calcification, bifurcation lesion, LVEF < 30%, chronic kidney disease with serum creatinine > 200µmol/L, chronic dialysis (peritoneal or haemodialysis), use of an intra-aortic balloon pump, previous CABG, or age ≥ 80 years. The study definitions used were adapted from the criteria used in the British Cardiovascular Intervention Society (BCIS) National PCI Dataset.[2-3] Patients who underwent primary or rescue PCI for ST-elevation myocardial infarction were excluded. Additionally, patients with missing data for ≥ 3 variables of interest with were excluded from the final analysis.

### Sample size

The sampling frame consisted of 161 patients identified from the general database. The minimum required sample size was calculated using the population to proportion method with the Raosoft® online calculator.[10] Using a 95% confidence interval, a 5% margin of error, a population size of 161, and a response distribution of 50% (to yield the maximum sample size), the minimum sample size required for analysis was determined to be 114.

### Statistical Analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), Version 25. Categorical data were expressed as numbers and percentages, while continuous data were presented as mean ± standard deviation (SD). Continuous variables were tested for normality; normally distributed data were expressed as mean ± SD, while non-parametric variables were presented as median and interquartile range (IQR). The comparison of categorical data between groups was performed using the Chi-square test, and continuous variables were compared across different groups using an independent t-test (for normally distributed data) or a Mann-Whitney U test (for non-normally distributed data). All variables with a p-value ≤ 0.3 in the univariate analysis were included in the multivariate analysis using binary logistic regression. For the multivariate analysis, a p-value < 0.05 was considered statistically significant. The final model's goodness-of-fit was assessed using the Hosmer-Lemeshow test (indicating good fit if p ≥ 0.05), the percentage of correctly classified cases (target > 70% accuracy), and the Nagelkerke $R^2$ value (moderate model fit if 0.5–0.7 and > 0.7 indicates a very good fit).

**Table I: Basic demography, laboratory data, echocardiography findings, coronary anatomy and procedural characteristics of the patients**

| Parameter | Overall N (%) n = 146 | Mortality N (%) n = 7 | No mortality N (%) n = 139 | p-value |
|---|---|---|---|---|
| Age (years) | 63.03 ± 10.19 | 69.00 [13.00] | 64.00 [12.00] | 0.30 |
| Gender | | | | |
| Male | 105 (71.9) | 6 (5.7) | 99 (94.3) | 0.67 |
| Female | 41 (28.1) | 1 (2.4) | 40 (97.6) | |
| LDL* (mmol/L) | 2.44 ± 1.13 | 2.60 [1.60] | 2.15 [1.33] | 0.38 |
| Not elevated | 45 (48.4) | 2 (4.4) | 43 (95.6) | 0.29 |
| Elevated | 48 (51.6) | 5 (10.4) | 43 (89.6) | |
| Serum creatinine (μmol/L) | 109.00 [384.00] | 99.00 [429.00] | 109.00 [381.00] | 0.97 |
| ≤ 200 | 90 (61.6) | 5 (5.6) | 85 (94.4) | |
| > 200 | 56 (38.4) | 2 (3.6) | 54 (96.4) | 0.71 |
| LVEF (%) | 48.39 ± 12.67 | 47.00 [30.00] | 47.00 [18.00] | 0.94 |
| < 30 | 14 (9.6) | 2 (14.3) | 12 (85.7) | 0.14 |
| ≥ 30 | 132 (90.4) | 5 (3.8) | 127 (96.2) | |
| Comorbidities | | | | |
| Diabetes Mellitus | 97 (66.4) | 4 (4.1) | 93 (95.9) | 0.69 |
| Hypertension | 122 (83.6) | 6 (4.9) | 116 (95.1) | 0.99 |
| ACS | 54 (37.0) | 3 (5.6) | 51 (94.4) | 0.99 |
| Cerebrovascular accident | 9 (6.2) | 1 (11.1) | 8 (88.9) | 0.37 |
| History of PCI | 32 (21.9) | 2 (6.2) | 30 (93.8) | 0.99 |
| History of CABG | 4 (2.7) | 0 | 4 (100) | 0.99 |
| Peripheral vascular disease | 1 (0.7) | 0 | 1 (100) | 0.99 |
| Chronic dialysis | 44 (30.1) | 2 (4.5) | 42 (95.5) | 0.99 |
| Number of lesions treated | 1.00 [0] | 1.00 [0] | 1.00 [0] | 0.88 |
| One | 118 (80.8) | 6 (5.1) | 112 (94.9) | |
| Two | 26 (17.8) | 1 (3.8) | 25 (96.2) | 0.99 |
| Three | 2 (1.4) | 0 | 2 (100) | |
| Stent length** (mm) | 45.89 ± 21.13 | 51.50 [21.00] | 42.00 [34.75] | 0.65 |
| Intracoronary Imaging | 64 (43.8) | 5 (7.8) | 59 (92.2) | 0.24*** |
| Intra-arterial balloon pump | 3 (2.1) | 1 (33.3) | 2 (66.7) | 0.14 |
| Access during PCI | | | | |
| Radial | 106 (72.6) | 5 (4.7) | 101 (95.3) | |
| Femoral | 35 (24.0) | 2 (5.7) | 33 (94.3) | 0.99 |
| Radial and femoral | 5 (3.4) | 0 | 5 (100) | |
| Atherectomy / Intravascular Lithotripsy | 57 (39.0) | 4 (7.0) | 53 (93.0) | 0.43 |
| Type of lesion | | | | |
| LMS | 30 (20.5) | 1 (3.3) | 29 (96.7) | 0.99 |
| Chronic total occlusion | 19 (13.0) | 0 | 19 (100) | 0.60 |
| Bifurcation | 10 (6.8) | 1 (10.0) | 9 (90.0) | 0.40 |
| Severe CAC | 68 (46.6) | 5 (7.4) | 63 (92.6) | 0.25 |
| CABG graft | 2 (1.4) | 0 | 2 (100) | 0.99 |
| Target vessel | | | | |
| LMS | 31 (21.2) | 1 (3.2) | 30 (96.8) | 0.99 |
| LAD | 118 (80.8) | 6 (5.1) | 112 (94.9) | 0.99 |
| LCx | 19 (13.0) | 1 (5.3) | 18 (94.7) | 0.99 |
| RCA | 19 (13.0) | 0 | 19 (100) | 0.60 |
| CABG graft | 2 (1.4) | 0 | 2 (100) | 0.99 |

Data are shown as number (percentage), mean ± standard deviation, median [interquartile range].
LDL low-density lipoprotein, LVEF left ventricular ejection fraction, ACS acute coronary syndrome, PCI percutaneous coronary intervention, CABG coronary artery bypass graft, CAC coronary artery calcification, LMS left main stem, LAD left anterior descending, LCx left circumflex, RCA right coronary artery. *53 missing, **24 missing, ***rejected univariate to be included in multivariate.

## RESULTS

A flow chart of the patient enrolment is provided as Fig. I. A total of 907 records were initially identified through database search. Following screening and eligibility assessment, 161 records were evaluated, of which 15 were excluded due to having ≥3 variables with missing data or being lost to follow-up (final outcomes unknown). This resulted in a final study population of 146 patients (90.7% of the extracted data). Table I shows the basic demography, laboratory and echocardiography findings as well as coronary anatomy and procedural characteristics.

The mean age of the cohort was 63.03 ± 10.19 years. Males constituted the majority (71.9%), reflecting the well-established male predominance in coronary artery disease. Cardiovascular comorbidities were highly prevalent: 66.4% of patients had diabetes mellitus and 83.6% had hypertension. A history of ACS was present in 37.0% of the patients while prior PCI was found in 21.9%. From the total, 6.2% had a history of stroke, and 2.7% had undergone CABG while 0.7% had peripheral vascular disease. Renal dysfunction was common, with 38.4% exhibiting baseline serum creatinine > 200μmol/L and 30.1% were undergoing chronic dialysis.

**Table II: 30-day MACE outcomes compared with mortality outcomes**

| Parameter | Overall N (%) n = 146 | Mortality N (%) n = 7 | No mortality N (%) n = 139 | p-value |
|---|---|---|---|---|
| Death | 7 (4.8) | 7 (100) | - | - |
| Stroke | 1 (0.7) | 0 | 1 (100) | 0.99 |
| Recurrent myocardial infarction | 0 | 0 | 0 | - |
| Re-admission | 7 (4.8) | 3 (42.9) | 4 (57.1) | < 0.001 |
| Major bleeding event | 1 (0.7) | 0 | 1 (100) | 0.99 |

**Table III: Multivariate logistic regression analysis comparing different univariate outcomes with the outcome of mortality**

| Parameter | OR (95% CI) | p-value | AOR (95% CI) | p-value |
|---|---|---|---|---|
| Age | 1.05 (0.96–1.14) | 0.30 | 1.13 (0.96–1.32) | 0.14 |
| Intra-arterial balloon pump | 11.42 (0.90–144.16) | 0.06 | 9.71 (0.16–592.11) | 0.28 |
| LVEF < 30% | 4.23 (0.74–24.20) | 0.14 | 41.11 (1.08–1563.83) | 0.04 |
| Severe CAC | 3.02 (0.57–16.08) | 0.25 | 28.18 (1.28–619.27) | 0.03 |
| Elevated LDL* | 2.50 (0.46–13.60) | 0.29 | 28.72 (1.18–701.13) | 0.04 |
| Re-admission | 25.31 (4.20–152.69) | < 0.001 | 81.69 (4.12–1618.32) | < 0.001 |

OR odds ratio, AOR adjusted odds ratio, CI confidence interval, LVEF left ventricular ejection fraction, CAC coronary artery calcification, LDL low-density lipoprotein. No intra-arterial balloon pump, LVEF ≥ 30%, no severe CAC, not elevated LDL level, and no re-admission were references. *53 missing.

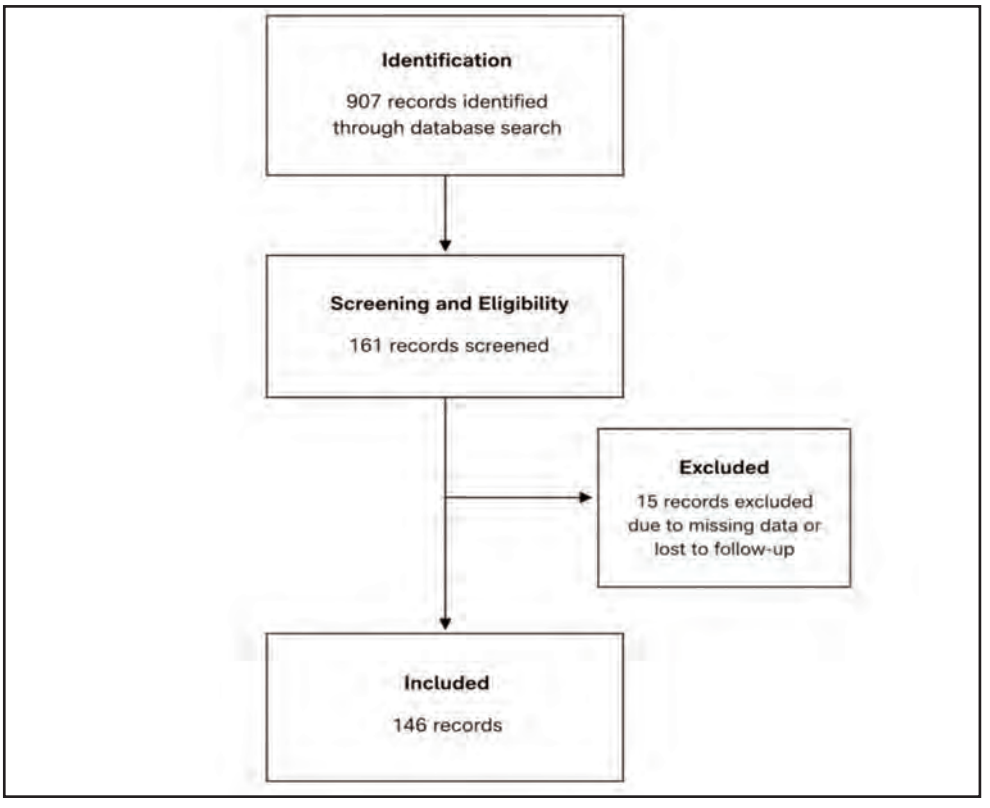



**Fig. 1:** Flow chart of patient enrolment

### Laboratory and Echocardiographic Findings

The mean LDL was 2.44 ± 1.13mmol/L, and more than half of the cohort (51.6%) had elevated LDL levels. LDL levels were categorised according to prior ACS history: for patients with a history of ACS, an elevated LDL was considered > 1.4mmol/L, whereas for those without a prior ACS history, elevated LDL was > 2.6mmol/L.[11] The mean LVEF was 48.39 ± 12.67%; however, 9.6% of patients presented with severely impaired systolic function with LVEF < 30%. The median serum creatinine was 109.0µmol/L (IQR: 384.0).

### Coronary Anatomy and Procedural Characteristics

The complexity of coronary lesions was notable. Severe coronary artery calcification was found in 46.6% of patients. PCI involved the left main stem (LMS) artery in 20.5% of cases, chronic total occlusion lesions in 13.0%, and bifurcation lesions in 6.8%. The mean stent length was 45.89 ± 21.13 mm, and most patients (80.8%) underwent single-lesion PCI. Lesions in the left anterior descending (LAD) artery were most frequently treated (80.8%), followed by the left circumflex artery (LCx) and right coronary artery (RCA),

each at 13.0%. Only 1.4% of procedures targeted coronary artery bypass grafts (CABG). The radial artery was the common access site (72.6%), whereas femoral access was used in 24.0% of the patients and combined radial–femoral access in 3.4%. Advanced calcium modification techniques were performed in 39.0% of patients and intracoronary imaging was used in 43.8% of cases. Use of mechanical circulatory support was uncommon, with only 2.1% of patients utilising intra-aortic balloon pump during PCI.

**30-Day Clinical Outcomes**

Table II compares the overall 30-days MACE outcomes with mortality outcomes. The MACE outcomes were low (5.5%) despite the high-risk profile of the cohort. Mortality occurred in 7 patients (4.8%), while stroke was reported in 1 patient (0.7%). All deaths were incidental cardiovascular in nature, with 6 deaths attributed to cardiogenic shock and 1 death due to ventricular tachycardia storm. Four deaths occurred during index hospitalisation whereas 3 occurred during subsequent readmission.

No recurrent myocardial infarction was observed. Non-MACE complications included hospital re-admission in 7 patients (4.8%) and a major bleeding event occurred in 1 patient (0.7%). Due to the small number of MACE events, which were driven predominantly by mortality rather than stroke or recurrent myocardial infarction, hence mortality alone was used as the final outcome measure.

**Exploratory analysis for variables associated with of 30-Day Mortality**

The model demonstrated good predictive accuracy, correctly classifying 92.5% of cases (target > 70%). The non-significant result (p=0.81) of the Hosmer–Lemeshow goodness-of-fit test suggested an adequate model, and the Nagelkerke $R^2$ of 0.53 indicated moderate explanatory power. Collectively, the developed model exhibited a moderate-good overall fit.

Univariate analyses indicated that several factors were potentially associated with 30-day mortality ($p \leq 0.30$), including advanced age (p=0.30), elevated LDL levels (p=0.29), LVEF<30% (p=0.14), severe coronary artery calcification (p=0.25), the use of an intra-aortic balloon pump (p=0.14), and hospital re-admission (p<0.001).

Hospital re-admission was included in the final outcome because previous studies have shown that re-admitted patients have a higher risk of mortality after PCI.[12] The variable of intracoronary imaging (p=0.24) was clinically rejected, as current guidelines recommend that PCI for anatomically complex lesions—left main stem, bifurcations, and long lesions—be guided by intravascular imaging.[13] The other statistically significant variables ($p \leq 0.3$) were included into a multivariate binary logistic regression model. The final exploratory analysis showed that LVEF < 30% (AOR: 41.11, 95% CI: 1.08–1563.83, p=0.04), severe coronary artery calcification (AOR: 28.18, 95% CI: 1.28–619.27, p=0.03), elevated LDL level (AOR: 28.72, 95% CI: 1.18–701.13, p=0.04), and hospital re-admission (AOR: 81.69, 95% CI: 4.12–1618.32, p<0.001) were potential factors associated with 30-day mortality. However, given the wide confidence intervals observed in the results, the data should be interpreted cautiously.

## DISCUSSION

This single-centre retrospective cohort study with 30-day follow-up provides valuable real-world insights into the clinical characteristics and short-term outcomes of patients undergoing CHIP-PCI in a non-surgical centre. The principal finding is that in a carefully selected high-risk cohort, CHIP-PCI can be performed with a low incidence of MACE of 5.5%. This study also identifies four exploratory variables potentially associated with 30-day mortality: severely reduced LVEF, severe coronary artery calcification, elevated LDL level, and hospital re-admission.

The patient cohort in this study aligns with the typical demographic and clinical profile of patients undergoing CHIP-PCI as documented in international literature.[2,14] More than two-thirds of patients were male and over 60 years of age, with a very high burden of diabetes mellitus, hypertension, and chronic kidney disease. Nearly half of all cases involved severe coronary calcification and one-fifth required left main stem intervention. These features are well recognised to increase procedural complexity and heighten the risk of periprocedural complications such as coronary perforation, suboptimal stent expansion, and peri-procedural myocardial infarction.[15-16] Notably, advanced calcium modification techniques was used in 39% of cases, underscoring the technical challenges posed by heavily calcified lesions. Contemporary plaque-modification tools such as rotational or orbital atherectomy, intravascular lithotripsy and specialised angioplasty balloons are essential to achieve adequate lesion preparation and stent expansion in this setting.[15,17] The high uptake of radial access despite lesion complexity reflects a growing preference for "radial-first strategies" even in CHIP-PCI, given their well-documented association with lower risk of all-cause mortality, major bleeding and major vascular complications.[18-19]

The MACE rate observed in the present cohort was similar when compared with outcomes reported in large-scale registries, including those from high-volume tertiary centres with on-site surgical backup. For instance, the retrospective analysis by Peles et al. of 1890 patients undergoing high-risk PCI - defined as unprotected left main disease, last patent vessel, or three-vessel disease with LVEF < 35% - reported a 30-day MACE rate of 14.2% and a 30-day all-cause mortality rate of 8.8%.[20] Similarly, the OPTIMUM registry by Salisbury et al., which investigated 726 patients with complex multivessel or left main coronary artery disease deemed ineligible for CABG, reported an all-cause mortality of 5.6% at 30 days.[21] Finally, Yeoh et al., analysing the Melbourne Interventional Group registry's data of 20,973 PCI patients stratified by a clinical and anatomical risk score, reported that the most complex and very high-risk patients had a 30-day mortality rate of 7.1%.[22] It is noteworthy that the MACE in our study was driven exclusively by mortality and stroke, with no reported cases of recurrent myocardial infarction. This finding may reflect successful procedural techniques that minimised periprocedural myocardial injury, a critical goal in CHIP-PCI. While the differences in study inclusion criteria prevent a direct head-to-head comparison of all results, the MACE rate from our study provides a useful benchmark for subsequent investigations.

Multivariate analysis identified several potential variables of short-term mortality. Reduced LVEF exhibited a high adjusted odds ratio, suggesting a potential association with increased odds of adverse outcomes in this patient population. This finding aligns with established cardiovascular literature documenting the strong association between left ventricular systolic dysfunction and increased adverse outcomes, as independently reported by Ye et al. and Mankerious et al. in their observational studies demonstrating higher rates of in-hospital MACE associated with reduced LVEF.[23-25] The challenge of CHIP-PCI in this group is rooted in their limited physiological reserve, rendering them poorly tolerant of repeated procedural myocardial ischaemia and significantly increasing their vulnerability to haemodynamic compromise, worsening heart failure, and ultimately, incomplete revascularisation.[26-28] Despite this inherent risk, Abudukeremu et al. reported in a meta-analysis of 25 observational studies (mean LVEF 30%) that PCI is a reasonable revascularisation strategy for patients with coronary artery disease and severe left ventricular systolic dysfunction, demonstrating acceptable short- and long-term outcomes, with no significant difference in long-term mortality compared with CABG.[29] Consequently, the high-risk profile necessitates meticulous procedural planning and the selective utilisation of haemodynamic support devices to mitigate MACE risk and achieve optimal revascularisation.[26]

Severe coronary artery calcification similarly emerged as a potential variable associated with 30-day mortality. The presence of severe coronary artery calcification significantly complicates PCI and is independently associated with an increased incidence of MACE.[15,30] The technical challenge posed by these lesions heightens the probability of procedural failure (e.g., balloon uncrossability or stent underexpansion), acute complications (e.g., coronary dissection or perforation, or balloon rupture), and higher periprocedural morbidity and mortality.[30] Consequently, this frequently necessitates advanced calcium modification techniques. While these techniques, such as mechanical atherectomy or intravascular lithotripsy (used in 39.0% of this cohort), may improve procedural success, they may not completely mitigate the inherent risk associated with severe coronary artery calcification, which remained potentially associated with adverse outcomes in this study. This highlights the essential role of intravascular imaging, meticulous technique selection, and clinical judgment based on individual lesion characteristics for optimal treatment of calcified lesions.[15]

A finding from our analysis was that elevated LDL level emerged as a potential variable associated with 30-day mortality. While LDL is a cornerstone of long-term cardiovascular risk management, its role as a predictor of acute outcomes is less clearly defined, and prior studies highlighted the nuanced nature of this association. For instance, Pres et al. reported that elevated admission LDL-C predicted in-hospital mortality in diabetic ST-elevation myocardial infarction (STEMI) patients treated with PCI, but not in their non-diabetic counterparts.[31] Similarly, Zhong et al. reported that a high LDL-C/HDL-C ratio was an independent predictor for 1-year MACE following PCI.[32] Although there is an important methodological distinction between the LDL-C measurement used in the cited studies and the less specific LDL measurement (as used in this present study), these collective evidences suggest that elevated admission LDL likely serves as a surrogate marker for a constellation of high-risk features, such as heightened systemic inflammation, plaque instability or poorly managed atherosclerotic disease.[33] While this association warrants further investigation, our findings suggest that baseline lipid status could be an important component of immediate risk assessment in the CHIP-PCI population.

In this study, it was observed that hospital re-admission was a potential variable associated with 30-day mortality and should be interpreted not as an independent baseline risk factor, but rather as a post-procedural complication that may indicate subsequent adverse outcomes. Large-scale analyses, such as Kwok et al., demonstrated that 30-day unplanned readmission following PCI occurs in nearly 1 in 10 patients and is associated with a higher risk of subsequent mortality and adverse events.[34] This association likely reflects that patients requiring re-admission are experiencing a decompensation of their fragile physiological state, often manifesting as significant, immediate postprocedural complications (e.g. major bleeding, stent thrombosis, or access-site complications) or acute clinical deterioration (e.g. worsening heart failure or infection). This underscores the necessity of multidisciplinary post-discharge surveillance and the implementation of transitional care protocols to mitigate the elevated risk of early mortality in this vulnerable patient population.

The authors acknowledge that several factors demonstrated very wide confidence intervals, likely due to the low number of mortality events observed in this study, resulting in statistical instability of the multivariable model. Although some variables appeared to be associated with increased odds of 30-day mortality, the magnitude of these associations should be interpreted with caution. For example, the adjusted odds ratio (AOR) for readmission was 81.69 (95% CI: 4.12–1618.32, $p<0.001$). While this suggests a possible association, the extremely wide confidence interval indicates substantial uncertainty around the effect estimate despite statistical significance. Therefore, these findings should be regarded as exploratory and hypothesis-generating rather than definitive evidence of independent predictors of mortality. Accordingly, terms implying strong or definitive associations should be interpreted cautiously within the context of the study's limited event rate and sample size.

## LIMITATIONS

Several limitations merit consideration. First, the single-centre retrospective cohort study with 30-day follow-up design limits the generalisability of the findings and allows only the identification of associations rather than causation. Second, the relatively small number of mortality events (the outcome of interest) resulted in wide confidence intervals for the odds ratios, and these findings should therefore be interpreted with caution. Third, although the exclusion of patients with incomplete data was methodologically necessary, it may have influenced the observed outcomes, particularly as some excluded patients had unknown 30-day outcomes due to loss to follow-up. Fourth, the 30-day follow-

up period does not provide insight into the long-term outcomes and safety of CHIP-PCI in this cohort. Fifth, elevated LDL levels as a potential variable associated with mortality may reflect an underlying high-risk comorbidity burden rather than a direct causal relationship. Additionally, the substantial proportion of missing LDL data (approximately 36%) limits confidence in the observed association between elevated LDL levels and 30-day mortality. Therefore, this finding should be interpreted cautiously. Sixth, re-admission as a potential variable may have been related to non-cardiac conditions (e.g., pneumonia) that were not captured in the database. Lastly, Firth's penalized logistic regression was not applied despite the small number of outcome events, due to limitations in the statistical package used for the analysis.

**Future Directions**

Future studies should incorporate larger, multicentre cohorts with extended follow-up periods to validate these findings and identify modifiable factors of adverse outcomes. Prospective evaluation of structured post-discharge care pathways and early implementation of intensive lipid-lowering strategies may further enhance clinical outcomes.

## CONCLUSION

In this single non-surgical centre experience, CHIP-PCI was associated with a low 30-day incidence of MACE despite the high clinical and procedural complexity of the patient cohort. Exploratory variables potentially associated with 30-day mortality included severely reduced LVEF, severe coronary artery calcification, elevated LDL levels, and hospital re-admission.

Overall, this study suggests that CHIP-PCI may be feasible in non-surgical centres with acceptable short-term outcomes in carefully selected patients. The findings add to the growing body of evidence indicating that, with experienced operators, meticulous procedural planning, and the use of contemporary interventional techniques, CHIP-PCI may be performed safely even in centres without on-site surgical backup.7 It also highlights the potential importance of aggressive lipid management and early detection of post-discharge complications. However, these observations should be regarded as exploratory and interpreted cautiously. The researchers acknowledge that 30-day mortality does not reflect long-term outcomes or overall long-term safety of CHIP-PCI. Therefore, larger multicentre studies with extended follow-up are warranted to validate these findings and further refine risk stratification and management strategies for this complex and expanding patient population.

## ACKNOWLEDGMENTS

The authors would like to thank the Director General of Health of Malaysia for his permission to publish this article.

## CONFLICT OF INTEREST

All authors of this study have no conflict of interest to declare.

## FUNDING

This study was conducted without the support of any external funding sources.

## ETHICAL APPROVAL

Ethical approval was obtained from Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia (NMRR ID-25-01644-KLT). Permission was obtained from the hospital authorities to assess the medical records.

## REFERENCES

1. Wennberg E, Abualsaud AO, Eisenberg MJ. Patient Management Following Percutaneous Coronary Intervention. JACC Adv 2024; 4(1): 42-7
2. Shamkhani W, Rashid M, Moledina S, Ludman P, Curzen N, Wijeysundera HC, et al. Complex High-Risk Percutaneous Coronary Intervention Types, Trends, and Outcomes in Nonsurgical Centres. Can J Cardiol 2024; 40(7): 1237-46.
3. Protty M, Sharp ASP, Gallagher S, Farooq V, Spratt JC, Ludman P, et al. Defining Percutaneous Coronary Intervention Complexity and Risk: An Analysis of the United Kingdom BCIS Database 2006-2016. JACC Cardiovasc Interv 2022; 15(1): 39-49.
4. Kinnaird T, Gallagher S, Spratt JC, Ludman P, de Belder M, Copt S, et al. Complex high-risk and indicated percutaneous coronary intervention for stable angina: Does operator volume influence patient outcome? Am Heart J 2020; 222: 15-25.
5. Achim A, Marc M, Ruzsa Z. Surgical Turned-Downed CHIP Cases-Can PCI Save the Day? Front Cardiovasc Med 2022; 9: 872398.
6. Abubakar M, Javed I, Rasool HF, Raza S, Basavaraju D, Abdullah RM, et al. Advancements in Percutaneous Coronary Intervention Techniques: A Comprehensive Literature Review of Mixed Studies and Practice Guidelines. Cureus 2023; 15(7): e41311
7. Grines CL, Box LC, Mamas MA, Abbott JD, Blankenship JC, Carr JG, et al. SCAI Expert Consensus Statement on Percutaneous Coronary Intervention Without On-Site Surgical Backup. JACC Cardiovasc Interv 2023; 16(7): 847-60
8. Bosco E, Hsueh L, McConeghy KW, Gravenstein S, Saade E. Major adverse cardiovascular event definitions used in observational analysis of administrative databases: a systematic review. BMC Med Res Methodol 2021; 21(1): 241
9. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011; 123(23): 2736-47
10. Raosoft. ® Sample size calculator [Internet]. Raosoft. 2025. Available from: http://www.raosoft.com/samplesize.html, accessed on 10 April 2025
11. Ministry of Health Malaysia; Academy of Medicine Malaysia; National Heart Association of Malaysia. Management of dyslipidemia 2023: clinical practice guidelines. 6th ed. Kuala Lumpur: National Heart Association of Malaysia; 2023. Table 4, Target LDL-C levels; p. 23.
12. Khawaja FJ, Shah ND, Lennon RJ, Slusser JP, Alkatib AA, Rihal CS, et al. Factors associated with 30-day readmission rates after percutaneous coronary intervention. Arch Intern Med. 2012 Jan 23;172(2):112-7.
13. Vrints C, Andreotti F, Koskinas KC, Rossello X, Adamo M, Ainslie J, et al. 2024 ESC Guidelines for the management of chronic coronary syndromes. Eur Heart J 2024; 45(36): 3415-537. Erratum in: Eur Heart J. 2025 Apr 22;46(16):1565.
14. Kheifets M, Vons SA, Bental T, Vaknin-Assa H, Greenberg G, Samara A, et al. Temporal Trends in Complex Percutaneous Coronary Interventions. Front Cardiovasc Med 2022; 9: 913588.
15. Sung JG, Lo ST, Lam H. Contemporary Interventional Approach to Calcified Coronary Artery Disease. Korean Circ J 2023; 53(2): 55-68.

16. Mohammad MA, Persson J, Buccheri S, Odenstedt J, Sarno G, Angerås O, et al. Trends in Clinical Practice and Outcomes After Percutaneous Coronary Intervention of Unprotected Left Main Coronary Artery. J Am Heart Assoc 2022; 11(7): e024040
17. Mohan J, Shams P, Bhatti K, Zeltser R. Coronary Artery Calcification. In: StatPearls. Treasure Island (FL): StatPearls Publishing; November 8, 2024.
18. Kolkailah AA, Alreshq RS, Muhammed AM, Zahran ME, Anas El-Wegoud M, Nabhan AF. Transradial versus transfemoral approach for diagnostic coronary angiography and percutaneous coronary intervention in people with coronary artery disease. Cochrane Database Syst Rev 2018; 4(4): CD012318.
19. Lindner SM, McNeely CA, Amin AP. The Value of Transradial: Impact on Patient Satisfaction and Health Care Economics. Interv Cardiol Clin 2020; 9(1): 107-115.
20. Peles I, Barrett O, Cafri C, Garcia-Garcia H, Tsaban G, El-Nasasra A, et al. Predictors of Adverse Outcome in High-Risk Percutaneous Coronary Interventions Patients. Can J Cardiol 2023; 39(10): 1369-79.
21. Salisbury AC, Grantham JA, Brown WM, Ballard WL, Allen KB, Kirtane AJ, et al; OPTIMUM Investigators. Outcomes of Medical Therapy Plus PCI for Multivessel or Left Main CAD Ineligible for Surgery. JACC Cardiovasc Interv 2023; 16(3): 261-273.
22. Yeoh J, Hamilton GW, Dinh D, Brennan A, Reid CM, Stub D, et al; Melbourne Interventional Group. Understanding long-term risk in Percutaneous Coronary Intervention (PCI) in the Australian contemporary era with a focus on defining Complex Revascularisation in High-Risk Indicated Patients (CHIP). Cardiovasc Revasc Med 2025; 77: 22-28.
23. Parikh PB, Bhatt DL, Bhasin V, Anker SD, Skopicki HA, Claessen BE, et al. Impact of Percutaneous Coronary Intervention on Outcomes in Patients With Heart Failure: JACC State-of-the-Art Review. J Am Coll Cardiol 2021; 77(19): 2432-47.
24. Ye Z, Lu H, Li L. Reduced Left Ventricular Ejection Fraction Is a Risk Factor for In-Hospital Mortality in Patients after Percutaneous Coronary Intervention: A Hospital-Based Survey. Biomed Res Int 2018 ; 2018: 8753176.
25. Mankerious N, Hemetsberger R, Toelg R, Abdel-Wahab M, Richardt G, Allali A. Acute and Long-Term Outcomes of Patients with Impaired Left Ventricular Systolic Function Undergoing Rotational Atherectomy: A Single-Center Observational Retrospective Study. Cardiol Ther 2019; 8(2): 267-281.
26. Di Muro FM, Bellino M, Esposito L, Attisano T, Meucci F, Mattesini A, et al. Role of Mechanical Circulatory Support in Complex High-Risk and Indicated Percutaneous Coronary Intervention: Current Indications, Device Options, and Potential Complications. J Clin Med 2024; 13(16): 4931.
27. Truesdell AG, Davies R, Eltelbany M, Megaly M, Rosner C, Cilia LA. Mechanical Circulatory Support for Complex High-risk Percutaneous Coronary Intervention. US Cardiol 2023; 17: e03.
28. Noordali H, Loudon BL, Frenneaux MP, Madhani M. Cardiac metabolism - A promising therapeutic target for heart failure. Pharmacol Ther 2018; 182: 95-114
29. Abudukeremu N, Yu ZX, Yang YN, Chan SP, Ma YT, et al. GW27-e1103 An Updated Systematic Review and Meta-analysis of the Short- and Long-term Outcomes of Percutaneous Coronary Intervention for Patients with Severe Left Ventricular Systolic Dysfunction. J Cardiovasc Med (Hagerstown) 2016, 68 (16_Supplement) C88; 5(4): 073-080.
30. Angsubhakorn N, Kang N, Fearon C, Techorueangwiwat C, Swamy P, Brilakis ES, et al. Contemporary Management of Severely Calcified Coronary Lesions. J Pers Med 2022; 12(10): 1638.
31. Pres D, Gasior M, Lekston A, Gierlotka M, Hawranek M, Tajstra M, et al. Relationship between low-density lipoprotein cholesterol level on admission and in-hospital mortality in patients with ST-segment elevation myocardial infarction, with or without diabetes, treated with percutaneous coronary intervention. Kardiol Pol 2010; 68(9): 1005-12.
32. Zhong Z, Hou J, Zhang Q, Zhong W, Li B, Li C, et al. Assessment of the LDL-C/HDL-C ratio as a predictor of one year clinical outcomes in patients with acute coronary syndromes after percutaneous coronary intervention and drug-eluting stent implantation. Lipids Health Dis. 2019; 18(1): 40.
33. Wolf D, Ley K. Immunity and Inflammation in Atherosclerosis. Circ Res. 2019; 124(2): 315-27.
34. Kwok CS, Rao SV, Potts JE, Kontopantelis E, Rashid M, Kinnaird T, et al. Burden of 30-Day Readmissions After Percutaneous Coronary Intervention in 833,344 Patients in the United States: Predictors, Causes, and Cost: Insights from the Nationwide Readmission Database. JACC Cardiovasc Interv 2018; 11(7): 665-74.

ORIGINAL ARTICLE

# Prevalence of contact sensitisation among patients with hand eczema and factors associated with contact sensitisation and disease severity

**Benjamin Liong Chee Seng, MRCP[1], Adawiyah Jamil, AdvMDerm[2], Ng Ting Guan, AdvMDerm[3], Norazura Mohamad, AdvMDerm[4]**

[1]Hospital Putrajaya, Putrajaya, Malaysia, [2]Hospital Pusat Perubatan Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia, [3]Hospital Tengku Ampuan Rahimah, Klang, Selangor, Malaysia, [4]Hospital Sultanah Nur Zahirah, Kuala Terengganu, Terengganu, Malaysia

## ABSTRACT

**Introduction: Chronic hand eczema is a debilitating skin disease. The aetiology of hand eczema can be due to irritant contact, allergic contact or a manifestation of endogenous eczema. Identification of sensitisers and subsequent avoidance of relevant sensitisers may improve care of chronic hand eczema patients. We aimed to study the prevalence and pattern of sensitisation, factors associated with sensitisation and severity of hand eczema.**

**Materials and Methods: A cross sectional study was conducted over a six month period between January to June 2025 at the Department of Dermatology in a tertiary hospital located in the capital of Selangor. Patients with predominantly hand eczema aged above 18 years old were interviewed, examined and patch tested with Standard European Baseline Series from Chemotechnique Diagnostics. Patients with contraindications for patch test and uncertain diagnosis were excluded. Hand eczema morphology was classified according to the Danish Contact Dermatitis Group classification. Hand eczema severity was determined using Hand Eczema Severity Index (HECSI). Patch test results were interpreted according to International Contact Dermatitis Research Group (ICDRG) guidelines.**

**Results: A total of 54 patients aged 44± 15.29years old participated. Female to male ratio was 2.6:1 and 79.6% had positive patch test. The most common sensitisers were nickel sulphate (29.63%), fragrance mix 1 (25.93%), potassium dichromate (14.8%) and formaldehyde (14.8%). Polysensitisation was seen in 41.6%. Sensitisation was not associated with age, history of atopy, hand washing >10 times/day, hand wetting activities > two hours/day, use of non-permeable gloves, hand sanitiser use, fragrances and smoking. Cosmetic use showed seven times increased odds of polysensitisation (p=0.033). Hand eczema morphology was not associated with sensitisation. HECSI was significantly higher with use of non-permeable gloves. HECSI was not associated with atopy, frequency of hand washing and duration of wet hands.**

**Conclusion: Patch test sensitisation was common in hand eczema patients. Polysensitisation was associated with use of cosmetics. Use of non-permeable gloves may worsen hand eczema.**

**KEYWORDS:**
*Hand eczema; patch test; sensitisation; allergic contact dermatitis*

## INTRODUCTION

Chronic hand eczema has a yearly prevalence of 9.1%.[1] A significant number of patients with hand eczema in multiple studies in Europe reported persistence of disease for 12 weeks or longer, had long durations of sick days, reported inability to work, had job changes due to hand eczema and even had early retirement.[1] In Sweden, the mean duration of sick leave was 18.9 weeks while in Denmark, 44% of patients with occupational hand eczema required job change and 15% of occupational hand eczema patients went into early retirement.[1]

The most common symptom in hand eczema is itching.[1] Primary acute skin lesions can include erythema, oedema, oozing, crusting papules and vesicles.[1] Secondary skin lesions that follow will include lichenification, hyperkeratosis and fissuring.[1] Chronic hand eczema is diagnosed when the eczematous changes described above last longer than three months or are recurrent within a year.[1] Involvement of the feet is present in 20% of patients.[1]

The aetiology of hand eczema can be due to irritant contact, allergic contact or a manifestation of endogenous eczema.[1] There can be an overlap between these conditions. Irritant contact dermatitis is a non-specific inflammatory dermatosis mainly due to the toxicity of chemicals on the skin and does not require sensitisation.[1-2] Allergic contact dermatitis is a delayed hypersensitivity response after sensitisation by an allergen/sensitiser and subsequently recreated by elicitation.[2] The process in which a patient develops an allergic contact reaction to an allergen/sensitiser is called sensitisation.

Patch testing aims to reproduce "in miniature" an eczematous reaction by applying allergens under occlusion in patients who are suspected to be allergic.[2] It attempts to elicit a reaction in a delayed hypersensitivity reaction and in the process, identify a "culprit" allergen. Sensitisers or

*This article was accepted: 02 June 2026*
*Corresponding Author: Benjamin Liong Chee Seng*
*Email: liongcheeseng@gmail.com*

allergens are inserted into patch test chambers which are then applied to intact skin under occlusion and given time for the elicitation reaction to occur. Typically, the patch chambers with sensitisers are removed after 48 hours and the first reading is made. The second reading is made after 96 hours to determine if a significant reaction is present. A typical allergic contact reaction will present after 24-72 hours and typically worsens (crescendo pattern) before resolution over time.[2]

Patch testing is recommended in patients with chronic hand eczema and those who are non-responsive to adequate treatment to investigate for relevant sensitisations to aid the diagnosis of allergic contact dermatitis.[1]

Common sensitisers in hand eczema include nickel sulfate, preservatives, fragrances, cobalt, rubber chemicals, potassium dichromate and p-phenylenediamine.[3] Up to 63% of the patients developed sensitisation to at least one allergen.[3] Sensitisation with three or more sensitisers (polysensitisation) has been linked to atopic diseases such as bronchial asthma, allergic rhinitis and hand eczema.[4-6]

Multiple factors have been associated with sensitisation. Skin barrier function, inherent skin susceptibility, size, duration and extent of allergen exposure, sensitising potency and occlusion/skin irritation are factors associated with sensitisation.[7] Role of atopic dermatitis in the pathophysiology of contact sensitisation is unclear; atopic dermatitis being Th2 driven may impede contact sensitisation and elicitation which are Th1 driven.[7] A meta-analysis identified frequent hand washing and long duration of wet works as risk factors for hand eczema, while suggesting use of occlusive gloves may have a role.[8] Body piercing is associated with nickel sensitisation, which lowers the threshold for elicitation in hand eczema or presents as a secondary eruption in hand eczema.[9] Other sources of nickel exposure include diet, accessories, utensils and occupation related exposure.[9] Fragrance allergens are common allergens in hand eczema.[10] Toiletries, perfumes, deodorants, essential oils and cosmetics are sources for fragrance allergens.[10] Use of cosmetics and hand eczema was also reported by Heede et al (10) in 2016.[11] Severity of hand eczema has been associated with age, atopic dermatitis, and the presence of sensitisers.[12] Although no single morphological classification is universally accepted, higher rates of sensitisation have been reported in the recurrent vesicular type of hand eczema.[13]

Studies on hand eczema that report contact sensitisation, factors associated with contact sensitisation, disease severity and morphology of hand eczema are lacking. We studied the above mentioned in a local setting.

## MATERIALS AND METHODS

### Study Design

The study was a cross-sectional observational study conducted on patients diagnosed by dermatologists and a dermatology fellow with chronic hand eczema who were conveniently sampled from the dermatology clinic at a government tertiary hospital in Selangor from 1st January 2025 to 30th June 2025.

The patients were screened for inclusion and exclusion criteria prior to enrolment. Patients aged 18 years old or older with eczema predominantly affecting the hands were included. Patients who were contraindicated for patch testing (e.g. pregnancy, on prednisolone above 10mg per day), patients whose diagnosis was uncertain, or had concomitant conditions such as tinea manuum, scabies, or hand psoriasis were excluded. Informed consent was obtained.

The patients were interviewed to collect data on demography, eczema history, their hand washing habits, duration of hand wetting activities, use of hand sanitisers, use of non-permeable gloves, body piercing, use of fragrance, use of cosmetics and smoking habits which were deemed to be factors associated with contact sensitisation or severity of hand eczema. Hand wetting was defined as wet work activities, which were defined by having wet hands by either hand washing, performing work or tasks that contribute to wet hands. Non permeable gloves were defined by specifically asking if the patient wore rubber, nitrile or latex gloves. Fragrance use was defined as use of fragrances used in perfumes, cosmetics, soaps, lotions and sanitisers. Food preparation was defined as preparing raw ingredients and cooking.

Physical examination was performed. Hand eczema morphology was classified according to the Danish Contact Dermatitis Group classification for hand eczema morphology; recurrent vesicular, chronic fissuring, hyperkeratotic, pulpitis, interdigital, nummular and unclassified as proposed by Danish guidelines on hand eczema.[14] Severity of hand eczema was assessed using Hand Eczema Severity Index (HECSI), a validated tool to measure hand eczema severity.[15]

Patients were then patch tested with 30 sensitisers from the standard European Baseline Series by Chemotechnique Diagnostics. Patients were required to attend the clinic on Monday for application of patch chambers. Patch test results were read on Wednesday and Friday (according to the International Contact Dermatitis Research Group Guide).[2] Patients with three or more positive results were categorised as polysensitisation while patients with one or two positive patch test results were categorised as oligosensitisation.

Sample size was calculated based on the primary objective to explore the prevalence of contact sensitisation using single proportion formula using the Scalex SP calculator. A systematic review reported the prevalence of contact sensitisation as 20.1%.[16] For the expected prevalence of 20% among patients with hand eczema, the required sample size was 80 for the margin of error or absolute precision of ±10% in estimating the prevalence with 95% confidence and considering the potential loss/attrition of 20%. With this sample size, the anticipated 95% CI was 10% - 30%.

Data were analysed using SPSS version 26.0. Continuous variables were presented as mean and standard deviation for normally distributed data, otherwise median and interquartile range. Categorical variables were presented as frequency and percentage. The various risk factors associated with contact sensitisation and hand eczema severity and the

**Table I: Characteristics of the study participants and patch test sensitisation pattern**

| Characteristics | | N= n(%) or mean±SD |
|---|---|---|
| Age in years, mean ± SD | | 43.76 ± 15.29 |
| Sex, n (%) | Female | 39 (72.2) |
| | Male | 15 (27.8) |
| Race, n (%) | Malay | 35 (64.8) |
| | Chinese | 8 (14.8) |
| | Indian | 9 (16.7) |
| | Others | 2 (3.7) |
| Household Income, n (%) | B40 (<RM5250) | 41 (75.9) |
| | M40 (RM5250-RM11819) | 12 (22.2) |
| | T20 (>RM11819) | 1 (1.9) |
| Occupation, n (%) | Unemployed | 16 (29.6) |
| | Blue collar | 12 (22.2) |
| | White collar | 20 (37.0) |
| | Pink collar | 4 (7.4) |
| | Gold collar | 2 (3.7) |
| History of atopy, n (%) | Yes | 26 (48.1) |
| Type of atopy | Bronchial asthma | 5 (19.2) |
| | Allergic rhinitis | 13 (50.0) |
| | Dermatitis | 15 (57.7) |
| Family history of atopy, n (%) | Yes | 29 (53.7) |
| Clinical diagnosis, n (%) | Hand eczema | 33 (61.1) |
| | Hand and Feet eczema | 21 (38.9) |
| Factors associated with sensitisation: | | |
| Hand washing frequency per day, n (%) | 0-9 | 24 (44.4) |
| | 10-19 | 18 (33.3) |
| | >20 | 12 (22.2) |
| Duration of Hands being wet per day, n (%) | <1 hour | 7 (13.0) |
| | 1-2 hour | 18 (33.3) |
| | >2 hour | 29 (53.7) |
| Sanitiser use, n (%) | | 17 (31.5) |
| Non-permeable glove use, n (%) | | 20 (37.0) |
| Body piercing, n (%) | | 33 (61.1) |
| Metal braces, n (%) | | 14 (25.9) |
| Dental implant, n (%) | | 5 (9.3) |
| Metal accessories, n (%) | | 9 (16.7) |
| Cosmetic use, n (%) | | 22 (40.7) |
| Fragrance use, n (%) | | 45 (83.3) |
| Food preparation, n (%) | | 42 (77.8) |
| Care for child under 4 years old, n (%) | | 9 (16.7) |
| Gardening, n (%) | | 17 (31.5) |
| Car repair, n (%) | | 7 (13.0) |
| Building or renovation, n (%) | | 2 (3.7) |
| Smoking, n (%) | | 8 (14.8) |
| Drug allergy, n (%) | | 9 (16.7) |
| Morphology | Recurrent Vesicular | 21(39.6) |
| | Chronic Fissuring | 12(22.6) |
| | Nummular | 7(13.2) |
| | Unclassified | 6(11.3) |
| | Interdigital | 4(7.5) |
| | Hyperkeratotic | 2(3.8) |
| | Pulpitis | 2(3.8) |
| Sensitisation rate, n (%) | Sensitised to at least 1 antigen | 43 (79.6) |
| | No sensitisation | 11 (20.4) |
| | Oligo-sensitisation | 25 (46.3) |
| | Polysensitisation | 18 (33.3) |

association between morphological patterns of hand eczema with the presence of contact sensitisation were tested using independent sample t test, Mann Whitney U test, Pearson chi-squared test, Fisher Exact test and simple regression analysis. All the tests were two sided and statistical significance was denoted by $p<0.05$.

This study was registered with the National Medical Research Registry (Research ID: RSCH ID-23-04790-YJR). Ethical approval was obtained from the Medical Research and Ethics Committee, Ministry of Health, Malaysia (Research ID: RSCH ID-23-04790-YJR).

**Table II: Positivity rate of allergens causing contact sensitisation, ranked from highest to lowest**

| Allergen | N | % | 95% CI of % |
|---|---|---|---|
| 1. Nickel sulphate | 16 | 29.63 | 17.98, 43.61 |
| 2. Fragrance mix I | 14 | 25.93 | 14.96, 39.65 |
| 3. Potassium dichromate | 8 | 14.81 | 6.62, 27.12 |
| 4. Formaldehyde | 8 | 14.81 | 6.62, 27.12 |
| 5. Methyldibromo Glutaronitrile | 7 | 12.96 | 5.37, 24.90 |
| 6. Benzisothiazolinone | 7 | 12.96 | 5.37, 24.90 |
| 7. Fragrance mix II | 6 | 11.11 | 4.19, 22.63 |
| 8. Cobalt chloride | 5 | 9.26 | 3.08, 20.30 |
| 9. Peru Balsam | 5 | 9.26 | 3.08, 20.30 |
| 10. Methylisothiazolinone + Methylchloroisothiazolinone | 5 | 9.26 | 3.08, 20.30 |
| 11. Methylisothiazolinone | 5 | 9.26 | 3.08, 20.30 |
| 12. Colophonium | 3 | 5.56 | 1.16, 15.39 |
| 13. Sodium Metabisulfite | 3 | 5.56 | 1.16, 15.39 |
| 14. Propolis | 3 | 5.56 | 1.16, 15.39 |
| 15. Neomycin sulphate | 2 | 3.7 | 0.45, 12.75 |
| 16. Paraben mix | 2 | 3.7 | 0.45, 12.75 |
| 17. N-Isopropyl-N-phenyl-p-phenyuledediamine | 2 | 3.7 | 0.45, 12.75 |
| 18. 2-Mercaptobenzothiazole | 2 | 3.7 | 0.45, 12.75 |
| 18. Decyl glucoside | 2 | 3.7 | 0.45, 12.75 |
| 19. p-Phenyldiamine | 1 | 1.85 | 0.05, 9.89 |
| 20. Thiuram mix | 1 | 1.85 | 0.05, 9.89 |
| 21. Caine mix | 1 | 1.85 | 0.05, 9.89 |
| 22. 2-hydroxyethyl methacrylate | 1 | 1.85 | 0.05, 9.89 |
| 23. Lanolin | 1 | 1.85 | 0.05, 9.89 |

**Table III: Factors associated with contact sensitisation**

| Factors | No sensitisation vs oligo-sensitisation | | No sensitisation vs polysensitisation | |
|---|---|---|---|---|
| | OR (95% CI) | p-value | OR (95% CI) | p-value |
| Age | 0.98 (0.93, 1.03) | 0.406 | 1.00 (0.95, 1.05) | 0.998 |
| Sex | | | | |
| Female | Ref | | Ref | |
| Male | 0.68 (0.15, 3.07) | 0.617 | 0.50 (0.10, 2.62) | 0.500 |
| Race | | | | |
| Malay | Ref | | Ref | |
| Chinese | 0.86 (0.12, 6.01) | 0.877 | 0.40 (0.05, 3.53) | 0.409 |
| Indian | 0.71 (0.13, 4.00) | 0.702 | 0.13 (0.01, 1.55) | 0.107 |
| Income | | | | |
| B40 (<RM5250) | Ref | | Ref | |
| M40 (RM5220 - RM11819) | 2.84 (0.30, 27.26) | 0.365 | 3.46 (0.34, 34.84) | 0.292 |
| T20 (>RM11819) | - | - | - | - |
| Occupation | | | | |
| Unemployed | Ref | | Ref | |
| Blue collar | 1.43 (0.24, 8.64) | 0.698 | 1.25 (0.16, 9.92) | 0.833 |
| White collar | 2.14 (0.38, 12.20) | 0.390 | 3.33 (0.52, 21.58) | 0.206 |
| Pink collar | - | - | - | - |
| Gold collar | - | - | - | - |
| History of atopy | | | | |
| No | Ref | | Ref | |
| Yes | 1.11 (0.27, 4.60) | 0.888 | 1.20 (0.27, 5.40) | 0.812 |
| Family history of atopy | | | | |
| No | Ref | | Ref | |
| Yes | 0.77 (0.19, 3.19) | 0.718 | 1.31 (0.28, 5.98) | 0.728 |
| Hand washing frequency | Ref | | Ref | |
| 0-9 | 2.55 (0.41, 15.65) | 0.313 | 4.67 (0.70, 31.04) | 0.111 |
| 10-19 | 1.91 (0.30, 12.26) | 0.496 | 2.33 (0.31, 17.55) | 0.410 |
| ≥20 | | | | |
| Hand washing frequency | | | | |
| <10 | Ref | | Ref | |
| ≥10 | 2.23 (0.52, 9.59) | 0.283 | 3.50 (0.73, 16.85) | 0.118 |
| Hand wet duration | | | | |
| <1 hour | Ref | | Ref | |
| 1-2 hour | 0.75 (0.09, 6.23) | 0.790 | 4.00 (0.27, 58.56) | 0.311 |
| >2 hour | 1.50 (0.21, 10.82) | 0.688 | 3.60 (0.26, 50.33) | 0.341 |

**Table III: Factors associated with contact sensitisation (Continued)**

| Factors | No sensitisation vs oligo-sensitisation | | No sensitisation vs polysensitisation | |
|---|---|---|---|---|
| | OR (95% CI) | p-value | OR (95% CI) | p-value |
| Hand wet duration | | | | |
| <1hour | Ref | | Ref | |
| ≥1hour | 1.17 (0.18, 7.56) | 0.872 | 3.78 (0.30, 47.56) | 0.304 |
| Sanitiser use | | | | |
| No | Ref | | Ref | |
| Yes | 0.67 (0.13, 3.47) | 0.630 | 2.67 (0.53, 13.43) | 0.234 |
| Non-permeable glove use | | | | |
| No | Ref | | Ref | |
| Yes | 1.50 (0.32, 7.12) | 0.610 | 2.13 (0.42, 10.78) | 0.359 |
| Body piercing | | | | |
| No | Ref | | Ref | |
| Yes | 1.25 (0.30, 5.23) | 0.760 | 1.67 (0.36, 7.77) | 0.515 |
| Metal braces | | | | |
| No | Ref | | Ref | |
| Yes | 2.53 (0.45, 14.37) | 0.294 | 0.90 (0.13, 6.46) | 0.917 |
| Metal accessories | | | | |
| No | Ref | | Ref | |
| Yes | 1.13 (0.18, 6.94) | 0.899 | 0.56 (0.07, 4.70) | 0.595 |
| Cosmetic use | | | | |
| No | Ref | | Ref | |
| Yes | 2.53 (0.45, 14.37) | 0.294 | 7.07 (1.17, 42.85) | 0.033 |
| Fragrance use | | | | |
| No | Ref | | Ref | |
| Yes | 0.70 (0.12, 4.20) | 0.700 | 3.78 (0.30, 47.56) | 0.304 |
| Prepare food | | | | |
| No | Ref | | Ref | |
| Yes | 0.70 (0.12, 4.20) | 0.700 | 0.78 (0.12, 5.16) | 0.795 |
| Care for child <4 years | | | | |
| No | Ref | | Ref | |
| Yes | 0.61 (0.09, 4.31) | 0.624 | 1.29 (0.19, 8.53) | 0.795 |
| Gardening | | | | |
| No | Ref | | Ref | |
| Yes | 0.82 (0.19, 3.65) | 0.798 | 0.67 (0.14, 3.35) | 0.629 |
| Car repair | | | | |
| No | Ref | | Ref | |
| Yes | 0.86 (0.13, 5.55) | 0.872 | 0.27 (0.02, 3.33) | 0.304 |
| Smoking | | | | |
| No | Ref | | Ref | |
| Yes | 1.13 (0.18, 6.94) | 0.899 | 0.27 (0.02, 3.33) | 0.304 |
| Drug allergy | | | | |
| No | Ref | | Ref | |
| Yes | 0.33 (0.07, 1.70) | 0.186 | 0.10 (0.01, 1.09) | 0.059 |

Simple linear regression

## RESULTS

A total of 57 patients were recruited, but three dropped out as they were not able to commit to the schedule of the patch testing.

The remaining 54 patients were included in the study. Their mean age was 44±15.29 years old. Female patients outnumber male patients by a 2.6:1 ratio. The majority were Malay (64.8%) with household income in the lower socioeconomic group i.e. B40 category (75.9%). About half reported history of atopy (48.1%) and family history of atopy (53.7%). Thirty three (61.1%) presented with hand eczema, and 21 (38.9%) presented with both hand and feet eczema.

Majority of the patients wash their hands 0-9 times daily (44.4%), had their hands wet for a duration of more than 2 hours (53.7%) per day, do not use sanitiser (68.5%) and do not use non-permeable glove (63.0%). The number of patients with body piercing, metal braces, dental implant, metal accessories, cosmetics use, and fragrance use were 33 (61.1%), 14 (25.9%), 5 (9.3%), 9 (16.7%), 22 (40.7%), and 45 (83.3%) respectively. There were 42 (77.8%) who prepared food and 9 (16.7%) cared for children under 4 years old. Seventeen (31.5%) did gardening, 7 (13.0%) did car repairs, and 2 (3.7%) were in construction related work. The characteristics of our patients are represented in Table I.

### Contact sensitisers and sensitisation pattern

The most common sensitisers observed were nickel sulphate (29.63%), followed by fragrance mix 1 (25.93%), potassium dichromate and formaldehyde (both 14.81%). Other sensitisers and their frequencies are summarised in Table II. There were 11 (20.4%) patients with negative test, 25 (46.3%) had oligo-sensitisation and the rest had polysensitisation (33.3%). Forty three (79.6%) patients had at least one positive reaction in their patch test, and 58.1% were clinically relevant. Of the 43 patients who reported at least one positive patch test, 41.8% were in the polysensitisation group.

**Table IV: Factors associated with severity of hand eczema**

| Factors | HECSI | p-value | Simple linear regression | |
|---|---|---|---|---|
| | | | Coef (95% CI) | p-value |
| Age ( Mean ± SD) | 17.07 ± 16.66 | 0.781[c] | -0.04 (-0.35, 0.26) | 0.781 |
| Sex (Median (IQR) | | | | |
| Female | 12 (5, 24) | 0.692[a] | Ref | |
| Male | 12 (7, 26) | | 4.61 (-5.57, 14.78) | 0.368 |
| History of atopy (Median (IQR) | | | | |
| No | 12 (6, 22) | 0.671[a] | Ref | |
| Yes | 16 (4,30) | | 4.68 (-4.42, 13.78) | 0.307 |
| Family history of atopy (Median (IQR) | | | | |
| No | 12 (7, 27) | 0.289[a] | Ref | |
| Yes | 12 (4, 24) | | -3.81 (-12.96, 5.34) | 0.407 |
| Hand washing frequency (Median (IQR) | | | | |
| 0-9 | 11 (5, 24) | 0.395[a] | Ref | |
| 10-19 | 16 (7, 30) | | 8.67 (-1.78, 18.92) | 0.103 |
| ≥20 | 9 (5, 29) | | 3.79 (-7.94, 15.53) | 0.520 |
| Hand washing frequency (Mean ± SD) | | | | |
| <10 | 13.38 ± 10.39 | 0.146[b] | Ref | |
| ≥10 | 20.03 ± 20.03 | | 6.66 (-2.40, 15.71) | 0.146 |
| Hand wet duration (Median (IQR) | | | | |
| <1 hour | 4 (0, 7) | 0.069[a] | Ref | |
| 1-2 hour | 12 (6, 27) | | 12.36 (-2.43, 27.14) | 0.099 |
| >2 hour | 12 (7, 25) | | 8.96 (-5.02, 22.94) | 0.204 |
| Hand wet duration (Median (IQR) | | | | |
| <1 hour | 4 (0, 7) | 0.019[a] | Ref | |
| ≥1 hour | 12 (6, 26) | | 10.26 (-3.11, 23.63) | 0.130 |
| Sanitiser use (Median (IQR) | | | | |
| No | 9 (5, 24) | 0.188[a] | Ref | |
| Yes | 16 (9, 27) | | 6.50 (-3.22, 16.22) | 0.185 |
| Non-permeable glove use (Mean ± SD) | | | | |
| No | 12.82 ± 10.00 | 0.013[b] | Ref | |
| Yes | 24.30 ± 22.65 | | 11.48 (0.81, 22.15) | 0.013 |

Mann Whitney U test; bIndependent sample t test; cPearson correlation; dSimple linear regression

**Table V: Association between presence of contact sensitisation with morphological pattern of hand eczema**

| | Morphology, n (%) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Chronic Fissuring | Hyper-keratotic | Interdigital | Nummular | Pulpitis | Recurrent vascular | Unclassified | p-value |
| Sensitisation | | | | | | | | |
| No | 4 (33.3) | 0 (0.0) | 0 (0.0) | 1 (14.3) | 0 (0.0) | 5 (23.8) | 1 (16.7) | 0.874 |
| Oligosensitisation | 6 (50.0) | 2 (100.0) | 3 (75.0) | 3 (42.9) | 1 (50.0) | 7 (33.3) | 3 (50.0) | |
| Polysensitisation | 2 (16.7) | 0 (0.0) | 1 (25.0) | 3 (42.9) | 1 (50.0) | 9 (42.9) | 2 (33.3) | |
| Sensitisation | | | | | | | | |
| No | 4 (33.3) | 0 (0.0) | 0 (0.0) | 1 (14.3) | 0 (0.0) | 5 (23.8) | 1 (16.7) | 0.910 |
| Yes | 8 (66.7) | 2 (100.0) | 4 (100.0) | 6 (85.7) | 2 (100.0) | 16 (76.2) | 5 (83.3) | |

Fisher Exact test

**Factors associated with contact sensitisation**

There was no significant association in age, gender, presence of atopy, family history of atopy, hand washing ≥10 times a day, duration of hand wetting of ≥ one hour a day, non-permeable glove use, sanitiser use, body piercing, metal bracers/dental implants, metal accessories use, fragrance use and smoking with oligosensitisation or polysensitisation groups. Cosmetics use was observed to significantly increase the odds for polysensitisation by 7.07 times rather than no sensitisation [OR (95% CI): 7.07 (1.17, 42.85); p= 0.033]. The results are presented in Table III.

**Factors associated with hand eczema severity**

The use of non-permeable gloves was significantly associated with a higher HECSI score (12.82± 10.00 vs 24.30 ± 22.65; p=0.013).

Hand eczema severity was not significantly associated with age, gender, presence of atopy, family history of atopy, frequency of hand washing ≥10times a day, duration of wet hands of ≥ one hour a day and presence of at least one sensitiser. The results are presented in Table IV.

**Morphology**

The morphological types of hand eczema observed in our study population were as follows: Twenty one (38.9%) patients had recurrent vesicular eczema, 12 (22.2%) chronic fissuring, 7 (13.0%) nummular, 6 (11.1%) unclassified, 4 (7.4%) interdigital, 2 (3.7%) hyperkeratotic and 2 (3.7%) had pulpitis. Morphology was not associated with a positive patch test (p value = 0.910) and no one particular sensitiser was associated with any morphology. The breakdown of hand eczema morphology is presented in Table I. The association with sensitisers was shown in Table V.

## DISCUSSION

The overall rate of patch test positivity among our study population is comparable to previous results from this region, which was between 76.6%-81.2%.[17-18] The most common sensitisers in our study were similar to those previously observed locally and in neighbouring countries.[17,18] Globally, preservatives had a more significant presence as a common sensitiser alongside metals and fragrance which ranked 4th and 5th in our study.[19]

Polysensitisation in hand eczema was reported to be higher by Gosnell, Schmotzer, and Nedorost[20] at 48% and in our study (41.7%) compared to the 16.7% expected by Carlsen et al[4] of all positive patch test results.[4,20] The higher incidence of polysensitisation in hand eczema could be due to the hands being the primary way in which the patients interact with the environment.[20] Data from the Spanish Contact Dermatitis Registry showed hand dermatitis had 46% higher risk of developing polysensitisation compared to facial dermatitis.[19]

### Factors associated with sensitisation

We did not find any significant differences in patients-related factors between non sensitised, oligosensitised and polysensitised groups in contrast to other studies showing the highest sensitisation rates among middle aged adults with facial, hand and leg dermatitis.[21] There were significantly higher percentages of females who were sensitised in other studies attributed to higher prevalence of cosmetics and topical products use and better health seeking habits among female patients.[22] Although females outnumber males, no significant correlation with gender was seen in our study.

We found no significant association between atopy/family history of atopy with sensitisation which echoes the findings of Boonchai & Iamtharachai.[18] An earlier longitudinal study by Uehara & Sawai[23] found severity of atopic dermatitis to be negatively associated with contact sensitisation with dinitrochlorobenzene, suggesting suppressed contact sensitivity in patients with atopic dermatitis.[23] To further elaborate, contact sensitisation and elicitation are primarily driven by Th1 which can be suppressed by atopic dermatitis which is Th2 driven.[7] In contrast, Kirchof and de Gannes[24] found atopy to be associated with sensitisation, emphasising the combination of barrier dysfunction from filaggrin mutation and exposure to irritants and allergens to be important factors in contact sensitisation.[24] The above contrasting views highlight the unclear relationship between atopic dermatitis and contact sensitisation. It is also possible that mild atopic dermatitis is associated with higher sensitisation while moderate to severe atopic dermatitis is associated with lower sensitisation.[7] However, the above is not covered in our study.

A meta-analysis of 45 studies identified hand washing habits, wet work, and occlusion to be risk factors for hand eczema while use of alcohol based hand rubs was not associated with hand eczema.[8] These risk factors likely contribute to hand eczema through their effect on the skin barrier function and subsequent irritant contact dermatitis. Yüksel[7] proposed a disrupted skin barrier to facilitate entry of allergens for sensitisation of T cells leading to allergic contact dermatitis but we did not find a significant association between these factors and sensitisation.[7] It is possible that frequent hand washing and prolonged hand wetting activities have an indirect association with sensitisation but are more highly associated with irritant contact dermatitis rather than allergic contact dermatitis. Hamnerius et al[25] reported kitchen work to be associated with hand eczema while caring for children below five was not.[25] We did not find any statistically significant association between caring for children aged four and below, or kitchen work with sensitisation.

We did not find any significant association between sanitiser use and sensitisation. Contact allergy to alcohol in sanitisers is deemed rare although possible.[26] This is supported by data from a 10-year surveillance study in Switzerland which reported no documented contact allergy (estimated incidence density of 1:35,000 person-years) to commercial alcohol based hand rubs.[27] Impurities and non-active ingredients such as fragrances, tocopherol and sodium benzoate can contribute to contact allergy as well.[26] However, there is less allergen per sanitiser product compared to water based soaps and some sanitisers were in fact declared allergen free as per list from American Contact Dermatitis Society.[28]

Nickel sensitisation is complex and has been shown to be higher in patients with body piercings.[9,29] However, pinpointing a single source of sensitisation and elicitation in nickel allergies is difficult as multiple sources such as jewellery, occupational, diet and implants can contribute simultaneously and hand eczema can be a presentation of secondary eruption in nickel allergy.[9] Conversely, early oral exposure to nickel may confer a protective benefit against nickel sensitisation.[9] While the mechanism is not fully understood, it was observed that patients who develop tolerance to nickel from oral exposure were patients who have CD4 T helper cells stimulated in isolation, leading to IL-10 expression which was anti-inflammatory.[9]

We did not find a significant association between body piercing, dental brace or use of metal accessories with sensitisation. Beyond contact with nickel, frequency and duration of contact with nickel, presence of occlusion, sweating, dose of nickel released from the source and diet may have affected the results of this study.[9] There were discrepant findings on the association between nickel contact allergy and smoking.[30-32] Thyssen et al.[30] showed a positive association between smoking and nickel sensitisation but smoking was not an independent risk factor in that study.[31] Our study results did not show an association but the number of smokers in our study was small.

Despite our high collective positive rate of 44% of patients with fragrance allergy compared to previous local studies, we did not find a significant association between fragrance use and sensitisation. We infer that sensitisation to fragrances is beyond exposure to products specifically used for the purpose of smelling nice but due to hidden fragrances added to mask the 'chemical odour' of most skin care products which may have been missed during the interview with our patients.

We found that polysensitisation was associated with cosmetic use. Polysensitisation frequently involved fragrances and preservatives which are common allergenic ingredients in

cosmetic products as reported by the European Surveillance System on Contact Allergies 2009-2014.[33-34] We observed the same trend as our most common sensitisers excluding nickel in the polysensitisation group were fragrances and preservatives. While we are unsure if fragrances or preservatives have intrinsic properties that promote polysensitisation, we propose polysensitisation in cosmetics to be associated with the habitual use of multiple products in cosmetics.

**Factors associated with hand eczema severity**

Hand eczema severity has been associated with older age, atopic dermatitis, frequent eruptions, wet works > five hours, presence of chapped fingers, higher transepidermal water loss and presence of at least one positive patch test.[12,35-36] However, these associations were not consistently observed.[35-36]

Our study found non significantly higher HECSI scores in patients with atopy, frequent hand washing and duration of hand wetting. The lack of statistical significance with hand wetting may be related to the duration, as a significant increase in HECSI scores was reported with duration > five hours a day while we recorded up to two hours or longer.[36]

We showed significantly higher HECSI scores in patients who used non permeable gloves which may be explained by increased transepidermal water loss and increased Staphylococcus colonisation observed in some other studies.[37] However, there were inconsistent findings with regards to the effect of Staphylococcus colonisation and severity of hand eczema. Nørreslet et al[38] did not find an association while Mernelius et al39 found otherwise.[38-39]

The lack of association between the presence of at least one sensitiser and higher HECSI scores in our study is in line with previous reports and reiterates the importance of evaluating irritants as well as allergens in patients with hand eczema.

**Relationship between morphology of hand eczema with risk of sensitisation**

Recurrent vesicular hand eczema compared to other hand eczema morphologies was reported by Boonstra et al[13] to have a higher risk for contact allergy.[13] Sensitisation was less likely with hyperkeratotic palmar eczema and pulpitis.[13] The most common hand eczema morphologies are recurrent vesicular and chronic fissuring which are also seen in our patients.[13] However, we did not find any morphology to be significantly associated with sensitisation.

## LIMITATIONS

Clinical relevance was assessed based on patients' recall which was subject to recall bias. Some relevant sensitisations may have been missed with the use of a single standard series without additional relevant extended series or testing with own products. Cross reacting sensitisers were still included as polysensitisation, as there is no reliable method with this study design to ascertain cross reactivity from true polysensitisation and this may overestimate the number of patients with polysensitisation. This study is underpowered as the sample size for power of 80% was not achieved.

## CONCLUSION

The prevalence of sensitisation in hand eczema patients was very high. Nickel, fragrance mix 1, potassium dichromate and formaldehyde were the most common sensitisers. Atopy, family history of atopy, frequency of hand washing, morphology of hand eczema and duration of hand wetting activity were not associated with sensitisation. Polysensitisation was associated with cosmetics use. Use of non-permeable gloves was associated with increased hand eczema severity. Patients with hand eczema should be subjected to patch testing as part of their management to identify possible irritants or allergens which may be avoided to improve their condition.

## ACKNOWLEDGEMENTS

The authors would like to thank the Director General of Health Malaysia for his permission to publish this article. We would also like to thank the Director, Head of Department, the clinical and administrative staff of the Dermatology Department at a tertiary hospital in the capital of Selangor for their support throughout the study. Special thanks are also given to the patients who participated in this study.

## CONFLICT OF INTEREST

None declared.

## FUNDING

No funding was received for conducting this study.

## ETHICAL APPROVAL

Approval from the Medical Research and Ethics Committee (MREC) of the Ministry of Health (MOH) Malaysia was obtained prior to initiation of the study (Research ID: RSCH ID-23-04790-YJR). The study was conducted in compliance with ethical principles outlines in the Declaration of Helsinki and Malaysian Good Clinical Practice guidelines.

## DATA AVAILABILITY

Data are available on request from the authors.

## REFERENCES

1. Thyssen JP, Schuttelaar MLA, Alfonso JH, Andersen KE, Angelova-Fischer I, Arents BWM, et al. Guidelines for diagnosis, prevention, and treatment of hand eczema. Contact Dermatitis. 2022; 86(5): 357-78.
2. Lachapelle J-M, Maibach HI. Patch testing and prick testing. A practical guide Berlin: Ed Springer. 2003: 6, 24, 56.
3. Agner T, Andersen KE, Brandao FM, Bruynzeel DP, Bruze M, Frosch P, et al. Contact sensitisation in hand eczema patients-relation to subdiagnosis, severity and quality of life: a multi-centre study. Contact Dermatitis. 2009; 61(5): 291-6.
4. Carlsen BC, Andersen KE, Menné T, Johansen JD. Patients with multiple contact allergies: a review. Contact Dermatitis. 2008; 58(1): 1-8.
5. Ha EK, Baek JH, Lee SY, Park YM, Kim WK, Sheen YH, et al. Association of Polysensitization, Allergic Multimorbidity, and Allergy Severity: A Cross-Sectional Study of School Children. Int Arch Allergy Immunol 2016; 171(3-4): 251-60.

6. Boonstra M, Rustemeyer T, Middelkamp-Hup MA. Both children and adult patients with difficult-to-treat atopic dermatitis have high prevalences of concomitant allergic contact dermatitis and are frequently polysensitized. J Eur Acad Dermatol Venereol 2018; 32(9): 1554-61.
7. Yüksel Y, Nørreslet L, Thyssen J. Allergic Contact Dermatitis in Patients with Atopic Dermatitis. Curr Dermatol Rep 2021; 10(3): 67-76.
8. Loh EW, Yew YW. Hand hygiene and hand eczema: A systematic review and meta-analysis. Contact Dermatitis 2022; 87(4): 303-14.
9. Ahlström MG, Thyssen JP, Wennervaldt M, Menné T, Johansen JD. Nickel allergy and allergic contact dermatitis: A clinical review of immunology, epidemiology, exposure, and treatment. Contact Dermatitis 2019; 81(4): 227-41.
10. Tai V, Sharifah Rosniza SNC, Tang MM. Contact sensitization to fragrance allergen: a 5-year review in the Department of Dermatology, Hospital Kuala Lumpur. Med J Malaysia 2023; 78(5): 583-8.
11. Heede NG, Thyssen JP, Thuesen BH, Linneberg A, Johansen JD. Predictive factors of self-reported hand eczema in adult Danes: a population-based cohort study with 5-year follow-up. Br J Dermatol 2016; 175(2): 287-95.
12. Hald M, Agner T, Blands J, Veien NK, Laurberg G, Avnstorp C, et al. Clinical severity and prognosis of hand eczema. Br J Dermatol 2009; 160(6): 1229-36.
13. Boonstra MB, Christoffers WA, Coenraads PJ, Schuttelaar ML. Patch test results of hand eczema patients: relation to clinical types. J Eur Acad Dermatol Venereol 2015; 29(5): 940-7.
14. Menné T, Johansen JD, Sommerlund M, Veien NK. Hand eczema guidelines based on the Danish guidelines for the diagnosis and treatment of hand eczema. Contact Dermatitis 2011; 65(1): 3-12.
15. Held E, Skoet R, Johansen JD, Agner T. The hand eczema severity index (HECSI): a scoring system for clinical assessment of hand eczema. A study of inter- and intraobserver reliability. Br J Dermatol 2005; 152(2): 302-7.
16. Alinaghi F, Bennike NH, Egeberg A, Thyssen JP, Johansen JD. Prevalence of contact allergy in the general population: A systematic review and meta-analysis. Contact Dermatitis 2019; 80(2): 77-85.
17. How KN, Tang MM, Kaur R, Johar A. Contact sensitisation in adults: a 5-year retrospective review in hospital Kuala Lumpur. Med J Malaysia 2017; 72(2): 113-8.
18. Boonchai W, Iamtharachai P. Risk factors for common contact allergens and patch test results using a modified European baseline series in patients tested during between 2000 and 2009 at Siriraj Hospital. Asian Pac J Allergy Immunol 2014; 32(1): 60-5.
19. Pesqué D, Borrego L, Zaragoza-Ninet V, Sanz-Sánchez T, Miquel-Miquel FJ, González-Pérez R, et al. Polysensitization in the Spanish Contact Dermatitis Registry (REIDAC): A 2019-2022 prospective study with cluster and network analysis. J Eur Acad Dermatol Venereol 2025; 39(1): 126-35.
20. Gosnell AL, Schmotzer B, Nedorost ST. Polysensitization and individual susceptibility to allergic contact dermatitis. Dermatitis 2015; 26(3): 133-5.
21. Pesqué D, Planella-Fontanillas N, Borrego L, Sanz-Sánchez T, Zaragoza-Ninet V, Serra-Baldrich E, et al. Patch test results to the Spanish baseline patch test series according to age groups: A multicentric prospective study from 2019 to 2023. Contact Dermatitis 2025; 92(2): 120–30.
22. Teo HG, Syed Nong Chek SR, Tang MM. Contact sensitisation pattern of patients with eczema at the face and neck region: A retrospective study in Kuala Lumpur. Med J Malaysia 2024; 79(5): 525-30.
23. Uehara M, Sawai T. A longitudinal study of contact sensitivity in patients with atopic dermatitis. Arch Dermatol 1989; 125(3): 366-8.
24. Kirchhof MG, de Gannes GC. Atopy Associated With Positive Patch Test and Possible Allergic Contact Dermatitis. J Cutan Med Surg 2018; 22(4): 405-10.
25. Hamnerius N, Svedman C, Bergendorff O, Björk J, Bruze M, Pontén A. Wet work exposure and hand eczema among healthcare workers: a cross-sectional study. Br J Dermatol 2018; 178(2): 452-61.
26. World Health Organization. WHO Guidelines Approved by the Guidelines Review Committee. WHO Guidelines on Hand Hygiene in Health Care: First Global Patient Safety Challenge Clean Care Is Safer Care. Geneva: World Health Organization.; 2009. p. 63.
27. Widmer AF. Replace hand washing with use of a waterless alcohol hand rub? Clin Infect Dis 2000; 31(1): 136-43.
28. Rodriguez-Homs LG, Atwater AR. Allergens in Medical Hand Skin Cleansers. Dermatitis 2019; 30(6): 336-41.
29. Ehrlich A, Kucenic M, Belsito DV. Role of body piercing in the induction of metal allergies. Am J Contact Dermat 2001; 12(3): 151-5.
30. Linneberg A, Nielsen NH, Menné T, Madsen F, Jørgensen T. Smoking might be a risk factor for contact allergy. J Allergy Clin Immunol 2003; 111(5): 980-4.
31. Thyssen JP, Johansen JD, Menné T, Nielsen NH, Linneberg A. Effect of tobacco smoking and alcohol consumption on the prevalence of nickel sensitization and contact sensitization. Acta Derm Venereol 2010; 90(1): 27-33.
32. Alotaibi GF, Alsalman HH, Alhallaf RA, Ahmad RA, Alshareef HA, Muammar JM, et al. The Association of Smoking with Contact Dermatitis: A Cross-Sectional Study. Healthcare (Basel) 2023; 11(3): 427.
33. Dittmar D, Uter W, Bauer A, Fortina AB, Bircher AJ, Czarnecka-Operacz M, et al. European Surveillance System on Contact Allergies (ESSCA): polysensitization, 2009-2014. Contact Dermatitis 2018; 78(6): 373-85.
34. Diepgen T, Weisshaar E. Contact dermatitis: epidemiology and frequent sensitizers to cosmetics. J Eur Acad Dermatol Venereol 2007; 21 Suppl 2: 9-13.
35. Handa S, Kaur I, Gupta T, Jindal R. Hand eczema: correlation of morphologic patterns, atopy, contact sensitization and disease severity. Indian J Dermatol Venereol Leprol 2012; 78(2): 153-8.
36. Qu Z, Jiang Q, Wang B, Yao C, Jiang R, Chen K, et al. A cross-sectional study of clinical characteristics and risk factors for hand eczema in the general Chinese population. Sci Rep 2024; 14(1): 29733.
37. Ramsing DW, Agner T. Effect of glove occlusion on human skin (II). Contact Dermatitis 1996; 34(4): 258-62.
38. Nørreslet LB, Edslev SM, Flachs EM, Ebbehøj NE, Andersen PS, Agner T. Wearing Occlusive Gloves Increases the Density of Staphylococcus aureus in Patients with Hand Eczema. Acta Derm Venereol 2021; 101(8): adv00515.
39. Mernelius S, Carlsson E, Henricson J, Löfgren S, Lindgren PE, Ehricht R, et al. Staphylococcus aureus colonization related to severity of hand eczema. Eur J Clin Microbiol Infect Dis 2016; 35(8): 1355-61.

ORIGINAL ARTICLE

# Diagnostic accuracy of zero Coronary Artery Calcium (CAC) score in a Malaysian cohort: A 20-year retrospective analysis

**Lee Jun Tsien, BSc, Muhammad Muaz Md Hazali, BSc, Siew Jit Ping, PhD**

Life Care Diagnostic Medical Centre Sdn. Bhd., Kuala Lumpur, Malaysia

## ABSTRACT

**Introduction: The Agatston coronary artery calcium (CAC) score is a widely used screening tool. However, its negative predictive value (NPV) in the Southeast Asian population, prone to premature non-calcified atherosclerosis, is not well defined.**

**Materials and Methods: We analysed paired data from 5,375 asymptomatic patients who underwent concurrent CAC scoring and Coronary CT Angiography (CCTA) at a tertiary center in Kuala Lumpur over 20 years. This cohort was selected to study plaque missed by CAC. A validated automated pipeline (weighted Cohen's Kappa = 0.978) was used to determine stenosis severity.**

**Results: Zero CAC yielded a negative predictive value of 76.1% for any plaque; 23.9% of calcium-negative patients harboured hidden atherosclerosis, including 3.5% with obstructive disease. While odds increased linearly with age (OR 1.22 per decade, p=0.004), missed disease peaked in males aged 40–44 and peri-menopausal women aged 55–59. These age groups represent a window during which lipid-rich plaques accumulate before calcifying.**

**Conclusion: Zero CAC can mask a "pre-calcific window" of active, radiolucent atheroma accumulation. Rather than a state of biological protection, this Zero CAC cohort harbours hidden risk driven by the same demographic engines as calcified disease, simply operating at an earlier phenotypic stage. Confirmatory CCTA is critical for high-risk younger males and peri-menopausal women to bridge this inherent diagnostic blind spot.**

**KEYWORDS:**
*Coronary artery calcium score; coronary computed tomography angiography; coronary artery disease; non-calcified plaque; diagnostic imaging*

## INTRODUCTION

In 1990, Agatston et al. introduced coronary artery calcium (CAC) scoring via computed tomography (CT) to non-invasively quantify atherosclerotic burden.[1] While a significant improvement over fluoroscopy, diagnostic sensitivity varies across age groups. Today, although the CAC score is a widely accepted screening tool, its reliance on calcification as the sole surrogate for atherosclerosis creates a "silent gap" or "pre-calcific window".[2-3]

This gap arises from the pathophysiology of atherosclerosis. Non-calcified plaques, composed of a lipid-rich necrotic core and fibrous cap, are radiolucent on non-contrast CT and invisible to the Agatston algorithm.[4-5] Calcification typically represents a late-stage healing response to chronic inflammation; thus, Zero CAC indicates "no calcified disease," not "no disease".[6-7] Consequently, vulnerable non-calcified plaques may proliferate undetected in patients mistakenly categorized as low-risk.

Despite this, large-scale Western trials such as SCOT-HEART[8] and PROMISE3 have heavily influenced the "power of zero" paradigm, prompting a 5 to 15 year "warranty period" for patients with Zero CAC.[9-10] However, emerging data suggest that the prevalence of non-calcified plaque may vary across populations.[11] Currently, there is a lack of large-scale data characterizing this disease burden in Southeast Asia, a population known for earlier disease onset and a severe cardiometabolic phenotype.[12-14]

To address this, we analysed 20-year retrospective data from 5,375 asymptomatic patients who underwent paired CAC and CCTA at a private medical centre in Kuala Lumpur, Malaysia. Contrasting with Agatston's foundational cohort,[1] we aim to leverage this large regional dataset to quantify the CAC "diagnostic blind spot" and identify demographic patterns missed by standard CAC screening.

## MATERIALS AND METHODS

### Study Design and Sample Population

This retrospective observational study analysed 5,375 patients who underwent paired CAC scoring and CCTA at a private medical centre in Kuala Lumpur, Malaysia. This cohort was selected to evaluate the prevalence of atherosclerosis missed by CAC. All included patients were asymptomatic per referral records, defined by the absence of documented chest pain, dyspnoea, Acute Coronary Syndrome (ACS), or positive stress testing.

**Inclusion criteria:**

- Adults aged ≥25 years;
- Patients who underwent both non-contrast CAC scanning and contrast-enhanced CCTA during the same imaging session.

**Exclusion criteria** were applied to focus strictly on native coronary atherosclerosis and included:

- Prior coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting);

*This article was accepted: 06 July 2026*
*Corresponding Author: Siew Jit Ping*
*Email: siewjp@lifecare.com.my*

- Incomplete imaging data (CAC or CCTA only);
- Reports lacking interpretable coronary findings.

No experimental interventions were performed. All data were derived from routine clinical care as detailed in Figure 1C.

**Imaging Acquisition and CCTA Status Classifications**
Scans were acquired using multidetector CT systems (≥64-slice), initially utilizing the 64-slice GE LightSpeed VCT and later transitioning to the 128-slice GE Optima CT660 (GE Healthcare, USA). All imaging adhered to evolving institutional cardiac CT Standard Operating Procedures throughout the 20-year study period.15 While scanner generations evolved, interpretation criteria remained consistent.

**Step 1: Non-Contrast CT for Calcium Scoring**
A non-contrast scan quantified coronary artery calcium burden using the Agatston method.[1] Scores were categorized:
- **0 (Zero):** No identifiable calcification.
- **1–100 (Mild):** Minimal atherosclerotic burden.
- **101–400 (Moderate):** Significant burden.
- **>400 (Severe):** Extensive burden, often correlating with high probability of ischemia.

**Step 2: Contrast-Enhanced CCTA**
Contrast-enhanced CCTA was performed with target heart rate ≤70 bpm; beta-blockers were administered as needed. Iodinated contrast medium was administered using a weight-adapted protocol: Ultravist 370 (Bayer Healthcare, Germany) for patient weight ≥80 kg and Xenetix 350 (Guerbet, France) for patient weight <80 kg.

CCTA images were reconstructed and interpreted by a Malaysia Medical Council–certified senior consultant radiologist, consistent with Society of Cardiovascular Computed Tomography (SCCT) guidelines,16 where disease severity was determined by the maximal luminal narrowing observed in any major epicardial vessel (Left Main, Left Anterior Descending, Left Circumflex, or Right Coronary Artery). Under this framework, patients were categorized as having **Normal Coronaries** (0% stenosis with a fully patent lumen), **Non-Obstructive CAD** (1%–49% stenosis with identifiable plaque), or **Obstructive CAD** (significant burden causing ≥50% luminal stenosis).

**Automated Extraction Pipeline**
An automated extraction pipeline was constructed using Python (version 3.9.11) with regular expression library (regex). The system operates by identifying specific linguistic patterns to categorize radiologist findings according to the classifications defined in Figure 1B. The high-level processing flow is defined as follows:

**Radiologist Findings** (Clinical Notes) → **Extraction Pipeline** (RegEx Algorithm) → **CCTA Status Classification** (Normal, Non-Obstructive, Obstructive, Outlier)

Text patterns were derived from SCCT reporting guidelines[16] and historical radiologist reporting syntax. Five functional categories processed raw findings into final classifications:

a) **Anchors Terms (A)**
Quantitative severity descriptors are only valid when syntactically linked to a predefined target clinical concept nouns set: "Stenosis", "Narrowing", "Obstruction", "Plaque".
Example: "Mild calcified plaque burden with mild (25-49%) luminal stenosis" → Extracted Anchor Term (A): {Plaque, Stenosis}

b) **Stenosis Severity Terms (K)**
An ordinal taxonomy of severity descriptors mapped to integer values (0-100%) based on SCCT reporting guidelines16 as shown in Figure 1B, where keywords took precedence over numeric ranges.
Example: "Severe calcified plaque burden with severe (70-99%) luminal stenosis" → Extracted Stenosis Severity Term (K): {Severe, 70-99%} Logic: Keywords take precedence over numeric ranges. → Final Value: 70%

c) **Exclusion terms (E)**
A comprehensive set of patterns used to remove false positives and non-target findings. This category unifies four specific filtering logic gates:

i. **Anatomical Exclusion:** Removes findings from non-coronary structures (e.g., "Aorta", "Mitral Valve").
Example: "The calcium plaque initially identified... located predominantly in the aorta rather than in the LMS" → Action: The presence of the exclusion keyword "aorta" invalidates the findings in this sentence, preventing the calcium burden from being incorrectly assigned to the Left Main Stem (LMS).

ii. **Contextual Disambiguation:** Neutralizes size descriptors that mimic severity terms (e.g., "Small vessel").
Example: "The left main coronary artery (LM) is a medium size vessel and bifurcates in LAD and LCX." → Action: Phrase "medium size vessel" is neutralized to prevent false-positive sizing.

iii. **Negation:** Identifies and excludes findings modified by negative qualifiers (e.g., "No evidence of").
Example: "No significant stenosis or plaque" → Action: Matches Negation Driver. Phrase "No significant" triggers null value (0%).

iv. **Artifacts:** Removes adjectives associated with image quality issues (e.g., "Motion artifact").
Example: "The calcium speck identified is likely an artifact" → Action: Matches Artifact keyword. The phrase is neutralized and excluded from scoring.

d) **Stenosis/Plaque type identifier terms (M)**
A hierarchical set of plaque composition descriptors are used: "Calcified","Mixed","Soft".
Example: "Severe non-calcified atherosclerotic plaque..." →Extracted (M): {Non-calcified}

e) **CCTA Status Classification (C):**
The final classification derived from the maximum stenosis value, mapped to one of three risk classes (Normal, Non-obstructive, Obstructive) as illustrated in Figure 1B.

The extraction pipeline executes a sequential processing routine (Figure 1). First, the raw text is normalized and segmented into sentences, preventing context leakage. The

engine then iterates through each sentence, applying the Exclusion Terms (E) to discard non-coronary, negated, or artifact-related statements. For remaining valid sentences, it extracts Stenosis Severity Terms (K) only if anchored to an Anchor Term (A). Stenosis/Plaque Type Identifier Terms (M) are extracted from non-negated sentences as supplementary metadata for qualitative review but were not utilized in the primary statistical analysis. Finally, the maximum severity value (Smax) detected across all valid segments is aggregated and mapped to SCCT stenosis grades, then to the final Clinical Category (C).

To illustrate this aggregation logic, consider a composite case based on the extraction definitions detailed above. If a patient report contains findings mapped to 25%, 0%, and 70% severity, the system computes the global maximum:
$S_{max}$ = max (25, 0, 70) = 70%

This value is then processed through the clinical mapping logic:
1. **SCCT Grade:** 70% maps to Severe.
2. Clinical Output Category (C): Severe maps to Obstructive (Threshold ≥ 50%).
∴ Input (Radiologist Findings) → (Smax= 70%, SCCT Grade = {Severe}, C = {Obstructive})

The extraction pipeline was validated against a 350-report manual review, achieving excellent reliability (weighted Cohen's Kappa = 0.978; 100% sensitivity; 97.6% specificity in validation sample). This perfect sensitivity is inherent to the deterministic, rule-based design.

### Statistical Analysis and Validation Protocol

#### Cohort Stratification and Demographics

Data aggregation and statistical analysis were performed using Python (pandas, scipy, statsmodels). The cohort was stratified by CAC status (Zero CAC vs. Positive CAC). Continuous variables (e.g., age) are presented as mean ± standard deviation (SD) and compared using independent samples t-tests. Categorical variables (e.g., sex) are presented as frequencies and percentages and evaluated using Pearson's Chi-square ($\chi^2$) test of independence. To ensure statistical robustness for prevalence estimates, particularly in smaller subgroups, 95% confidence intervals (CI) for proportions were calculated using the Wilson Score Interval. Two-tailed p-values <0.05 were considered statistically significant.

#### Multivariable Predictive Modelling

To determine if age and sex serve as predictors of plaque in the absence of calcium, a multivariable binary logistic regression was performed on the Zero CAC cohort (n=1,382). Traditional cardiovascular risk factors (hypertension, diabetes, dyslipidaemia, smoking) were incompletely documented in imaging reports and could not be included in multivariable modelling. The primary predictive model therefore focused on the high-fidelity demographic variables of Age and Sex, which were consistently recorded. This approach represents a demographic risk stratification model rather than a comprehensive clinical risk model. Results are reported as Odds Ratios (OR) with associated 95% CIs, with the explicit understanding that unmeasured confounding may influence estimates. A penalized (Firth-style) logistic regression was utilized to stabilize point estimates given the event rate.

#### Diagnostic Performance Metrics

Using CCTA classification as the reference standard,[11] diagnostic accuracy (Sensitivity, Specificity, Positive and Negative Predictive Values) was calculated for CAC scoring. A CAC>0 was defined as positive for calcification. CCTA classifications of "Normal," "Non-obstructive," and "Obstructive" were determined by the radiologist's clinical notes, where terms are utilized as defined in Figure 1B.

In this study, the metrics are defined as:
- True Positive (TP): CAC>0 and CCTA shows plaque
- False Positive (FP): CAC>0 but CCTA normal coronaries
- True Negative (TN): Zero CAC and CCTA normal coronaries
- False Negative (FN): Zero CAC but CCTA shows plaque

All metrics were computed with exact binomial 95% confidence intervals to assess the precision of CAC as a predictor for CCTA-defined atherosclerosis.

#### Clinical Discordance Analysis

A manual root-cause analysis of the 21 discordant outliers (0.4% of cohort) presenting with positive CAC scores but normal CCTA confirmed the CCTA interpretations were correct. These false-positive CAC readings were attributed to known non-contrast CT limitations, including motion artifacts (n=12), sub-resolution micro-calcifications (n=5), and mis-indexed extra-coronary calcification (n=4) located in the adjacent aorta, pulmonary trunk, or outside the vasculature.[16-18] This confirms discordance in this direction is driven by inherent specificity limitations rather than missed pathology.

## RESULTS

### Demographics

The baseline characteristics of the study population (N=5,375) are detailed in Table I. Patients with Zero CAC were significantly younger than those with positive scores (49.2 ± 9.9 vs. 58.4 ± 9.9 years, p<0.001). Male sex predominated across the cohort (69.5%), particularly within the positive CAC group (72.9% vs. 59.7% in the Zero CAC group, p<0.001). A small number of patients (n=21) had positive CAC, but no plaque detected on CCTA, reflecting differences in detection between calcium scoring and plaque visualization (refer Section 2.4.4 for explanation).

The association between CAC categories and CCTA-defined stenosis was highly significant ($\chi_2$ = 1153.14, p<0.001), with higher scores correlating strongly with obstructive CAD, reaching 95.5% (95% CI: 93.7–96.7%) in the severe (>400) group. Conversely, among the Zero CAC cohort, CCTA identified 330 patients (23.9%; 95% CI: 21.7–26.2%) with plaque. Within this "blind spot," 281 patients (20.3%; 95% CI: 18.3–22.5%) had non-obstructive CAD and 49 (3.5%; 95% CI: 2.7–4.7%) harboured obstructive CAD (≥50% stenosis).

### Diagnostic Performance Metrics

To quantify the reliability of CAC as a screening tool, diagnostic performance metrics were evaluated against CCTA classifications for Any Plaque and Obstructive CAD (Table II).

**Table I: Overall demographics of CaC & CCTA Results**

| CAC Group | N | Age (years) | Male, n (%) | CCTA Classification | | |
|---|---|---|---|---|---|---|
| | | | | Positive CCTA (Any Plaque) | Non-Obstructive CAD (<50%), n (%) | Obstructive CAD (≥50%), n (%) |
| Zero CAC Score | 1382 | 49.2 ± 9.9 | 825 (59.7%) | 330 (23.9%) [21.7–26.2] | 281 (20.3%) [18.3–22.5] | 49 (3.5%) [2.7–4.7] |
| Positive CAC (>0) | 3993 | 58.4 ± 9.9 | 2,912 (72.9%) | 3,972 (99.5%) [99.2–99.7] | 1,737 (43.5%) [42.0–45.0] | 2,235 (56.0%) [54.4–57.5] |
| Mild (1-100) | 2125 | 55.6 ± 9.4 | 1,510 (71.1%) | 2,109 (99.2%) [98.8–99.5] | 1,414 (66.5%) [64.5–68.5] | 695 (32.7%) [30.8–34.7] |
| Moderate (101-400) | 1119 | 60.0 ± 9.5 | 816 (72.9%) | 1,116 (99.7%) [99.2–99.9] | 291 (26.0%) [23.5–28.7] | 825 (73.7%) [71.1–76.2] |
| Severe (>400) | 749 | 63.5 ± 9.4 | 586 (78.2%) | 747 (99.7%) [99.0–99.9] | 32 (4.3%) [3.0–6.0] | 715 (95.5%) [93.7–96.7] |
| Total Cohort | 5375 | 56.0 ± 10.7 | 3,737 (69.5%) | 4,302 (80.0%) [78.9–81.1] | 2,018 (37.5%) [36.2–38.8] | 2,284 (42.5%) [41.2–43.8] |
| Statistic | N/A | -29.51 | 84.46 | 3666.56 | N/A | 1153.14 |
| P-Value (0 vs >0) | N/A | <0.001* | <0.001† | <0.001† | N/A | <0.001† |

Data Presentation: Continuous variables are presented as mean ± standard deviation; categorical variables are presented as n (%) with [95% Wilson Score Confidence Intervals].
* Welch's t-test: Used for continuous comparison between Zero and Positive CAC group.
† Pearson's Chi-Square ($\chi 2$): Used for categorical comparisons between Zero and Positive CAC groups.
These comparisons are presented to characterize cohort differences and are not intended to imply causal inference.

**Table II: Diagnostic Utility of CAC Score against Clinical Thresholds**

| Metric / Test Threshold | Any Plaque (> 0%) CAC > 0 | Obstructive CAD (≥50%) | | |
|---|---|---|---|---|
| | | CAC > 0 | CAC > 100 | CAC > 400 |
| Sensitivity | 92.3% [91.5-93.1] | 97.9% [97.2-98.4] | 67.4% [65.5-69.3] | 31.3% [29.4-33.2] |
| Specificity | 98.0% [97.0-98.7] | 43.1% [41.4-44.9] | 89.4% [88.2-90.4] | 98.9% [98.5-99.2] |
| Likelihood Ratio (LR+) | 46.2 | 1.72 | 6.36 | 28.5 |
| Likelihood Ratio (LR-) | 0.08 | 0.05 | 0.36 | 0.69 |
| PPV | 99.5% [99.2-99.7] | 56.0% [54.4-57.5] | 82.4% [80.6-84.1] | 95.5% [93.7-96.7] |
| NPV | 76.1% [73.8-78.3] | 96.5% [95.3-97.3] | 78.8% [77.4-80.1] | 66.1% [64.7-67.4] |
| Accuracy | 93.5% [92.8-94.1] | 66.4% [65.1-67.6] | 80.1% [79.0-81.1] | 70.2% [68.9-71.4] |

**Table III: Multivariable Predictors of Coronary Plaque**

| Feature | Model 1: Full Dataset Model (CAC Positive Prediction) | Model 2: Zero CAC Subset Model (CCTA Plaque Prediction) |
|---|---|---|
| Model Fit (LLR) | p<0.0001 | p=0.0020 |
| VIF (Age / Sex) | 1.05/1.05 | 1.11/1.11 |
| Intercept (β0) | -5.98 | -2.35 |
| Age (β1) | 1.14 (p<0.001) | 0.192 (p=0.004) |
| Age (OR per decade) | 3.13 [ 2.88, 3.39] | 1.21 [1.10, 1.34] |
| Male Sex (β2) | 1.37 (p<0.001) | 0.3952 (p=0.004) |
| Male Sex (OR) | 3.94 [3.35, 4.62] | 1.48 [1.13, 1.95] |
| Regression: | ln(p/(1-p)) = β0+β1(Age)+β2(Sex [Male]) | |

Diagnostic utility shifted significantly across clinical thresholds. When evaluating for obstructive CAD, utilizing a standard positive threshold of CAC>0 yielded a high sensitivity of 97.9% but a reduced specificity of 43.1%. Conversely, increasing the threshold to CAC>400 served as a highly specific metric, maximizing specificity (98.9%), PPV (95.5%), and yielding a strong LR+ of 28.5. However, when evaluating for the presence of any atherosclerotic plaque, Zero CAC yielded an NPV of only 76.1%. This low NPV implies that while the CAC score remains highly sensitive for calcified lesions, it has limited ability to detect active, non calcified plaque, particularly in younger Malaysian patients where metabolic risk factors drive early non calcified atheroma formation.[12,19]

**Characteristics of Patients with Zero CAC Score but with Plaque**

Age and male sex are significant independent predictors of coronary calcification within the study population. In the full cohort baseline, multivariable analysis (Model 1) identified age (OR 3.13 per decade; p<0.001) and male sex (OR 3.94; p<0.001) as strong independent predictors with negligible multicollinearity (VIF 1.05/1.05) as shown in Table III.

These variables also predict hidden non-calcified plaque in the Zero CAC subset, albeit with a notably attenuated age effect. Model 2 demonstrated a significant overall fit (LLR p=0.002) and identified both age (OR 1.21 per decade; p=0.004) and male sex (OR 1.48; p=0.004) as significant

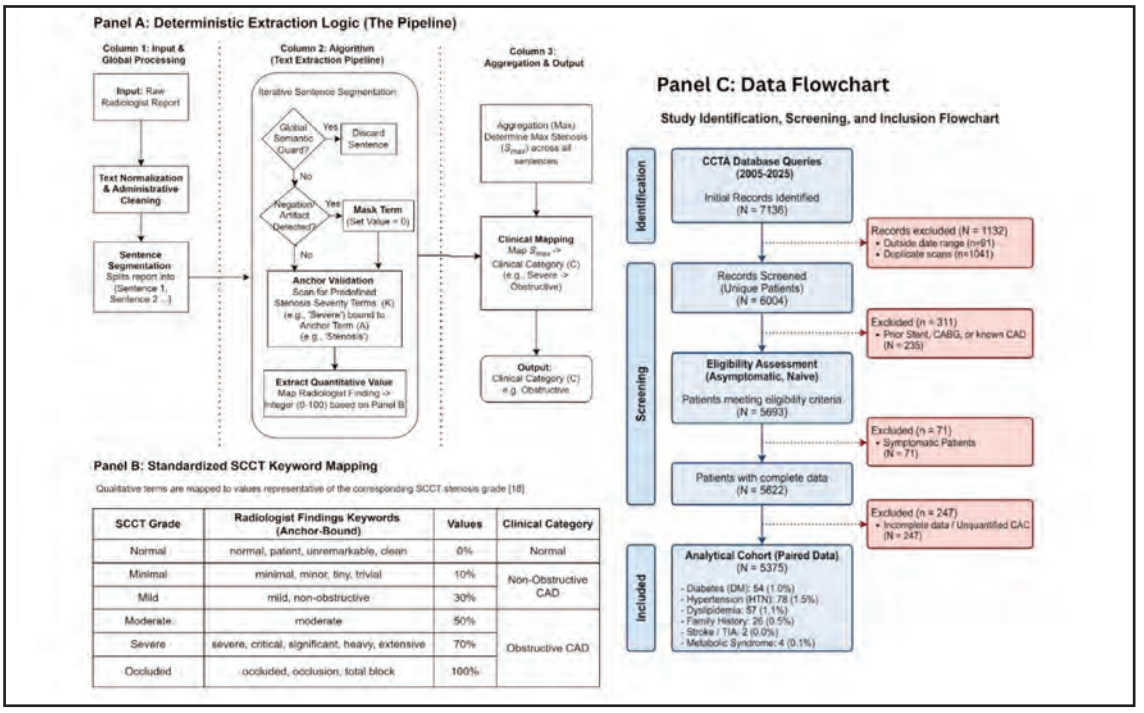



**Fig. 1:** Automated text extraction pipeline. (A) Processing workflow transforms raw radiology text into CCTA status classifications through normalization, filtering, and severity aggregation. (B) Keyword mapping table converts clinical descriptors to standardized SCCT stenosis grades. (C) Study cohort data flow: systematic attrition of the initial 7,136 records to the final analytical cohort of 5,375 asymptomatic patients, excluding duplicate scans and symptomatic cases
(Cardiovascular risk factor data incomplete; not included in analysis)

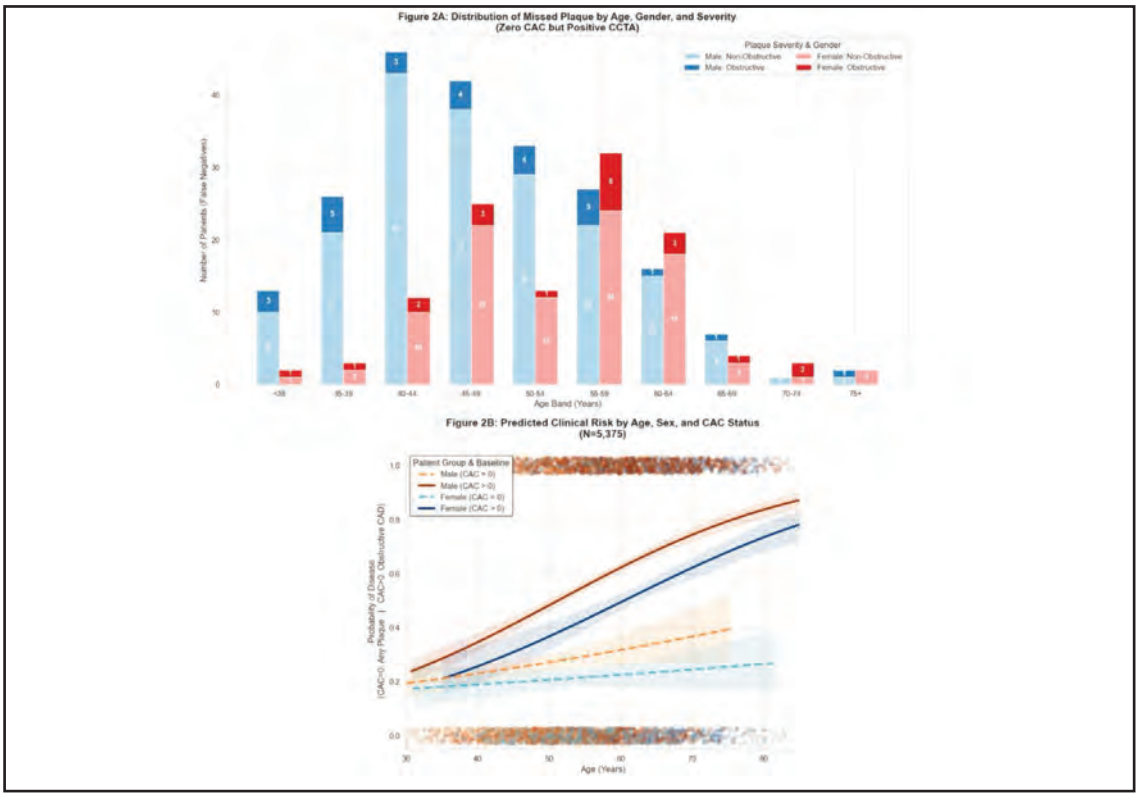



**Fig. 2:** CAD Distribution and Predicted Risk (A) Prevalence of Missed Plaque by Age and Sex: CCTA-derived characterization of the Zero CAC cohort, showing the distribution of non-obstructive versus obstructive disease. (B) Predicted Probability of CAD: Multivariable logistic regression curves comparing the risk of Any Plaque in Zero CAC patients (dashed lines) against Obstructive CAD in CAC>0 patients (solid lines). Note the distinct risk trajectories for Zero versus non zero CAC scores across age deciles

independent predictors (VIF 1.11/1.11) of hidden plaque. The reduction in the age coefficient (β1=0.192) indicates a less dominant age-driven trajectory in the Zero CAC cohort compared to the full-cohort baseline. While the male sex effect remained a strong risk driver (OR 1.48).

The Zero CAC cohort with plaque exhibited a distinct age-sex dimorphism (Figure 2A). Males predominated (68.9%) and demonstrated earlier disease onset, with non-obstructive CAD peaking in the 40 – 44 year band. Females showed delayed onset, clustering in the 55 – 59 year band. Risk followed a sustained linear escalation across the observed age spectrum (Figure 2B) without an apparent biological threshold, reflecting continuous plaque accumulation throughout the pre-calcific window.

Within this "blind spot," obstructive CAD was identified in 49 patients (3.5%). This hidden cohort was descriptively middle-aged (51.3 ± 11.2 years) and evenly distributed between sexes (55.1% male). These findings indicate that while Zero CAC is generally reassuring, a minority of patients harbour obstructive disease requiring confirmatory CCTA for detection.[20]

## DISCUSSION AND CONCLUSION

While Zero CAC as a diagnostic gatekeeper is well-validated in Western populations,[3,8,10] its role as a clinical gatekeeper is increasingly contested in the Southeast Asian context. In this cohort, 23.9% of patients with Zero CAC had non-calcified plaque, with a 3.5% prevalence of hidden obstructive CAD. This burden of non-calcified disease is substantially higher than rates reported in major Western registries such as CONFIRM.[11]

This disparity highlights a notable finding driven by Malaysia's high cardiometabolic burden. With metabolic syndrome prevalence reaching 43% in adults under 40,[19,21] this milieu accelerates the formation of lipid-rich, non-calcified atheromas before osteogenic calcification becomes detectable on non-contrast CT.[22-24] Consequently, the traditional 5–15 year "warranty period" for Zero CAC is effectively reduced in this context.[9,10,14,24] These findings identify younger males and peri-menopausal women as high-yield groups for confirmatory CCTA, where Zero CAC score provides insufficient clinical reassurance.[12-13,25-26]

### Association between Age and Plaque Development

The age gap between zero and positive CAC patients (49.2 vs. 58.4 years) reflects a well-characterised stage of atherosclerosis in which lipid-rich plaque accumulates prior to osteogenic calcification.[5,7] Aging subsequently drives calcific conversion, transitioning older patients into positive CAC cohorts and sequestering potential false negatives within younger groups where soft-plaque formation is most active.[27] While Western guidelines typically cite a 5–15 year "warranty period" for a zero score,[9-10] the 23.9% prevalence of non calcified plaque in our Zero CAC group suggests that this warranty is less reliable in this population. Consistent with Malaysia's metabolic syndrome burden clustering in adults under 40,[19,21] a milieu that accelerates lipid rich atheroma formation before calcification occurs.[14,24]

### Sex and Age Patterns in Non-Calcified Plaque

The 23.9% of Zero CAC patients harbouring hidden plaque exhibited a distinct sex dimorphism in disease onset, marking a critical "pre-calcific window". In men, non-obstructive CAD volume peaked in the 40–44 year band (n=43), whereas females demonstrated a delayed clustering in the 55–59 band (n=8 obstructive cases). This early male peak is consistent with fibrofatty atheroma formation driven by high regional prevalence of metabolic syndrome in adults under 40.[19,21] As these lesions age, they undergo osteogenic hardening and shift patients into calcified cohorts.[7,20] In women, the 55–59 clustering aligns with the post-menopausal loss of hormonal cardioprotection.[28]

Notably, the independent male sex effect (OR 1.48) confirms this dimorphism persists after adjusting for age, reinforcing that male sex is a distinct risk driver for non-calcified burden in this setting. Both patterns diverge from broader Asian registry data, where Zero CAC cohorts typically demonstrate later onset and lower non-calcified plaque prevalence.[24,29] While the magnitude of the age effect appeared smaller in Zero CAC patients (OR 1.21 vs. 3.13 per decade). This suggests that a zero score identifies patients with delayed calcification rather than a fundamentally different biology of aging. The reduced age coefficient indicates that in this "blind spot," plaque formation is likely accelerated by unmeasured metabolic stressors and genetic predisposition rather than chronological aging alone. Consequently, these findings identify Malaysian males under 50 and peri-menopausal women as high-yield groups for confirmatory CCTA, where Zero CAC provides insufficient clinical reassurance.

### Diagnostic Performance and Clinical Significance

While CAC scoring shows high sensitivity (97.9%) for detecting obstructive CAD, its specificity is limited (43.1%) largely due to blooming artifacts where dense calcification exaggerates stenosis severity.[1,16,18] More clinically important is the 76.1% NPV for Any Plaque: 23.9% of patients with zero calcium had non-calcified plaque missed by CAC alone. Detecting this non-calcified burden matters because, as the SCOT-HEART trial demonstrated, identifying subclinical atherosclerosis enables preventive therapies that reduce cardiovascular events.[8]

The number needed to scan (NNS) with CCTA to detect one obstructive case in the Zero CAC cohort is 29. This does not justify routine CCTA for all Zero CAC patients, as CCTA involves radiation and contrast, but supports its use when metabolic risk factors or clinical suspicion suggest higher pretest probability. CAC scoring remains a useful filter for calcified disease, but CCTA adds prognostic value in younger patients where plaque may still be non-calcified.

## LIMITATIONS

This single-centre retrospective study excluded documented symptomatic patients and prior revascularization, but undocumented symptoms and referral bias remain inherent limitations. Although patients were classified as asymptomatic based on referral documentation, same-session CAC and CCTA suggests possible undocumented symptoms or higher clinical suspicion, which may

overestimate plaque prevalence in a truly asymptomatic population. Data on traditional cardiovascular risk factors were incomplete and not included in multivariable modelling, which was restricted to age and sex. Residual confounding factors such as differential smoking rates (NHMS 2023: 44.2% male vs. 1.1% female) may explain observed associations rather than true sex-specific biology. The subgroup of Zero CAC patients with detectable plaque (n=330) limits the statistical power for granular analyses. These results should be interpreted as hypothesis-generating demographic patterns rather than causal predictors.

## CONCLUSION

In this analysis of 5,375 Malaysian patients, a Zero CAC score effectively ruled out obstructive stenosis (NPV 96.5%) but missed atherosclerotic plaque in 23.9% of calcium-negative patients, including 3.5% with obstructive disease. Multivariable analysis confirmed that age and male sex remain significant predictors.

These findings demonstrate a critical "diagnostic gap." While a Zero CAC score provides strong reassurance, it does not guarantee the absence of disease, as the odd of hidden plaque climbs continuously by 22% every decade. Ultimately, clinicians must recognize the limitations of CAC screening, where radiolucent atheroma escapes detection.

## REFERENCES


1. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 1990; 15(4): 827-32.
2. Shams P, Sultan FAT, Sultan A, Javed U. Prognosis of Zero Coronary Artery Calcium Score in Symptomatic Patients of South Asian Descent - an Experience from a Tertiary Care Center in Pakistan. Glob Heart 2024; 19(1): 80.
3. Budoff MJ, Mayrhofer T, Ferencik M, Bittner D, Lee KL, Lu MT, et al. Prognostic Value of Coronary Artery Calcium in the PROMISE Study (Prospective Multicenter Imaging Study for Evaluation of Chest Pain). Circulation 2017; 136(21): 1993-2005.
4. Wang W, Yang L, Wang S, Wang Q, Xu L. An automated quantification method for the Agatston coronary artery calcium score on coronary computed tomography angiography. Quant Imaging Med Surg 2022; 12(3): 1787-99.
5. Alyami B, Santer M, Seetharam K, Velu D, Gadde E, Patel B, et al. Non-Calcified Coronary Artery Plaque on Coronary Computed Tomography Angiogram: Prevalence and Significance. Tomography 2023; 9(5): 1755-71.
6. Hanneman K, Gulsin GS. Significance of a Coronary Artery Calcium Score of 0 in Stable Chest Pain. Radiology 2024; 310(3): e240073.
7. Sheppard JP, Lakshmanan S, Lichtenstein SJ, Budoff MJ, Roy SK. Age and the power of zero CAC in cardiac risk assessment: overview of the literature and a cautionary case. Br J Cardiol 2022; 29(3): 23.
8. Osborne-Grinter M, Kwiecinski J, Doris M, McElhinney P, Cadet S, Adamson PD, et al. Association of coronary artery calcium score with qualitatively and quantitatively assessed adverse plaque on coronary CT angiography in the SCOT-HEART trial. Eur Heart J Cardiovasc Imaging 2022; 23(9): 1210-21.
9. Valenti V, Ó Hartaigh B, Heo R, Cho I, Schulman-Marcus J, Gransar H, et al. A 15-Year Warranty Period for Asymptomatic Individuals Without Coronary Artery Calcium: A Prospective Follow-Up of 9,715 Individuals. JACC Cardiovasc Imaging 2015; 8(8): 900-9.
10. Dzaye O, Dardari ZA, Cainzos-Achirica M, Blankstein R, Agatston AS, Duebgen M, et al. Warranty Period of a Calcium Score of Zero: Comprehensive Analysis From MESA. JACC Cardiovasc Imaging 2021; 14(5): 990-1002.
11. Hadamitzky M, Achenbach S, Al-Mallah M, Berman D, Budoff M, Cademartiri F, et al. Optimized prognostic score for coronary computed tomographic angiography: results from the CONFIRM registry (COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter Registry). J Am Coll Cardiol 2013; 62(5): 468-76.
12. Gami A, Nasir K, Patel J. Coronary plaque burden among South Asians using CCTA: "See disease, treat disease." Atherosclerosis 2025; 409: 120502.
13. Kanaya AM, Vittinghoff E, Lin F, Kandula NR, Herrington D, Liu K, et al. Incidence and Progression of Coronary Artery Calcium in South Asians Compared With 4 Race/Ethnic Groups. J Am Heart Assoc 2019; 8(2): e011053.
14. Agarwala A, Patel J, Blaha M, Cainzos-Achirica M, Nasir K, Budoff M. Leveling the playing field: The utility of coronary artery calcium scoring in cardiovascular risk stratification in South Asians. Am J Prev Cardiol 2022; 13: 100455.
15. Life Care Diagnostic Medical Centre. Standard operating procedure – computed tomography scan. SOP No. LCD-IMG-05, Version 2.0; 2020.
16. Cury RC, Abbara S, Achenbach S, Agatston A, Berman DS, Budoff MJ, et al. CAD-RADS(TM) Coronary Artery Disease - Reporting and Data System. An expert consensus document of the Society of Cardiovascular Computed Tomography (SCCT), the American College of Radiology (ACR) and the North American Society for Cardiovascular Imaging (NASCI). Endorsed by the American College of Cardiology. J Cardiovasc Comput Tomogr 2016; 10(4): 269-81.
17. Pack JD, Xu M, Wang G, Baskaran L, Min J, De Man B. Cardiac CT blooming artifacts: clinical significance, root causes and potential solutions. Vis Comput Ind Biomed Art 2022; 5(1): 29.
18. Willemink MJ, de Jong PA, Leiner T, de Heer LM, Nievelstein RA, Budde RP, et al. Iterative reconstruction techniques for computed tomography Part 1: technical principles. Eur Radiol 2013; 23(6): 1623-31.
19. Wan KS, Mohd Yusoff MF, Mat Rifin H, Chan WK, Yoga Ratnam KK, Ganapathy SS, et al. The prevalence of metabolic syndrome and the associated factors in a multiethnic upper-middle-income country in Asia: findings from a nationwide community-based study in 2023. BMC Public Health 2025; 25(1): 1482.
20. Mortensen MB, Gaur S, Frimmer A, Bøtker HE, Sørensen HT, Kragholm KH, et al. Association of Age With the Diagnostic Value of Coronary Artery Calcium Score for Ruling Out Coronary Stenosis in Symptomatic Patients. JAMA Cardiol 2022; 7(1): 36-44.
21. Mohamud WN, Ismail AA, Sharifuddin A, Ismail IS, Musa KI, Kadir KA, et al. Prevalence of metabolic syndrome and its risk factors in adult Malaysians: results of a nationwide survey. Diabetes Res Clin Pract 2011; 91(2): 239-45.
22. Wang X, Le EPV, Rajani NK, Hudson-Peacock NJ, Pavey H, Tarkin JM, et al. A zero coronary artery calcium score in patients with stable chest pain is associated with a good prognosis, despite risk of non-calcified plaques. Open Heart. 2019; 6(1): e000945.
23. Fattouh M, Kuno T, Pina P, Skendelas JP, Lorenzatti D, Arce J, et al. Interplay Between Zero CAC, Quantitative Plaque Analysis, and Adverse Events in a Diverse Patient Cohort. Circ Cardiovasc Imaging. 2023; 16(8): e015236.
24. Chen CL, Wu YJ, Yang SC, Wu FZ. New look at the power of zero coronary artery calcium (CAC) in Asian population: a systemic review and meta-analysis. Cardiovasc Diagn Ther. 2024; 14(3): 377-87.
25. Biavati F, Saba L, Boussoussou M, Kofoed KF, Benedek T, Donnelly P, et al. Coronary Artery Calcium Score Predicts Major Adverse Cardiovascular Events in Stable Chest Pain. Radiology 2024; 310(3): e231557.

26. Miller T, Hana D, Patel B, Conte J, Velu D, Avalon JC, et al. Predictors of non-calcified plaque presence and future adverse cardiovascular events in symptomatic rural Appalachian patients with a zero coronary artery calcium score. J Cardiovasc Comput Tomogr 2023; 17(5): 302-9.
27. Aggarwal A, Srivastava S, Velmurugan M. Newer perspectives of coronary artery disease in young. World J Cardiol 2016; 8(12): 728-34.
28. San Miguel L, Masoli O, Redruello M, Blanco JM, Collaud C, Sodor E, et al. Factors associated with non-calcified plaques in patients with coronary artery calcium score of zero. Rev Argent Cardiol 2020; 88(4): 324-330.
29. Shen YW, Wu YJ, Hung YC, Hsiao CC, Chan SH, Mar GY, et al. Natural course of coronary artery calcium progression in Asian population with an initial score of zero. BMC Cardiovasc Disord 2020; 20(1): 212.

ORIGINAL ARTICLE

# Awareness and disposal practices of unused or expired medications among patients with type 2 diabetes in Ipoh, Malaysia

**Theingi Maung Maung, PhD (Medical Community Medicine)[1], Aung San Phyo, MMed (Surgery)[2], Win Mar Aye, MMed (Surgery)[2], Ahmad Yusuf Wildan Rosharudin[3], Arief Zuhaily Arman[3], Nurul Elyanasofia Mohd Satar[3], Nur Husna Nabila Bt Badrul Hisham[3]**

[1]Community Based Department, Universiti Kuala Lumpur Royal College of Medicine Perak (UniKL RCMP), [2]Surgical Based Department, Universiti Kuala Lumpur Royal College of Medicine Perak (UniKL RCMP), [3]Faculty of Medicine, Universiti Kuala Lumpur Royal College of Medicine Perak (UniKL RCMP)

## ABSTRACT

**Introduction: Improper disposal of unused or expired medications poses significant public health and environmental risks. Despite Malaysia's "Return Your Medicines Program," improper disposal practices persist, particularly among Type 2 diabetic patients on long-term therapies. This study aimed to determine awareness and disposal practices of unused or expired medications among Type 2 diabetic patients in Ipoh and identify factors influencing improper disposal.**

**Materials and Methods: A cross-sectional study was conducted at three government clinics in the Kinta District of Ipoh, Malaysia. Data were collected from 241 participants using structured questionnaires and analysed using descriptive statistics and Pearson's chi-square tests.**

**Results: A total of 34.4% of respondents reported having unused or expired medications, primarily due to overprescription (36.1%). Among the diabetic patients surveyed, 68% demonstrated satisfactory awareness regarding the disposal of unused prescribed medications, while 32% showed unsatisfactory awareness. In terms of disposal practices, 43.37% of participants followed proper methods, whereas 56.63% engaged in poor disposal practices. A statistically significant association was observed between the level of awareness and the disposal practices adopted by the participants(p=0.000). It is recommended that health authorities enhance public education campaigns and implement accessible, well-publicized medication take-back programs to promote proper disposal of unused or expired medicines.**

**Conclusion: The study identifies a strong association between awareness levels and proper disposal practices of unused or expired medications, emphasizing the need for targeted educational initiatives to promote safe disposal among patients.**

**KEYWORDS:**
*Type 2 diabetes; medication disposal; awareness; Malaysia; public clinic*

## INTRODUCTION

Healthcare systems strive to offer patients the best quality of service through maximum utilization of the available resources, while simultaneously minimizing any possible monetary losses.[1] One definition of waste is, "Any substance or object the holder discards, intends to discard, or is required to discard". Unused medications include expired, spilled, and contaminated pharmaceutical products, drugs, vaccines, and sera that are no longer required and need to be disposed of appropriately.[2] Overprescription, therapy changes, and patient non-adherence were contributing factors to unused medications. Socioeconomic factors, such as lower income correlating with improper disposal, highlight disparities in access to take-back programs.[3]

Diabetes Mellitus is among the four leading non-communicable diseases and is responsible for more than 2 million deaths globally, according to the World Health Organization.[4] In Malaysia, the burden of diabetes mellitus has been increasing, with a prevalence of 21.1% reported in 2024, indicating that approximately 4.75 million adults were living with the condition.[5] The Malaysian government has been subsidizing medications for diabetic type 2 patients to ensure that they have access to essential treatments. However, the issue of unused medications persists, as reflected by significant increase in the total value of medicines returned to three tertiary hospitals although the Ministry of Health in Malaysia launched the "Return Your Medicines Program" in 2010.[6]

Type 2 diabetic patients, often on long-term regimens, are particularly prone to accumulating unused drugs, exacerbating risks of improper disposal. The patients' practices toward the disposal of unused medications are influenced by several factors, including their awareness, attitudes, and accessibility to proper disposal methods. Additional barriers include unnecessary prescriptions and low medication adherence, which silently contribute to the wastage of valuable resources.[7]

Despite raising awareness, improper disposal methods are still widespread among patients and the return of medicine

*This article was accepted: 3 June 2026*
*Corresponding Author: Theingi Maung Maung*
*Email: theingi.maung@unikl.edu.my , drtheingi68@gmail.com*

through the programs was not satisfactory. A lack of awareness, home storage of medications, and inappropriate disposal practices have been reported in Asian countries, largely due to the absence of official guidelines.[8] A cross-sectional study in Malaysia reported that 35.1% of respondents returned unused medications, whereas 38.3% disposed of them in household trash.[9] A study done in Kuwait had ranked throwing unused or unwanted medicines into the garbage being their most common method of disposal (76.5%) followed by flushing them down the sink or toilet (11.2%).[10] Diabetes Mellitus has become a major issue in this country, with the number of cases steadily increasing and affecting a large portion of the population. A study conducted among Type 2 diabetic patients in Kelantan, Malaysia found that only 11.5% of patients disposed of sharps at a healthcare facility, while the majority (88.6%) discarded them using plastic bags.[11] Improper disposal of expired or unused medications by diabetic patients can harm public health, ecosystems, and contaminate water systems.[12] Several studies have investigated unused medications within the general population. However, limited research has been conducted in Malaysia on the issue of unused medications among diabetic patients. This study aimed to determine the awareness and disposal practices of unused medications among individuals with Type 2 diabetes. The findings may serve as baseline data to inform and support the development of more effective government initiatives addressing unused medication management.

## MATERIALS AND METHODS

### Study area and duration

A cross-sectional study was carried out among Type 2 diabetic patients registered in the government health clinics( Klinik Kesihatan ) in Kinta district of Malaysia. The duration of the study was from 3/2/2025 to 16/5/2025. The selected clinics were Klinik Kesihatan Greentown, Klinik Kesihatan Gunung Rapat, and Klinik Kesihatan Chemor.

### Sample size and sampling method

Three health clinics located within the Kinta district were selected simple random sampling by using Research Randomizer and participants were recruited to ensure the inclusion of individuals with specific experiences and knowledge related to diabetic medication use. Participants were identified using purposive sampling from three clinics, with approximately equal proportions obtained from each clinic.

The sample size was calculated using OpenEpi with a 5% margin of error and a 95% confidence interval. The population size was based on registered active diabetic individuals, as reported by the Kinta District Health Office in 2023.[13] The prevalence of proper disposal practice of unused medication was 15% according to the previous study in Malaysia.[14] Based on these parameters, the sample size required for this study was 191 participants. Allowing a 20% attrition rate, the study recruited 241 participants.

### Inclusion and exclusion criteria

This study included individuals aged 18 and above with Type 2 Diabetes Mellitus (T2DM) who were registered in the Kinta district and consented to participate. Patients with conditions other than T2DM or those registered at clinics outside the Kinta district were excluded from the study.

### Data Collection

Data collection was conducted through face-to-face interviews using both printed questionnaires and a Google Form. A QR code linking to the Google Form was provided to enhance accessibility and convenience for participants.

To minimise interviewer bias, all interviewers used a structured questionnaire with consistent wording and sequence of questions. Interviewers were instructed to remain neutral and avoid leading participants' responses. Participants were assured of the confidentiality of their responses to encourage honest reporting.

### Materials

The questionnaire was divided into three sections: Section A gathered sociodemographic information, Section B assessed awareness regarding the disposal of unused or expired prescribed medications, and Section C focused on the disposal practices of unused medications.

Both English and Malay versions of the questionnaire were used. Content validity was established through expert review by a panel comprising specialists in Public Health, Internal Medicine, and Pharmacy. The panel evaluated the questionnaire for relevance, clarity, comprehensiveness, and appropriateness of the items. Based on their feedback, revisions were made to ensure that the questionnaire adequately covered all relevant domains related to diabetic medication use and disposal practices. A pre-test was subsequently conducted, and the questionnaire demonstrated acceptable internal consistency, with a Cronbach's alpha value of 0.76. For language adaptation, the questionnaire was translated from English into Malay by a bilingual expert. A separate independent bilingual translator then performed back-translation into the original language to ensure conceptual equivalence. Any discrepancies identified during the translation process were reviewed and resolved by the research team prior to data collection.

### Statistical analysis

Data were analysed using IBM SPSS version 25. Binary logistic regression was employed to assess associations between variables, with a p-value of less than 0.05 considered statistically significant.

### Ethical considerations

Ethical approval was sought from the National Medical Research and Ethics Committee (MREC) and the Ethics Committee of UniKL Royal College of Medicine Perak (UniKLRCMP/MREC/2024-2025/SRP-091) before commencing the study. Informed consent was obtained from all participants, and the study was conducted in accordance with the principles of the Declaration of Helsinki.

**Table I: Awareness of disposal of unused or expired prescribed medications among diabetic patients**

| Awareness questions | No | Yes |
|---|---|---|
| Improper disposal of medicines has adverse effects on the environment? | 13.7% | 86.3% |
| Is it acceptable to dispose of solid medicines such as tablets and capsules into the garbage? | 77.2% | 22.8% |
| Is it acceptable to dispose of needles and syringes into the garbage? | 81.7% | 18.3% |
| Is it acceptable to dispose of liquid medicines into the sink or toilet? | 73.0% | 27.0% |
| Do you think the medicines disposed of in the sink or toilet can reach and contaminate the groundwater? | 27.4% | 72.6% |
| Is it appropriate to return unused or expired medicines to the local pharmacy or hospital? | 6.6% | 93.4% |
| Do you know about the "Return Your Medicines Program"? | 44.8% | 55.2% |

**Table II: Nature of unused medication disposal among the respondents**

| Variable | | Frequency | Percentage |
|---|---|---|---|
| Do you have any unused or expired medicines at home? (N = 241) | Yes | 83 | 34.4 |
| | No | 158 | 65.6 |
| Why do you have unused or expired prescribed medicines at home? (N=83) | Prescribed more than needed | 30 | 36.1 |
| | Doctor changed treatment | 5 | 6 |
| | Self-discontinuation after the condition | 22 | 26.5 |
| | Passed expiry date | 11 | 13.3 |
| | Adverse effects of prescribed drug | 4 | 4.8 |
| | Non-compliance | 11 | 13.3 |
| What is the form of the unused or expired prescribed medicines at home? (N=83) | Inhaler | 1 | 1.2 |
| | Capsules | 2 | 2.4 |
| | Injection | 1 | 1.2 |
| | Syrup | 1 | 1.2 |
| | Tablets | 78 | 94 |
| How do you dispose of unused or expired prescribed medicines? (N=83) | Continue to use since not yet expire | 3 | 3.6 |
| | Return to pharmacy/clinic | 36 | 43.4 |
| | Thrown away in the trash/garbage | 32 | 38.6 |
| | Rinsing down a toilet/sink | 3 | 3.6 |
| | Given away to friends/charity | 3 | 3.6 |
| | Stored/never disposed | 6 | 7.2 |
| Practice of unused medicine disposal(N=83) | Poor | 47 | 56.63 |
| | Good | 36 | 43.37 |

N=number of individuals

**Table III: Association between socio-demographic factors and awareness of unused medicine disposal**

| Predictor | B | SE | Wald | p-value | OR | 95% CI for OR | |
|---|---|---|---|---|---|---|---|
| Older than 60 | Ref. | | | | | | |
| 30-60 yrs | -0.396 | 0.31 | 1.629 | 0.202 | 0.673 | 0.367 | 1.236 |
| Younger than 30 | -0.227 | 1.261 | 0.033 | 0.857 | 0.797 | 0.067 | 9.434 |
| Female | Ref. | | | | | | |
| Male | 0.15 | 0.281 | 0.286 | 0.593 | 1.162 | 0.67 | 2.017 |
| Tertiary education | Ref. | | | | | | |
| Secondary education | 0.174 | 0.331 | 0.278 | 0.598 | 1.191 | 0.622 | 2.277 |
| Primary education | 0.083 | 0.427 | 0.038 | 0.845 | 1.087 | 0.471 | 2.51 |
| >11000 RM | Ref. | | | | | | |
| 4500-11000 RM | -0.642 | 0.659 | 0.95 | 0.33 | 0.526 | 0.145 | 1.914 |
| <4500 RM | -0.264 | 0.612 | 0.187 | 0.666 | 0.768 | 0.231 | 2.547 |
| Model summary | | | | | | | |
| Hosmer and Lemeshow X2 | 3.177 | | | | | | |
| df | 8 | | | | | | |
| p | 0.923 | | | | | | |

B=Unstandardized coefficient, SE=Standard Error, OR=Odds Ratio, CI=Confidence Interval

**Table IV: Association between socio-demographic factors, respondents' awareness and disposal practice of unused medicine**

| Predictor | B | SE | Wald | p-value | OR | 95% CI for OR | |
|---|---|---|---|---|---|---|---|
| Older than 60 | Ref | | | | | | |
| 30-60 yrs | -0.84 | 0.524 | 2.572 | 0.109 | 0.432 | 0.155 | 1.205 |
| Younger than 30 | -21.249 | 40192.97 | 0 | 1 | 0 | 0 | |
| Female | Ref | | | | | | |
| Male | 0.392 | 0.573 | 0.468 | 0.494 | 1.481 | 0.481 | 4.555 |
| Tertiary edu | Ref | | | | | | |
| Secondary edu | 0.208 | 0.677 | 0.094 | 0.759 | 1.231 | 0.327 | 4.641 |
| Primary edu | 0.408 | 0.934 | 0.19 | 0.663 | 1.503 | 0.241 | 9.377 |
| >11000 RM | Ref | | | | | | |
| 4500-11000 RM | -1.416 | 1.719 | 0.679 | 0.41 | 0.243 | 0.008 | 7.052 |
| <4500 RM | -2.148 | 1.604 | 1.793 | 0.181 | 0.117 | 0.005 | 2.708 |
| Unsatisfactory attitude | Ref | | | | | | |
| Satisfactory attitude | 3.058 | 0.726 | 17.751 | 0.000* | 21.282 | 5.131 | 88.267 |
| Model summary | | | | | | | |
| Hosmer and Lemeshow $c^2$ | 3.454 | | | | | | |
| df | 7 | | | | | | |
| p | 0.84 | | | | | | |

B=Unstandardized coefficient, SE=Standard Error, OR=Odds Ratio,CI=Confidence Interval
* Significant

## RESULTS

A total of 241 diabetic patients participated in the study, with the majority being female (55.6%), over the age of 60 (63.9%), having a secondary level of education (46.5%), and earning a monthly income below RM4500 (70.5%).

Table I presents the findings on awareness regarding the disposal of unused or expired prescribed medications among the diabetic patients. Although most respondents were aware of proper disposal methods, approximately one-fourth were not aware of appropriate practices for disposing of unused medicines. Some believed it was acceptable to discard medications in the trash or down the sink, unaware of the potential health risks. Notably, 93.4% of diabetic patients knew that unused or expired medications should be returned to a pharmacy or hospital. However, nearly half (44.8%) were unfamiliar with the 'Return Your Medicine Program.'

The awareness questionnaire consisted of 7 binary items, with each correct response scored as 1 and each incorrect response scored as 0, resulting in a total score range of 0–7. Since the awareness score was derived from summed binary items and represented an ordinal/discrete distribution, participants were categorized based on the median total score. A score above the median value of 5 was considered satisfactory awareness, while scores at or below the median were categorized as unsatisfactory awareness.In this study, 68% of diabetic patients demonstrated satisfactory awareness regarding the disposal of unused prescribed medications, whereas 32% showed unsatisfactory awareness.

Approximately one-third (34.4%) of respondents had unused prescribed medications at home. Among these individuals, 36% cited overprescription as the main reason. The vast majority (94%) of unused medications were in tablet form. The most common disposal method was returning unused medications to a pharmacy or clinic (43.3%). However, a considerable proportion of respondents disposed of medications in household trash (38.6%), while a smaller percentage discarded them via the toilet or sink (3.6%). Disposal methods were categorized as either good or poor. Returning unused medications was considered a good practice, while all other methods were classified as poor practices. As mentioned in Table II, 56.63% of diabetic patients demonstrated poor disposal practices, whereas 43.37% were found to follow good disposal practices.

A binary logistic regression was performed to find out the impact of socio-demographic factors on the likelihood of awareness of unused medicine disposal. Based on Table III, socio-demographic factors did not have any effect on the awareness of disposal practices. Hosmer and Lemeshow $c^2$ showed non-significant p-value, suggesting a good model fit. A binary logistic regression was carried out in Table IV to find out the impact of socio-demographic factors and participant's awareness on the likelihood of disposal practice of unused medicine. A non-significant Hosmer and Lemeshow $c^2$ suggests the model fits the data adequately. Nagelkerke R Square indicates 43.8% variance is explained by the model. Respondent's awareness is a significant predictor of disposal practices for unused medicines among diabetic patients (B=3.058, SE=0.726, p<0.001, OR=21.282, 95%CI [5.13,88.26]). Lower awareness was significantly associated with improper disposal practices.

## DISCUSSION

Malaysia has made strong progress in health, with good coverage and risk protection. However, the country still faces health problems caused by social and environmental issues. Government clinics (Klinik Kesihatan) make up 28% of primary healthcare but handle 64% of outpatient visits. Still, only 2.2% of the country's GDP is spent on the current health expenditure (CHE), showing that health is underfunded. One major reason for rising health costs is the growing demand for medicines and medical supplies.[15]

In 2010, Ministry of Health Malaysia introduced "The Return Your Medicine Program" to encourage safe disposal of unused or excessed medicine among patients. This program helps patients safely dispose of unused medicines in an environmentally friendly way, following proper guidelines, through a joint effort between government and private pharmacies.[16-17]

This study aimed to assess how aware patients with Type 2 Diabetes (T2DM) are about disposing of unused medications and how they actually dispose of them. Most of the participants were from low-income groups and had a secondary education level. Klinik Kesihatan play a key role in Malaysia's healthcare system by offering affordable and accessible services. They charge low consultation fees and are especially important for low- and middle-income families.18 Although most respondents knew that unused or expired medicines should be returned to a hospital or pharmacy, about 13% to 27% were not properly aware of how to dispose of them in the current study. Almost half were still unaware that the Medication Return Programme is available at all government hospitals and clinics. A study in Terengganu, Malaysia also found low awareness of the program, with 60% to 70% of people throwing unused or expired medicines in the trash.[19] Ling et al. (2024) also reported that 71.5% of respondents disposed of unused medications in rubbish bins, making it the most common method among Malaysians. The study also found that awareness of how pharmaceuticals can harm the environment was strongly linked to proper disposal practices.[20]

Although Malaysia has been promoting awareness programs for rational drug use for over a decade, Lim (2016) reported that fewer than 50% of respondents demonstrated satisfactory awareness. Findings from the current study support previous research, revealing that only 32% of diabetic patients are aware of proper disposal methods for unused medications. This highlights the ongoing need to raise public awareness about the safe disposal of medications.[21]

In this study, 43.3% of participants returned unused medications to a pharmacy or clinic, indicating awareness of the "Return Your Medicines Program" and appropriate medication disposal practices. Compared with a study conducted in Saudi Arabia, participants in the present study demonstrated greater awareness regarding the proper disposal of unused medications (43.3% versus 14.9%).[22] The Saudi study targeted the general public, whereas the current study focused on patients with Diabetes Mellitus. These patients may have better awareness of medication disposal practices due to more frequent exposure to healthcare providers.[23]

Findings reported that one-third of the respondents reported disposing of unused or expired medications in the trash, while 3.6% admitted to discarding them in sinks or toilets. These findings indicate that poor disposal practices are prevalent among more than half of the patients with Type 2 Diabetes Mellitus (T2DM). Improper disposal methods, such as discarding medications in the trash or flushing them, can lead to environmental pollution, accidental poisoning, and potential drug misuse. These practices may contaminate water sources, posing risks not only to human health but also to wildlife. Furthermore, pathogens and toxic substances from pharmaceutical waste can contribute to climate impact through environmental degradation.[24]

Awareness and disposal patterns of unused medications were not significantly associated with sociodemographic factors in the current study. Our findings are consistent with a study conducted in the United Arab Emirates (UAE), which also found no significant relationship between age, gender, or education level and knowledge or practices related to the disposal of unused medications.[25] However, in a survey conducted among the general public in Saudi Arabia, gender and educational level were found to be significantly associated with unused medication disposal patterns. That study included a larger sample size and a higher proportion of respondents with tertiary education compared to the current study.[26]

A cross-sectional survey conducted among the Malaysian public in 2023 revealed that individuals with greater awareness of health and environmental hazards were more likely to practice safe disposal of unused medications.20 Similar findings were observed in the current study, where participants with better knowledge regarding medication disposal reported safer disposal practices.

To improve public awareness, targeted health education campaigns can be implemented at local health clinics, reaching not only patients with chronic conditions such as Type 2 Diabetes Mellitus, but also their family members. Additionally, pharmacists can play a vital role by providing brief, personalized guidance on proper disposal methods at the point of prescription. Educational materials such as pamphlets or handy flyers can further reinforce this information. Moreover, incorporating animated sticker labels on medication packaging that demonstrate correct disposal methods can serve as a cost-effective and visually engaging reminder for patients.

## LIMITATION

This study has several limitations that should be acknowledged. The use of nonprobability sampling limits the generalizability of the findings, as participants were selected based on their availability and willingness rather than random selection, which may not fully represent the broader population of Type 2 diabetic patients in the Kinta district. Additionally, reliance on self-reported responses introduces the possibility of recall bias and social desirability bias, potentially affecting the accuracy of reported disposal practices.

Furthermore, the study was conducted only in three health clinics, which may not fully reflect the practices of patients in other clinics or healthcare settings. To address these limitations, future research should consider using probability sampling methods to improve representativeness and reduce selection bias, while expanding the study to include more clinics across different districts or states to obtain a broader understanding of disposal practices among diabetic patients in Malaysia.

## CONCLUSIONS

This study reveals that one-third of Type 2 diabetes patients registered at government clinics in Ipoh possess unused or expired prescribed medications, primarily due to overprescription and self-discontinuation of treatment. These

findings provide important insight into the initial steps needed to address improper medication waste disposal among patients.

The study identifies a statistically significant association between awareness levels and proper disposal practices of unused or expired medications, emphasizing the need for targeted educational initiatives to promote safe disposal among patients. Enhancing public knowledge, increasing accessibility to medication take-back programs, and strengthening communication between healthcare providers and patients regarding medication management are critical steps in reducing pharmaceutical waste and its associated environmental and health risks. Lower awareness was significantly associated with improper disposal practices, underscoring the importance of sustained awareness efforts.

## ACKNOWLEDGEMENTS

The authors would like to express their sincere gratitude to all the participants of this study for their time, cooperation, and willingness to share valuable information. We also extend our appreciation to the staff of the government clinics in the Kinta District, Ipoh, for their support and assistance during the data collection process. We would also like to acknowledge Universiti Kuala Lumpur, Royal College of Medicine Perak, for providing resources and opportunities.

## REFERENCES

1. Mbau R, Musiega A, Nyawira L, Tsofa B, Mulwa A, Molyneux S, et al. Analysing the efficiency of health systems: a systematic review of the literature. Appl Health Econ Health Policy. 2023; 21(2): 205-24.
2. Environment Agency. Check if your material is waste [Internet]. London: GOV.UK; 2021 Aug 31 [updated 2024 Jul 11; cited 2026 Jun 25]. Available from: https://www.gov.uk/government/publications/legal-definition-of-waste-guidance/definition-of-waste-2018-waste-framework-directive-amendments
3. Calise TV, Martin SL, Wingerter C. Safely disposing unused and unwanted prescription and over-the-counter medications: a public health, housing, and safety partnership in Framingham, MA. Journal of Pharmaceutical Policy and Practice 2022; 15(1): 1-8.
4. Noncommunicable diseases [Homepage on the Internet]. [cited 2026 Apr 8];Available from: https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases
5. Malaysia - International Diabetes Federation [Homepage on the Internet]. [cited 2026 Apr 8];Available from: https://idf.org/our-network/regions-and-members/western-pacific/members/malaysia/
6. Returning Unwanted Medicine To Pharmacies – Monash University Malaysia - CodeBlue [Homepage on the Internet]. [cited 2025 Jun 6];Available from: https://codeblue.galencentre.org/2022/05/returning-unwanted-medicine-to-pharmacies-monash-university-malaysia/
7. Alharbi H. Drug Consumers Behaviors toward the Disposal of Unused and Expired Medicines in Qassim Province/Saudi Arabia. J Pharm Biomed Sci 2018; 8(1): 8-13.
8. Borhan Uddin M, Al Samir R, Golam Mehebub Pantho GM. Practice of Expired and Unused Drug Disposal in South Asian and Southeast Asian Countries. Waste Management for a Sustainable Future - Technologies, Strategies and Global Perspectives. 2024 Sep 26;
9. Wang LS, Aziz Z, Chik Z. Disposal practice and factors associated with unused medicines in Malaysia: a cross-sectional study. BMC Public Health 2021;21:1695.
10. Abahussain EA, Ball DE, Matowe WC. Practice and Opinion towards Disposal of Unused Medication in Kuwait. Medical Principles and Practice 2006; 15(5): 352-7.
11. Hasan UA, Hairon SM, Yaacob NM, Daud A, Hamid AA, Hassan N, et al. Factors contributing to sharp waste disposal at health care facility among diabetic patients in North-East Peninsular Malaysia. Int J Environ Res Public Health 2019; 16(13): 2251.
12. Tong AYC, Peake BM, Braund R. Disposal practices for unused medications around the world. Environment International 2011; 37(1): 292-8.
13. Pejabat Kesihatan Daerah [Homepage on the Internet]. [cited 2025 Jun 6];Available from: https://jknperak.moh.gov.my/jkn/v2/index.php/perkhidmatan/pejabat-kesihatan-daerah-pkd
14. Hassali MA, Shakeel S. Unused and Expired Medications Disposal Practices among the General Public in Selangor, Malaysia. Pharmacy: Journal of Pharmacy Education and Practice [homepage on the Internet] 2020 [cited 2026 Apr 8];8(4):196.
15. Ministry of Health Malaysia. Health White Paper for Malaysia. Putrajaya: Ministry of Health Malaysia; 2023. [cited 2026 Jun 25]. Available from: https://www.moh.gov.my/images/04-penerbitan/kertas-putih/Kertas_Putih_Kesihatan_ENG_compressed.pdf
16. The Proper Practice of Medicine Disposal | CARiNG Pharmacy [Homepage on the Internet]. [cited 2025 Jun 7];Available from: https://www.caring2u.com/health-center/health-info/the-proper-practice-of-medicine-disposal/
17. Keowmani T, Liew JE, Tan SL. Knowledge, attitude and practice related to unused medicines among doctors, pharmacists and nurses: developing and validating a tool. Pharm Res Rep 2024; 7(1): 18-32.
18. Understanding Malaysia's Healthcare System [Homepage on the Internet]. [cited 2025 Jun 7];Available from: https://www.internationalinsurance.com/health/systems/malaysia.php?srsltid=AfmBOoqyUHvd5XLrHWZgHvECu_geCewbT9XhuCMI8LsRAYS5ytMJ15zx
19. Saharuddin NA, Noordin ZM, Hospital TA, et al. Original Research Article Assessing Public Awareness and Practices in Medicine Disposal : A Cross- Sectional Study on the Utilisation of the ' Return Your Medicines ' Program in. 2024; 7: 34-47.
20. Ling JY, Ng PY, Shamsuddin AS, Zulkifli A, Lee KE. Medication Disposal Patterns and Practices with Awareness of Environmental Contamination Caused by Pharmaceuticals among the General Public in Malaysia. Asian Pacific Journal of Cancer Prevention 2024; 25(8): 2723-34.
21. Lim MT. Disposal Practices of Unused and Unwanted Medications among Patients in a Tertiary Hospital. Education in Medicine Journal 2016; 8(3): 49-59.
22. Bani Hani S, Al Omar S, Abu Zaid A, et al. Preoperative predictors of complications in pediatric laparoscopic appendectomy: a retrospective cohort study. J Pediatr Surg 2022; 57(6): 1171-7.
23. Aljeezan MK, Altaher YY, Boushal TA, Alsultan AM, Khan AS. Patients' Awareness of Their Rights and Responsibilities: A Cross-Sectional Study From Al-Ahsa. Cureus 2022; 14(12).
24. World Health Organization. Health care waste [Internet]. Geneva: World Health Organization; 2024 Oct 24 [cited 2026 Jun 25]. Available from: https://www.who.int/news-room/fact-sheets/detail/health-care-waste
25. Dweik R Al, Ajaj R, Hafez W. Public awareness of medication disposal and its impact on environmental and public health: A cross-sectional study in the United Arab Emirates. Informatics in Medicine Unlocked 2024; 50: 101580.
26. Khan NA, Easwaran V, Orayj K, Venkatesan K, Alavudeen SSA, Alhadeer SA, et al. A cross-sectional study on perceptions towards safe disposal of unused/expired medicines and its associated factors among the public in Saudi Arabia—a threat to the environment and health. PeerJ 2025; 13: e19258.

ORIGINAL ARTICLE

# Transabdominal cervical length measurement as primary screening method for short cervix in the mid-trimester: A prospective observational cohort diagnostic accuracy study

**LP Sii, MRCOG[1], HY Voon, MRCOG[1,3], Bujang Mohd Adam, PhD[2], LN Tan, MRCOG[1], Rafaie Amin, MMed (O&G)[1,3]**

[1]Department of Obstetrics and Gynecology, Sarawak General Hospital, Kuching, Sarawak, Malaysia, [2]Institute for Clinical Research, National Institute of Health, Ministry of Health Malaysia, [3]Department of Obstetrics & Gynecology, Faculty of Medicine and Health Science, Universiti Malaysia Sarawak

## ABSTRACT

**Introduction: Preterm birth (PTB) is a leading cause of neonatal morbidity and mortality, with cervical insufficiency being a major contributor. While transvaginal ultrasound is the gold standard, concerns over invasiveness, resource requirements, and acceptability limit its universal use. Transabdominal cervical length measurement may offer a pragmatic alternative, particularly in conservative populations. We aim to compare transabdominal versus transvaginal cervical length measurement for screening of short cervix during the mid-trimester, and to determine the feasibility and clinical utility of using transabdominal ultrasound as a primary screening tool, especially in populations with reservations about undergoing transvaginal scans.**

**Materials and Methods: This was a prospective observational cohort diagnostic accuracy study involving pregnant women undergoing routine mid-trimester anomaly scans. Cervical length was measured using transabdominal and transvaginal ultrasound by experienced sonographers. Statistical analysis: correlation assessed with Spearman's coefficient. Agreement evaluated with intraclass correlation and Bland-Altman plots. Diagnostic accuracy metrics (sensitivity, specificity, PPV and NPV) were calculated for transabdominal thresholds. Confounding factors, including bladder filling, maternal body mass index (BMI), and prior caesarean delivery on visualisation, were also evaluated.**

**Results: Of the 266 women eligible to participate in the study, 6.0% were excluded as they declined a transvaginal scan. Postvoid transabdominal (TA) measurements demonstrated better agreement with transvaginal (TV) values but were associated with higher rate of non-visualization (10.0%). Bland-Altman plots showed good agreement without systematic bias. The mean prevoid TA cervical length and postvoid TA cervical length were 35.7 mm and 35.6 mm respectively, compared to 39.3 mm on TV measurement. Non-visualization occurred more often postvoid (10%) than prevoid (6.4%), while postvoid TA measurements showed stronger agreement with TV (ICC=0.818). Agreement of measurements was higher among Maternal-Fetal Medicine (MFM) consultants than among MFM fellows. Body mass index (BMI) and prior caesarean section scars did not significantly affected visualization or measurement accuracy.**

**Conclusion: TA cervical length measurement is a reliable initial screening approach for identifying women at risk of short cervix during mid-trimester when performed by experienced operators. It serves as a pragmatic alternative in settings where TV scans are declined or not feasible, facilitating timely referral for TV confirmation and early initiation of preventive interventions such as progesterone therapy or cerclage. However, its application may be limited in untrained hands.**

**KEYWORDS:**
*Cervical length; transabdominal ultrasound; transvaginal ultrasound; mid-trimester screening; short cervix; conservative populations; diagnostic accuracy*

## INTRODUCTION

The World Health Organization (WHO) reported that approximately 15 million babies were born too soon annually, with Malaysia contributing more than 34,000 of these preterm births.[1-2] The majority of preterm births (PTB) were spontaneous (as opposed to medically-indicated), resulting from preterm labour (40 to 50 percent) or preterm prelabour rupture of membranes (20 to 30%); with cervical insufficiency recognised as one of the significant contributors.[3] In fact, the International Federation of Gynaecology and Obstetrics (FIGO) Working Group for Preterm Birth identified cervical insufficiency as one of the "low-hanging fruits" and issued recommendations on its intervention.[4]

For an intervention to be implemented, cervical length screening must first take place. Most studies on cervical length in the prediction of PTB were performed via transvaginal (TV) ultrasound, which has also been shown to be reproducible and less prone to technical issues.[5-6] However, introducing routine TV ultrasound in a centre at the outset may add considerable assessment time and clinicians may be reluctant to comply, in the absence of data supporting a clinical advantage.[6] From a resource perspective, allocation of an additional chaperone during the TV scan and,

*This article was accepted: 7 June 2026*
*Corresponding Author: LP Sii*
*Email: lehping81@gmail.com*

**Table I: Demographic and Socioeconomic Characteristics of Participants**

| Characteristic | | Value |
|---|---|---|
| Age (year) | | 33.4 ± 6.6 |
| Race | Bidayuh | 26 (10.4) |
| | Chinese | 28 (11.2) |
| | Iban | 55 (22.0) |
| | Malay | 133 (53.2) |
| | None of the above | 8 (3.2) |
| Gestational age (weeks) | | 21.3 ± 1.3 |
| Parity | Nulliparous | 62 (24.8) |
| | Multiparous | 188 (75.2) |
| Booking BMI (kg/m$^2$) | <18.5 | 18 (7.2) |
| | 18.5-24.9 | 66 (26.4) |
| | 25.0-29.9 | 77 (30.8) |
| | 30.0-34.9 | 55 (22.0) |
| | 35.0-39.9 | 19 (7.6) |
| | ≥40 | 1 (0.4) |
| | Not available | 14 (5.6) |
| Previous cesarean section | | 54 (21.6) |
| Previous preterm birth | | 25 (10) |
| History of cervical conization/ loop excision | | 0 (0) |
| Household income | Top 20 | 7 (2.8) |
| | Middle 40 | 43 (17.2) |
| | Bottom 40 | 173 (69.2) |
| | Not available | 27 (10.8) |

Data represent mean (Standard deviation) or n (%) unless stated

disassembly and disinfectant of an additional transducer can be prohibitive. TV ultrasound is invasive and some women find the procedure distressing.[7] Furthermore, in some culturally-conservative societies such as the authors', TV ultrasound is regarded as a highly intimate examination, with some women compelled to request for their partner's approval.[8] Studies among Asian patients reported 7.7 to 22.9% of women declining TV ultrasound.[9-10] Lastly, performing an intimate examination on mostly young women in a vulnerable position with dim lighting, subjects the clinician to threats of litigation if workplace protocols are not strictly adhered to.[10]

Technically, the sonographic assessment of cervical length can also be performed using a transabdominal (TA) or transperineal approach. TA ultrasound is associated with reduced scanning time, use of resources and discomfort for the patients. However, whether TA is sufficiently accurate as a surrogate for TV in screening of women with shortened cervical length remains in equipoise, based on existing studies.[4,5,11] We sought to (1) compare TA and TV measurements of cervical length to assess the efficacy of an initial TA assessment in defining a group of women that should have further TV evaluation; (2) assess inter-observer variation of both TA and TV measurement; (3) investigate if bladder filling or body mass index (BMI) affected the ability to visualize the cervix using TA ultrasound.

## MATERIALS AND METHODS

We conducted a prospective observational cohort diagnostic accuracy study, evaluating pregnant women who underwent mid-trimester fetal anomaly screening in the Maternal-Fetal Medicine (MFM) unit of Sarawak General Hospital, Malaysia. Women ≥18 years of age with singleton pregnancies between 18+0 and 23+6 weeks of gestation were eligible. Exclusion criteria included symptoms of threatened preterm labour, uterine anomalies, pre-existing cerclage in-situ, or progesterone therapy. Women declining TV scans and their reasons were documented. Written informed consent was obtained. A bilingual patient information leaflet was also made available and women who did not understand English or Bahasa Malaysia were counselled in the presence of an interpreter.

TA cervical length was measured pre- and post-void. Visualization was defined by the identification of both internal and external os. Three TA measurements were obtained; the shortest was used for analysis. TV measurements were performed as per Fetal Medicine Foundation guidelines.[12] To reduce measurement bias, TV and TA scans were performed independently by different operators, who were blinded to the other's findings. Inter-observer reliability was assessed. Bladder volume was estimated using a standard formula previously described.[13,14] Sample size was determined using Bujang & Adnan (2016), requiring 264 participants to achieve 90% sensitivity with 85% power for TV cervical length of 25 mm, based on a target significance level of 0.05.[15] A cut-off of 25 mm measured transvaginal was used as the reference standard as cervical length below this cut-off is associated with increased risks of preterm deliveries.[16] Data collected were analysed with SPSS version 26.0 (SPSS Inc, Chicago, IL). Statistical analysis: correlation assessed with Spearman's coefficient. Agreement evaluated with intraclass correlation and Bland-Altman plots. Diagnostic accuracy metrics (sensitivity, specificity, PPV and NPV) were calculated for transabdominal thresholds. Regression models explored effects of BMI and prior

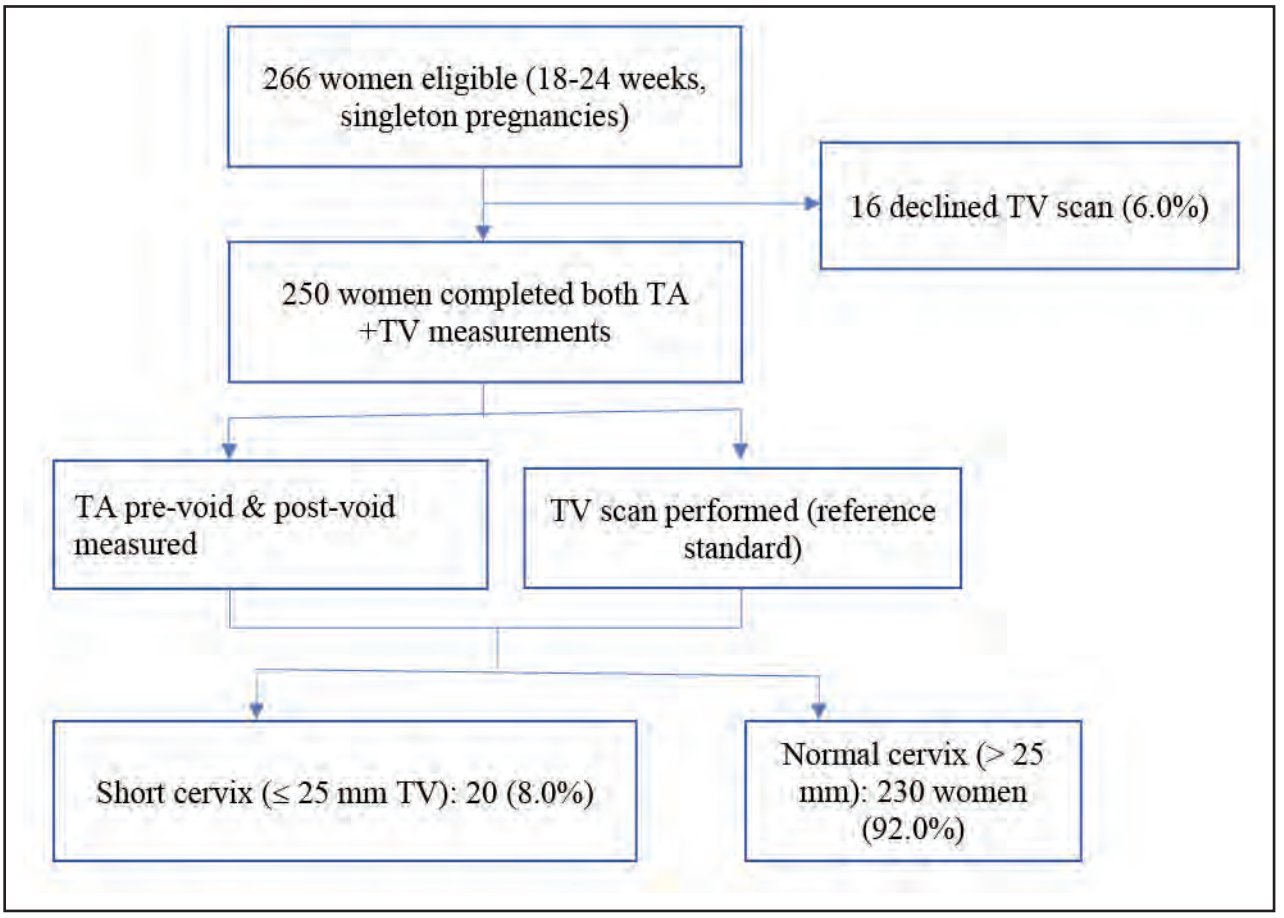



**Fig. 1:** Participant flow diagram for the study cohort

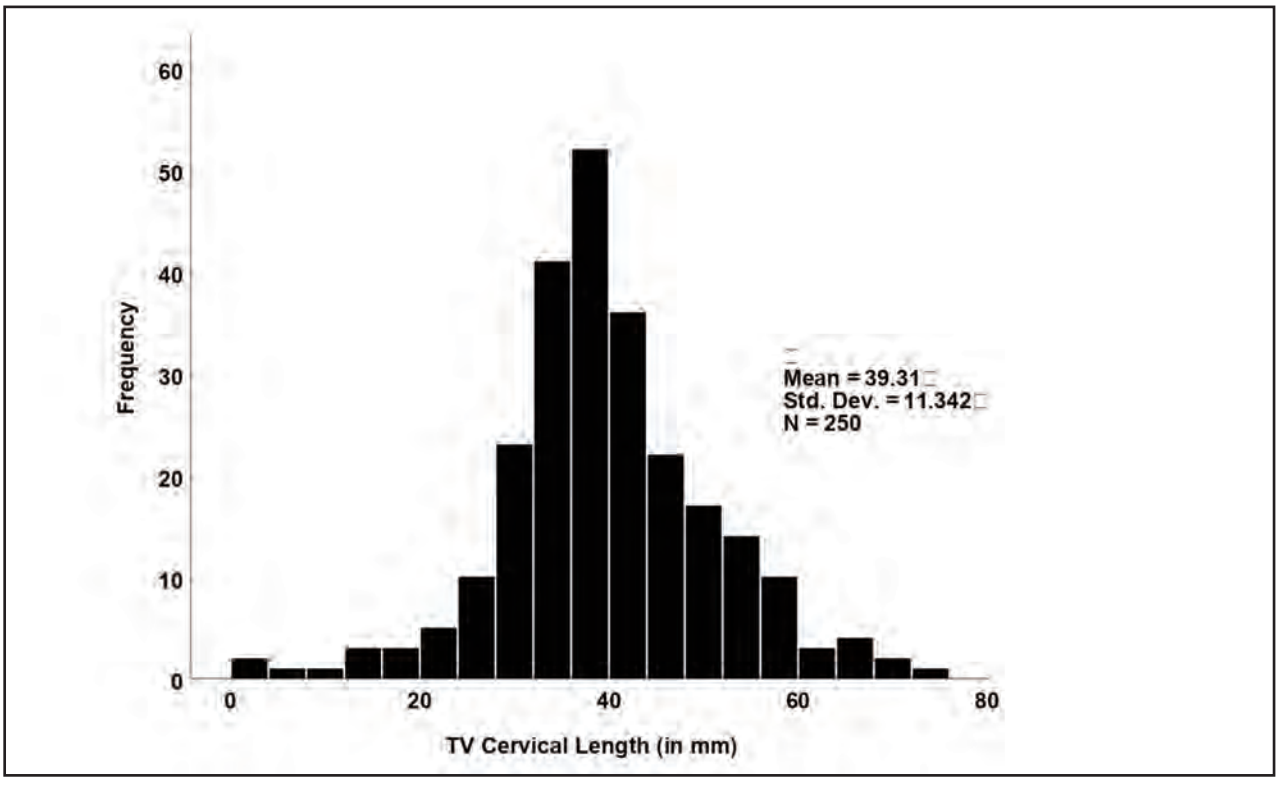



**Fig. 2:** Distribution of transvaginal cervical length measurements

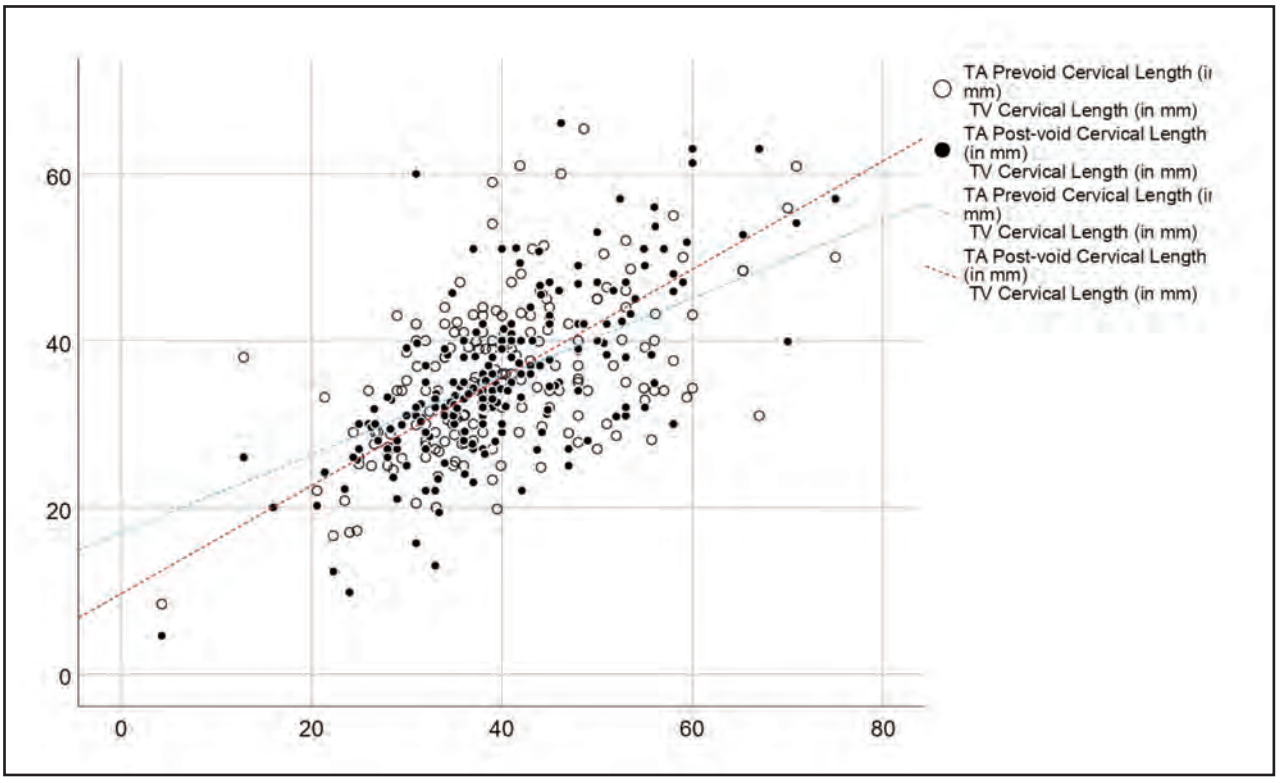



**Fig. 3:** Prevoid and postvoid transabdominal cervical length measurement compared with transvaginal measurement

caesarean scar. Refusals were documented to reduce selection bias. Women with non-visualised cervix on TA were included in analysis as missing data; no imputation was performed. Statistical analysis excluding these cases was undertaken. A flow diagram of participants, exclusions, and refusals is provided. (Figure 1).

This study received no external funding. Ethical approval was obtained from the Medical Research & Ethics Committee (MREC) and registered with the National Medical Research Register Malaysia (NMRR ID-22-02567-BGW). Authors declare no conflicts of interest.

## RESULTS

Of 266 recruited, 250 completed both TA and TV measurements. 16 (6.0%) women declined TV ultrasound. Demographic data and preterm birth risk factors among the women screened are shown in Table I.

Self-reported mean household income, categorized based on the Department of Statistics' data, was used as a surrogate for socioeconomic status.17 Mean prevoid TA cervical length was 35.7 mm (95% CI 34.5 - 36.9 mm) and postvoid TA cervical length was 35.6 mm (95% CI 34.3 - 36.9) compared to 39.3 mm (95% CI 37.9 - 40.7) (Figure 2) when measured through TV. Short cervix (TV cervical length of ≤ 25 mm) was observed in 8.0%. Non-visualization occurred in 17 (6.4%) prevoid and 25 (10.0%) postvoid TA scans and these are excluded from analysis. Postvoid TA had stronger agreement with TV (ICC=0.818) than prevoid TA (ICC=0.765) (Figure 3). The agreement of measurements was higher amongst Maternal-Fetal Medicine consultants 0.762 (95% CI 0.646 - 0.840; p<0.001) compared to MFM fellows 0.697 (95% CI 0.55-0.781; p<0.001). In a multivariate analysis, maternal BMI and presence of previous caesarean section scar, two potential confounders for visualization of cervical length TA did not affect the agreement of measurements (p>0.05).

## DISCUSSION

Our study shows TA cervical length measurement can be used as a surrogate to TV scan in detection of short cervix. The mean cervical length in our study and incidence of short cervix in our cohort was consistent with previously published studies.[5,11,18-19] Postvoid TA was more accurate than prevoid TA but associated with higher non-visualization rates. A cut-off of 30 mm improved sensitivity to 87.5% with acceptable trade-off in specificity. Previous authors have suggested a higher cut-off of 30 mm to 32 mm be used when the cervix was measured transabdominally.[5,16,20] Importantly, TA high negative predictive value supports its use as triage tool in population where TV is declined.

The strength of this study includes its prospective design, standardized protocol, blinded measurements, and assessment of confounders. Limitations includes single-centre setting and experienced operators performing the scan, which may limit generalisability. A transperineal scan was not included as a separate arm in this study as it is an equally intimate examination like TV and technically more challenging.

Clinically, TA scans as first-line screening allows identification of women requiring TV confirmation, enabling timely interventions such as vaginal progesterone or cerclage. This may help reduce preterm birth burden in settings when TV acceptance or availability is limited.

## CONCLUSION

TA cervical length measurement has a high negative predictive value and is a reasonable first-line strategy for identifying women with a short cervix. It can be used to triage women for TV confirmation, particularly in culturally-conservative or resource-limited settings. As the scans were performed by trained operators, the findings may not be generalizable to all clinical settings.

## REFERENCES


1. World Health Organization. Born too soon: the global action report on preterm birth. Geneva: WHO; 2012.
2. Malaysian National Neonatal Registry. Report of the Malaysian National Neonatal Registry 2020: a study of critically ill babies in neonatal intensive care units. Kuala Lumpur: Malaysian National Neonatal Registry; 2023.
3. Prediction and Prevention of Spontaneous Preterm Birth: ACOG Practice Bulletin, Number 234. Obstet Gynecol. 2021 Aug 1; 138(2): e65-90.
4. Jacobsson B, Simpson JL; FIGO Working Group for Preterm Birth. FIGO good practice recommendations for reducing preterm birth and improving child outcomes. Int J Gynaecol Obstet 2021; 1 55(1): 1-4.
5. Friedman AM, Srinivas SK, Parry S, Elovitz MA, Wang E, Schwartz N. Can transabdominal ultrasound be used as a screening test for short cervical length? Am J Obstet Gynecol 2013; 208(3): 190.e1-7.
6. Bennett CC, Richards DS. Patient acceptance of endovaginal ultrasound. Ultrasound Obstet Gynecol 2000; 15(1): 52-5.
7. Chawanpaiboon S, Titapant V, Anuwutnavin S, Kanjanapongporn A, Pooliam J. Identifying the Barriers to Universal Cervical Length Screening for Preterm Birth Prevention at a Tertiary Hospital in Thailand (Physician Perspectives): Implementation Research. Healthcare (Basel) 2023; 11(7): 1039.
8. Nambiar JM, Pai MV, Reddy A, Kumar P. Can Transabdominal Scan Predict a Short Cervix by Transvaginal Scan? Obstet Gynecol Int 2017; 2017: 3035718.
9. Peng CR, Chen CP, Wang KG, Wang LK, Chen CY, Chen YY. The reliability of transabdominal cervical length measurement in a low-risk obstetric population: Comparison with transvaginal measurement. Taiwan J Obstet Gynecol 2015; 54(2): 167-71.
10. Collins K, Hamlyn T, Bruxner G, Kothari A. Dangers in the dark: Calling for a safer practice of transvaginal ultrasonography. Australas J Ultrasound Med 2020; 24(1): 5-12.
11. To MS, Skentou C, Liao AW, Cacho A, Nicolaides KH. Cervical Assessment at the Routine 23-Weeks' Scan: Problems with Transabdominal Sonography. Ultrasound Obstet Gynecol 2000; 15(4): 292-6.
12. Fetal Medicine Foundation. Cervical Assessment: FMF Certification. Available from: https://fetalmedicine.org/fmf-certification-2/cervical-assessment-1.
13. Saul LL, Kurtzman JT, Hagemann C, Ghamsary M, Wing DA. Is transabdominal sonography of the cervix after voiding a reliable method of cervical length assessment? J Ultrasound Med 2008; 27(9): 1305-11.
14. Poston GJ, Joseph AE, Riddle PR. The accuracy of ultrasound in the measurement of changes in bladder volume. Br J Urol 1983; 55(4): 361-3.
15. Bujang MA, Adnan TH. Requirements for Minimum Sample Size for Sensitivity and Specificity Analysis. J Clin Diagn Res 2016; 10(10): YE01-06.
16. Iams JD, Goldenberg RL, Meis PJ, Mercer BM, Moawad A, Das A, et al. The length of the cervix and the risk of spontaneous premature delivery. National Institute of Child Health and Human Development Maternal Fetal Medicine Unit Network. The New England journal of medicine 1996; 334(9): 567-72.
17. Carvalho M. B40, M40 categorisation being phased out, subsidies to be based on net disposable income [Internet]. The Star. 2023 Jun 14 [cited 2024 Jun 18]. Available from: https://www.thestar.com.my/news/nation/2023/06/14/subsidies-to-be-based-on-net-disposable-income-govt-phasing-out-use-of-b40-m40-categories-says-rafizi
18. Stone PR, Chan EH, McCowan LM, Taylor RS, Mitchell JM; SCOPE Consortium. Transabdominal scanning of the cervix at the 20-week morphology scan: comparison with transvaginal cervical measurements in a healthy nulliparous population. Aust N Z J Obstet Gynaecol 2010; 50(6): 523-7.
19. Stamilio D, Carlson LM. Transabdominal ultrasound is appropriate. Am J Obstet Gynecol. 2016 Dec;215(6):739-743.e1.
20. Hernandez-Andrade E, Romero R, Korzeniewski SJ, Ahn H, Aurioles-Garibay A, Garcia M, et al. Cervical strain determined by ultrasound elastography and its association with spontaneous preterm delivery. J Perinat Med 2014; 42(2): 159-69.

ORIGINAL ARTICLE

# Medication adherence and medication concordance among chronic illness patients in selected suburban areas in Johor, Malaysia: A cross-sectional study

**Thurairaj Arvin, MBBS[1], Swe Kye Mon Min, PhD[2,3], Radha Krishnan Nithya Vaisnavi, MBBS[4], Hon Mei Jing, MBBS[5], Ng Wen Min, MBBS[6], Goo Jie Ler, MBBS[7], Yeong Livia Lin Lee, MBBS[8], Wong Ing Zhi, MBBS[9]**

[1]Hospital Sultan Ismail, Johor Bahru, Johor, Malaysia, [2]Newcastle University Medicine Malaysia, Iskandar Puteri, Johor, Malaysia, [3]Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, United Kingdom, [4]Cumberland Infirmary, Carlisle, United Kingdom, [5]Royal Derby Hospital, Derby, United Kingdom, [6]Wexham Park Hospital, Berkshire, United Kingdom, [7]Queen Elizabeth Hospital, Gateshead, United Kingdom, [8]Hospital Queen Elizabeth, Kota Kinabalu, Sabah, Malaysia, [9]Sarawak General Hospital, Kuching, Sarawak, Malaysia

## ABSTRACT

**Introduction: Inadequate medication adherence is a significant problem globally, affecting up to 50% of chronic illness patients. The complications can also be significant, with increased rates of disease complications and hospitalisations due to lack of adherence. This research study seeks to find the medication adherence rate across select suburban areas in Johor, Malaysia, and to identify the relationship between medication adherence and treatment concordance.**

**Materials and Methods: A community-based cross-sectional study was conducted among patients with chronic diseases across various locations in Johor. A validated questionnaire, the Malaysia Medication Adherence Assessment Tool (MyMAAT) and a Modified Concordance Scale were used to explore the study objectives.**

**Results: Medication adherence is defined as a MyMAAT score of ≥54. A total of 82 chronic illness patients participated in this study, with males (48.8%) and females (51.2%). The mean age of the participants is 57.5 years old. The study reported 41.5% adherence (MyMAAT ≥54). Female vs male OR was calculated via logistic regression adjusting for confounding factors, with adherence (MyMAAT≥54) as a binary factor (OR=4.23; 95% CI 1.38-12.91; p=0.011). A statistically significant weak correlation was found between the MyMAAT score and the Modified Concordance Scale score (SR ρ=0.286, p=0.009).**

**Conclusion: In conclusion, the study shows a potential relationship between medication concordance and improved patient adherence in the Malaysian setting. More research should be conducted to further verify these findings.**

**KEYWORDS:**
*Medication adherence; medication concordance; chronic illness; Malaysia; shared decision making*

## INTRODUCTION

Optimal adherence to prescribed medication regimens is the key to sustaining good health outcomes, as it ensures the effective management of medical conditions and minimizes the risk of disease progression or complications. Authorities at all levels have invested significant effort to improve public health outcomes; however, in developed countries, patient adherence to chronic disease management averages only 50%.[1] The World Health Organization (WHO) has defined medication adherence as the degree to which an individual's actions regarding medication intake, dietary control, or lifestyle modifications align with agreed prescriptions from healthcare professionals.[1] Poor medication adherence results in reduced clinical effectiveness, allowing the disease to deteriorate, which can lead to more complications, increase hospitalisations and elevate mortality rates. Consequently, inadequate medication adherence has become a costly economic burden worldwide, with a reported amount of a few million ringgit per year of unused subsidised medications from a single hospital in Malaysia.[2] Reduced adherence may stem from an individual's health literacy, socioeconomic factors, and the complexity of the treatment regimen. A patient with chronic illness with complex medication regimens was reported to be adherent at a rate of only 30%.[3] Medication concordance, therefore, is a process of shared decision-making that considers a patient's ideas, concerns, and expectations to tailor the treatment to the individual better. The 2015 European Patients Forum position paper describes medication concordance as an approach in which patients and prescribers work together and the degree to which the prescription represents a shared decision.[4] When the recognition of the patient's views is paramount, evidence shows that improved concordance leads to better patient satisfaction and medication adherence.[5-6]

Several studies have explored medication adherence within the Malaysian setting, including a 2022 scoping review and meta-analysis that included 64 studies.[7] The included studies were designed to measure the prevalence of poor medication adherence, validate medication adherence scales, and

*This article was accepted: 7 June 2026*
*Corresponding Author: Swe Kye Mon Min*
*Email: kye-mon.min-swe@newcastle.edu.my*

evaluate interventions to improve medication adherence. Other studies focused on different sub-populations such as older adults,[8] people with hypertension,[9] type 2 diabetes mellitus[7] and subsidized versus self-paying patients.[10] There is limited quantitative evidence on the relationship between medication adherence and concordance in Malaysia.

This study examines the relationship between medication concordance and adherence in Malaysia using a quantitative approach. Limited quantitative evidence exists on this topic within the Malaysian context. Only 2 qualitative studies have been done, one in 2018 by Ng et al.[11] and one in 2022 by Abdullah et al.[12] which touched on the topics of patient-centered care and the importance of communication between healthcare professionals and patients for better medication adherence. This is a significant gap that this study addressed.

The global literature is increasingly moving towards treatment concordance, yet literature in this area is minimal in Malaysia. The objective of this study is to determine the medication adherence rate across selected suburban areas in Johor and to investigate the relationship between medication concordance and adherence using a quantitative method in the Malaysian setting. Our primary research question is, "What is the relationship between medication concordance and medication adherence in Malaysia?" This will provide evidence to support clinicians in engaging with treatment concordance to improve adherence rates.

## MATERIALS AND METHODS

### Design, Setting, and Participants.

A community-based cross-sectional study was conducted among patients with chronic illnesses across various locations in Johor, including Iskandar Puteri, Kluang, Pontian, Taman Mount Austin, and Johor Bahru. The participants were recruited from the community using convenience sampling. The data collection period was from May 2024 to September 2024. The data were collected by the investigators, who were final-year medical students at Newcastle University Medicine Malaysia. They were guided by a supervisor who was a lecturer and an MMC-registered medical practitioner. A 30-minute Zoom session was held prior to data collection to educate the investigators on data collection methodology. No specific quality control procedures were implemented, and a total of 8 investigators were involved in data collection. The five regions above were chosen because they were the locations where the investigators were posted for their medical postings. The investigators would visit houses door-to-door in nearby neighbourhoods to source respondents. Only odd-numbered houses were visited to randomize data collection. Data collection happened between 9 am to 8 pm and included both weekdays and weekends. The target sample size was 383, calculated with Cochran's formula.

A total of 82 responses were collected face-to-face using physical questionnaires, and informed consent was taken. The target sample size was not achieved due to difficulties with sourcing appropriate respondents. This study did not involve medication review, and only patients were interviewed to evaluate medication concordance. Inclusion criteria were being aged 18 years or older, physically residing in Johor, having a diagnosed chronic condition, and being on medications for at least 1 month. Patients on only dietary control regimens and those with memory impairments were excluded; respondents were screened for memory impairment by asking whether they had any diagnosed conditions that could affect short- or long-term memory, such as Alzheimer's disease, Parkinson's disease, or space-occupying lesions of the brain. A 1-month cutoff for medication use was used as an adherence measure, consistent with adherence studies that often use a 1-month observation window.[13] Furthermore, evidence shows that medication adherence behaviour in the first 1 month strongly predicts subsequent behaviour over the next year,[14] which supports our decision to operationalize chronic illness as medication use for at least 1 month.

The primary outcome was to measure the relationship between medication concordance (measured using the Modified Concordance Scale) and medication adherence (measured using the MyMAAT), the secondary outcome is the prevalence of poor medication adherence as measured by the MyMAAT.

### Study instruments

The first part of the questionnaire collected demographic information such as age, sex, race, education level, source of medications, the diagnosed chronic disease, and number of medications. All diagnoses were self-reported by respondents, and medical records or prescriptions were not requested. The source of medications question consisted of 3 options: "public hospitals and clinics," "private hospitals and clinics," and "private pharmacies." This categorization is based on 3 main factors: the healthcare sector, access to doctors, and funding mechanisms. Public hospitals and clinics are very affordable for Malaysian citizens, which extends coverage to those with low socioeconomic status. However, patients often experience long wait times and limited consultation time due to high patient volume, which may affect a doctor's ability to involve patients in decision-making. Private hospitals and clinics are more expensive because they require out-of-pocket payments or insurance coverage, and doctors in these settings usually have adequate time for patient consultations. Some patients are also known to continue prescriptions at private pharmacies without seeing their doctors, which limits contact with doctors and reduces chances for counselling on medication adherence.

The validated Malaysia Medication Adherence Assessment Tool (MyMAAT), developed by Hatah et al.[15] used to assess medication adherence. The Cronbach's alpha value was 0.910, and the instrument consisted of 12 questions with a 5-point Likert scale from "Strongly Disagree" to "Strongly Agree". A MyMAAT score cut-off of ≥54 was used to define adherence, in line with the validation study by Hatah et al., which reported a statistically significant correlation with HbA1c levels.[15]

The Modified Concordance Scale was adapted from the Concordance Scale by Clucas et al.[6] The Concordance Scale was created with HIV-specific wording, which the researchers modified to suit chronic illnesses. The Cronbach's alpha value was 0.910 for the Concordance Scale. The Modified

**Table I: Demographic and clinical characteristics of Participants (n =82)**

| Variables | | Frequency, N (Percentage, %) |
|---|---|---|
| Gender | Male | 40 (48.8) |
| | Female | 42 (51.2) |
| Race | Chinese | 34 (41.5) |
| | Malay | 31 (37.8) |
| | Indian and other | 17 (20.7) |
| Age | Adult (18-47) | 18 (21.4) |
| | Older adult (48-67) | 42 (50.0) |
| | Senior (≥68) | 22 (26.2) |
| Source of medication* | Government Hospitals and Clinics | 58 (70.7) |
| | Private Hospitals and Clinics | 28 (34.1) |
| | Private Pharmacies | 14 (17.1) |
| Number of Types of Medications | 1-4 | 59 (72.0) |
| | >4 | 23 (28) |
| Education level | Primary school and below | 16 (19.5) |
| | Secondary school and higher | 66 (80.5) |
| Types of chronic illness** | Hypertension | 52 (63.4) |
| | Dyslipidaemia | 37 (45.1) |
| | Type 2 diabetes mellitus | 34 (41.5) |
| | Others*** | 47 (57) |

*Multiple responses allowed for source of medications question
**Many participants had more than one chronic health issue; as such, the total percentages will not add up to 100. The denominator is equal to the total sample size of 82.
***Other conditions include depression, asthma, anemia, rheumatoid arthritis, hyperthyroidism, heart failure, benign prostatic hyperplasia, ischaemic heart disease and end-stage renal failure.

**Table II: MyMAAT Scores obtained by respondents (n =82)**

| Question Number | Question | Mean±SD |
|---|---|---|
| 1 | In the past one month, I frequently failed to take my medication in accordance with the doctor's instruction. | 4.01±1.27 |
| 2 | In the past one month, I reduced my medication intake when I felt better. | 3.66±1.48 |
| 3 | In the past one month, I took my medication alternately. | 3.88±1.40 |
| 4 | I was often late on / missed the appointment date to get the supplies of my follow-up medication at the pharmacy counter. | 3.99±1.35 |
| 5 | I have excess supply of the prescribed medication at home. | 3.78±1.43 |
| 6 | I did not fully comply with the prescriptions because I felt it was unnecessary/insignificant. | 4.27±1.27 |
| 7 | In the past one month, I frequently failed to remember to take my medication. | 3.94±1.31 |
| 8 | I regularly take less medication than prescribed for fear of the side effects to my body. | 4.04±1.40 |
| 9 | I will miss/not take my medication if no one reminds me to do so. | 4.15±1.25 |
| 10 | I am uncertain about my daily medication doses. | 4.37±1.20 |
| 11 | I am unable to manage my medication intake properly. | 4.29±1.21 |
| 12 | Without support or help from the loved ones, I lack motivation to take my medication as prescribed by the doctor. | 4.22±1.24 |

Concordance Scale consists of 10 items with a 4-point Likert Scale. The options ranged from "Did not happen" to "Very good". The Modified Concordance Scale was used to measure doctor-patient concordance from the patient's perspective. No pilot testing was done prior to administering this questionnaire. Permission was obtained from the authors of both questionnaires for use in this study for the MyMAAT and Modified Concordance Scales, respectively.

### Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics software (version 29; IBM Corp., Armonk, NY). A Kolmogorov–Smirnov test was conducted to assess the normality of data, as both the Modified Concordance Scale and MyMAAT scores were non-normal. A Spearman's rank correlation was performed to determine the relationship between concordance scores and medication adherence scores. Subgroup means by sex, age, race, source of medications, number of medication types, and education level were also compared using Kruskal-Wallis tests to assess statistical differences in medication adherence. Demographic and patient characteristic factors were then included in a final logistic regression to adjust for confounding variables. Responses with missing data were excluded from the analysis, in line with a complete-case analysis.

## RESULTS

### Sociodemographic Characteristics of the Respondents.

A total of 82 responses were collected over five months. The sample distribution across the different regions is as follows: 24.4% from Iskandar Puteri, 14.6% from Kluang, 13.4% from Pontian, 26.8% from Taman Mount Austin, and 20.7% from Johor Bahru. The sample consisted of almost equal numbers

**Table III: Modified Concordance Scale Scores obtained by respondents (n = 82)**

| Question Number | Question | Mean±SD | Correlation with MyMAAT scores* |
|---|---|---|---|
| 1 | Doctor described the reason you need long-term medication. | 3.32±0.887 | 0.001** |
| 2 | Doctor clarified that there is more than one treatment option. | 2.49±1.189 | 0.018** |
| 3 | Doctor outlined all the options available. | 2.67±1.187 | 0.037** |
| 4 | Doctor provided information in a format you found useful. | 3.12±1.011 | 0.025** |
| 5 | Doctor checked your full understanding of all the issues. | 2.89±1.077 | 0.141 |
| 6 | Doctor explored your concerns, expectations and options. | 2.67±1.077 | 0.169 |
| 7 | Doctor checked the role you wanted to take in making decisions. | 2.76±1.182 | 0.020** |
| 8 | Doctor gave you time to talk to others before reaching a decision. | 2.79±1.214 | 0.250 |
| 9 | Doctor made a final decision | 3.18±0.970 | 0.973 |
| 10 | Doctor reviewed the decision after a while. | 3.23±1.010 | 0.084 |

*Correlation calculated via Spearman Rho
** Statistically significant correlation

**Table IV: Subgroup Comparison of MyMAAT Score means**

| Variables | | Mean MyMAAT Score | p-value |
|---|---|---|---|
| Gender | Male | 45.8 | 0.014* |
| | Female | 51.24 | |
| Race | Chinese | 48.09 | 0.962 |
| | Malay | 48.81 | |
| | Indian and other | 49.18 | |
| Age | Adult (18-47) | 47.28 | 0.975 |
| | Older Adult (48-67) | 48.57 | |
| | Senior (≥68) | 49.68 | |
| Source of medication | Government Hospitals and Clinics | 47.64 | 0.158 |
| | Private Hospitals and Clinics | 48.64 | 0.447 |
| | Private Pharmacies | 43.36 | 0.214 |
| Number of Types of Medications | ≤4 | 49.00 | 0.214 |
| | ≥5 | 47.52 | |
| Education Level | Primary school and below | 46.19 | 0.304 |
| | Secondary school and higher | 49.17 | |
| Types of chronic illness | Hypertension | 48.77 | 0.774 |
| | Dyslipidaemia | 50.32 | 0.436 |
| | Type 2 diabetes mellitus | 47.40 | 0.183 |
| | Others | 47.10 | 0.340 |

of male and female respondents, as shown in Table I: 51.2% female and 48.8% male. The mean age of the participants was 57.5 years.

**The MyMAAT Score**

The MyMAAT total score can range from 12 to 60. Adherence is defined as a MyMAAT score of ≥54. We can see an adherence rate of 41.5% (95% CI 31%-52%). The mean MyMAAT score is 48.59. Table II shows the mean scores by question.

**Modified Concordance Scale Scores**

The total scores can range from 10 (low concordance) to 40 (high concordance), with an average score of 29.12. 45.1% (95% CI 34%-56%) of patients achieved high concordance scores (30-40). The Modified Concordance Scale had a Cronbach Alpha of 0.852. Table III shows the mean scores by question.

**Correlation between treatment concordance and medication adherence**

Spearman's rank correlation was used to identify the correlation between medication adherence and treatment concordance. This was because the medication adherence scores, as measured via the MyMAAT, showed a left-skewed distribution, and the one-sample Kolmogorov-Smirnov test was significant ($p<0.001$). As the data were not normal, a non-parametric test was chosen. There is a statistically significant weak correlation between the MyMAAT score and the Modified Concordance Scale score ($\rho=0.286$, 95% CI 0.06584-0.4799; $p=0.009$).

Items 1, 2, 3, 4 and 7 from the Modified Concordance Scale have statistically significant correlations with MyMAAT scores. Item 1 also has the largest effect size, Rs 0.35, indicating a weak correlation.

**Impact of demographic factors on medication adherence**

There is a statistically significant difference in MyMAAT scores between males and females, as shown in Table IV. Female vs male OR was calculated via logistic regression adjusting for confounding factors, with adherence (MyMAAT≥54) as a binary factor (OR=4.23; 95% CI 1.38-12.91; $p=0.011$), the model is presented in Table V. The "Other" race category in this study includes 2 respondents of Siamese origin.

**Table V: Logistic regression of demographic factors and clinical characteristics of participants with adherence defined as MyMAAT ≥54**

| Variables | | B | S.E. | Wald | df | Sig. | Exp(B) | 95% CI for Exp(B) | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Lower | Upper |
| Age | 18-47 | 0.25 | 1.03 | 0.06 | 1 | 0.809 | 1.28 | 0.17 | 9.62 |
| | 48-67 | 0.23 | 0.71 | 0.11 | 1 | 0.743 | 1.26 | 0.31 | 5.08 |
| Race | Malay | 0.01 | 0.72 | 0.00 | 1 | 0.989 | 1.01 | 0.25 | 4.15 |
| | Chinese | 0.21 | 0.87 | 0.06 | 1 | 0.812 | 1.23 | 0.22 | 6.83 |
| Education Level | Primary and lower | 0.02 | 0.77 | 0.00 | 1 | 0.978 | 1.02 | 0.23 | 4.61 |
| Gender | Female | 1.44 | 0.57 | 6.41 | 1 | 0.011 | 4.23 | 1.38 | 12.91 |
| Medication source | Government clinics and hospitals | -0.57 | 1.25 | 0.21 | 1 | 0.646 | 0.56 | 0.05 | 6.49 |
| | Private hospitals and clinics | -0.11 | 1.26 | 0.01 | 1 | 0.933 | 0.90 | 0.08 | 10.58 |
| | Private pharmacies | -0.74 | 0.77 | 0.91 | 1 | 0.339 | 0.48 | 0.10 | 2.18 |
| Chronic medical conditions | Hypertension | -0.35 | 0.64 | 0.30 | 1 | 0.582 | 0.70 | 0.20 | 2.47 |
| | Dyslipidemia | 0.58 | 0.64 | 0.83 | 1 | 0.363 | 1.79 | 0.51 | 6.29 |
| | Type 2 diabetes mellitus | -0.27 | 0.67 | 0.16 | 1 | 0.688 | 0.77 | 0.21 | 2.82 |
| | Other medical conditions | -0.57 | 0.60 | 0.90 | 1 | 0.342 | 0.57 | 0.18 | 1.83 |
| Number of medications | 1-4 | 1.08 | 0.94 | 1.32 | 1 | 0.250 | 2.95 | 0.47 | 18.62 |
| Constant | - | -0.52 | 1.49 | 0.12 | 1 | 0.727 | 0.59 | | |

Notes:
1. Reference subcategories for the variables are as follows: Age: >67; Race: Indian and others; Education level: Secondary and higher; gender: male; medication source and chronic medical conditions: respondents who did not choose that option; number of medications: 5-8
2. Model Nagelkerke R2=0.22, Overall classification accuracy 69.5%

All other demographic factors did not have a statistically significant influence on MyMAAT scores. For the source of medications question and types of chronic illness question, respondents were allowed more than one response; as such, each subgroup was compared with respondents who did not choose that option. A number of subgroups were combined before comparison due to low numbers.

**Chronic illnesses as reported by respondents**

The top 5 chronic illnesses reported by respondents were hypertension (63.4%), dyslipidaemia (45.1%), type 2 diabetes mellitus (41.5%), asthma (7.3%) and heart failure (4.9%). 49% of respondents had 2 or more comorbidities. There is no statistically significant difference in MyMAAT scores between those with and without multiple comorbidities.

## DISCUSSION

We have found that there is a statistically significant weak correlation between medication concordance as measured by the Modified Concordance Scale and medication adherence as measured by the MyMAAT scale (ρ=0.286, p=0.009). This is in line with a 2002 qualitative study that used a concordance-based consultation model to improve clinical outcomes in non-adherent patients, which showed improvement in 14 of the 22 study participants.16 However, the weak correlation points to limited clinical predictive value and must be interpreted with caution. A 2023 Systematic review on the impact of shared decision-making on medication adherence found no significant effect of shared decision-making interventions on adherence among patients with chronic illness. This systematic review included 2 studies, both of which used decision aids as an intervention to improve shared decision-making; however, the studies reported high medication adherence even before the intervention, which may explain the lack of a significant effect.[17] Another 2020 retrospective study[18] also found no significant effect of shared decision-making on medication adherence; this may be due to cultural differences, as the study was conducted in the USA. Furthermore, adherence was measured using the Medication Possession Ratio, calculated as the ratio of total days of medication supplied to the number of days in a specified time interval. This is a more objective measure of adherence compared to the MyMAAT questionnaire, which relies on patient self-reporting. While these studies focused on shared decision-making, medication concordance is a component of shared decision-making, and they remain a useful comparison for our findings.

Our analysis showed that Item 1 of the Modified Concordance Scale, "Doctor described the reason you need long-term medication," had the strongest correlation with MyMAAT scores among the items, with a p-value of 0.01. This demonstrates that when patients understand the rationale behind their prescriptions, adherence rates improve. This may provide evidence for the use of face-to-face health education and information flyers to improve adherence, in line with a 2025 review that identified studies with statistically significant outcomes for both interventions.[19] This is in contrast to technology-assisted methods to improve adherence, as was investigated by Pratiwi et al.[20] in their systematic review; these technology-assisted methods focus on improving memory and compensating for disabilities in the patient, which may impair adherence, in contrast to concordance, which is more concerned with understanding, cooperation, and partnership.

Furthermore, an adherence rate of 41.5% was reported (defined as a MyMAAT score of ≥54).[7,15] This is on the lower end of previous findings, which reported 65.8% (a meta-analysis of 12 studies in 2022 focusing on patients with Type 2 diabetes mellitus) [7], 49% (focusing on older adults in Pahang in 2024),[21] 60.3 (conducted in a Health Clinic in Pagoh, Johor in 2023).[22] This may be due to the smaller sample size in this study. Furthermore, this study was focused only on populations within Johor. This may indicate a lower regional prevalence of medication adherence. Moreover, this

study was conducted in a community setting with door-to-door visits, which may have allowed us to capture patients who had defaulted on their clinic follow-ups, in contrast to most existing studies, which were conducted in clinical settings.

Additionally, we found that sex had a statistically significant impact on medication adherence, with females 4.23 times more likely to be adherent than males. This contrasts with previous studies, which generally showed a lack of relationship between sex and medication adherence.[23-25] It is important to interpret this finding in context, as the study's small sample size reduces precision. Therefore, this finding is of limited clinical value. However, a 2021 study by Chang et al. in Taiwan shows that females have a higher rate of medication adherence.[26] They also note the conflicting past evidence when it comes to the relationship between sex and medication adherence.

The main implication for practice from this paper is the importance of achieving concordance with patients when prescribing medications to improve medication adherence. For example, in this study, based on the responses to the Modified Concordance Scale, 52.4% of respondents chose "Did not happen" or "Not very good" for the statement "Doctor clarified that there is more than one treatment option.", and 45.1% chose similarly for the statement "Doctor explored your concerns, expectations and options.". This shows that a significant number of patients feel that doctors are not fully explaining the available treatment options. Furthermore, patients perceive a lack of exploration of their concerns and expectations, which is crucial to patient-centered care. We therefore need to ensure adequate explanation and promotion of patient choice in treatment decisions to improve patient outcomes.

## LIMITATIONS

The most significant limitation of this study is the small sample size of 82 respondents. This means that the study is underpowered and that there is an important limitation on its precision. There is also limited ability to accurately represent the Johor population, as our sampling methodology is convenience sampling rather than random. This was primarily due to the difficulty of sourcing respondents in the community. This study should be expanded to cover more respondents from different areas across Johor to improve representability and should be conducted in primary healthcare settings as a longitudinal analysis to further explore the observed findings.

Secondly, this study used patient-reported measures of concordance and medication adherence, which are likely subject to both recall bias leading to inaccurate reporting and social desirability bias which could skew results and inflate the adherence estimates. As the chronic illness diagnoses were also self-reported there is a further risk of misclassification bias. It would be fruitful to repeat this study with perspectives on medication concordance from physicians and independent observers.

Thirdly, medication concordance is built along with the doctor-patient relationship; as such, it is suboptimal to measure it based on a single consultation; a study with a longer time frame and follow-ups will be better able to capture this. More research can also be done on the relationship between gender and medication adherence in the local context.

Fourthly, the study uses a convenience sampling method, which may introduce selection bias. Participants who are willing to respond may be better informed about the underlying medical conditions and, consequently, have better medication adherence.

Fifthly, the Modified Concordance scale was adapted from the original study, where it was used in the context of HIV patients; it did not undergo pilot testing or validation prior to use in the chronic disease population, which serves as a limitation as to the reliability of this instrument.

## STRENGTHS

This study has 3 primary strengths: firstly, with current clinical practice moving towards shared decision-making and medication concordance, it is both timely and relevant to address this topic. Secondly, this study helps fill a critical gap in the literature by providing quantitative evidence in the Malaysian context. Thirdly, this study has generated useful hypotheses for further exploration in larger-scale studies.

## CONCLUSION

In conclusion, our study found that the rate of medication adherence across 5 suburban communities in Johor is approximately 41.5%. There is also a weak and statistically significant relationship between medication concordance and medication adherence. Furthermore, our study points to a statistically significant relationship between female sex and medication adherence, which should be interpreted with caution. This finding may have implications for clinical practice by highlighting the need for practitioners to include additional interventions for male patients in routine care to improve medication adherence. Future research on this topic can be enhanced by including larger sample sizes and by utilizing more objective measures of medication adherence, especially via the utilisation of electronic monitoring devices. Physician responses can also be solicited when measuring medication concordance.

## ACKNOWLEDGEMENTS

Firstly, we are grateful to Newcastle University Medicine Malaysia (NUMed) for granting permission to conduct this study and for providing funding support for publication. The NUMed RMC project number for this study is RMC_NUIR_2024_12. We would like to acknowledge the help of Ms. Karen Ang in translating the Modified Concordance Scale. We would also like to thank Dr. Ernieda Hatah from Universiti Kebangsaan Malaysia for providing permission to use the Malaysia Medication Adherence Assessment Tool.(15) Further, we would like to extend our gratitude to Dr. Claudine Clucas from Evidera, United Kingdom, for permission to use the Concordance Scale. (6)

## CONFLICT OF INTEREST
None.

## FUNDING
None.

## ETHICAL APPROVAL
Ethical approval was obtained from the Newcastle University Ethics Committee (Ref: 43616/2023) prior to the data collection.

## REFERENCES
1. Sabaté E. Adherence to long-term therapies: evidence for action. Geneva: World Health Organization; 2003. p. 198.
2. Hassali MA, Supian A, Ibrahim MI, Al-Qazaz HK, Al-Haddad M, Saleem F, et al. The Characteristics of Drug Wastage at the Hospital, Tuanku Jaafar Seremban, Malaysia: A Descriptive Study. J Clin Diagn Res 2012; 6(5): 787-90.
3. Donnan PT, MacDonald TM, Morris AD. Adherence to prescribed oral hypoglycaemic medication in a population of patients with Type 2 diabetes: a retrospective cohort study. Diabet Med 2002; 19(4): 279-84.
4. European Patients' Forum. Adherence and concordance: EPF position paper. Belgium: European Patients' Forum; 2015.
5. Ikeda Y, Sasaki T, Kuwahata S, Imamura M, Tanoue K, Komaki S, et al. Questionnaire Survey From the Viewpoint of Concordance in Patient and Physician Satisfaction Concerning Hypertensive Treatment in Elderly Patients - Patients Voice Study. Circ J 2018; 82(4): 1051-61.
6. Clucas C, Harding R, Lampe FC, Anderson J, Date HL, Johnson M, et al. Doctor-patient concordance in HIV treatment-switching decision-making. HIV Med 2011; 12(2): 87-96.
7. Teng CL, Chang WC, Wong PS. Medication Adherence of Persons with Type 2 Diabetes in Malaysia: A Scoping Review and Meta-Analysis. J ASEAN Fed Endocr Soc 2022; 37(1): 75-82.
8. Neoh CF, Long CM, Lim SM, Ramasamy K, Shahar S, Majeed ABA. Medication use and adherence among multi-ethnic community-dwelling older adults in Malaysia. Geriatr Gerontol Int 2017; 17(8): 1214-20.
9. Ramli A, Ahmad NS, Paraidathathu T. Medication adherence among hypertensive patients of primary health clinics in Malaysia. Patient Prefer Adherence 2012; 6: 613-22.
10. Aziz H, Hatah E, Makmor-Bakry M, Islahudin F, Ahmad Hamdi N, Mok Pok Wan I. A comparison of medication adherence between subsidized and self-paying patients in Malaysia. Malays Fam Physician 2018; 13(2): 2-9.
11. Ng YK, Shah NM, Loong LS, Pee LT, Hidzir SAM, Chong WW. Attitudes toward concordance and self-efficacy in decision making: a cross-sectional study on pharmacist-patient consultations. Patient Prefer Adherence 2018; 12: 615-24.
12. Abdullah NF, Khuan L, Theng CA, Sowtali SN. Prevalence and reasons influenced medication non-adherence among diabetes patients: A mixed-method study. J Diabetes Metab Disord 2022; 21(2): 1669-78.
13. Coleman CI, Limone B, Sobieraj DM, Lee S, Roberts MS, Kaur R, et al. Dosing Frequency and Medication Adherence in Chronic Disease. J Manag Care Pharm 2012; 18(7): 527-39.
14. Lauffenburger JC, Franklin JM, Krumme AA, Shrank WH, Matlin OS, Spettell CM, et al. Predicting Adherence to Chronic Disease Medications in Patients with Long-term Initial Medication Fills Using Indicators of Clinical Events and Health Behaviors. J Manag Care Spec Pharm 2018; 24(5): 469-77.
15. Hatah E, Rahim N, Makmor-Bakry M, Mohamed Shah N, Mohamad N, Ahmad M, et al. Development and validation of Malaysia Medication Adherence Assessment Tool (MyMAAT) for diabetic patients. PloS One 2020; 15(11): e0241909.
16. Dowell J, Jones A, Snadden D. Exploring medication use to seek concordance with "non-adherent" patients: a qualitative study. Br J Gen Pract 2002; 52(474): 24-32.
17. Salakay ENH, Mahu GFPH, Rahayu AS. Assessing the Effectiveness of Shared Decision-Making in Enhancing Medication Adherence among Chronic Disease Patients in Primary Healthcare - A Systematic Literature Review. Rev Prim Care Pract Educ 2024; 6(2): 54-9.
18. Milky G, Thomas J 3rd. Shared decision making, satisfaction with care and medication adherence among patients with diabetes. Patient Educ Couns 2020; 103(3): 661-9.
19. Wang M, Lee K, Thew HZ, Sowtali SN, Jiang Q, Cao Y, et al. Medication Adherence Interventions Among People Living with Diabetes: A Systematic Review. Patient Prefer Adherence 2025; 19: 3095-112.
20. Pratiwi H, Kristina SA, Widayanti AW, Prabandari YS, Kusuma IY. A Systematic Review of Compensation and Technology-Mediated Strategies to Maintain Older Adults' Medication Adherence. Int J Environ Res Public Health 2023; 20(1): 803.
21. Al Haqimy Mohammad Yunus MA, Akkawi ME, Fata Nahas AR. Investigating the association between medication regimen complexity, medication adherence and treatment satisfaction among Malaysian older adult patients: a cross-sectional study. BMC Geriatr 2024; 24(1): 447.
22. Chin SS, Lau SW, Lim PL, Wong CM, Ujang N. Medication adherence, its associated factors and implication on glycaemic control in patients with type 2 diabetes mellitus: A cross-sectional study in a Malaysian primary care clinic. Malays Fam Physician 2023; 18: 14.
23. Ahmad NS, Ramli A, Islahudin F, Paraidathathu T. Medication adherence in patients with type 2 diabetes mellitus treated at primary health clinics in Malaysia. Patient Prefer Adherence 2013; 7: 525-30.
24. Krass I, Schieback P, Dhippayom T. Adherence to diabetes medication: a systematic review. Diabet Med 2015; 32(6): 725-37.
25. Chew BH, Hassan NH, Sherina MS. Determinants of medication adherence among adults with type 2 diabetes mellitus in three Malaysian public health clinics: a cross-sectional study. Patient Prefer Adherence 2015; 9: 639-48.
26. Chang SM, Lu IC, Chen YC, Hsuan CF, Lin YJ, Chuang HY. Behavioral Factors Associated with Medication Nonadherence in Patients with Hypertension. Int J Environ Res Public Health 2021; 18(18): 9614.

# Contributing factors for episiotomy in primiparous women in a tertiary hospital in Perak, Malaysia

**Aruku Naidu Apana, FRCOG[1], Soe Lwin, M. Med Sc (O&G)[1], Harpreet Kaur Harbans Singh, MBBS[2], Hafizzuddin Mohamad[1], Misha Mustafa[1], Massuri Anusar[1], Dini Hamid[1], Huzair Shaharani[1]**

[1]Faculty of Medicine, Universiti Kuala Lumpur - Royal College of Medicine Perak, Malaysia. [2]Clinical Research Centre, Hospital Raja Permaisuri Bainun, Ipoh, Perak, Malaysia

## ABSTRACT

**Introduction: Episiotomy is a surgical incision of the perineum performed during vaginal delivery. Although previously routine, current evidence supports a selective approach due to associated maternal morbidity. Despite this, episiotomy remains common among primiparous women. This study aimed to determine the prevalence and contributing factors for episiotomy among primiparous women in a tertiary hospital in Perak, Malaysia.**

**Materials and Methods: A cross-sectional study was conducted using secondary data from the obstetric delivery registry of Hospital Raja Permaisuri Bainun, Ipoh. Records of primiparous women who underwent vaginal delivery with episiotomy between 1 January and 31 December 2024 were reviewed. Maternal demographics and clinical indications were analysed. Associations between demographic variables and type of episiotomy were assessed using chi-square tests.**

**Results: Of 346 eligible cases, 311 were analysed. Routine episiotomy accounted for 76.5% of cases, while 23.5% were selective. The most common indications for selective episiotomy were cord around the neck (45.2%) and preterm delivery (39.7%). No significant association was found between type of episiotomy and maternal age (p=0.378) or ethnicity (p=0.981).**

**Conclusion: Routine episiotomy remains the predominant practice among primiparous women in this tertiary Malaysian hospital. These findings highlight the need for institutional review and adherence to evidence-based selective episiotomy guidelines.**

**KEYWORDS:**
*Episiotomy; primiparous; tertiary hospital; obstetric practice; Malaysia*

## INTRODUCTION

Episiotomy is a surgical incision of the perineum performed during vaginal delivery to enlarge the vaginal opening and facilitate childbirth.[1] Historically, routine episiotomy was widely practiced with the intention of preventing severe perineal trauma, preserving pelvic floor function and improving neonatal outcomes. However, accumulating evidence has shown that routine episiotomy may increase maternal morbidity, including pain, haemorrhage, infection and obstetric anal sphincter injury, without providing substantial benefits to either the mother or the neonate.[2] Selective mediolateral episiotomy has been reported to reduce the risk of severe perineal trauma in selected cases, particularly during operative vaginal delivery.[3-4]

Current international guidelines advocate restrictive rather than routine use of episiotomy. The World Health Organization (WHO) recommends selective episiotomy as part of evidence-based intrapartum care for a positive childbirth experience.[5] Similarly, the International Federation of Gynecology and Obstetrics (FIGO) supports restrictive use of episiotomy and discourages routine practice.[6] Studies conducted in different countries have demonstrated considerable variation in episiotomy rates, reflecting differences in clinical practice, training and institutional policies.[7-8] Several maternal and obstetric factors, including younger maternal age, primiparity, prolonged labour and increased fetal birth weight, have been associated with a higher likelihood of episiotomy.[9-12]

Despite international recommendations favouring selective episiotomy, the procedure continues to be commonly performed in many settings. In Malaysia, studies have reported variations in episiotomy practice among tertiary hospitals and suggested that selective mediolateral episiotomy may offer protection against spontaneous perineal trauma and obstetric anal sphincter injury.[13] Nevertheless, local evidence regarding factors associated with episiotomy practice among primiparous women remains limited. Furthermore, differences in patient characteristics and institutional practices may contribute to variations in episiotomy rates and clinical outcomes.

Therefore, this study was undertaken to determine the prevalence of episiotomy and to identify maternal and clinical factors associated with its use among primiparous women in a Malaysian tertiary hospital. The findings of this study may provide valuable information to support evidence-based obstetric practice and contribute to strategies aimed at reducing unnecessary episiotomy and its associated maternal morbidity.

## MATERIALS AND METHODS

### Study Design and Setting

This cross-sectional study utilised secondary data from the obstetric delivery registry of Hospital Raja Permaisuri Bainun,

*This article was accepted: 03 June 2026*
*Corresponding Author: Associate Professor Dato' Dr Aruku Naidu Apana*
*Email: aruku1964@gmail.com*

**Table I: Maternal demographic characteristics of primiparous women who underwent episiotomy (n = 311)**

| Variable | Routine episiotomy n (%) | Selective episiotomy n (%) | Total n (%) |
|---|---|---|---|
| Age group (years) | | | |
| 18–25 | 71 (29.8) | 18 (24.7) | 89 (28.6) |
| 26–35 | 122 (51.4) | 38 (52.1) | 160 (51.4) |
| 36–45 | 8 (3.4) | 2 (2.7) | 10 (3.2) |
| Ethnicity | | | |
| Malay | 156 (65.5) | 48 (65.8) | 204 (65.6) |
| Chinese | 21 (8.8) | 6 (8.2) | 27 (8.7) |
| ndian | 18 (7.6) | 5 (6.8) | 23 (7.4) |
| Orang Asli | 15 (6.3) | 4 (5.5) | 19 (6.1) |
| Others | 28 (11.8) | 10 (13.7) | 38 (12.2) |

Data are presented as number (percentage).

**Table II: Association between maternal demographics and type of episiotomy**

| Variable | $\chi^2$ | p-value |
|---|---|---|
| Age group | – | 0.378 |
| Ethnicity | – | 0.981 |

$p < 0.05$ considered statistically significant.

**Table III: Indications for selective episiotomy among primiparous women (n = 73)**

| Indication | n (%) |
|---|---|
| Cord around the neck | 33 (45.2) |
| Preterm labour | 29 (39.7) |
| Prolonged labour | 5 (6.8) |
| Instrumental delivery | 2 (2.7) |
| Fetal distress | 1 (1.4) |
| Large fetal size | 1 (1.4) |
| Shoulder dystocia | 1 (1.4) |
| Others | 1 (1.4) |

Ipoh, a tertiary referral hospital in Perak, Malaysia, for the period 1 January to 31 December 2024.

### Study Population
Primiparous women who delivered vaginally and underwent episiotomy during the study period were included. Multiparous women and those delivered by caesarean section were excluded.

### Sample Size and Sampling
Based on a finite population of 3,385 primiparous vaginal deliveries, a minimum sample size of 346 was calculated using OpenEpi (95% confidence level, 5% margin of error). Simple random sampling was applied. After exclusion of incomplete records, 311 cases were analysed.

### Data Collection
Extracted variables included maternal age, ethnicity, gestational age, labour characteristics, and indications for episiotomy. Episiotomy was classified as routine or selective based on documented clinical indications. A random 10% of records was rechecked for data accuracy.

### Statistical Analysis
Data were analysed using SPSS version 29. Descriptive statistics were presented as frequencies and percentages. Associations between maternal demographics and type of episiotomy were analysed using Pearson's chi-square or Fisher's exact test. A p-value <0.05 was considered statistically significant.

### Ethical Approval
Ethical approval was obtained from the Ethical Committee of the Faculty of Medicine, Universiti Kuala Lumpur – Royal College of Medicine Perak. Permission to access medical records was obtained from the Clinical Research Centre and hospital administration. Patient confidentiality was maintained.

## RESULTS
### Prevalence of Episiotomy Practice
Among the 311 primiparous women analysed, 238 (76.5%) underwent routine episiotomy, while 73 (23.5%) underwent selective episiotomy. [Table I]

### Maternal Demographics
Most women were aged 26–35 years. Malay women constituted the majority (65.6%). Routine episiotomy predominated across all age groups and ethnicities. [Table 1]
Association Between Demographics and Type of Episiotomy
No statistically significant association was observed between maternal age group and type of episiotomy ($p = 0.378$), nor between ethnicity and type of episiotomy ($p = 0.981$). [Table II]

### Indications for Selective Episiotomy
Among selective episiotomy cases, the most common indications were cord around the neck (45.2%) and preterm labour (39.7%). Other indications were infrequent. [Table III]

## DISCUSSION

This study demonstrated that routine episiotomy remains highly prevalent among primiparous women in a Malaysian tertiary hospital despite current recommendations favouring selective use. Maternal age and ethnicity were not significantly associated with episiotomy practice, suggesting that clinical decision-making may be influenced more by institutional practice patterns and healthcare providers' preferences than by maternal demographic characteristics. Variations in episiotomy rates across different settings have been reported previously, reflecting differences in clinical protocols, training and obstetric practices.[7-8]

The high prevalence of routine episiotomy observed in the present study is inconsistent with current evidence and international recommendations advocating restrictive use. The World Health Organization and the International Federation of Gynecology and Obstetrics recommend selective rather than routine episiotomy because routine use has been associated with increased maternal morbidity without significant neonatal benefit.[5-6] Similarly, population-based studies and systematic reviews have demonstrated that changes in clinical practice and adherence to evidence-based guidelines are important determinants of declining episiotomy rates.[7-8]

The common indications for selective episiotomy in this study included cord around the neck and preterm delivery, reflecting clinicians' concerns regarding expedited delivery and prevention of fetal compromise. However, previous studies have shown that routine episiotomy does not necessarily improve neonatal outcomes and should be reserved for specific obstetric indications.[2,14] These findings further support the recommendations advocating restrictive episiotomy practice.[5-6]

The absence of a significant association between episiotomy type and maternal age or ethnicity suggests that episiotomy practice may be largely provider-driven rather than individualised according to patient characteristics. Similar observations have been reported in studies from Africa, where clinicians' experience, training and institutional protocols were found to influence episiotomy rates.[11,15] Strengthening adherence to evidence-based guidelines and promoting selective episiotomy based on objective clinical indications may therefore help minimise unnecessary maternal morbidity. Furthermore, mediolateral episiotomy has been shown to reduce the risk of obstetric anal sphincter injury, particularly during operative vaginal delivery, supporting its selective use when clinically indicated.[3-4]

Although maternal age was not significantly associated with episiotomy practice in the present study, previous studies have reported higher episiotomy rates among younger primigravid women, possibly because of reduced perineal compliance and concerns regarding severe spontaneous perineal tears.[12] Ethnicity was also not found to be a significant determinant in this study. Nevertheless, variations in obstetric practice and differences in maternal characteristics may contribute to differences in episiotomy rates among diverse populations. Local evidence from Malaysian tertiary hospitals has suggested that selective mediolateral episiotomy may provide protection against spontaneous perineal trauma and obstetric anal sphincter injury.[13]

Clinical factors such as increased fetal size and prolonged labour were associated with episiotomy use, findings that are consistent with previous reports.[9-10,15] Increased fetal size may impose greater mechanical stress on the maternal perineum, whereas prolonged labour may prompt clinicians to perform episiotomy to facilitate delivery and reduce the risk of fetal compromise.[16] These observations highlight the continuing role of clinical judgement in obstetric decision-making and reinforce the importance of adopting a selective and evidence-based approach to episiotomy practice.

Overall, the findings of this study highlight the need for continued reinforcement of evidence-based guidelines, regular professional education and clinical audit mechanisms to reduce unnecessary episiotomy and its associated maternal morbidity. Greater emphasis on restrictive rather than routine episiotomy practice may improve maternal outcomes and align local obstetric practice with current international recommendations.[5,6,8] Further multicentre studies are warranted to evaluate contemporary episiotomy practices in Malaysia and to identify strategies that may facilitate greater adherence to evidence-based recommendations.

## LIMITATIONS

The retrospective design and reliance on secondary data limited assessment of certain clinical variables. As a single-centre study, generalisability is limited. Multi-centre prospective studies are recommended.

## CONCLUSION

Routine episiotomy remains the predominant practice among primiparous women in this tertiary hospital. No association was found between episiotomy practice and maternal age or ethnicity. Institutional review and adherence to selective episiotomy guidelines are warranted.

## ACKNOWLEDGEMENTS

The authors thank the Research Unit of Universiti Kuala Lumpur – Royal College of Medicine Perak and the Department of Obstetrics and Gynaecology, Hospital Raja Permaisuri Bainun, for their support.

## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

## REFERENCES

1. Kalis V, Laine K, De Leeuw JW, Ismail KM, Tincello DG. Classification of episiotomy: towards a standardisation of terminology. BJOG: an international journal of obstetrics & gynaecology. 2012; 119(5): 522-6.
2. Jiang H, Qian X, Carroli G, Garner P. Selective versus routine use of episiotomy for vaginal birth. Cochrane Database of Systematic Reviews. 2017(2).

3. De Leeuw JW, De Wit C, Kuijken JP, Bruinse HW. Mediolateral episiotomy reduces the risk for anal sphincter injury during operative vaginal delivery. BJOG: An International Journal of Obstetrics & Gynaecology 2008; 115(1): 104-8.
4. Revicky V, Nirmal D, Mukhopadhyay S, Morris EP, Nieto JJ. Could a mediolateral episiotomy prevent obstetric anal sphincter injury? European Journal of Obstetrics & Gynecology and Reproductive Biology 2010; 150(2): 142-6.
5. World Health Organization. WHO recommendations on intrapartum care for a positive childbirth experience. Geneva: WHO; 2018.
6. Nassar AH, Visser GH, Ayres-de-Campos D, Rane AJ, Gupta S, Barnea ER, de Bernis L, et al. FIGO Statement: Restrictive use rather than routine use of episiotomy.
7. Goueslard K, Cottenet J, Roussot A, Clesse C, Sagot P, Quantin C. How did episiotomy rates change from 2007 to 2014? Population-based study in France. BMC pregnancy and childbirth 2018; 18(1): 208.
8. Hussein SA, Dahlen H, Schmied V. What makes episiotomy rates change? a systematic review of the literature. Int J Childbirth 2012; 2(1): 29-39.
9. Beyene F, Nigussie AA, Limenih SK, Tesfu AA, Wudineh KG. Factors associated with episiotomy practices in Ethiopia. Risk Manag Healthc Policy 2020; 13: 2281-9.
10. Bekele H, Tamiru D, Debella A, Getachew A, Yohannes E, Lami M, et al. Magnitude of episiotomy practice and associated factors among women who gave birth at Hiwot Fana Specialized University Hospital, Eastern Ethiopia. Frontiers in global women's health 2022; 3: 911449.
11. Woldegeorgis BZ, Obsa MS, Tolu LB, Bogino EA, Boda TI, Alemu HB. Episiotomy practice and its associated factors in Africa: A systematic review and meta-analysis. Frontiers in Medicine 2022; 9: 905174.
12. Saeid MS, Muhammad AK, Mohamed NR. A Study of necessity of episiotomy in primigravida. Journal of Zankoy Sulaimani-Part A 2014; 16(4): 75-81.
13. Karalasingam SD, Jeganathan R, Jegasothy R, Soelar SA, Reidpath D. Is Selective Mediolateral Episiotomy Protective Against Spontaneous Perineal Trauma and OASIS in Malaysian Tertiary hospitals? A Cross-Sectional Study from the National Obstetrics Registry.
14. Amani N, Tajuddin NA, Suhaimi J, Ramdzan SN, Abd Malek K, Ismail IA, et al. Why women chose unassisted home birth in Malaysia: A qualitative study.
15. Bekele H, Tamiru D, Debella A, Getachew A, Yohannes E, Lami M, et al. Magnitude of episiotomy practice and associated factors among women who gave birth at Hiwot Fana Specialized University Hospital, Eastern Ethiopia. Frontiers in global women's health 2022; 3: 911449.
16. Djusad S, Permatasari II, Futihandayani A, Shahnaz P, Hadiwinata D, Herianti HF. Analysis of episiotomy incidence and risk factors in vaginal deliveries: a single center. AJOG Global Reports 2024; 4(3): 100371.

# Clinical presentation of aspergillus and candida in otomycosis: A cross-sectional study at a tertiary hospital in Central Java, Indonesia

**Anton Budhi Darmawan, PhD[1], Nia Krisniawati, MD[2], Bella Jovita Darmayan, MD[1]**

[1]Department of Otorhinolaryngology, Head and Neck Surgery, Faculty of Medicine Universitas Jenderal Soedirman-Margono Soekarjo Hospital, Purwokerto, Indonesia, [2]Department of Microbiology, Faculty of Medicine Universitas Jenderal Soedirman, Purwokerto, Indonesia

## ABSTRACT

**Introduction: Otomycosis is a common fungal infection of the external auditory canal, particularly in tropical regions. *Aspergillus* and *Candida* are the main causative agents, yet their clinical differentiation remains challenging due to overlapping manifestations. This study aimed to identify the distribution of fungal etiologies, and to compare clinical manifestations and predisposing factors between *Aspergillus* and *Candida* infections in a tertiary hospital in Central Java, Indonesia.**

**Materials and Methods: A cross-sectional study was conducted at a tertiary hospital, including patients aged 17 years and above with clinically and microbiologically confirmed otomycosis. Demographic data, symptoms, physical findings, and predisposing factors were collected. Fungal identification was performed using culture and microscopy. Comparative analyses were conducted using chi-square or Fisher's exact test.**

**Results: A total of 41 patients (56 fungal isolates) were included. Aspergillus spp. accounted for 58.9% of isolates, while Candida spp. comprised 41.1%, with mixed infections observed in 16.1%. Itching, hearing loss, and ear fullness were the most common symptoms in both groups. No statistically significant differences were found in clinical manifestations or physical examination findings between *Aspergillus* and *Candida* infections (all p>0.05). Although whitish debris was more frequent in *Candida* and brownish debris in *Aspergillus*, these patterns were not discriminatory. Ear drop use and cotton bud manipulation were significantly associated with Aspergillus infections (p<0.05).**

**Conclusion: Substantial clinical overlap exists between *Aspergillus* and *Candida* otomycosis, underscoring the importance of microbiological confirmation for accurate diagnosis.**

**KEYWORDS:**
*Aspergillus; candida; external ear canal; otomycosis*

## INTRODUCTION

Otomycosis is a fungal infection of the external auditory canal (EAC) and tympanic membrane that may present in acute, subacute, or chronic forms.[1-2] It accounts for approximately 9 - 30% of EAC infection.[2] The incidence is higher in tropical and subtropical with humid climate regions.[3-4] Although generally not life-threatening, the condition is often characterized by recurrence and may require prolonged management.[5]

The most common causative agents of otomycosis are *Aspergillus* and *Candida*.[2,4] Accurate identification of the underlying fungal etiology is clinically important. Several studies have reported reduced sensitivity to commonly used antifungal agents.[6] Early recognition of potential differences in clinical presentation may help guide more appropriate empirical therapy while awaiting microbiological confirmation.[2]

However, differentiating between *Aspergillus* and *Candida* infections based solely on clinical manifestations and predisposing factors remains challenging due to their non-specific and overlapping features. In addition, comparative data evaluating these differences are limited.[2,4,7] Regional data from Indonesia, particularly from tertiary healthcare settings, are also scarce. Therefore, this study aimed to identify the distribution of fungal etiologies in otomycosis and to evaluate differences in clinical characteristics and predisposing factors between infections caused by *Aspergillus* and *Candida* in a tertiary hospital in Central Java, Indonesia.

## MATERIALS AND METHODS

### Study Design, Participants, and Data Collection

This cross-sectional study was conducted at the otorhinolaryngology clinic of Margono Soekarjo General Hospital from April to September 2022. This hospital is a tertiary referral center in Central Java, Indonesia. Patients were included if they were aged 17 years and above, clinically diagnosed with otomycosis based on typical otoendoscopic findings by an otorhinolaryngologist, had fungal elements confirmed through microbiological examination, and had complete clinical and demographic data available. Patients who had received antifungal treatment prior to sampling, had contaminated specimens, or had fungal isolates other than *Aspergillus* spp. or *Candida* spp. were excluded. Data on demographic characteristics, clinical manifestations, and predisposing factors were obtained through structured patient interviews and review of medical records.

*This article was accepted: 11 April 2026*
*Corresponding Author: Associate Professor Dato' Dr Aruku Naidu Apana*
*Email: aruku1964@gmail.com*

### Specimen Collection and Microbiological Examination

Ear swab specimens were obtained from patients who had been clinically diagnosed with otomycosis based on otoendoscopic examination by an otorhinolaryngologist. Following diagnosis, samples were collected from the EAC using sterile flocked swabs and transported in Amies medium to the microbiology laboratory.

All specimens were cultured on appropriate fungal media and incubated under standard conditions. Identification of fungal isolates was performed based on macroscopic colony characteristics and microscopic morphology. Direct microscopic examination was also conducted using Gram staining and 10% KOH preparation to support identification.[8]

### Statistical Analysis

Data were analyzed using IBM SPSS version 25. Descriptive analysis was used to present the distribution of variables. Comparative analysis between *Aspergillus* and *Candida* groups was performed using the chi-square test or Fisher's exact test, as appropriate, with statistical significance defined as $p < 0.05$.

## RESULTS

### Study Population and General Characteristics

A total of 41 patients were included in this study, of whom 6 presented with bilateral involvement. Due to the presence of mixed fungal infections, an additional nine isolates were identified, resulting in a total of 56 fungal isolates (Table I). All subsequent analyses were conducted on an isolate basis.

The age of the subjects ranged from 11 to 80 years, with the highest proportion of isolates observed in the 31–40-year age group (28.6%). The mean age was 38.9 years, with a median age of 36 years. Of the 56 isolates, 51.8% (29/56) were obtained from female patients, while 48.2% (27/56) were from male patients.

The age distribution differed descriptively between fungal groups. The highest proportion of Aspergillus isolates was observed in the 31–40-year age group (27.3%), while Candida isolates were most frequently identified in the 21–30-year age group (34.0%). Regarding gender distribution, *Candida* isolates were more commonly obtained from female patients (60.9%), whereas *Aspergillus* isolates were more frequently identified in male patients (54.5%). However, these differences were not statistically significant for either age group (p=0.364) or gender (p=0.388) (Table II).

### Distribution of Fungal Isolates

The distribution of fungal isolates is presented in Table I. *Aspergillus* spp. constituted the majority of isolates (58.9%, 33/56), while *Candida* spp. accounted for 41.1% (23/56). Mixed infections were identified in 16.1% (9/56) of isolates, comprising combinations of *Candida-Candida*, *Aspergillus-Aspergillus*, and *Aspergillus-Candida*. The most frequently observed mixed species combinations were *C. parapsilosis* with *C. tropicalis* and *A. flavus* with *C. parapsilosis*, each identified in two samples.

Within the *Aspergillus* group, *A. flavus* was the predominant species (48.5%, 16/33), followed by *A. niger* (27.3%, 9/33) and *A. fumigatus* (9.1%, 3/33). Other *Aspergillus* species accounted for a small proportion of isolates (3.0%, 1/33).

Within the Candida group, *C. parapsilosis* was the most frequently identified species (39.1%, 9/23), followed by *C. tropicalis* (26.1%, 6/23) and *C. krusei* (13.0%, 3/23). Less common species included *C. kefyr* (8.7%, 2/23) and other Candida species (4.3%, 1/23).

### Comparison of Clinical Manifestations

The distribution of clinical manifestations according to fungal group is presented in Table III. Overall, itching was the most frequently reported symptom in both groups, observed in 78.8% of *Aspergillus* and 87.0% of *Candida* isolates. Hearing loss was reported in 78.8% of *Aspergillus* cases and 82.6% of *Candida* cases. A sensation of ear fullness was noted in 72.7% of *Aspergillus* and 73.9% of *Candida* infections.

Ear discharge was reported in 54.5% of *Aspergillus* and 65.2% of *Candida* cases, while otalgia occurred in 48.5% and 56.5%, respectively. Tinnitus and headache were more frequently observed in the *Aspergillus* group (54.5% and 43.2%) compared to the *Candida* group (39.1% and 39.1%, respectively). Vertigo was uncommon in both groups.

None of the clinical manifestations showed a statistically significant difference between *Aspergillus* and *Candida* infections (all p-values >0.05). Despite this, several symptoms were numerically more frequent in the *Candida* group, suggesting a tendency toward more pronounced clinical manifestations, although these differences were not statistically significant (Table III).

### Comparison of Physical Examination Findings

The comparison of otoendoscopic findings between fungal groups is presented in Table III. Fungal debris was identified in all cases (100%). The predominant appearance in both groups was whitish debris, observed in 57.6% of *Aspergillus* and 70.0% of *Candida* infections. Brownish debris was the second most common morphology, found in 30.3% of *Aspergillus* and 13.0% of *Candida* cases. Mixed appearances, including whitish debris with brown or black spores, were less frequently observed.

Ear discharge was present in 54.5% of *Aspergillus* and 65.2% of *Candida* infections. Tympanic membrane perforation was observed in 57.6% of *Aspergillus* and 56.5% of *Candida* cases. Erythema and edema of the EAC were identified in a smaller proportion of isolates, and tragus tenderness was uncommon in both groups.

Whitish debris was more frequently observed in *Candida* infections, whereas brownish debris was relatively more common in the Aspergillus group. However, no statistically significant differences were found in any of the physical examination findings between Aspergillus and *Candida* infections (all p-values >0.05) (Table III).

**Table I: Profile and frequency of isolated fungi**

| Isolate | n=56 (%) |
|---|---|
| **Aspergillus** | n=33 (58.9%) |
| *Aspergillus flavus* | 16 (48.5%) |
| *Aspergillus niger* | 9 (27.3%) |
| *Aspergillus fumigatus* | 3 (9%) |
| *Aspergillus oryzae* | 1 (3%) |
| *Aspergillus galucus* | 1 (3%) |
| *Aspergillus tamarii* | 1 (3%) |
| *Aspergillus terreus* | 1 (3%) |
| *Aspergillus candidus* | 1 (3%) |
| **Candida** | n=23 (41.1%) |
| *Candida parapsilosis* | 9 (39.1%) |
| *Candida kefyr* | 2 (8.7%) |
| *Candida albicans* | 1 (4.3%) |
| *Candida utilis* | 1 (4.3%) |
| *Candida tropicalis* | 6 (26.1%) |
| *Candida glabrata* | 1 (4.3%) |
| *Candida krusei* | 3 (13%) |
| **Mixed Infection** | n=18 |
| *C. parapsilosis & C. albicans* | 1 |
| *C. parapsilosis & C. tropicalis* | 2 |
| *C. parapsilosis & C. crusei* | 1 |
| *A. flavus & A. fumigatus* | 1 |
| *A. flavus & C. parapsilosis* | 2 |
| *A. flavus & C. glabrata* | 1 |
| *A. niger & C. tropicalis* | 1 |

**Table II: Age group and gender classification of subjects**

| Variables | Aspergillus n (%) | Candida n (%) | Total n (%) | p-value |
|---|---|---|---|---|
| Age | | | | |
| 11-20th | 3 (9.1%) | 3 (13%) | 6 (10.7%) | 0.364 |
| 21-30th | 6 (18.2%) | 8 (34.8%) | 14 (25%) | |
| 31-40th | 9 (27.3%) | 7 (30.4%) | 16 (28.6%) | |
| 41-50th | 3 (9.1%) | 3 (13%) | 6 (10.7%) | |
| 51-60th | 8 (24.2%) | 2 (8.7%) | 10 (17.9%) | |
| 61-70th | 3 (9.1%) | 0 | 3 (5.4%) | |
| 71-80th | 1 (3%) | 0 | 1 (1.8%) | |
| Gender | | | | |
| Male | 18 (54.5%) | 9 (39.1%) | 27 (48.2%) | 0.388 |
| Female | 15 (45.5%) | 14 (60.9%) | 29 (51.8%) | |

### Comparison of Predisposing Factors

The most frequently reported predisposing factors included a history of ear infection (80.4%), water exposure during bathing (78.6%), ear drop use (76.8%), and ear manipulation with cotton buds (75.0%). Among patients with a history of ear infection, 72.3% were diagnosed with chronic suppurative otitis media. A history of recent swimming (within one month) and prior ear surgery were reported in 16.1% and 14.3% of isolates, respectively. No patients reported hearing aid use.

Comparative analysis demonstrated that ear drop use and cotton bud manipulation were significantly associated with fungal group (p=0.042 and p=0.041, respectively), with both factors more frequently reported in *Aspergillus* isolates compared to *Candida*. In contrast, the distribution of previous ear infection, water exposure, recent swimming, and prior ear surgery did not differ significantly between the two groups (all p-values >0.05) (Table III).

## DISCUSSION

This study demonstrated that *Aspergillus spp.* were the predominant causative agents of otomycosis, consistent with previous reports in which *A. flavus* and *A. niger* constituted the majority of isolates.[3] This predominance may be attributed to the ubiquitous environmental presence and saprophytic nature of *Aspergillus*, as well as the favorable microenvironment of the EAC, which provides organic substrates for fungal growth, including keratin debris and glycoprotein- and polysaccharide-containing components of cerumen and epithelial cells.[3,9]

However, studies from other regions, such as Spain, have reported *Candida* as the leading etiological agent, suggesting the influence of geographic variation, environmental conditions, and local practices, including ear hygiene and topical medication use.[2] The presence of mixed infections in this study further supports the polymicrobial nature of otomycosis.[10]

**Table III: Clinical manifestations and predisposing factors of otomycosis**

| Variables | Aspergillus n=33 (%) | Candida n=23 (%) | Total n=56 (%) | p-value |
|---|---|---|---|---|
| Clinical Manifestation | | | | |
| Itching | | | | |
| Yes | 26 (78.8%) | 20 (87%) | 46 (82.1%) | 0.5 (>0.05)* |
| No | 7 (21.2%) | 3 (13%) | 10 (17.9%) | |
| Hearing loss | | | | |
| Yes | 26 (78.8%) | 19 (82,6%) | 45 (80.4%) | 1 (>0.05)* |
| No | 7 (21.2%) | 4 (17.4%) | 11 (19.6%) | |
| Ear Discharge | | | | |
| Yes | 19 (57.6%) | 14 (60.9%) | 33 (58.9%) | 1 (>0.05) |
| No | 14 (42.4%) | 9 (39.1%) | 23 (41.1%) | |
| Tinnitus | | | | |
| Yes | 18 (54.5%) | 9 (39.1%) | 27 (48.2%) | 0.388 (>0.05) |
| No | 15 (45.5%) | 14 (60.9%) | 29 (51.8%) | |
| Ear fullness | | | | |
| Yes | 23 (69.7%) | 18 (78.3%) | 41 (73.2%) | 0.685 (>0.05) |
| No | 10 (30.3%) | 5 (21.7%) | 15 (26.8%) | |
| Otalgia | | | | |
| Yes | 16 (48.5%) | 13 (56.5%) | 29 (51.8%) | 0.749 (>0.05) |
| No | 17 (51.1%) | 10 (43.5%) | 27 (48.2%) | |
| Headache | | | | |
| Yes | 14 (42.4%) | 9 (39.1%) | 23 (41.1%) | 1 (>0.05) |
| No | 19 (57.6%) | 14 (60.9%) | 33 (58.9%) | |
| | | | | |
| Physical Examination | | | | |
| Fungi identified with otoendoscopic examination | | | | |
| Yes | 33 (100%) | 23 (100%) | 56 (100%) | -+ |
| No | 0 | 0 | 0 | |
| Morphology of fungi | | | | |
| White debris | 19 (57.6%) | 16 (70%) | 35 (62.5%) | 0.247 (>0.05) |
| Brownish debris | 10 (30.3%) | 3 (13%) | 13 (23.2%) | |
| Black spores | 0 (0%) | 2 (9%) | 2 (3.6%) | |
| White debris with brown spores | 3 (9%) | 1 (4%) | 4 (7.1%) | |
| White debris with black spores | 1 (3%) | 1 (4%) | 2 (3.6%) | |
| Edematous EAC | | | | |
| Yes | 4 (12.1%) | 3 (13%) | 7 (12.5%) | 1 (>0.05)* |
| No | 29 (87.8%) | 20 (87%) | 49 (87.5% | |
| Hyperemic EAC | | | | |
| Yes | 7 (21.2%) | 4 (17.4%) | 11 (19.6%) | 1 (>0.05)* |
| No | 26 (78.8%) | 19 (82.6%) | 45 (80.5%) | |
| Tragus pain | | | | |
| Yes | 1 (3%) | 2 (8.7%) | 3 (5.4%) | |
| No | 32 (97%) | 21 (91.3%) | 53 (94.6%) | 0.562 (>0.05)* |
| Discharge in EAC | | | | |
| Yes | 18 (54.5%) | 15 (65.2%) | 33 (58.9%) | 0.601 (>0.05) |
| No | 15 (45%) | 8 (34.8%) | 23 (41.1%) | |
| Tympanic membrane | | | | |
| Perforated | 17 (51.5%) | 15 (65.2%) | 32 (57.1%) | 0.55 (>0.05) |
| Intact | 13 (39.4%) | 7 (30.4%) | 20 (35.7%) | |
| Cannot be assed (patient with history of mastoidectomy surgery) | 3 (9.1%) | 1 (4.3%) | 4 (7.1%) | |
| Predisposing Factors | | | | |
| History of water exposure during bathing | | | | |
| Yes | 24 (72.7%) | 20 (87%) | 44 (78.6%) | 0.322 (>0,05)* |
| No | 9 (27.3%) | 3 (13%) | 12 (21.4%) | |
| History of swimming | | | | |
| Yes | 4 (12.1%) | 5 (21.7%) | 9 (16.1%) | 0.464 (>0.05)* |
| No | 29 (87.9%) | 18 (78.3%) | 47 (83.9%) | |
| History of ear drop usage | | | | |
| Yes | 29 (87.9%) | 14 (60.9%) | 43 (76.8%) | 0.042 (<0.05)[a] |
| No | 4 (12.1%) | 9 (39.1%) | 13 (23.2%) | |
| History of ear infection | | | | |
| Yes | | | | |
| No | 26 (78.8%) | 19 (82.6%) | 45 (80.4%) | 1 (>0.05)* |
| | 7 (21.2%) | 4 (17.4%) | 11 (19.6%) | |

**Table III: Clinical manifestations and predisposing factors of otomycosis**

| Variables | Aspergillus n=33 (%) | Candida n=23 (%) | Total n=56 (%) | p-value |
|---|---|---|---|---|
| History of ear surgery | | | | |
| Yes | 6 (18.2%) | 2 (8.7%) | 8 (14.3%) | 0.449 (>0.05)* |
| No | 27 (81.8%) | 21 (91.3%) | 48 (85.7%) | |
| History of ear manipulation with cotton buds | | | | |
| Yes | 21 (63.6%) | 21 (91.3%) | 42 (75%) | 0.041 (<0.05)[a] |
| No | 12 (36.4%) | 2 (8.7%) | 14 (25%) | |
| History of hearing aid usage | | | | |
| Yes | 0 | 0 | 0 | -+ |
| No | 33 (100%) | 23 (100%) | 56 | |

[a]significance in statistics
*fisher's extract test
+no statistics are computed because constant

Both *Aspergillus* and *Candida* infections were most frequently observed in the 31–40-year age group, followed by the 21–30-year group, corresponding to the working-age population.[11] This pattern suggests that exposure-related factors may play a greater role than species-specific susceptibility. In terms of gender, *Aspergillus* infections were more common in males, whereas *Candida* infections were more frequent in females, although no statistically significant association was identified. These findings indicate that gender is not a reliable distinguishing factor. The observed differences may instead reflect behavioral or environmental influences rather than inherent anatomical differences, such as in health-seeking behavior.[12]

The clinical manifestations were largely similar between the two groups, with itching, hearing loss, and aural fullness as the most common symptoms. Pruritus remains the hallmark feature of otomycosis due to fungal irritation of the EAC.[12] The high frequency of hearing loss and aural fullness may be attributed to the substantial proportion of patients with underlying chronic suppurative otitis media (72.3%), as well as mechanical obstruction from fungal debris.[7] In addition, chronic suppurative otitis media may further promote fungal colonization through epithelial maceration and the availability of nutrients from persistent discharge.[13] Although these symptoms were numerically more frequent in the *Candida* group, suggesting a tendency toward more pronounced presentation, the substantial overlap limits differentiation of fungal etiology based on clinical features alone.

Otoscopic or otoendoscopic examinations remain essential for the initial diagnosis of otomycosis, although classical findings such as a "blotting paper-like" appearance are not consistently observed.[1,14] In this study, whitish debris was predominantly observed in *Candida* infections (70%), consistent with previous descriptions of white or creamy deposits.[1] However, a similar appearance was also observed in a substantial proportion of *Aspergillus* cases (57.6%), possibly reflecting mixed infections or variability in fungal growth stages. Brownish debris was the second most frequent finding in *Aspergillus* infections (30.3%), aligning with the role of spore pigmentation, including melanin production in species such as *A. flavus*, which contributes to a darker colony appearance.[14-15]

Other physical findings, including ear discharge and tympanic membrane perforation, were commonly observed in both groups, likely reflecting the high prevalence of underlying chronic suppurative otitis media in this study. Although previous studies have suggested a higher association of tympanic membrane perforation with *Candida* infections, this distinction was not observed in the present study.[16] These findings indicate substantial overlap in clinical and otoscopic features between fungal species.

Regarding predisposing factors, ear drop use and cotton bud manipulation were significantly more frequent in *Aspergillus* infections. Mechanical trauma from ear manipulation may disrupt the epithelial barrier, while repeated use of ototopic medications can alter the local microenvironment, thereby facilitating fungal colonization.[11,14] Topical agents, particularly antibiotics and corticosteroids, may further disrupt the normal bacterial flora and increase canal pH, creating conditions favorable for fungal growth.[12] This association may reflect ecological selection pressure within the EAC. Other commonly recognized risk factors, including prior ear infection, water exposure, swimming, and previous ear surgery, were highly prevalent but did not differ significantly between fungal groups.[2] Previous studies have reported that otomycosis may involve the middle ear in approximately 10% of cases; however, a substantially higher proportion of middle ear disease was observed in this study (72.3%).

Overall, although differences were observed in fungal distribution and certain associated risk factors, the clinical and otoscopic presentations of otomycosis were largely comparable between *Aspergillus* and *Candida* infections. These findings underscore the importance of microbiological confirmation to ensure accurate diagnosis and appropriate management, particularly in settings with a high burden of chronic ear disease.

**Strengths and limitations**

This study directly addressed the primary objective by systematically comparing clinical manifestations, physical findings, and predisposing factors between *Aspergillus* and *Candida* otomycosis, an area that remains relatively underexplored in previous literature. The isolate-based analysis allowed for a more detailed evaluation of fungal-

specific patterns, including mixed infections. In addition, the study provides valuable regional data from a tertiary referral center in Central Java, Indonesia, contributing to the epidemiological understanding of otomycosis in a tropical setting.

However, this study also has limitations. The relatively small sample size may have limited the ability to detect statistically significant differences between groups. The cross-sectional design precludes causal inference, and associations between predisposing factors and fungal species should be interpreted cautiously. The isolate-based approach may introduce clustering effects in cases with bilateral or mixed infections, and the use of patient-reported data for predisposing factors carries a risk of recall bias.

## CONCLUSION

*Aspergillus* spp. were the predominant causative agents of otomycosis, followed by *Candida* spp., with a notable proportion of mixed infections. Despite differences in etiological distribution, clinical manifestations and physical examination findings showed substantial overlap between the two groups, with no statistically significant differences. Although certain descriptive trends were observed, these were not sufficient for reliable clinical differentiation. Ear drop use and cotton bud manipulation were significantly associated with Aspergillus infections, while other predisposing factors did not differ between groups. Overall, these findings indicate that clinical assessment alone is insufficient to distinguish between *Aspergillus* and *Candida* otomycosis, and microbiological examination remains essential for accurate diagnosis and appropriate management.

## ACKNOWLEDGEMENTS

The authors sincerely thank the Faculty of Medicine, Jenderal Soedirman University, Margono Soekarjo General Hospital, and all participants for their support and valuable contributions to this study.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## FUNDING

This study was supported by a research grant from Universitas Jenderal Soedirman, Indonesia.

## ETHICAL APPROVAL

This study was approved by the Health Research Ethics Committee of Jenderal Soedirman University (No. 018/KEPK/PE/II/2022). Written informed consent was obtained from all participants prior to data collection.

## REFERENCES

1. Sumbria D, Yousuf A, Ahmad R. Hospital based study on etiopathogenesis and treatment of otomycosis: ethnic Kashmiri population. International Journal of Otorhinolaryngology and Head and Neck Surgery 2019; 5(5): 1190-6.
2. Bojanović M, Stalević M, Arsić-Arsenijević V, Ignjatović A, Ranđelović M, Golubović M, et al. Etiology, Predisposing Factors, Clinical Features and Diagnostic Procedure of Otomycosis: A Literature Review. Journal of Fungi 2023; 9(6): 662.
3. Barati B, Okhovvat S, Goljanian A, Omrani MR. Otomycosis in Central Iran: A Clinical and Mycological Study. Iranian Red Crescent Medical Journal 2011; 13(12): 873-6.
4. Jing R, Yang WH, Xiao M, Li Y, Zou GL, Wang CY, et al. Species identification and antifungal susceptibility testing of Aspergillus strains isolated from patients with otomycosis in northern China. Journal of Microbiology, Immunology and Infection 2022; 55(2): 282-90.
5. Darmawan AB, Krisniawati N, Widhi APKN, Hestiyani RAN, Kurniawan DW, Darmayan BJ. Etiology and Antifungal Sensitivity Test in Otomycosis Caused by Candida Sp. Bandung Medical Journal 2023; 55(4): 220-6.
6. Gharaghani M, Halvaeezadeh M, Jalaee GA, Taghipour S, Kiasat N, Mahmoudabadi AZ. Antifungal susceptibility profiles of otomycosis etiological agents in Ahvaz, Iran. Current Medical Mycology 2020; 6(2): 18-22.
7. Anwar K, Gohar MS. Otomycosis; Clinical features, predisposing factors and treatment implications. Pakistan Journal of Medical Sciences 2014; 30(3).
8. Mathers, Amy J, et al. 2022. M100 Performance Standards for Antimicrobial. 32nd Edition. Clinical and Laboratory Standards Institute.
9. Shokry E, Filho NRA. Insights into cerumen and application in diagnostics: Past, present and future prospective. Biochemia Medica 2017; 27(3): 030503.
10. Tasić-Otašević S, Golubović M, Đenić S, Ignjatović A, Stalević M, Momčilović S, et al. Species distribution patterns and epidemiological characteristics of otomycosis in Southeastern Serbia. Journal de Mycologie Médicale 2020; 30(3).
11. Javidnia J, Ghotbi Z, Ghojoghi A, Solhjoo K, Alshahni MM, Jeddi SA, et al. Otomycosis in the South of Iran with a High Prevalence of Tympanic Membrane Perforation: A Hospital-Based Study. Mycopathologia 2022; 187(2–3): 225-33.
12. Ameye SA, Adeyemo A, Eziyi JA, Amusa YB. Clinical profile of otomycosis in a sub-saharan African tertiary health center. Int J Otorhinolaryngol Clin 2018; 10(2): 52-5.
13. Haq M, Deshmukh P. Review of Recurrent Otomycosis and Clotrimazole in Its Treatment. Cureus 2022 Oct 9.
14. Bojanović M, Ignjatović A, Stalević M, Arsić-Arsenijević V, Ranđelović M, Gerginić V, et al. Clinical Presentations, Cluster Analysis and Laboratory-Based Investigation of Aspergillus Otomycosis - A Single Center Experience. Journal of Fungi 2022; 8(3).
15. Koda K. Otomycosis caused by Aspergillus identified by characteristic otoscopic findings. J Gen Fam Med 2026; 27(2).
16. Koltsidopoulos P, Skoulakis C. Otomycosis with tympanic membrane perforation: a review of the literature. Ear Nose Throat J 2020; 99(8): 518-21.

# Service utilization of a novel statewide domiciliary palliative care program in Malaysia

**Yoke Yeng Leong, MRCP[1], Yoke Ling Choo, MRCP[1], Samuel Leong Kheng Wong, MMed Fam Med[2], Diana Suk Chin Law, MMed Fam Med[3], Audrey Ju Yeng Teo, FRACGP[4], Sie Zin Kong, MMed Fam Med[5], Norafini Salamon, MMed Fam Med[6], Rawa Bau, MMed Fam Med[7], Shaun AP Wyan, MMed Fam Med[8], Kia Miang Sii, MAFP/FRACGP[9], Aaron K Wong, PhD[10,11]**

[1]Department of Radiotherapy, Oncology and Palliative Care, Sarawak General Hospital, Malaysia, [2]Domiciliary Palliative Care, Petra Jaya Health Clinic, Sarawak, Malaysia, [3]Domiciliary Palliative Care, Siburan Health Clinic, Sarawak, Malaysia, [4]Domiciliary Palliative Care, Sri Aman Health Clinic, Sarawak, Malaysia, [5]Domiciliary Palliative Care, Sarikei Health Clinic, Sarawak, Malaysia, [6]Domiciliary Palliative Care, Jalan Merbau Health Clinic, Sarawak, Malaysia, [7]Domiciliary Palliative Care, Bintulu Health Clinic, Sarawak, Malaysia, [8]Domiciliary Palliative Care, Midlayar Health Clinic, Sarawak, Malaysia, [9]Domiciliary Palliative Care, Asajaya Health Clinic, Sarawak, Malaysia, [10]Sir Peter MacCallum Department of Oncology, University of Melbourne, Victoria, Australia, [11]The Royal Melbourne Hospital, Victoria, Australia

## ABSTRACT

**Introduction: Palliative care is a human right and key to universal health coverage, yet remains inaccessible for many cancer patients. By 2030, Malaysia is expected to experience a 240% surge in demand for palliative care, with Sarawak, its largest state, projected to bear the greatest burden of unmet need. A novel statewide domiciliary palliative care (DPC) program was implemented to meet this growing demand across a culturally diverse and geographically dispersed region. This study characterizes the patterns of DPC service use during the inaugural year of this novel statewide program to inform future planning.**

**Materials and Methods: This retrospective cohort study included adults with advanced illnesses referred to DPC services at eight health clinics across Malaysia's largest state of Sarawak from July 1, 2023, to June 30, 2024. Descriptive analysis was utilized.**

**Results: A total of 113 patients with terminal illness were seen, the majority (89%; n=101) of whom had advanced cancer. The commonest cancer types were gastrointestinal (25%; n=28) and thoracic (17%; n=19). Median time from referral to first DPC encounter was 4 days (IQR 2–7). Median time to death was 28 days (IQR 11-53). Most patients (72%; n=82) received care in urbanized locations.**

**Conclusion: This study demonstrates the wide reaching implementation of DPC across a geographically and culturally diverse region, particularly to cancer patients. Opportunities for strategic growth include expanding rural outreach, strengthening engagement with indigenous populations, and community engagement to enable more timely, inclusive, and equitable access to palliative care.**

**KEYWORDS:**
*Palliative care; home care services; health services accessibility; neoplasms; rural health*

## INTRODUCTION

Palliative care is an essential component of universal health coverage and is recognized as a fundamental human right.[1] It is a crucial component of healthcare, yet global access remains strikingly inadequate.[1-2] According to the World Health Organization, an estimated 56.8 million people require palliative care services annually, and approximately 78% of this global need arises from low- and middle-income countries.[2] Of all people who require palliative care services, only an estimated 14% actually receive it.[1] This means that the vast majority of people experience unnecessary suffering towards the end of their lives.

Global inequities in palliative care delivery are largely driven by systemic barriers in low- and middle-income countries.[3] According Global Atlas of Palliative Care highlights that palliative care access in Malaysia remains fragmented, particularly at the community level.[4] Yang et al. projected a 240% increase in demand for palliative care in Malaysia by 2030, with the state of Sarawak anticipated to experience one of the greatest needs.[5]

Sarawak, Malaysia's largest state, is located on the island of Borneo and spans a vast geographic area of 124,450 km², with a population of approximately 2.9 million.[6] In rural Sarawak, patients travel up to 100 km to access the nearest palliative care service, often originating from remote areas without road access and requiring up to 2.5 hours of travel by boat.[7]

Given the frailty and symptom burden commonly experienced by people requiring such care, these logistical barriers highlight the urgent need for further decentralization and targeted expansion of palliative care delivery. Although community-based palliative care offers a scalable solution for rural and remote regions like Sarawak, such models have yet to be systematically implemented.

*This article was accepted: 29 April 2026*
*Corresponding Author: Aaron K Wong*
*Email: Aaron.Wong@petermac.org*

Domiciliary Home Care services were first introduced in Malaysia in 2014, initially implemented across 160 selected health clinics.[8] At its inception, the program focused on providing nursing care and rehabilitation for patients with stroke, traumatic brain injury, spinal cord injury, cerebral palsy, and cancer. In 2016, its scope was expanded to include palliative care, namely domiciliary palliative care (DPC). This aligns with the Malaysian National Palliative Care Policy and Strategic Plan 2019–2030, which identifies the strengthening of community-based and primary care services as a core strategy for expanding access. This expansion is especially critical in Sarawak due to its widely dispersed geographical nature.

In 2023, eight public health clinics across Sarawak were selected for a statewide government DPC implementation program. The DPC program, aligned with global home-based palliative care models, enables patients to receive palliative care at home from 3-person teams comprising medical doctors, nurses and medical assistants who provide palliative services from public health clinics. Due to the state's unique landscape, catchment areas for public health clinics in Sarawak are not strictly delineated by distance. Instead, coverage is population-based with urban clinics serve smaller, densely populated zones, while rural clinics cover expansive areas encompassing multiple scattered villages. Patients are referred from hospitals and assessed holistically across physical, psychological, social, and spiritual domains, with specialist support as needed. Essential medicines such as morphine are dispensed, and patients are seen within three working days.[8] Admission criteria follow national DPC guidelines, including individuals with life-limiting illnesses and European Cooperative Oncology Group (ECOG) performance status of 3–4, or 1–2 if anticipated with rapid deterioration. The protocol defines that an initial visit should occur within 3 working days of receiving the referral, however the frequency of home visits is not specified and is appropriately based on clinical decision.

This study aimed to describe the patient demographics and key health service utilization data in the first year of this DPC implementation program. This will assist with a structured understanding of local healthcare needs and benchmarking against similar services to inform future directions of the DPC program.

## MATERIALS AND METHODS

### Study Design and Setting

This retrospective study included terminally ill adults receiving DPC from eight trained Sarawak health clinics (July 2023–June 2024), with ethical approval from Medical Research and Ethics Committee Malaysia (NMRR-24-01737-WNM (IIR)).

### Study Setting

The eight selected health clinics across Sarawak participated in the DPC training program, representing diverse regional locations – Petra Jaya, Sri Aman, Midlayar, Siburan, and Asajaya Health Clinics in the southwest region; Sarikei Health Clinic in the central region, and Jalan Merbau and Bintulu Health Clinics in the northeast regions of Sarawak.

### Data collection

Data were collected from local clinic databases using a standardized case report form and uniform data dictionary, reviewed by practitioners and verified by a senior author. Demographic variables (age, gender, ECOG status, primary diagnosis, Charlson Comorbidity Index (CCI) and health service utilization data (dates of referral, first DPC encounter, and death) were recorded. The interval from first DPC encounter to death was analyzed by diagnosis.

### Statistical Analysis

Baseline demographic data were analyzed using descriptive statistics (medians, interquartile ranges, frequencies) with SPSS version 26. Complete data were available for all patients. Time intervals from DPC referral to first encounter and from encounter to death were analysed by clinic size based on average daily attendance, diagnosis, and ECOG performance status across the eight participating health clinics.

## RESULTS

### Demographics

During its inaugural year, 113 patients were referred to the DPC service. The median age was 69 years (IQR 59–76) with a balanced gender distribution (48% males). Malays comprised 50% of patients, followed by Chinese (23%) and Ibans (20%). Most had ECOG 3 (36%) or 4 (55%) performance status. Cancer was the primary diagnosis in 89% of cases, mainly gastrointestinal (25%), thoracic (17%), and head and neck cancers (14%). Non-cancer conditions accounted for 11% of referrals. The median CCI was 8.

### Health Service Use

*Referrals According to Serviced Population Size*

Health clinics service classification is categorized based on their average daily attendance to clinic, ranging from Class 1 (population of >800) to Class 7 (population of <50).[10] The majority of referrals originated from Class 2 regions (50%) (population of 500 - 800), followed by one health clinic from each Class 1 region (population of > 800), Class 3 region (population of 300 – 500), Class 4 region (population of 150 – 300) and Class 5 region (population of 100 - 150) (Figure 1).

*Timing of Domiciliary Palliative Care Service Provision in Relation to Geographical Location*

The wait time from referral to the first DPC encounter varied across clinic classifications. The overall median wait time was 4 days (IQR: 2–7 days). The wait time was shortest for Class 3 region (median 2 days; IQR 1 – 4), and longest for Class 1 region (median 7 days; IQR 3 –9 days), followed by Class 5 region (median 6 days; IQR 4 – 10) (Table II).

*Timing Between Domiciliary Palliative Care Service Provision and Death in Relation to Primary Diagnosis*

Overall, patients died within 23 days (IQR 9.5–48 days) of first encounter. People with breast cancer, and neurodegenerative disorders survived the longest (median 29 days (IQR 19–78 days) and 27 days (IQR 20 – 85 days)) respectively. People with other cancers (hematological, genitourinary tract and melanoma) and end-stage renal failure (ESRF) had the shortest survival (9 days (IQR 4.5–27 days), and 9 days (IQR 2–22 days) respectively) (Table II).

**Table I: Baseline Demographic Characteristics**

| Demographic Variable | Total Cohort (n = 113) |
|---|---|
| **Gender, n (%)** | |
| Male | 54 (48) |
| Female | 59 (52) |
| **Age (years), Median (IQR)** | 69 [59- 76] |
| **Ethnicity, n (%)** | |
| Malay | 57 (50) |
| Chinese | 26 (23) |
| Iban | 25 (22) |
| Bidayuh | 4 (4) |
| Dayak | 2 (2) |
| Non-Malaysian | 1 (1) |
| **ECOG, n (%)** | |
| 1 | 1 (1) |
| 2 | 9 (8) |
| 3 | 41 (36) |
| 4 | 62 (55) |
| **Primary Cancer Diagnosis, n (%)** | |
| Gastrointestinal | 28 (25) |
| Thoracic | 19 (17) |
| Head and Neck | 16 (14) |
| Breast | 14 (12) |
| Gynaecological | 8 (7) |
| Genitourinary | 7 (6) |
| Other cancer1 | 9 (8) |
| **Primary Non- Cancer Diagnosis** | |
| End stage renal failure | 3 (3) |
| Advanced COPD | 2 (2) |
| Neurodegenerative disorder | 7 (6) |
| **Number of Referrals by Health Clinic, n (%)** | |
| **Class 1** | |
| Petra Jaya | 31 (27) |
| **Class 2** | |
| Sri Aman | 19 (17) |
| Sarikei | 16 (14) |
| Bintulu | 11 (10) |
| Jalan Merbau | 4 (4) |
| **Class 3** | |
| Siburan | 13 (12) |
| **Class 4** | |
| Asajaya | 15 (13) |
| **Class 5** | |
| Midlayar | 4 (3) |
| **CCI[2], Median [IQR]** | 8 [7 – 9] |

[1]Other cancer – leukaemia, myelofibrosis melanoma, sarcoma, brain
[2]CCI = Charlson Comorbidity Index

## DISCUSSION

This study describes the first-year outcomes of DPC service delivery in Sarawak and is the first to describe DPC implementation in Malaysia. Sarawak, the largest and most ethnically diverse in 30 different ethnic groups, faces challenges in equitable service delivery with only two palliative care physicians.[11] The DPC program has helped address these gaps, as community-based models effectively mitigate barriers from geographic isolation, limited healthcare infrastructure, and workforce shortages in rural and remote areas.[12] One of the recognized issues is lack of trained palliative care healthcare providers in the community.[13-14] This DPC program upskills clinicians from existing government-funded clinics to provide community-based palliative care which enables people to receive care in the home environment.

We observed that the volume of referrals to each DPC service was not necessarily related to the size of the population served by each clinic. The clinic with the largest number of referrals (Petra Jaya) was an outlier, accounting for over a quarter of all referrals. Its location in the state's capital, combined with its proximity to Sarawak's largest tertiary hospital likely contributed to this pattern, as it is also where both palliative care physicians are based. The authors postulate that referral trends may be more strongly influenced by community awareness of the service's availability rather than clinic population size alone.

The participating health clinics were located in urban areas with predominantly Malay (50%), Chinese (23%), and Iban (20%) populations, which does not reflect Sarawak's overall ethnic composition—Ibans (30%), Malays (25%), and Chinese (23%).[11] Indigenous minority groups were under-

**Table II: Domiciliary Palliative Care Health Service Utilisation by Clinic Classification**

| Timepoint | Time Interval (days), Median [IQR] |
|---|---|
| Time from referral to first DPC1 encounter | |
| Class 1 | 7 [ 3 – 9] |
| Class 2 | 3 [ 1 - 7] |
| Class 3 | 2 [1 - 4] |
| Class 4 | 3 [1 - 4] |
| Class 5 | 6 [4 - 10] |
| Total | 4 [2 – 7] |
| Time from first DPC1 encounter to death | |
| Primary cancer diagnosis | |
| Gastrointestinal Tract | 28 [14 – 71] |
| Thoracic | 21 [4 – 28] |
| Head and Neck | 18 [11 – 99] |
| Breast | 29 [19 – 78] |
| Gynaecological | 22 [15 – 38] |
| Other | 9 [ 2 – 22] |
| Primary non- cancer diagnosis | |
| Neurodegenerative | 27 [20 – 85] |
| End stage renal failure | 9 [4.5 – 27] |
| Chronic Obstructive Pulmonary Disease | 89 [89 – 89] |
| Time from referral to first DPC1 encounter by health clinic | |
| Sarikei | 0 [0 - 1] |
| Asajaya | 3 [ 2 - 4] |
| Siburan | 3 [2 – 4] |
| Sri Aman | 3[ 2 – 6] |
| Bintulu | 6 [5 – 9] |
| Midlayar | 6 [4 – 10] |
| Petra Jaya | 8 [3 – 9] |
| Jalan Merbau | 9 [3 - 14] |
| Time from referral to death by performance status | |
| ECOG 1 | 39 [39 – 39] |
| ECOG 2 | 114 [31 – 136] |
| ECOG 3 | 29 [20 – 46] |
| ECOG 4 | 25 [8 – 45.5] |
| Total | 28 [11 – 53] |

[1]DPC: Domiciliary Palliative Care

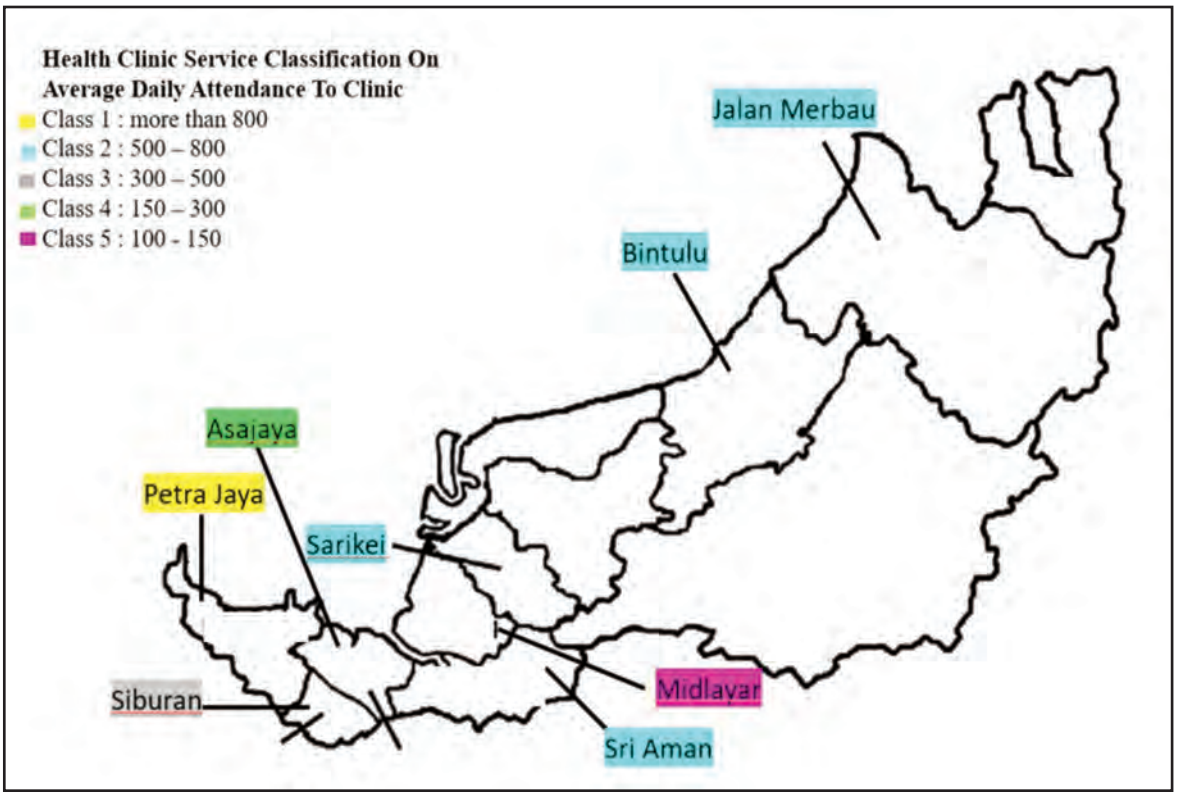



**Fig. 1:** Location of health clinics in Sarawak

represented, likely due to most referrals originating from urban areas.[12] In its first year, palliative care services may not yet be well established in rural regions, and clinics in these areas were not part of the initial implementation. These findings underscore the need to expand DPC services to rural clinics to enhance equitable access across communities.

Our findings showed that 88.4% of referrals involved cancer diagnoses, while only 11.6% were non-cancer. This aligns with Yip et al. and other studies showing most palliative care referrals in Malaysia and community settings are cancer-related.[13-14] Non-cancer conditions appear under-recognized, possibly due to limited awareness that end-organ failure also warrants palliative care.[15] As non-cancer illnesses often have prolonged, unpredictable trajectories, implementing validated tools such as the Supportive and Palliative Care Indicators Tool in health clinics may improve confidence and accuracy in identifying patients needing palliative care.[16]

Patients with non-cancer diagnoses, such as neurodegenerative diseases, had a median survival of 27 days, similar to cancer patients. While those with end-stage renal failure (ESRF) had the shortest at 9 days. ESRF referrals often follow dialysis withdrawal, reflecting limited prognosis and end-of-life care needs at home. Teno et al. reported that non-cancer patients generally have poorer functional status and outcomes, with lower-quality end-of-life care due to higher rates of life-sustaining treatments.[17-19] These findings underscore the need to strengthen DPC services for non-cancer patients through greater awareness at community and hospital levels.

Most patients (91%) had poor performance status (ECOG 3–4) and a high median CCI score of 8, reflecting frailty at referral. The median duration from DPC referral to death was 28 days, consistent with previous local findings.[13] Timely palliative care referrals allow for care that is tailored to patients' needs and delivered holistically, thereby optimising service provision in the community.[20] International studies show that early palliative care integration improves outcomes.[21] As the DPC service grows beyond its inaugural year, it will be important emphasise to the role of timely palliative care delivery.

In Malaysia, the Ministry of Health mandates that all health clinics provide the first DPC encounter within 3 days of referral.[8] However, our findings show variability, with response times ranging from 0 to 9 days, indicating challenges in meeting this target and highlighting the need for further improvement. It is expected that service delivery will increase significantly beyond this inaugural year. Service improvement efforts should focus on addressing the reasons for these slower response times and on how this may be improved, including the extent to which this is related to service demand and travel distance.

## CONCLUSION

This study provides the first insight into DPC service delivery in Sarawak, a geographically vast and ethnically diverse state. Building on this inaugural year, key areas for growth include strengthening community engagement, expanding access for indigenous populations, increasing involvement from non-cancer diagnosis, and reducing referral to assessment timelines to ensure more timely, inclusive, and equitable palliative care access.

## ACKNOWLEDGEMENTS

We acknowledge Dr. Hui Yi Lai from the Family Health Section, Family Health and Development Branch of Sarawak State Health Department for coordinating data collection, and Dr Mohamad Adam Bujang from the Clinical Research Centre, National Institutes of Health, Sarawak General Hospital, Ministry of Health, Malaysia for conducting the data analysis.

## CONFLICT OF INTEREST

The Author(s) declare(s) that there is no conflict of interest related to this work.

## FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors

## ETHICAL APPROVAL

The study was approved by the Medical Research Ethics Committee Malaysia (NMRR ID-24-01737-WNM (IIR)).

## PATIENT CONSENT STATEMENT

Patient consent was not required for this retrospective de-identified study.

## REFERENCES

1. World Health Organization. Palliative care. August 5, 2020. [cited October 2025]. Available from: https://www.who.int/news-room/fact-sheets/detail/palliative-care
2. World Health Organization. WHO takes steps to address glaring shortage of quality palliative care services. World Health Organization. October 5, 2021. [cited September 2025]. Available from: https://www.who.int/news/item/05-10-2021-who-takes-steps-to-address-glaring-shortage-of-quality-palliative-care-services
3. Hannon B, Zimmermann C, Knaul FM, Powell RA, Mwangi-Powell FN, Rodin G. Provision of Palliative Care in low- and middle-income countries: overcoming obstacles for effective treatment delivery. J Clin Oncol 2016 Jan; 34(1): 62–8.
4. Worldwide Hospice Palliative Care Alliance; World Health Organization. Global Atlas of Palliative Care. 2nd ed. WHPCA; 2020. [cited October 2025]. Available from: https://www.thewhpca.org/global-atlas-of-palliative-care
5. Yang SL, Woon YL, Teoh CCO, Leong CT, Lim RBL. Adult palliative care 2004-2030 population study: estimates and projections in Malaysia. BMJ Support Palliat Care 2022; 12(e1): e129-e136.
6. Sarawak Government. Official Portal of the Sarawak Government. Sarawak Government. 2025. [cited September 2025]. Available from: http://www.sarawak.gov.my/web/home/article_view/240/175/

7. Segarmurthy MV, Lim RB, Yeat CL, Ong YX, Othman S, Taher SW, Spence D, Ahmad F, Sullivan R, Rosa WE, Bhoo-Pathy N. Mapping palliative care availability and accessibility: a first step to eradicating access deserts in the low- and middle-income settings. J Palliat Care 2024; 39(4): 255-63.
8. Kementerian Kesihatan Malaysia. Garis Panduan Perkhidmatan Perawatan Domisiliari di Kesihatan Primer. Edisi ke-2. Bahagian Pembangunan Kesihatan Keluarga; 2020. [cited September 2025]. Available from: https://hq.moh.gov.my/bpkk/images/Kesihatan_Orang_Kurang_Upaya/PDF/Garis_Panduan/1_Garis_Panduan_Perkhidmatan_Perawatan_Domisiliari_Di_Kesihatan_Primer_Edisi_2_Tahun_2020.pdf
9. Ministry of Health Malaysia. National Palliative Care Policy and Strategic Plan 2019-2030. Putrajaya: Ministry of Health Malaysia; 2019 [cited May 2024]. Available from: https://hq.moh.gov.my/bpkk/index.php/component/jdownloads/?task=download.send&id=1118&catid=24&m=0&Itemid=1098
10. Kementerian Kesihatan Malaysia. Klasifikasi klinik kesihatan. Bahagian Pembangunan Kesihatan Keluarga. [cited September 2025]. Available from: https://hq.moh.gov.my/bpkk/index.php/klasifikasi-klinik-kesihatan
11. Sarawak Tourism Board. Ethnicities of Sarawak. Sarawak Tourism Hornbill Trail Newsletter. [cited September 2025]. Available from: https://enewsletter.sarawaktourism.com/ethnicities-of-sarawak/
12. Cai Y, Lalani N. Examining barriers and facilitators to palliative care access in rural areas: a scoping review. Am J Hosp Palliat Care 2022; 39(1): 123-130.
13. Yip YY, Hwong WY, McCarthy SA, Hassan Chin AA, Woon YL. Duration of referral-to-death and its associated factors among cancer and noncancer patients: retrospective cohort study of a community palliative care setting in Malaysia. J Palliat Care 2022; 38(2): 111-25.
14. Walshe C, Todd C, Caress A, Chew-Graham C. Patterns of access to community palliative care services: a literature review. J Pain Symptom Manage 2009; 37(5): 884-912.
15. Bostwick D, Wolf S, Samsa G, Bull J, Taylor DH, Johnson KS, et al. Comparing the palliative care needs of those with cancer to those with common non-cancer serious illness. J Pain Symptom Manage 2017; 53(6): 1079-1084.e1.
16. Lunardi L, Hill K, Crail S, Esterman A, Le Leu R, Drummond C. 'Supportive and Palliative Care Indicators Tool (SPICT) improves renal nurses' confidence in recognising patients approaching end of life'. BMJ Support Palliat Care 2024; 14(e1): e784-e9.
17. Teno JM, Gozalo PL, Bynum JPW, Leland NE, Miller SC, Morden NE, et al. Change in End-of-Life Care for Medicare Beneficiaries: Site of Death, Place of Care, and Health Care Transitions in 2000, 2005, and 2009. JAMA 2013; 309(5): 470-7.
18. Wachterman MW, Pilver C, Smith D, Ersek M, Lipsitz SR, Keating NL. Quality of end-of-life care provided to patients with different serious illnesses. JAMA Intern Med 2016; 176(8): 1095-102.
19. Temel JS, Sloan J, Zemla T, Greer JA, Jackson VA, El-Jawahri A, et al. Multisite, randomized trial of early integrated palliative and oncology care in patients with advanced lung and gastrointestinal cancer: Alliance A221303. J Palliat Med 2020 Jul 1; 23(7): 922-9.
20. Hui D, Heung Y, Bruera E. Timely palliative care: personalizing the process of referral. Cancers. 2022; 14(4): 1047.
21. Davis MP, Temel JS, Balboni T, Glare P. A review of the trials which examine early integration of outpatient and home palliative care for patients with serious illnesses. Ann Palliat Med 2015; 4(3): 99-121.

# Psychological distress and associated stressors with proposed stress reduction model for Chinese international postgraduate students in Malaysia: A cross-sectional study

**Ying Liu, MA[1,2], Velu Perumal, PhD[1,6], Subapriya Suppiah, MD[3,4], Poh Foong Lee, PhD[5], Abdul Rohim Tualeka, PhD[6]**

[1]Department of Industrial Design, Faculty of Design and Architecture, Universiti Putra Malaysia, Serdang, Selangor, Malaysia, [2]Faculty of Art and Design, Changsha Normal University, Changsha City, Hunan, China, [3]Department of Radiology, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang, Selangor, Malaysia, [4]Pusat Pengimejan Diagnostik Nuklear, Universiti Putra Malaysia, Serdang, Selangor, Malaysia, [5]Department of Mechanical and Material Engineering, Lee Kong Chian Faculty of Engineering and Science, Universiti Tunku Abdul Rahman, Bandar Sungai Long, Kajang, Selangor, Malaysia, [6]Department of Occupational Health and Safety, Kampus-C, Universitas Airlangga, Jl. Ir. Soekarno, Surabaya, Indonesia

## ABSTRACT

**Introduction: In recent years, there has been an exponential rise in students inbound to Malaysia to pursue their postgraduate studies. In particular, Chinese international postgraduate students (CIPS) represent a rapidly growing student population in this country, which is postulated to lead to substantial psychological distress resulting from academic, cultural, and financial adjustments that are required of the students immersing themselves in a new environment. Nevertheless, quantitative evidence regarding depression, anxiety, and stress among CIPS in Malaysian public universities remains limited.**

**Materials and Methods: A cross-sectional study was conducted among 347 Chinese international postgraduate students at Universiti Putra Malaysia (UPM) using mixed-mode convenience sampling. Data were collected using a structured questionnaire that included sociodemographic variables, stressors, stress-relieving activities, and the Depression Anxiety Stress Scales-21 (DASS-21). For the statistical analysis, we performed descriptive statistics, group comparisons, Pearson correlations, and hierarchical regression analyses.**

**Results: The prevalence of mild-to-extremely severe symptoms was 61.1% for depression, 67.1% for anxiety, and 56.2% for stress. Psychological distress was significantly associated with perceived discrimination, financial concerns, poorer self-rated health, and depression history. In the final hierarchical regression model, perceived discrimination emerged as the strongest predictor of distress ($\beta = .270$, $p < .001$). Furthermore, financial concerns, poorer self-rated health, and participation in artistic activities such as calligraphy classes were also positively associated with increasing DASS-21 scores, whereas positive future outlook scores showed a negative association. The final model explained 53.1% of the variance in psychological distress.**

**Conclusion: Psychological distress among CIPS at UPM was substantial and appeared to be strongly related to acculturative stress and resource-related pressures. A proposed model to overcome this should include university-driven, culturally responsive mental health services, anti-discrimination support, and financial and academic assistance to ensure the successful onboarding and orientation of international postgraduate students.**

**KEYWORDS:**
*Psychological distress; chinese international students; acculturative stress; DASS-21; Malaysia; postgraduate students*

## INTRODUCTION

Global cross-border higher education has expanded steadily over the past two decades, and Malaysia has emerged as a major destination for Chinese students.[1-2] Malaysia attracts many international postgraduate students because of its globally recognised qualifications, budget-friendly tuition and living expenses, including numerous world-class branch campuses. Our country offers an ideal environment for advanced studies, combining a safe, multicultural society with widespread proficient English-speaking locals. Interestingly, Chinese nationals have made up more than 40% of all international students in Malaysia during 2024, with total enrolments hitting 56,198. Specifically, in Universiti Putra Malaysia (UPM), our institutional data from the UPM School of Graduate Studies showed that as of 26th May 2023, there were 2,837 Chinese postgraduate students at UPM, including 1,105 master's students and 1,732 PhD students. Chinese postgraduate students accounted for approximately 27.6% of the listed postgraduate student population at UPM.

Although the two countries are culturally close, Chinese international postgraduate students (CIPS) still face challenges related to language, academic demands, financial pressure, daily adjustment, and social support.[3] Evidence from multiple countries points to growing concern about students' mental health. Nearly one in five students experiences a mental disorder, most commonly anxiety or depression.[4] In Malaysia, about 30% of local university

*This article was accepted: 24 June 2026*
*Corresponding Author: Velu Perumal*
*Email: velu@upm.edu.my*

students were reported to be at risk of anxiety.[5] Research also indicates that international students often report higher distress than local students but are less likely to use mental health services.[6-7] CIPS in Malaysia are part of South–South mobility and may face additional adaptation pressures related to language, social integration, and identity.[8-10]

Existing studies in Malaysian universities have mainly focused on local students,[5,11] while studies on CIPS have often examined emotional expression or psychological well-being using other instruments, including mixed international student samples without separate analysis of Chinese postgraduates, or used qualitative methods without standardised measures.[12-15] To date, no study in a Malaysian public research university has used the Depression, Anxiety, and Stress Scale (DASS-21) to assess depression, anxiety, and stress among CIPS while also examining major stressors and stress-relieving activities.[12-15] This study was conceptually informed by the acculturative stress framework and conservation of resources theory, which suggest that psychological distress among international students may arise from perceived discrimination, cultural adjustment difficulties, financial strain, and reduced social or psychological resources.

Despite the growing number of CIPS in Malaysia, quantitative evidence on their mental health remains limited. Despite the growing number of these international students in Malaysia, few quantitative studies have examined depression, anxiety, and stress simultaneously using a validated instrument while also investigating culturally relevant stressors and stress-relieving behaviours within a South–South educational mobility context. Based on this gap, this study focused on CIPS at UPM with the aim of identifying a model that can propose corrective measures to mitigate this problem. This study aimed to determine the prevalence and severity of depression, anxiety, and stress among CIPS at UPM; examine demographic and psychosocial correlates of psychological distress; and finally, to identify significant predictors of DASS-21 scores using hierarchical regression analysis.

## MATERIALS AND METHODS

### Study design and sampling criteria

We conducted a cross-sectional survey among CIPS at UPM in March 2025. Participants were recruited using a mixed-mode non-probability sampling strategy that combined offline campus-based recruitment and online dissemination via Chinese student WeChat groups. All eligible participants completed the survey via WeChat by scanning a QR code or opening the survey link.[16] WeChat was used as the main access channel because it is widely used among Chinese students. As the online link could be further shared through WeChat groups, the total number of students reached was unknown; therefore, an overall response rate could not be calculated. Inclusion criteria were enrolment in a master's or doctoral programme at UPM, Chinese nationality, age ≥18 years, and the ability to read Chinese or English. Sample size was estimated using a single-proportion formula for cross-sectional studies. Based on an expected prevalence of 50%,[17-18] $\alpha$=0.05, and a margin of error of 0.06, the minimum required sample size was 267. After adding 20% for possible non-response, the target sample was approximately 330. In total, 347 usable responses were obtained. This study was approved by the UPM Research Ethics Committee (JKEUPM-2023-1423) and was conducted in accordance with the Declaration of Helsinki. Participation was voluntary, responses were anonymous and confidential, and online informed consent was obtained from all participants.

### Instrument of measurement

The survey was conducted using a 55-item structured questionnaire administered through Questionnaire Star (Wenjuanxing), an online survey platform.[16] The stressor and stress-relieving activity items listed were analysed as individual indicators rather than latent psychometric scales. The questionnaire included:

1. **Demographic variables:** gender, age, student type, semester, sibling status, marital status, employment status, depression history, main financial source, and income range.
2. **Key factors, stressors, and stress-relieving activities:** Single-item measures were used for relationship with supervisor, English fluency, self-evaluation of current health, awareness of the counselling unit, and likelihood of seeking help; self-evaluation of current health referred to participants' overall current health status, with higher scores indicating poorer health. The questionnaire also included stressor and stress-relieving activity items, all rated on a five-point Likert scale (1=strongly disagree/never to 5=strongly agree/very often). Internal consistency was acceptable for the stressor and stress-relieving activity items (Cronbach's $\alpha$=0.854 and 0.703). These items were adapted from previous literature and expert-reviewed.
3. **Additional questionnaire using DASS-21:** Psychological distress over the past week was assessed using the DASS-21, which includes three subscales—depression, anxiety, and stress—with seven items each.[19] Items were rated on a four-point Likert scale (0=did not apply at all, 3=applied most of the time). For each subscale, the seven item scores were summed and then multiplied by two, yielding subscale scores ranging from 0 to 42. The total DASS-21 score ranged from 0 to 126, with higher scores indicating greater psychological distress. Internal consistency was excellent for the total scale and all subscales (Cronbach's $\alpha$=0.973; depression=0.934, anxiety=0.923, stress=0.920). Scores were classified into normal, mild, moderate, severe, and extremely severe according to the standard DASS severity cut-off scores. The DASS-21 is a screening instrument.

### Statistical analysis

Data were analysed using SPSS Statistics 26.0. Descriptive statistics were used to summarise the sample. Internal consistency was assessed using Cronbach's $\alpha$, and common method bias was examined using Harman's single-factor test. Group differences were tested using independent-samples t-tests and one-way ANOVA, associations using Pearson correlation coefficients, and factors associated with DASS-21 total score using hierarchical regression. Variables were entered in three conceptual blocks: sociodemographic variables, stressor variables, and stress-relieving activity

variables. Statistical significance was set at α=0.05. Prior to regression analysis, assumptions of normality, linearity, homoscedasticity, and multicollinearity were examined. Variance inflation factor values were below conventional thresholds, indicating no evidence of problematic multicollinearity

## RESULTS

### Sample characteristics and reliability

This study included 347 valid responses. Table I presents the sociodemographic characteristics. Overall, the sample was predominantly female, mainly aged 26–30 years, and consisted mostly of master's students. Most participants were in the early to middle stages of study, and over half reported no history of depression. In terms of financial background, nearly half were self-funded, and most reported a monthly income of RM 1,000-5,000. English communication ability was generally limited, with nearly half rating their fluency as poor or fair. Awareness and use of mental health services were also limited: most students had either not heard of or had only heard of the UPM counselling unit, and actual service use was low. Help-seeking intention was also generally low. Harman's single-factor test showed that the first unrotated factor explained 37.6% of the total variance, below the 40% threshold, suggesting that common method bias was not a major concern.

### Descriptive statistics and prevalence of DASS-21

The mean scores were 14.89 (SD=11.84) for depression, 15.48 (SD=11.40) for anxiety, and 17.29 (SD=11.37) for stress. The mean total DASS-21 score was 47.65 (SD=33.44). Among the 347 participants, the prevalence of mild-to-extremely severe symptoms was 61.1% for depression, 67.1% for anxiety, and 56.2% for stress. Anxiety showed the highest prevalence, followed by depression and stress. In terms of severity distribution, 33.7% of participants were in the severe-to-extremely severe range for depression, 50.7% for anxiety, and 29.1% for stress (Table II).

### Group differences

*Demographic differences in DASS-21 total scores*

We compared overall psychological distress (DASS-21 total score) across sociodemographic groups. Significant differences were found for gender, age, marital status, depression history, and income range. Males scored higher than females (t=3.82, p<0.001). Distress also varied significantly across age groups (F=5.26, p<0.01), with the 26–30 group showing the highest scores and the 31–39 and ≥40 groups showing lower scores. Marital status was significant (F=3.89, p<0.01), with divorced participants reporting the highest distress. Depression history showed the strongest group difference (F=35.29, p<0.001): participants with no history had the lowest scores, whereas those with undiagnosed, diagnosed, or uncertain history reported higher distress. Income range also differed significantly (F=4.94, p=0.01), with the middle-income group scoring higher in the DASS-21 scores than the high-income group. No significant differences were found for student type, semester, sibling status, employment status, or main financial source (p>0.05).

*Group differences in stressors across demographics*

This study compared nine stressors across sociodemographic groups, including homesickness, perceived discrimination, living conditions, academic pressure, financial concerns, social support, adaptation to a new culture, future outlook, and health. No significant differences were found for sibling status or main financial source across any stressor indicators (p>0.05). For gender, males scored significantly higher on perceived discrimination (t=3.17, p<0.01), whereas females scored higher on academic pressure (t=-3.13, p<0.001).

*Group differences in stress-relieving activities across demographics*

This study found significant differences across several stress-relieving activities among sociodemographic groups (Table III). No significant differences were found for sibling status or depression history across any stress-relieving activities (p>0.05). In addition, social entertainment and cooking/cleaning rooms showed no significant differences across demographic groups.

For gender, males reported higher participation in online gaming (t=4.75, p<0.001) and mindfulness meditation (t=3.92, p<0.001) than females. Age differences were also significant, with younger students reporting more frequent online gaming (F=17.17, p<0.001) and those aged 26-30 years reporting the highest mindfulness meditation scores (F=3.69, p=0.01). Master's students reported higher online gaming than PhD students (t=3.78, p<0.01). Semester differences were found for online gaming (F=8.81, p<0.001), which was highest in semesters 5-6, and mindfulness meditation (F=4.94, p<0.001), which was highest in semesters 1-2. Marital status showed a significant difference in online gaming, with divorced students reporting the highest scores (F=5.52, p<0.001). The main financial source was associated with online social networks (F=3.29, p=0.04), online gaming (F=14.48, p<0.001), and doing arts (F=4.99, p=0.01), with scholarship students reporting higher engagement than the other groups. Income range also showed significant differences: low- and middle-income students reported more frequent use of online social networks (F=3.59, p=0.03), while the middle-income group reported higher engagement in doing arts (F=3.27, p=0.04) and mindfulness meditation (F=3.60, p=0.03).

### Correlation analysis

Table IV shows the correlations between DASS-21 total score and the main stressors, stress-relieving activities, and sociodemographic variables. Overall, psychological distress was positively correlated with most stressors. Perceived discrimination showed the strongest correlation with DASS-21 total score (r=0.57, p<0.001), followed by poorer health (r=0.45, p<0.001), financial concerns (r=0.43, p<0.001), living condition (r=0.43, p<0.001), new culture adaptation (r=0.40, p<0.001), homesickness (r=0.39, p<0.001), and lower social support (r=0.37, p<0.001). Academic pressure and future outlook also showed weaker but significant correlations. For stress-relieving activities, higher psychological distress was significantly associated with more frequent online gaming (r=0.26, p<0.001), doing arts (r=0.29, p<0.001), and mindfulness meditation (r=0.22, p<0.001), whereas other stress-relieving activities were not significantly correlated. Among sociodemographic variables, gender (r=-0.20,

**Table I: Demographic Characteristics of Participants (N = 347)**

| Variables | Category | n (%) |
|---|---|---|
| Gender | Male | 145 (41.79) |
| | Female | 202 (58.2) |
| Age | 21-25 | 105 (30.26) |
| | 26–30 | 142 (40.92) |
| | 31–39 | 92 (26.51) |
| | ≥40 | 8 (2.31) |
| Student type | Master's | 199 (57.35) |
| | Doctoral | 148 (42.65) |
| Semester | 1-2 | 97 (27.95) |
| | 3-4 | 139 (40.06) |
| | 5-6 | 62 (17.87) |
| | ≥7 | 49 (14.12) |
| Marital status | Single | 208(59.9) |
| | Married | 106(30.5) |
| | Divorced | 14(4) |
| | Other | 19(5.4) |
| Depression history | No | 194 (55.91) |
| | Not sure | 101 (29.11) |
| | Yes, undiagnosed | 33 (9.51) |
| | Yes, diagnosed | 19 (5.48) |
| Main financial source | Scholarship | 46(13.2) |
| | Self-support | 166(47.8) |
| | Family or friends' aid | 135(38.9) |
| Income range | <1000RM/Month | 85(24.5) |
| | 1000-5000RM/Month | 205(59.1) |
| | >5000RM/ Month | 57(16.4) |
| Communication of English fluency | Poor | 16(4.6) |
| | Fair | 144 (41.50) |
| | Good | 136 (39.19) |
| | Very good | 43 (12.39) |
| | Excellent | 8 (2.30) |
| Awareness of counselling unit | No | 138(39.7) |
| | Heard of it | 161(46.3) |
| | Used it | 48(13.8) |
| Likelihood of seeking help from counselling service | Definitely not | 16(4.61) |
| | Not likely | 113(32.5) |
| | Somewhat likely | 146(42.0) |
| | Very likely | 56(16.1) |
| | Definitely | 16 (4.61) |

Note: The "Other" marital status category referred to participants who did not identify as single, married, or divorced, or who preferred not to specify their marital status.

**Table II: Severity distribution of depression, anxiety, and stress among CIPS at UPM**

| Severity | Depression n (%) | Anxiety n (%) | Stress n (%) |
|---|---|---|---|
| Normal | 135 (38.9) | 114 (32.9) | 152 (43.8) |
| Mild | 31 (8.9) | 16 (4.6) | 34 (9.8) |
| Moderate | 64 (18.4) | 41 (11.8) | 60 (17.3) |
| Severe | 49 (14.1) | 37 (10.7) | 68 (19.6) |
| Extremely severe | 68 (19.6) | 139 (40.1) | 33 (9.5) |
| Mild-to-extremely severe | 212 (61.1) | 233 (67.1) | 195 (56.2) |

**Table III: Significant group differences across stress-relieving activities**

| Activity | Gender | Age | Marital Status | Student Type | Semester | Sibling | Depression History | Financial Source | Income |
|---|---|---|---|---|---|---|---|---|---|
| Online social networks | — | — | — | — | — | — | — | Scholarship ↑ | Low & Middle ↑ |
| Online gaming | Male ↑ | 21–25 ↑ | Divorced ↑ | Master ↑ | 5–6 ↑ | — | — | Scholarship ↑ | — |
| Physical exercise | — | — | — | — | — | — | — | — | — |
| Do arts | — | — | — | — | — | — | — | Scholarship ↑ | Middle ↑ |
| Mindfulness meditation | Male ↑ | 26–30 ↑ | — | — | 1–2 ↑ | — | — | — | Middle ↑ |

Social entertainmentNo significant differences
Cooking/cleaning roomsNo significant differences
Note: ↑ indicates a higher frequency.

**Table IV: Correlations between DASS-21 and stressors, common ways of relieving stress, and sociodemographic variables**

| Category | Variables | M | SD | r | p |
|---|---|---|---|---|---|
| Stressors | Perceived Discrimination | 2.69 | 1.10 | 0.57*** | <0.001 |
| | Health (poorer health) | 3.28 | 1.00 | 0.45*** | <0.001 |
| | Financial Concerns | 3.41 | 0.97 | 0.43*** | <0.001 |
| | Living Condition | 3.36 | 1.03 | 0.43*** | <0.001 |
| | New Culture Adaptation | 3.31 | 0.98 | 0.40*** | <0.001 |
| | Homesickness | 3.43 | 1.04 | 0.39*** | <0.001 |
| | Social Support (higher scores = lower support) | 3.35 | 0.96 | 0.37*** | <0.001 |
| | Academic Pressure | 3.78 | 0.90 | 0.24*** | <0.001 |
| | Future Outlook | 3.73 | 0.92 | 0.15** | 0.01 |
| ways of relieving stress | Online gaming | 3.18 | 1.20 | 0.26*** | <0.001 |
| | Do arts (drawing, calligraphy, music) | 3.11 | 1.16 | 0.29*** | <0.001 |
| | Mindfulness meditation | 3.02 | 1.14 | 0.22*** | <0.001 |
| | Online social networks | 3.92 | 0.85 | 0.09 | 0.11 |
| | Physical exercise | 3.41 | 0.96 | 0.06 | 0.25 |
| | Participating in social entertainment | 3.69 | 0.79 | 0.10 | 0.08 |
| | Cooking or cleaning rooms | 3.71 | 0.95 | 0.09 | 0.11 |
| Sociodemographic | Gender | 1.58 | 0.49 | -0.20*** | <0.001 |
| | Age | 2.01 | 0.81 | -0.16** | 0.01 |
| | Marital status | 1.55 | 0.81 | 0.12* | 0.03 |
| | Depression History | 1.65 | 0.87 | 0.42*** | <0.001 |

Note: All stressor variables and stress-relieving activities are shown. Sociodemographic variables are shown only when significantly correlated with DASS-21 total score. Higher scores on social support indicate lower perceived support; higher scores on health indicate poorer self-rated health.
***p<0.001, **p<0.01, *p<0.05.

**Table V: Hierarchical regression analysis predicting DASS-21 from demographic factors, stressors, and ways of relieving stress (N = 347)**

| Model | Variable | Block I β | Block II β | Block III β |
|---|---|---|---|---|
| Block I | Gender | -0.192*** | -0.129** | -0.116** |
| | Age | -0.166** | -0.084* | -0.067 |
| | Marital status | 0.091 | 0.069 | 0.069 |
| | Depression History | 0.417*** | 0.264*** | 0.257*** |
| | Income range | -0.078 | -0.065 | -0.066 |
| Block II | Homesickness | | 0.069 | 0.061 |
| | Perceived Discrimination | | 0.288*** | 0.270*** |
| | Living Condition | | 0.072 | 0.065 |
| | Academic Pressure | | 0.030 | 0.056 |
| | Financial Concerns | | 0.113* | 0.109* |
| | Social Support | | 0.105* | 0.084 |
| | New Culture Adaptation | | -0.049 | -0.055 |
| | Future Outlook | | -0.096* | -0.097* |
| | Health | | 0.161** | 0.167** |
| Block III | Online social networks | | | 0.012 |
| | Online gaming | | | 0.027 |
| | Physical exercise | | | -0.015 |
| | Do arts | | | 0.123** |
| | Mindfulness meditation | | | 0.011 |
| | Participating in social entertainment | | | -0.036 |
| | Cooking or cleaning rooms | | | -0.022 |
| R2 | 0.258 | 0.518 | 0.531 | |
| ΔR2 | - | 0.260 | 0.013 | |
| F | 23.69*** | 25.45*** | 17.53*** | |
| df | 341 | 332 | 325 | |

Note: ***p<0.001, **p<0.01, *p<0.05

p<0.001), age (r=-0.16, p=0.01), marital status (r=0.12, p=0.03), and depression history (r=0.42, p<0.001) were significantly associated with DASS-21 total score.

### Hierarchical regression

Hierarchical regression was used to examine factors associated with DASS-21 total score among CIPS (Table V). Variables were entered in three blocks. Block I included sociodemographic variables and explained 25.8% of the variance in psychological distress ($R^2$=0.258, F(5,341) = 23.69, p<0.001). Gender (β=-0.192, p<0.001), age (β=-0.166, p<0.01), and depression history (β=0.417, p<0.001) were significant predictors. Block II added stressor variables and increased the explained variance to 51.8% ($R^2$=0.518, $\Delta R^2$=0.260, p<0.001). Perceived discrimination (β=0.288, p<0.001), financial concerns (β=0.113, p<0.05), and poorer health (β=0.161, p<0.01) were significant positive predictors, whereas future outlook was a significant negative predictor

(β=-0.096, p<0.05). Block III added stress-relieving activities and produced a small but significant increase in explained variance ($R^2$=0.531, $\Delta R^2$ =0.013, p<0.05). In the final model, perceived discrimination (β=0.270, p<0.001), financial concerns (β=0.109, p<0.05), poorer health (β=0.167, p<0.01), and doing arts (β=0.123, p<0.01) were significant positive predictors, whereas future outlook remained a significant negative predictor (β=-0.097, p<0.05). Overall, the final model explained 53.1% of the variance in psychological distress ($R^2$=0.531, p<0.001).

## DISCUSSION

This study found high levels of psychological distress among CIPS at UPM, with mild-to-extremely severe symptom rates of 61.1% for depression, 67.1% for anxiety, and 56.2% for stress. These findings should be interpreted cautiously in relation to previous studies because directly comparable evidence on Chinese international postgraduate students in Malaysia remains limited. Studies using DASS-21 among Malaysian university students have also reported substantial levels of depression, anxiety, and stress, suggesting that psychological distress is a broader concern in Malaysian higher education settings.[11,20] The findings suggest that psychological distress among CIPS deserves continued attention in the Malaysian higher education context. Available evidence from other host countries also suggests that the mental health burden of Chinese international students may vary across contexts.[21-22] In the United States, a study of Chinese international students reported prevalence rates of 24.5% for depression and 20.7% for anxiety.[22] In Singapore, a study of international students reported depressive and anxiety symptoms in 19.57% and 20.28% of participants, respectively, although the sample was not limited to Chinese students.[23] These figures should be treated as contextual reference points rather than direct cross-country prevalence comparisons. Cross-study differences may reflect methodological and contextual variation rather than actual prevalence differences. CIPS at UPM may face multiple challenges, including academic demands, cross-cultural adjustment, language difficulties, financial strain, and low willingness to seek help.[3,8,10] In our sample, many students were self-funded or from middle-income families, nearly half reported limited English fluency, and awareness and use of counselling services were low. The high prevalence in this group may reflect not only cross-cultural adjustment difficulties, but also limited access to support.[7,10] These findings suggest a need to improve mental health literacy and culturally sensitive help-seeking support.[7,24-25]

Several sociodemographic factors were associated with psychological distress. Male students reported higher distress than females, although previous findings remain mixed.26 Younger students also showed higher distress, consistent with earlier research on anxiety and adaptation difficulties in early adulthood.[27-28] Divorced students reported the highest distress scores, which may reflect greater social and economic vulnerability.[29] Depression history was one of the strongest predictors, consistent with evidence that symptoms may re-emerge under stress.[30] Students from middle-income families also reported higher distress, possibly reflecting greater financial pressure.[31] Language ability, self-rated health, supervisor relationship, and awareness of counselling services also differed across groups. Older students reported stronger supervisor relationships, whereas younger students were more aware of counselling services.[24,32] Students with a history of depression reported poorer health and weaker supervisor relationships.[30,32] Scholarship students showed higher awareness of counselling services and stronger help-seeking intention, while high-income students reported better English communication.[33]

Stressors also varied across demographic groups. Younger students reported greater perceived discrimination and more difficulty with new culture adaptation, whereas older students reported higher academic pressure, financial concerns, lower social support, and poorer health.[6,34-35] Stress among CIPS may change over time, with adaptation difficulties appearing more prominent earlier and practical or resource-related pressures becoming more salient later.[34] PhD students showed higher academic pressure, and students with a history of depression, especially those with undiagnosed symptoms, reported higher levels of most stressors.[36] Middle-income students also showed higher stressor scores compared to students from a more affluent background.[37] These findings show that distress among CIPS is shaped not only by academic adjustment but also by broader social, financial, and health-related pressures.

Group differences in stress-relieving activities were mainly observed in online gaming, mindfulness meditation, doing arts, and online social networks.[38] Male and younger students reported more online gaming, whereas those aged 26–30 years reported higher mindfulness meditation.[38] Scholarship and middle-income students showed higher engagement in several stress-relieving activities, while physical exercise, cooking, or cleaning rooms, and social entertainment did not show significant group differences.[38] Several stressors were positively associated with psychological distress, and perceived discrimination remained the strongest predictor, suggesting that social evaluation and exclusion may be particularly important in cross-cultural settings.[6,35] Financial concerns and poorer self-rated health also showed predictive effects, while future outlook showed a negative predictive effect.[37] Among stress-relieving activities, only artistic activities remained significant in the final model, suggesting that students with higher distress may have engaged more frequently in creative practices. We postulate that art-related activities may reflect reactive coping attempts among psychologically distressed students rather than protective behaviours. These findings suggest that distressed students may preferentially engage in creative activities for emotional self-regulation, although causal direction cannot be determined. These findings are broadly consistent with the acculturative stress framework and conservation of resources theory, suggesting that emotional distress among CIPS is shaped by discrimination, financial concerns, health-related pressures, and limited resources as observed in other similar international studies.[39-40] Universities should improve the visibility and accessibility of counselling services and provide culturally responsive support for CIPS. Male students, particularly those with a history of depression, middle-income students, and PhD candidates, may require special attention.

This study adds quantitative evidence on psychological distress among CIPS in a South–South mobility context. Despite this, the cross-sectional design does not allow causal inference, and self-reported data may introduce recall bias and subjective judgment. Additional limitations of this study caused by a mixed-mode convenience sampling strategy may have introduced selection bias; students with wider peer networks or greater interest in mental health topics may have been more likely to participate, whereas socially isolated students may have been underrepresented. Therefore, the prevalence estimates and group comparisons should be interpreted cautiously. Finally, because this study was conducted at a single university using a non-probability sample, the generalisability of the findings may be limited. Future studies should include multiple universities and use longitudinal or mixed-method designs to clarify changes in psychological distress and stress-relieving activities over time.

## CONCLUSION

This study identified substantial levels of depression, anxiety, and stress among Chinese international postgraduate students at Universiti Putra Malaysia, highlighting psychological distress as an important concern within the South–South international student mobility context. Perceived discrimination, financial concerns, poorer self-rated health, and previous depression history were significantly associated with higher psychological distress, suggesting that both acculturative and resource-related stressors play important roles in students' mental well-being. Although participation in artistic activities was positively associated with distress, the cross-sectional design does not allow conclusions regarding causality, and these activities may reflect reactive coping behaviours among distressed students rather than protective effects. The findings underscore the need for universities to strengthen culturally responsive mental health support, improve awareness and accessibility of counselling services, and develop interventions that address discrimination, financial strain, and cross-cultural adjustment difficulties among international postgraduate students.

## ACKNOWLEDGMENTS

We thank the students who took part in this study for their time and willingness to participate. We also thank Universiti Putra Malaysia for permitting us to conduct this research.

## REFERENCES

1. UNESCO. Record number of higher education students highlights global need for recognition of qualifications. 2025 [cited Dec 2025]. Available from: https://www.unesco.org/en/articles/record-number-higher-education-students-highlights-global-need-recognition-qualifications
2. Fleck A. Chinese students are pivoting to Asian countries. Statista Daily Data. 2025 [cited Dec 2025]. Available from: https://www.statista.com/chart/35133/number-of-inbound-international-students-from-china
3. Xue W, Singh MKM. Unveiling the academic, sociocultural, and psychological adaptation challenges of Chinese international students in Malaysia: a systematic review. J Int Stud 2025; 15(2): 69-86.
4. Auerbach RP, Alonso J, Axinn WG, Cuijpers P, Ebert DD, Green JG, et al. Mental disorders among college students in the World Health Organization world mental health surveys. Psychol Med 2016; 46(14): 2955-70.
5. Mohamad NE, Mohd Sidik SM, Akhtari-Zavare M, Gani NA. The prevalence risk of anxiety and its associated factors among university students in Malaysia: a national cross-sectional study. BMC Public Health 2021; 21: 438.
6. Xie L, Xu Y. A systematic review on the factors affecting Chinese international students' mental health. Int J Adv Couns 2024; 46(2): 343-68.
7. Shek CHM, Chan SWC, Stubbs MA, Tong Lee RL. Promoting international students' mental health unmet needs: an integrative review. Int J Ment Health Promot 2024; 26(11): 905-24.
8. Zhai X, Razali AB. Uncovering challenges mainland Chinese international students face in English language communication in Malaysian higher education institutions. Asian J Univ Educ 2022; 18(4): 1130-41.
9. Zhao W. Exploring the influence of social media use motivations on acculturation orientations and psychological adaptation among Chinese students in Malaysia. PLoS One 2025; 20(5): e0323407.
10. Xu X, Tran LT, Xie X. Between decolonization and recolonization: investigating Chinese doctoral students in Malaysia as a case of global South-South student mobility. High Educ 2024; 87(5): 1193-209.
11. Wong SS, Wong CC, Ng KW, Bostanudin MF, Tan SF. Depression, anxiety, and stress among university students in Selangor, Malaysia during COVID-19 pandemics and their associated factors. PLoS One 2023; 18(1): e0280680.
12. Xu M, Jaffri HB, Yang X, Chor SL, Ma X. Psychological well-being in students: cultural adaptation and revision of the Ryff model. Interacción y perspectiva: Revista de Trabajo Social 2025; 15(3): 879-900.
13. Ahmed A, Mohamed M. Factors affecting the mental health of international students in Malaysia during COVID-19 pandemic: evidences from Universiti Utara Malaysia. Int J Public Health Clin Sci 2021; 8: 135-56.
14. Yusliza YM, Othman AK. An early study on perceived social support and psychological adjustment among international students: the case of a higher learning institution in Malaysia. Int J Bus Soc 2011; 12(2): 1-15.
15. Yakin HSM, Totu A. Managing acculturative stress and building an effective intercultural relation: a case study among international students at Universiti Malaysia Sabah. J Adv Humanit Soc Sci 2018; 4(6): 244-57.
16. Guo Y, Cheng C, Zeng Y, Li Y, Zhu M, Yang W, et al. Mental health disorders and associated risk factors in quarantined adults during the COVID-19 outbreak in China: cross-sectional study. J Med Internet Res 2020; 22(8): e20328.
17. Wang S, Matsuda E. The effects of stressful life events and negative emotions in relation to the quality of sleep: a comparison between Chinese and Japanese undergraduate students and Chinese international students. Jpn Psychol Res 2023; 65(2): 99-111.
18. Ying Z, Kondo A, Piao M. Mental health challenges among Chinese international students during COVID-19: a systematic review and meta-analysis of depression and anxiety. J Int Stud 2025; 15(8): 209-30.
19. Henry JD, Crawford JR. The short-form version of the Depression Anxiety Stress Scales (DASS-21): construct validity and normative data in a large non-clinical sample. Br J Clin Psychol 2005; 44(Pt 2): 227-39.
20. Ismail A, Kahwa KM. Prevalence, associated factors, and help seeking behavior related to psychological distress among international students at Universiti Kebangsaan Malaysia. Malays J Public Health Med 2020; 20(2): 215-23.

21. Magnusdottir E, Thornicroft G. Mental health of Chinese international students: narrative review of experiences in the UK. NIHR Open Res 2022; 2: 52.
22. Lin C, Tong Y, Bai Y, Zhao Z, Quan W, Liu Z, et al. Prevalence and correlates of depression and anxiety among Chinese international students in US colleges during the COVID-19 pandemic: a cross-sectional study. PLoS One 2022; 17(4): e0267081.
23. Zeng F, John WCM, Qiao D, Sun X. Association between psychological distress and mental help-seeking intentions in international students of National University of Singapore: a mediation analysis of mental health literacy. BMC Public Health 2023; 23: 2358.
24. Cao H, Lin W, Chen P. Counselling services and mental health for international Chinese college students in post-pandemic Thailand. Educ Sci 2022; 12(12): 866.
25. Koutra K, Pantelaiou V, Mavroeides G. Breaking barriers: unraveling the connection between mental health literacy, attitudes towards mental illness, and self-stigma of psychological help-seeking in university students. Psychol Int 2024; 6(2): 590-602.
26. Atherton K, Cornwall J. Psychological distress and help-seeking behaviour: Chinese international students in New Zealand. JANZSSA 2022; 30: 48-62.
27. Remes O, Brayne C, Lafortune L. The prevalence of anxiety disorders across the life course: a systematic review of reviews. Lancet 2014; 384: S66.
28. Arnett JJ. Emerging adulthood: a theory of development from the late teens through the twenties. Am Psychol 2000; 55(5): 469-80.
29. Grundström J, Konttinen H, Berg N, Kiviruusu O. Associations between relationship status and mental well-being in different life phases from young to middle adulthood. SSM Popul Health 2021; 14: 100774.
30. Adams KL, Saunders KE, Keown-Stoneman CDG, Duffy AC. Mental health trajectories in undergraduate students over the first year of university: a longitudinal cohort study. BMJ Open 2021; 11(12): e047393.
31. Li C, Ning G, Wang L, Chen F. More income, less depression? Revisiting the nonlinear and heterogeneous relationship between income and mental health. Front Psychol 2022; 13: 1016286.
32. Ma L, Yao H, Hou J. Exploring the relationship between supervisor support and anxiety of graduate students in China: the mediating role of scientific research efficacy. Asia Pac Educ Res 2024; 33(2): 321-9.
33. Sarwari AQ, Wahab MNA. Relationship between English language proficiency and intercultural communication competence among international students in a Malaysian public university. Int J Lang Educ Appl Linguist [Internet]. 2016 [cited Nov 2025]. Available from: http://journal.ump.edu.my/ijleal/article/view/494
34. Ahrari S, Krauss SE, Suandi T, Haslinda H, Sahimi NAHA, Olutokunbo AS, et al. A stranger in a strange land: experiences of adjustment among international postgraduate students in Malaysia. Issues Educ Res 2019; 29(3): 611-32.
35. Bi K, Yeoh D, Jiang Q, Wienk MNA, Chen S. Psychological distress and everyday discrimination among Chinese international students one year into COVID-19: a preregistered comparative study. Anxiety Stress Coping 2023; 36(6): 727-42.
36. Yang CY, Bai L. Psychological adjustment of Chinese PhD students: a narrative study. Int J Dr Stud 2020; 15: 595-614.
37. Wilson S, Hastings C, Morris A, Ramia G, Mitchell E. International students on the edge: the precarious impacts of financial stress. J Sociol 2023; 59(4): 952-74.
38. Rasheed A, Ahsan S, Zaheer S. Impact of Internet gaming disorder on self-appraisal among university students: moderating role of gender. Pak J Psychol Res 2021; 36(3): 451-71.
39. Berry JW. Immigration, acculturation, and adaptation. Appl Psychol 1997; 46(1): 5-34.
40. Hobfoll SE. Conservation of resources: a new attempt at conceptualizing stress. Am Psychol 1989; 44(3): 513-24.

# Profile, risk factors, genotype and outcome of *Staphylococcus aureus* catheter related blood stream infection in a Malaysian tertiary hospital

**Nian Jye Tay, MPath (Microbiology, USM)[1], Wei Chuan Chua, MPath (Microbiology, USM)[1,2], Intan Baiduri Badri, (MSc, Nursing USM)[2,3], Habsah Hasan, MPath (Microbiology, USM)[1,2], Mohammed Hussain Abdulrazak, (MSc, BUK Nigeria)[1,4], Siti Asma' Hassan, MPath (Microbiology, USM)[1,2]**

[1]Department of Medical Microbiology & Parasitology, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia, [2]Hospital Pakar USM, Health Campus, USM, Kubang Kerian, Kelantan, Malaysia, [3]School of Health Sciences, Universiti Sains Malaysia, Health Campus, Kelantan, Malaysia, [4]Department of Pharmacology, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia

## ABSTRACT

**Introduction: *Staphylococcus aureus* is a commonly known causative agent of catheter related bloodstream infections (CRBSI) and complicated CRBSI. This study aimed to detect prevalence of *S. aureus* and complicated *S. aureus* CRBSI, their virulence genes and evaluate their association with development of complicated CRBSI, patient risk factors and outcomes.**

**Materials and Methods: A cross-sectional study involving retrospective record review of CRBSI cases was conducted from January 2019 to December 2021. A total of 139 CRBSI cases were identified. Patients' clinical data, risk factors and outcomes of *S. aureus* CRBSI were analyzed. Nineteen isolates from patients with complicated *S. aureus* CRBSI were selected for detection of *Cna, Chp* and *Cap8* gene using PCR. The association between the development of complicated *S. aureus* CRBSI and the presence of virulence genes was analyzed.**

**Results: Forty-three (31%, n=43) of CRBSI cases were caused by *S aureus*. Among these, nineteen cases (44.2%) were complicated. Patients with chronic kidney disease (CKD) or end-stage renal failure (ESRF) (adjusted OR 11.11, 95% CI: 2.86–33.33, p<0.001) were at significant risk of S.aureus CRBSI. Virulence genes detected were *Cap8* (89.5 %, n=17), *Cna* (47.4%, n=9) and *Chp* (26.3%, n=5). The presence of these genes was not significantly associated with the development of complicated *S.aureus* CRBSI. *S. aureus* CRBSI were associated with higher mortality (p=0.035).**

**Conclusion: *S. aureus* was the predominant agent for CRBSI and 44.2% of them were complicated. CKD/ESRF were the comorbidities associated with *S. aureus* CRBSI. Although cap8 was the most frequently detected virulence gene, it was not associated with the development of complicated *S. aureus* CRBSI.**

**KEYWORDS:**
*Staphylococcus aureus; catheter related bloodstream infection; risk factor; virulence gene; complicated catheter related bloodstream infections*

## INTRODUCTION

The use of intravascular central catheters has become an important component of patient care and management. They function by providing secure access to the circulation for procedures like hemodialysis and administration of medication or chemotherapy. The undesired side effect associated with catheter use is the increase in cases of Catheter Related Bloodstream Infections (CRBSI). In the years 2008 to 2013, the incidence was estimated to be around 30,100 in intensive care units and acute care wards.[1] It poses burden to both patients and the healthcare system as it results in significant mortality, longer hospital stays and higher hospital costs.[2] Among the organisms that cause CRBSI, *S. aureus* was the most frequent isolate.[3] *S. aureus* is a Gram-positive aerobic bacterium that has a niche preference for the anterior nares.[4] Community-acquired *S. aureus* was associated with native and prosthetic valve endocarditis, skin, and soft tissue infections, and osteoarticular infection; while healthcare-acquired *S. aureus* infection was associated with devises or procedure in the form of ventilator-associated pneumonia, CRBSI and surgical site infection.[3] The mortality rate associated with invasive *S. aureus* bacteremia has been found to range between 20-37%.[5-6] Apart from high mortality, *S. aureus* that caused CRBSI also causes complicated CRBSI. Complicated CRBSI is defined according to van der Vaart et al[7] as the presence of either one of the following:

a) Development of endocarditis (according to modified Duke criteria)
b) Septic thrombophlebitis (persistent *S. aureus* bacteremia for >72 hours after the initiation of active therapy associated with the documentation of a thrombus at the site of catheter insertion).
c) Septic metastatic infection, including arthritis, spondylodiscitis, infection involving vascular osteoarticular prostheses or end-organ hematogenous seeding to other location.
d) Persistent bacteremia >72 hours or
e) persistent fever for more than four days after extraction of the first blood culture yielding *S. aureus*, provided that alternative cause had been reasonably excluded.[7] The development of complicated *S. aureus* CRBSI in certain patients but sparing others had led to doubts regarding pathogen factor that affect the different outcome. San-

*This article was accepted: 24 June 2026*
*Corresponding Author: Associate Professor Dr. Siti Asma' Hassan*
*Email: sitiasmakb@usm.my*

Juan et al had demonstrated in their multicenter research the pathogen factor for developing complicated *S. aureus* CRBSI was *Cap*8, *Cna* and *Chp* gene.[8]

The *Cna* gene encodes a collagen binding protein, a structure that is part of the microbial surface components recognizing adhesive matrix molecule (MSCRAMMS) They are cell wall adhesins that function by binding to host collagen. The catheter placement into blood vessel is followed by subsequent coating with patient serum that is rich in fibrin. Collagen will enhance collagen-binding protein expression and contribute to the biofilm formation. Meanwhile the *Cap*8 gene encodes capsule polysaccharide 8, which plays a role in evading the human immune response through its antiphagocytic function. The *Chp* gene encodes a chemotaxis inhibitory protein that impairs the neutrophil recruitment. Data pertaining to the above aspects were limited and therefore, this study objectives of this study were to describe the profile of CRBSI in our health center, analyze the risk factors and outcomes of *S. aureus* CRBSI and identify the proportion of complicated *S. aureus* CRBSI and *S. aureus* virulence genes (*Cap*8, *Cna* and *Chp*), as well as the association between the two.

## MATERIALS AND METHODS

This study received approval from local research ethics committee (Reference No: USM/JEPeM/21020189) for data collection from patients' medical record. A cross-sectional study involving retrospective record review of CRBSI cases which were carried out from January 2019 till December 2021 at a tertiary teaching hospital which has a capacity of 800 bedded patients. Convenience sampling was used for sample collection. Inclusion criteria include cases that were clinically diagnosed with CRBSI, and the paired culture result that fulfilled the differential time to positivity between central and peripheral of two hours or more. Exclusion criteria were cases with inadequate clinical history. A total of 139 isolates from cases of CRBSI were collected over the study period. All the *S. aureus* isolate were identified based on phenotypic characteristics; round convex colony with or without beta hemolysis on blood agar, Gram-stain showing Gram positive cocci in cluster, biochemical test catalase, and coagulase positive; and positive with latex agglutination test Staphaurex Plus (Thermo Fisher Scientific, Waltham, U.S.A.). Only methicillin sensitive *S.aureus* (MSSA) will be included in the research. The antibiotic sensitivity testing for methicillin was carried out using disc diffusion (Kirby Bauer) method, with interpretive breakpoint provided by Clinical and Laboratory Standards Institute (CLSI M100 31st edition. All 19 samples of complicated *S. aureus* CRBSI were selected and subjected to exploratory subset analysis using molecular PCR to detect the presence of the gene *Cna, Chp* and *Cap*8.

### DNA extraction

Nineteen phenotypically confirmed *S. aureus* colonies were subjected to DNA extraction via DNA lysate boiling method. Two loopful of the colonies were taken from blood agar plate of *S. aureus* incubated overnight in $CO_2$. It was mixed into 100µl of distilled water and stirred adequately until no sediment was observed. The mixture was then boiled at 100ºC for ten minutes, followed by centrifugation at 12,000 rpm for five minutes to remove all the cell debris. The supernatant formed after centrifugation was transferred into a new tube while the cell debris was discarded. The lysate was then stored and kept in 4ºC while waiting for subsequent PCR analysis.

### PCR analysis

Each PCR reaction mixture (total volume 25 µl) was prepared by pipetting 3µl of DNA lysate, 7.5µl distilled water, 1µl of 25 µM forward and reverse primer, 12.5µl of MyTaq Red Mix DNA polymerase buffer (Bioline, Cincinnati, U.S.A). The sequence for the primer used in the study are listed in Table I. The temperature and time required for denaturation and elongation are the same for the three target genes and one housekeeping gene, which were initially denatured at 95ºC for five minutes, with subsequent denaturation at 95ºC for 30 second, annealing at 60ºC for 30 second, elongation at 72ºC for 30 second, followed by final elongation at 72ºC C for 5 minutes. This was followed by 35 cycles of denaturation, annealing, and extension. Post amplification analysis was carried out with gel electrophoresis method by detection of present of band.

### Data collection and statistical analysis

The medical record of all the patients diagnosed with CRBSI was retrieved and reviewed. Patient data including demographic information, comorbidity and outcome were extracted from medical records for analysis.

All the data were analyzed using IBM SPSS Statistic version 27. The profile of *S. aureus*, the proportion of virulence gene in complicated *S. aureus* CRBSI and proportion of complicated CRBSI were presented as descriptive statistics. The association between risk factor for *S. aureus* CRBSI were analyzed using univariate analysis, the risk factors with p-value of <0.25 were further analysed using multiple logistic regression. While outcome of *S. aureus* CRBSI and association between complicated *S. aureus* CRBSI with virulence gene were analyzed using Pearson Chi Square.

## RESULTS

A total of 139 CRBSI cases were included in the study. Forty-three cases (31%, n=43) were caused by *S. aureus* and nineteen of them (44.2 %) developed complicated *S aureus* CRBSI. The demographic data of study participants is summarized in Table II. The mean age for patient with CRBSI was 46-year-old, with male being slightly more common than female More than half of them have comorbidity of diabetes mellitus and CKD or ESRF. The most common reason for intravascular catheterization was for indication of hemodialysis, and the insertion of catheter over the internal jugular or subclavian chemoport was more frequently seen than femoral catheter.

*Staphylococcus aureus* was the most frequent organism causing CRBSI followed by another Gram-positive organism which was coagulase-negative *Staphylococcus*. Association between *S. aureus* CRBSI with its risk factors are as shown in Table III. Multiple regression analysis showed that the development of S. aureus CRBSI was significantly associated with patient having CKD/ESRF (adjusted OR 11.11, 95% CI:

2.86–33.33, p<0.001), while hematological malignancy and diabetes mellitus were not significantly associated with *S. aureus* CRBSI. The site of catheter did not have a significant association with development of *S. aureus* CRBSI. With regards to outcome, *S. aureus* CRBSI patient was significantly associated with outcome of death (p=0.035) (Table IV). The mortality rate for S.aureus CRBSI is this study was 32.6% (95% CI : 18.6- 46.6%). About 15.9% of the risk of death in CRBSI can be attributed to the *S. aureus* infection, compared to the control group.

All nineteen cases of complicated *S.aureus* CRBSI were selected for molecular detection of virulence gene namely *Chp, Can* and *Cap*8.The results were as shown in Figure 1a and b. *Cap*8 gene was most commonly present (n=17,89%) followed by *Cna* gene (n=9, 47%) and *Chp* gene (n=5,26%).

## DISCUSSION

In this retrospective analysis of over a three years duration in patients diagnosed with CRBSI, *S. aureus* was found to be the most common etiological agent. This finding is in accordance with other studies that describe the common pathogen causing CRBSI.[9] However, some studies showed a decreasing trend in cases of *S. aureus* causing CRBSI.[10]

There are limited Southeast Asian studies specifically focusing on complicated S.aureus CRBSI and bacteremia. A Singapore tertiary-hospital study of 100 patients with community-onset MSSA bacteremia found that 46% developed complicated bacteremia and 18% developed infective endocarditis. The attributable mortality was 11%.[11]

Intravascular access over internal jugular vein was usually preferred over femoral vein due to its direct path into superior vena cava and hence is less technically challenging. It is also more convenient for the patient to ambulate and move around. Thus, it was not surprising that it was being used more commonly in this study compared to femoral catheter. A published randomized controlled trial that compared the site of intravascular catheterization between jugular vein and femoral vein found that the rates of CRBSI (2.3 vs. 1.5 per 1000 catheter days, respectively; p=0.42) and catheter colonization (35.7 vs. 40.8 per 1000 catheter days, respectively; p=0.031) were similar in both groups.[12] This explains the finding where the site of vascular access was not found to be significantly associated with *S. aureus* CRBSI.

Renal replacement therapy has become a life-sustaining option for patients with renal failure. The 26th Report of the Malaysian Dialysis and Transplant Registry 2018 revealed that haemodialysis was a more common choice compared to peritoneal dialysis, where among 8431 newly dialyzed patient, 7200 used hemodialysis while 1231 patients used peritoneal dialysis.[13] Among the three types of vascular access for haemodialysis, namely arteriovenous fistula, arteriovenous graft and central venous catheter, the latter was less desired due to complications including catheter-related infection. In the HEMO study, a multicenter randomized clinical trial designed to evaluate the effect of haemodialysis dose and flux on morbidity and mortality, access-related infection was present in 32% of study patients despite central venous catheter being used for 7.2% of vascular access.[14] The increase in negative outcomes associated with central venous catheters was also shown in a systematic review of 62 cohort studies, where individuals using catheters had higher risks for fatal infections when compared to those with fistula (2.12, CI 1.79–2.52) and to those with graft (1.49, CI 1.15–1.93).[15] The microorganism that was responsible for CRBSI among renal failure patients was commonly found to be *S. aureus*, as shown from a literature published by one of the local university hospitals as well as a 12-year review from a tertiary referral hospital.[16-17] This finding was in concordance with the result from this study that showed statistical association between *S. aureus* and patients with CKD or ESRF. Apart from catheter-related bacteraemia, the nasal carriage rate of *S. aureus* was also high among dialysis patients and can be found in up to 41% of the cases.[18] This colonization eventually became the route of acquiring *S. aureus* CRBSI where the infection was endogenously acquired.[19] A genotypic study was able to demonstrate the correlation where in more than 80% of the cases of bacteremia strain was genotypically similar to the strain carried in the patient's nasal cavity.[20] This correlation had led to the use of antimicrobials for nasal eradication of the *S. aureus* reservoir, and a meta-analysis showed that the use of mupirocin for eradication was associated with a 59% (cpRR, 0.41; 95% confidence interval [CI], 0.36–0.48) reduction in *S. aureus* infection among dialysis patients.[21]

Diabetes mellitus is a metabolic disease with potential systemic complication. It affects the innate and acquired immunity and causes patients to become susceptible to infection.[22] However, the association between diabetes and developing *S. aureus* bacteraemia due to CRBSI was less straightforward. The association between the two was found in a retrospective study carried out in a university-affiliated hospital.[23] However, the diabetic patients included in the study were also dialysis-dependent (as discussed earlier, ESRF was associated with *S. aureus* CRBSI), and only univariate analysis was done causing it to be affected by other confounding variables. This was seen in our study where the association between the two was statistically significant with Pearson Chi Square test but found to be insignificant when using multiple logistic regression.

A recent retrospective study that compared two groups of cancer patients from 1999 to 2000 and 2013 to 2014 that was published by Chaftari et al showed that Gram-negative organism made up 41% of the CRBSI cases.[24] Furthermore, another study demonstrated the change in epidemiology of causative organisms from predominantly Gram-positive to Gram-negative.[25] This was in concordance with our study that found *S. aureus* to be not significantly associated with CRBSI in patients with hematological malignancy.

*S. aureus* bacteraemia is known to be associated with substantial mortality. In a study where nosocomial *S. aureus* bacteraemia was predominantly catheter-related (61%), the mortality rate was found to be 20%.[26] Another ten-year prospective cohort study showed that CRBSI cases with *S. aureus* as the etiological organism were associated with significant mortality. This was in accordance with the findings from this study.[27]

**Table I: List of Primers used for the optimization of PCR Assay**

| Target gene | Sequence | Primer size | Reference |
|---|---|---|---|
| Chp- F | 5′- ACG GCA GGA ATC AGT ACA CA- 3′ | 291 | de Haas CJ et al 2004 |
| Chp- R | 5′- TCT ATC TTC AGC AAG TGG TGT- 3′ | 291 | |
| Cap 8- F | 5′- TGG CGC AAG AGG TTC AAA GT-3′ | 307 | Sau, S et al year 1996 |
| Cap 8- R | 5′- ACT GCT GTA CCG TCT GCT TT- 3′ | 307 | |
| Cna- F | 5′-CCA AGG CTC CTA TAG CTA ATG T -3′ | 310 | Yamamoto et al., 2006 |
| Cna- R | 5′-TGA GTG CCT TCC CAA ACC TT -3′ | 310 | |
| Arc- F | 5′-TTG ATT CAC CAG CGC GTA TTG TC -3′ | 456 | Buttimer et al 1995 |
| Arc- R | 5′-AGG TAT CTG CTT CAA TCA GCG -3′ | 456 | |

**Table II: Demographic data of CRBSI cases during the study period.(n=139)**

| Variable | Frequency (n,%) |
|---|---|
| Age (Mean) | 46 |
| Gender | |
| Male | 78 |
| Female | 61 |
| Comorbidities | |
| Diabetes mellitus | 77, 55% |
| Chronic kidney disease/End stage renal failure | 77, 55% |
| Solid tumour | 14, 10% |
| Haematological malignancy | 25, 18% |
| Catheter Site | |
| IJC catheter | 84, 60% |
| Femoral catheter | 55, 40% |
| Indication for catheterization | |
| Antibiotic | 23, 17% |
| Chemotherapy | 32, 22% |
| Haemodialysis | 76, 55% |
| Total Parental Nutrition | 8, 6% |
| Microorganisms | |
| Staphylococcus aureus | 43, 31% |
| Coagulase negative Staphylococci | 21, 15% |
| Other Gram positive organisms | 17, 12% |
| Enterobacterales | 24, 17% |
| Non Enterobacterales | 23, 17% |
| Yeast | 11, 8% |
| ICU admission | |
| Yes | 33, 24% |
| Nil | 106, 76% |
| Outcome | |
| Death | 109, 22% |
| Survive | 30, 78% |

**Table III: S. aureus CRBSI with its associated risk factors**

| | Crude ORa (95% CI) | p-value | Adjusted ORb (95% CI) | p-value | Wald statistics (df) | p-value |
|---|---|---|---|---|---|---|
| Chronic kidney disease/ End stage renal failure | 11.1 (4.0, 30.7) | <0.001 | 11.11 (2.86–33.33) | <0.001 | 12.19 | <0.001 |
| Non chronic kidney disease/End stage renal failure | 1.0 | | 1.0 | | | |
| Diabetes mellitus | 3.4 (1.6, 7.6) | 0.02 | 0.9 (0.3,2.6) | 0.889 | 0.02 | 0.889 |
| Non diabetes mellitus | 1.0 | | 1.0 | | | |
| Haematological malignancy | 0.16 (0.04, 0.69) | 0.06 | 1.0 (0.15,6.84) | 0.989 | <0.01 | 0.989 |
| Non haematological malignancy | 1.0 | | 1.0 | | | |
| Femoral catheter | 0.137 (0.19,0.139) | 0.137 | - | - | - | - |
| Non femoral catheter | - | - | - | - | - | - |

*Simple logistic regression and multiple logistic regressionb was applied. All the assumption met (Classification table=69.1; Hosmer Lemeshow value=0.74; Area under the curve ROC=0.74(0.83,0.66)
Adjusted OR 11.11 (95% CI: 2.86–33.33).

**Table IV: S. aureus CRBSI with its associated outcome**

| | Staphylococcus aureus | Non-Staphylococcus aureus | $X^2$(df) | p-value |
|---|---|---|---|---|
| Death | 14 | 16 | 1 | 0.035 |
| Survive | 29 | 80 | | |

Attributable Risk = 0.326–0.167=0.159 (15.9%)
Mortality rate = 32.6% (95% CI = 18.6% - 46.6%)

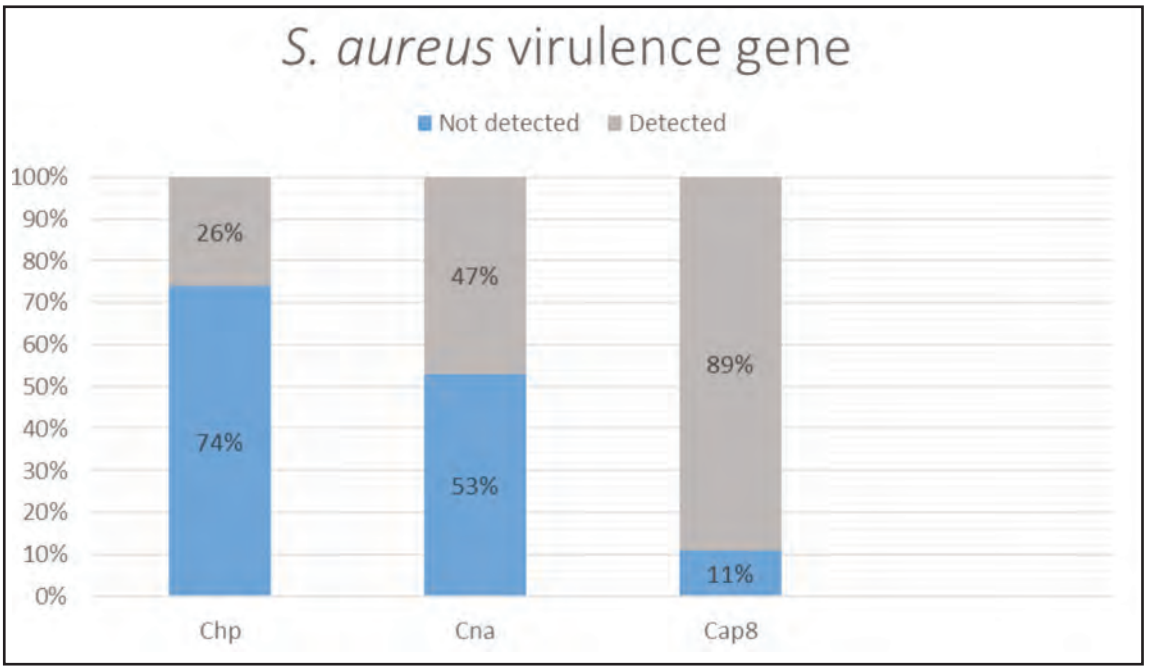



**Fig. 1a:** Virulence gene detected among selected *S. aureus* CRBSI (n=19)

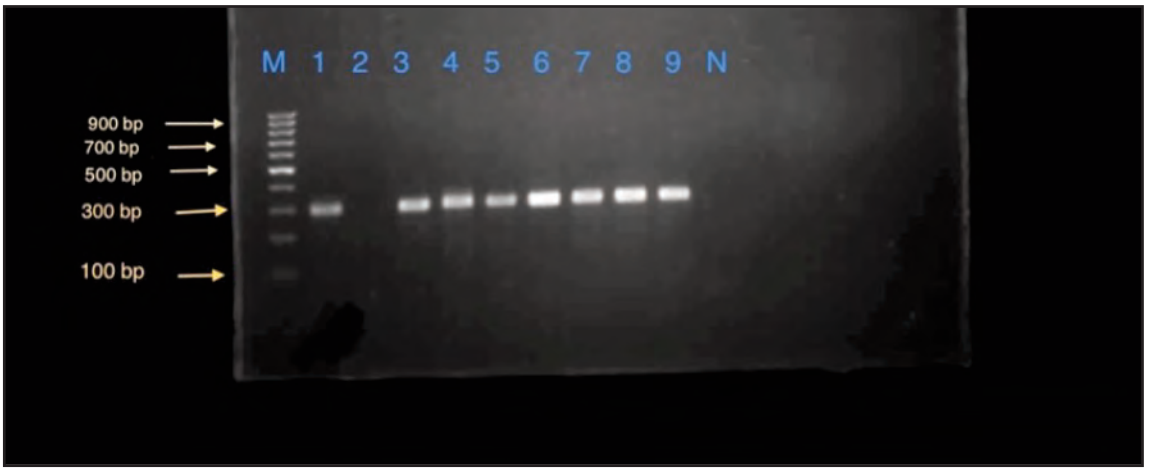



**Fig. 1b:** Representative image of agarose gel electrophoresis of monoplex PCR assay targeting *S.aureus* DNA amplicon using virulence gene Cap8 primer
Lane M: 100bp DNA ladder, Lane 1: STAU 001, Lane 2:STAU 002, Lane 3:STAU 003, Lane 4:STAU 004, Lane 5:STAU005, Lane 6:STAU 006, Lane 7:STAU 007, Lane 8:STAU 008, Lane 9: STAU 009, Lane N: Negative control

Patients without complicated CRBSI were more frequent than patients with complicated CRBSI, with this study recording 44.2% among *S. aureus* CRBSI patients, a percentage higher than that recorded by San-Juan et al[8] of 31.3%. However other findings like the most common virulence gene (*Chp* gene in San-Juan et al[8], *Cap*8 in this study) and the association between the three virulence genes and the development of complicated CRBSI (*Chp, Cna, Cap*8 respectively was not found to be statistically significant in this study) could be due to the molecular detection being only an exploratory subset analysis in a single center study with smaller sample size.

*S.aureus* colonization has several important implications in healthcare. This study showed that patients with renal failure have a significant risk of developing *S. aureus* CRBSI. This group of patients with ESRF may benefit from nasal swab screening for *S. aureus* colonisation. The same applies to other immunocompromised patients such as patients with malignancy. This is supported by published systematic reviews and meta-analyses indicating that nasal screening for *S. aureus* in haemodialysis patients could help to identify carriers, and when combined with decolonization therapy, could significantly reduce catheter infections and bloodstream infections.[28-29]

## CONCLUSION

This study shows that CKD or ESRF was the comorbidity associated with the development of *S. aureus* CRBSI. Complicated *S. aureus* CRBSI contributed about 44.2% of total *S. aureus* CRBSI. The most common virulence gene was *Cap*8. The retrospective design, single-center setting and small genotypic sample size could be the limiting factors for finding significant association between the virulence gene and complicated CRBSI.

## ACKNOWLEDGMENTS

The authors would like to acknowledge the Department of Medical Microbiology and Parasitology and Hospital Pakar USM for allowing the project to be conducted in their laboratory facility and for giving access to patients' data from medical records. The laboratory experiments for this project were conducted using University Research Grant: RUI:1001/PPSP/8012258

## REFERENCES

1. CDC. 2014 HAI Progress Report. Centers for Disease Control and Prevention; 2014 [cited 2025 Sep 4]. Available from: https://www.cdc.gov/hai/data/archive/2014-progress-report.html
2. Al-Rawajfah OM, Hewitt JB, Stetzer F, Cheema J. Length of stay and charges associated with health care-acquired bloodstream infections. Am J Infect Control 2012; 40(3): 227-32.
3. Weiner-Lastinger LM, Abner S, Edwards JR, Kallen AJ, Karlsson M, Magill SS, et al. Antimicrobial-resistant pathogens associated with adult healthcare-associated infections: summary of data reported to the National Healthcare Safety Network, 2015–2017. Infect Control Hosp Epidemiol 2020; 41(1): 1-18.
4. Sakr A, Brégeon F, Mège JL, Rolain JM, Blin O. Staphylococcus aureus nasal colonization: an update on mechanisms, epidemiology, risk factors, and subsequent infections. Front Microbiol 2018; 9: 2419.
5. Fätkenheuer G, Preuss M, Salzberger B, Schmeißer N, Cornely OA, Wisplinghoff H, et al. Long-term outcome and quality of care of patients with Staphylococcus aureus bacteremia. Eur J Clin Microbiol Infect Dis 2004; 23(3): 157-62.
6. Hill PC, Birch M, Chambers S, Drinkovic D, Ellis-Pegler RB, Everts R, et al. Prospective study of 424 cases of Staphylococcus aureus bacteraemia: determination of factors affecting incidence and mortality. Intern Med J 2001; 31(2): 97-103.
7. van der Vaart TW, Prins JM, Goorhuis A, Lemkes BA, Sigaloff KCE, Spoorenberg V, et al. The utility of risk factors to define complicated Staphylococcus aureus bacteremia in a setting with low methicillin-resistant S. aureus prevalence. Clin Infect Dis 2024; 78(4): 846-54.
8. San-Juan R, Pérez-Montarelo D, Viedma E, Lalueza A, Fortún J, Loza E, et al. Pathogen-related factors affecting outcome of catheter-related bacteremia due to methicillin-susceptible Staphylococcus aureus in a Spanish multicenter study. Eur J Clin Microbiol Infect Dis 2017; 36(10): 1757-65.
9. Kaur M, Gupta V, Gombar S, Chander J, Sahoo T. Incidence, risk factors, microbiology of venous catheter associated bloodstream infections: a prospective study from a tertiary care hospital. Indian J Med Microbiol 2015; 33(2): 248-54.
10. Buetti N, Lo Priore E, Atkinson A, Widmer AF, Kronenberg A, Marschall J. Catheter-related infections: does the spectrum of microbial causes change over time? A nationwide surveillance study. BMJ Open 2018; 8(12): e023824.
11. Chia JWZ, Hsu LY, Chai YA, Tambyah PA. Epidemiology and outcomes of community-onset methicillin-susceptible Staphylococcus aureus bacteraemia in a university hospital in Singapore. BMC Infect Dis 2008; 8: 14.
12. Parienti JJ, Thirion M, Mégarbane B, Souweine B, Ouchikhe A, Polito A, et al. Femoral vs jugular venous catheterization and risk of nosocomial events in adults requiring acute renal replacement therapy: a randomized controlled trial. JAMA 2008; 299(20): 2413-22.
13. National Renal Registry. 26th report of the Malaysian Dialysis and Transplant Registry 2018. Malaysian Society of Nephrology; 2018 [cited 2025 Sep 4]. Available from: https://www.msn.org.my/nrr/26th-report-of-the-malaysian-dialysis-and-transplant-registry-2018/
14. Allon M, Depner TA, Radeva M, Bailey J, Beddhu S, Butterly D, et al. Impact of dialysis dose and membrane on infection-related hospitalization and death: results of the HEMO Study. J Am Soc Nephrol 2003; 14(7): 1863-70.
15. Ravani P, Palmer SC, Oliver MJ, Quinn RR, MacRae JM, Tai DJ, et al. Associations between hemodialysis access type and clinical outcomes: a systematic review. J Am Soc Nephrol 2013; 24(3): 465-73.
16. Shahar S, Mustafar R, Kamaruzaman L, Periyasamy P, Pau KB, Ramli R. Catheter-related bloodstream infections and catheter colonization among haemodialysis patients: prevalence, risk factors, and outcomes. Int J Nephrol 2021; 2021: 5562690.
17. Fitzgerald SF, O'Gorman J, Morris-Downes MM, Crowley RK, Donlon S, Bajwa R, et al. A 12-year review of Staphylococcus aureus bloodstream infections in haemodialysis patients: more work to be done. Clin Nephrol 2011; 75(5): 401-6.
18. Lederer SR. Nasal carriage of methicillin resistant Staphylococcus aureus: the prevalence, patients at risk and the effect of elimination on outcomes among outclinic haemodialysis patients. Eur J Med Res 2007; 12(7): 284-8.
19. Lemaire X, Morena M, Leray-Moragués H, Henriet-Viprey D, Chenine L, Defez-Fougeron C, et al. Analysis of risk factors for catheter-related bacteremia in 2000 permanent dual catheters for hemodialysis. Blood Purif 2009; 28(1): 21-8.
20. von Eiff C, Becker K, Machka K, Stammer H, Peters G. Nasal carriage as a source of Staphylococcus aureus bacteremia. N Engl J Med 2001; 344(1): 11-6.
21. Nair R, Perencevich EN, Blevins AE, Goto M, Nelson RE, Schweizer ML. Clinical effectiveness of mupirocin for preventing Staphylococcus aureus infections in nonsurgical settings: a meta-analysis. Clin Infect Dis 2016; 62(5): 618-30.

22. Daryabor G, Atashzar MR, Kabelitz D, Meri S, Kalantar K. The effects of type 2 diabetes mellitus on organ metabolism and the immune system. Front Immunol 2020; 11: 1582.
23. Shahani L, Noggle C, Khardori N. Changing microbiology of indwelling venous catheter related infection. Clin Res 2018; 2018: 224.
24. Chaftari AM, Hachem R, Jiang Y, Shah P, Al Hamal Z, Hussain A, et al. Changing epidemiology of catheter-related bloodstream infections in cancer patients. Infect Control Hosp Epidemiol 2018; 39(6): 727-9.
25. Braun E, Hussein K, Geffen Y, Rabino G, Bar-Lavie Y, Paul M. Predominance of Gram-negative bacilli among patients with catheter-related bloodstream infections. Clin Microbiol Infect 2014; 20(10): O627-9.
26. Kaech C, Elzi L, Sendi P, Frei R, Laifer G, Bassetti S, et al. Course and outcome of Staphylococcus aureus bacteraemia: a retrospective analysis of 308 episodes in a Swiss tertiary-care centre. Clin Microbiol Infect 2006; 12(4): 345-52.
27. Saliba P, Hornero A, Cuervo G, Grau I, Jimenez E, García D, et al. Mortality risk factors among non-ICU patients with nosocomial vascular catheter-related bloodstream infections: a prospective cohort study. J Hosp Infect 2018; 99(1): 48-54.
28. BC Young, AA Votintseva, D Foster, H Godwin, RR Miller, LW Anson, et al. Multi-site and nasal swabbing for carriage of Staphylococcus aureus: what does a single nose swab predict? Journal of Hospital Infection Volume 96, Issue 3, July 2017, Pages 232-37.0
29. Grothe C, Taminato M, Belasco A, Sesso R, Barbosa D. Screening and treatment for Staphylococcus aureus in patients undergoing hemodialysis: a systematic review and meta-analysis. BMC nephrology 2014; 15(1): 202.

ORIGINAL ARTICLE

# Factors associated with non-attendance at initial tuberculosis screening among contacts in Kudat, Sabah

**Holly Girlchy Jastin, MPH[1], Veshny Ganesan, MPH[1], Mohd Helmi Abdul Hamid, MBBS[2], Richard Avoi, MPH[1]**

[1]Faculty of Medicine and Health Sciences, Universiti Malaysia Sabah, Kota Kinabalu, Sabah, Malaysia, [2]Kudat District Health Office, Kudat, Sabah, Malaysia

## ABSTRACT

**Introduction: Tuberculosis (TB) contact screening is a key strategy for early case detection and prevention of transmission. However, non-attendance at initial TB screening among contacts remains a persistent challenge, particularly in high-burden settings such as Sabah, Malaysia. This study aimed to determine factors associated with non-attendance at initial TB screening among contacts in Kudat, Sabah.**

**Materials and Methods: A case–control study was conducted using primary and secondary data from the National Tuberculosis Registry involving 468 TB contacts registered between June and December 2023. Cases were contacts who failed to attend initial screening within one month, while controls attended screening within the same period. Data were analysed using descriptive statistics and multiple logistic regression.**

**Results: Multivariable logistic regression analysis revealed that factors associated with lower odds of non-attendance included contacts of male TB index patients (OR: 0.30, 95% CI: 0.194–0.470), contacts of extrapulmonary TB index patients (OR: 0.09, 95% CI: 0.050–0.179), and higher attitude scores (OR: 0.88, 95% CI: 0.818–0.952). In contrast, contacts with secondary education had higher odds of non-attendance compared to those with no formal education (OR: 1.86, 95% CI: 1.080–3.209).**

**Conclusion: Non-attendance at initial TB screening among contacts was associated with index case sex and TB form, contact education level, and attitudes towards TB. Targeted interventions addressing behavioural and structural barriers are essential to improve TB contact screening uptake in high-burden settings.**

**KEYWORDS:**
*Tuberculosis; contact screening; non-attendance; risk factors; Sabah*

## INTRODUCTION

Tuberculosis (TB) remains one of the world's most persistent infectious diseases and a leading cause of death globally. According to the WHO Global Tuberculosis Report, Malaysia has an intermediate TB burden with an estimated incidence of 50–99 cases per 100,000 population per year, which is consistent with national notification data reporting 77.8 cases per 100,000 population.[1] The burden is disproportionately higher in certain states, with Sabah recording one of the highest TB notification rates in the country, largely attributed to socioeconomic factors, population density, and cross-border migration.[2]

A TB contact is defined as a person who has been exposed to an individual with infectious tuberculosis, typically through sharing airspace, including household members, coworkers, classmates, and other close contacts.[3] The effectiveness of contact screening programs largely depends on the active participation of identified contacts in the screening process. However, non-attendance at initial screening appointments has emerged as a critical barrier to successful TB control efforts globally.[4] Studies from various countries have reported non-attendance rates ranging from 20% to 60%, significantly undermining the potential impact of contact screening programs.[5] Delayed or missed screening opportunities are particularly concerning, as they may lead to undetected active TB cases continuing to transmit infection within communities, while individuals with latent TB infection (LTBI) lose the chance to benefit from preventive treatment.[6]

The factors influencing attendance at TB contact screening are complex and multifaceted, encompassing individual, social, economic, and health system-related determinants. Sociodemographic characteristics such as age, gender, education level, and socioeconomic status have been consistently identified as important predictors of screening attendance across different settings. Additionally, psychosocial factors including knowledge about TB, attitudes toward the disease and its prevention, and TB-related stigma play crucial roles in shaping health-seeking behaviors among TB contacts.[7]

In Malaysia, limited research has explored factors influencing TB contact screening attendance, particularly in high-burden areas such as Sabah. Kudat District, with its diverse ethnic communities, indigenous populations, and varied socioeconomic conditions, presents unique challenges for TB control. Identifying modifiable factors like knowledge, attitudes, and stigma, alongside non-modifiable factors such as demographics and index case characteristics, is crucial for designing targeted interventions. This study aims to address these gaps in Kudat using a case-control design, generating evidence to inform culturally appropriate strategies that enhance screening uptake and strengthen TB control efforts.

*This article was accepted: 24 June 2026*
*Corresponding Author: Richard Avoi*
*Email: richard.avoi@ums.edu.my*

## MATERIALS AND METHODS

### Study Design and Setting

A case-control study was conducted from February to June 2024 in Kudat District, Sabah, Malaysia. The study covered all five subdistricts of Kudat: Banggi, Tiga Papan, Tambuluran, Matunggong, and Dualog.

### Study Population

Cases were defined as TB contacts who failed to attend their initial screening within one month of being listed as a contact on Tuberculosis Information System (TBIS 10C-1). Controls were TB contacts who attended their initial screening within the same one-month timeframe.

Although national TB guidelines recommend screening within two weeks of notification, this study utilised a one-month timeframe to better reflect real-world programme implementation in rural settings such as Kudat. Evidence from Sabah indicates that delays in health-seeking behaviour are common, with a proportion of TB contacts reporting that they would wait up to 3–4 weeks before seeking care.[8] In addition, operational challenges such as work commitments, time constraints, and accessibility barriers have been identified as key factors affecting timely attendance in TB contact investigation.[8] Therefore, a one-month timeframe was considered appropriate to capture actual screening behaviour and minimise misclassification of delayed attenders as non-attenders.

### Study Variables

Variables in this study were categorised into TB index case characteristics and TB contact characteristics.

TB contacts were defined as individuals who had been exposed to a person with active TB disease, typically through shared airspace, including both household and non-household contacts identified through routine contact investigation.

TB index case variables included age, sex, form of tuberculosis, level of education, and nationality. The classification of TB form was based on the anatomical site of disease, categorised into pulmonary TB (PTB) and extrapulmonary TB (EPTB), in accordance with standard TB classification used in the National Tuberculosis Registry (NTBR). All forms of pulmonary TB, including smear-positive and smear-negative cases, were grouped under the PTB category, as both involve pulmonary disease and are relevant for contact investigation and transmission risk assessment.

TB contact variables included age, sex, nationality, category of contact (household or non-household), monthly income, level of education, and region. Education level was categorised into no formal education, primary education (7–12 years), secondary education (13–17 years), upper secondary education (pre-university level, including matriculation, STPM, O-Level, A-Level or equivalent), and tertiary education (diploma, bachelor's degree, master's degree, or doctoral level) based on the Malaysian education system. In addition, psychosocial variables including knowledge, attitude, and stigma towards TB were assessed using the validated KAPS-TB questionnaire.

The outcome variable was attendance at initial TB screening, categorised as non-attenders (cases) and attenders (controls).

### Study Settings

TB contacts were identified from all five subdistricts of Kudat District, namely Matunggong, Banggi, Dualog, Tambuluran, and Tiga Papan, based on available registry data from the NTBR. The distribution of cases and controls across subdistricts reflected the actual distribution of TB contacts recorded during the study period, rather than a predetermined or equal sampling allocation. As such, cases and controls were included proportionately based on real-world programme data, ensuring that the study sample was representative of the underlying population of TB contacts in Kudat District.

### Inclusion and Exclusion Criteria

Inclusion criteria included all adults aged 18 years and older, contacts of index TB cases with all forms of tuberculosis, contacts of deceased index TB cases, individuals able to understand Malay language, and consented participants. Exclusion criteria comprised contacts of TB patients with severe mental illness affecting ability to give informed consent.

### Sample Size Calculation

The required sample size was estimated for an unmatched case-control design based on detecting a minimum mean difference in knowledge, attitude, and stigma scores between contacts who attended and those who did not attend the initial tuberculosis screening. Standard deviations from previous literature were used for estimation.[8] Using a two-sided $\alpha$=0.05, power=80%, and a 1:1 control-to-case ratio, the largest calculated sample size across all domains was selected. After adding a 20% allowance for non-response, the final required sample size was 468 participants.

### Data Collection

Both primary and secondary data were utilized. Secondary data were extracted from NTBR, while primary data were collected through both Google Forms and hard copy questionnaires. TB healthcare staff facilitated recruitment via WhatsApp, phone calls, or home visits. Participants were provided with study information and gave informed consent before participation.

### Study Tools

Data was collected using a validated Malay version of the KAPS-TB (Knowledge, Attitude, Practice, and Stigma-TB) questionnaire. The questionnaire comprised four sections: sociodemographic characteristics, knowledge domain (25 items, Cronbach's alpha ≥0.65), attitude domain (5 items using 5-point Likert scale, Raykov's rho=0.557), and stigma domain (11 items using 5-point Likert scale, Raykov's rho=0.889).[9] Internal consistency of the KAPS-TB instrument was assessed using Cronbach's alpha.

### Statistical Analysis

Data was entered and analyzed using SPSS Version 29.0. Descriptive statistics summarized characteristics of both index TB cases and their contacts. Univariable associations were first explored using simple logistic regression, with

**Table I: Descriptive Analysis of the TB Index Characteristics**

| Variables | Frequency, n | Percentage, (%) |
|---|---|---|
| Age | | |
| mean (SD) | 43.6 (23.9) | - |
| Sex | | |
| Male | 45 | 60.0 |
| Female | 30 | 40.0 |
| Nationality | | |
| Malaysian | 68 | 90.7 |
| Non-Malaysian | 7 | 9.3 |
| Relationship | | |
| Spouse | 12 | 16.0 |
| Father/mother/child/uncle / aunt | 38 | 50.7 |
| Sibling/ first cousin | 7 | 9.3 |
| Grandparent/Grandchildren | 6 | 8.0 |
| No family Relation | 12 | 16.0 |
| Form of TB | | |
| Pulmonary | 62 | 82.7 |
| Extrapulmonary | 13 | 17.3 |
| Level of Education | | |
| No formal education | 26 | 34.7 |
| Primary Education | 18 | 24.0 |
| Secondary Education | 25 | 33.3 |
| Upper Secondary Education | 1 | 1.3 |
| Tertiary Education | 5 | 6.7 |
| Region | | |
| Matunggong | 16 | 21.3 |
| Banggi Dualog | 7 | 9.3 |
| Tambuluran | 6 | 8.0 |
| Tiga Papan | 7 | 9.3 |
| | 39 | 52.0 |

SD= Standard Deviation

variables having p<0.25 included in the multivariable analysis.

Multivariable logistic regression was conducted using the Enter method, as well as comparisons with stepwise forward and backward LR methods. Model fitness was assessed using the Hosmer–Lemeshow test (p=0.668) and Nagelkerke $R^2$=0.357, indicating acceptable fit.

**Ethical Considerations**

The study adhered to the Declaration of Helsinki and Malaysian Good Clinical Practice Guidelines. Anonymity was maintained by replacing patient names with research IDs. All data was stored on password-protected systems. Ethical approval was obtained from MREC.NMRR ID-24-00193-JED.

## RESULTS

A total of 75 TB index cases were included in the study. Table I presents the sociodemographic and clinical characteristics of the TB index cases.

Table II summarises the characteristics of TB contacts according to non-attendance at initial TB screening. Non-attenders were slightly younger (mean 40.1±13.3 years) compared to attenders (43.2±15.1 years). A higher proportion of non-attenders were female, had lower income, and were from non-household contact categories. Non-attenders also showed slightly lower knowledge scores and lower stigma scores compared to attenders, while attitude scores were similar between groups.

**Reliability of the Questionnaire**

The internal consistency of the KAPS-TB questionnaire was assessed using Cronbach's alpha. The knowledge domain demonstrated good reliability (Cronbach's alpha=0.84), while the stigma domain showed acceptable reliability (Cronbach's alpha=0.77). The attitude domain demonstrated lower internal consistency (Cronbach's alpha=0.54).

**Inferential Analysis**

Simple logistic regression was used to screen predictors of non-attendance at the initial TB screening (outcome coded 1=non-attender, 0=attender). Results are presented in Table III and Table IV. Odds ratios (OR), 95% confidence intervals (CI), and p-values are reported; OR > 1 indicates higher odds of non-attendance; OR < 1 indicates lower odds. Continuous variables were modelled for a per-unit increase. Variables with p<0.25 were carried forward to multivariable analysis.

**Factors Associated with Non-Attendance at Initial Tuberculosis Screening**

Simple logistic regression analysis identified several variables associated with non-attendance at initial TB screening. Variables with p-values < 0.25 were considered for inclusion in the multivariable analysis.[10] A total of 12 variables were included in the final model selection process using both forward and backward stepwise logistic regression. The enter method was used for the final model to adjust for potential confounding factors. The final model demonstrated good fit (Hosmer–Lemeshow p=0.668) with a Nagelkerke $R^2$ of 0.357, indicating that 35.7% of the variability in non-attendance was explained by the included predictors. Significant

**Table II: Descriptive Analysis of TB Contact Sociodemographic and Psychosocial Characteristics**

| Variables | Case (Non-attender), n = 224 (%) | Control (Attender), n = 252 (%) |
|---|---|---|
| Age | | |
| mean (SD) | 40.1 (13.3) | 43.2 (15.1) |
| Sex | | |
| Male | 115 (51.3) | 150 (59.5) |
| Female | 109 (49.7) | 102 (40.5) |
| Nationality | | |
| Malaysian | 211 (94.0) | 233 (92.5) |
| Non-Malaysian | 13 (5.8) | 19 (7.5) |
| Category of Contacts | | |
| Household | 92 (41.1) | 109 (43.3) |
| non-household | 132 (58.9) | 143 (56.7) |
| Monthly Income | | |
| <Rm 2500 | 175 (78.1) | 167 (66.3) |
| Rm2500-Rm3169 | 31 (13.8) | 37 (14.7) |
| Rm3170-Rm3969 | 4 (1.8) | 32 (12.7) |
| Rm3970-Rm4846 | 11 (4.9) | 11 (4.4) |
| >Rm4500 | 4 (1.8) | 5 (2.0) |
| Level of Education | | |
| Primary Education | 26 (11.6) | 49 (19.4) |
| Secondary Education | 135 (60.3) | 128 (50.8) |
| Upper Secondary Education | 9 (4.0) | 14 (5.6) |
| Tertiary Education | 14 (6.3) | 9 (3.6) |
| No formal education | 40 (17.9) | 52 (20.6) |
| Region | | |
| Matunggong | 53 (23.7) | 45 (17.9) |
| Banggi | 16 (7.1) | 22 (8.7) |
| Dualog | 1 (0.4) | 14 (5.6) |
| Tambuluran | 13 (5.8) | 39 (15.5) |
| Tiga Papan | 141 (62.9) | 132 (52.4) |
| Knowledge | | |
| median (IQR) | 18.5 (6) | 19.0 (4) |
| Attitude | | |
| median (IQR) | 21.0 (4) | 21.0 (4) |
| Stigma | | |
| median (IQR) | 40.0 (9) | 42.0 (6) |

SD= Standard Deviation, IQR= Interquartile Range

predictors included index sex, index TB form, contact education level, and contact attitude. Relationship type and TB contact stigma were not statistically significant (Table V).

Contacts of male TB index cases were significantly less likely to be non-attenders compared to those of female index cases (AOR=0.300; 95% CI: 0.194–0.470; p<0.001). Similarly, contacts of extrapulmonary TB index cases had lower odds of non-attendance compared to those of pulmonary TB index cases (AOR=0.090; 95% CI: 0.050–0.179; p<0.001).

Among TB contact characteristics, secondary education was associated with higher odds of non-attendance compared to no formal education (AOR=1.860; 95% CI: 1.080–3.209; p=0.025). In contrast, higher attitude scores were significantly associated with lower odds of non-attendance (AOR=0.880; 95% CI: 0.818–0.952; p=0.001).

Other variables, including relationship type and stigma, were not statistically significant.

## DISCUSSION

This study provides important insights into the factors associated with non-attendance at initial TB contact screening in Kudat, Sabah, contributing to the limited body of evidence on this critical public health issue in the Malaysian context. The findings reveal a complex interplay of demographic, clinical, educational, and psychosocial factors that influence screening attendance, with significant implications for TB control program design and implementation.

### Index Case Gender and Contact Screening Attendance

This finding may reflect sociocultural dynamics within the local context of Sabah, where male household members often assume decision-making roles and greater authority in family matters.

Contacts of male TB index patients were significantly less likely to be non-attenders compared to those of female index patients, with approximately 70% lower odds of non-attendance.

This observation is consistent with findings from various settings, including low- and middle-income countries, where gender roles influence health-seeking behaviour and healthcare utilisation, particularly in relation to family decision-making and access to resources.[11] This may be particularly relevant in Asian contexts, where traditional gender roles can influence healthcare engagement.

**Table III: Univariate Analysis of TB Contact Sociodemographic and TB Index Characteristics**

| Variables | COR | 95% CI | p-value |
|---|---|---|---|
| | TB Contact Sociodemographic | | |
| Age | 0.990 | 0.973-0.998 | 0.027 |
| Sex | | | |
| Male | 0.720 | 0.499-1.032 | 0.073 |
| Female | | | |
| Nationality | | | |
| Malaysian | | | |
| Non-Malaysian | 0.760 | 0.364-1.567 | 0.451 |
| Monthly income | | | |
| > Rm3170 | 0.360 | 0.200-0.640 | <0.001* |
| Rm2500-Rm3169 | 0.800 | 0.474-1.348 | 0.401 |
| <Rm2500 | | | |
| Level of Education | | | |
| Secondary Education and above | 1.360 | 0.851-2.174 | 0.198 |
| Primary Education | 0.690 | 0.368-1.294 | 0.247 |
| No formal Education | | | |
| Category of contacts | | | |
| Household | 1.090 | 0.759-1.575 | 0.630 |
| Non-household | | | |
| | TB Index Characteristics | | |
| Age | 1.020 | 1.006-1.023 | <0.001* |
| Sex | | | |
| Male | 0.230 | 0.157-0.342 | <0.001* |
| Female | | | |
| Relationship | | | |
| Spouse | 0.460 | 0.183-1.153 | 0.098 |
| Father/mother/child/Aunt/Uncle | 1.080 | 0.715-1.620 | 0.731 |
| Sibling/1stcousin/Grandfather/grandchildren | 1.030 | 0.614-1.737 | 0.903 |
| No Family relationship | | | |
| Form of TB | | | |
| Extrapulmonary | 0.110 | 0.062-0.198 | <0.001* |
| Pulmonary | | | |
| Level of Education | | | |
| Secondary Education and above | 0.750 | 0.492-1.153 | 0.192 |
| Primary Education | 0.740 | 0.431-1.500 | 0.260 |
| No formal education | | | |
| Nationality | | | |
| Malaysian | 0.810 | 0.320-2.055 | 0.659 |
| Non-Malaysian | | | |

COR = Crude Odds Ratio; CI = Confidence Interval; *p < 0.05 indicates statistical significance
Reference categories: Female (Sex), Non-Malaysian (Nationality), B1 <RM2500 (Monthly income), No Formal Education (Level of Education), Non-household (Category of contacts), Female (Index Sex), Pulmonary TB (Index Form of TB), No Formal Education (Index Education), No Family Relationship (Relationships).

**Table IV: Univariate Analysis of Knowledge, Attitude, and Stigma Among TB Contacts**

| Variables | COR | 95%CI | p-value |
|---|---|---|---|
| Knowledge | 0.960 | 0.920-1.004 | 0.075 |
| Attitude | 0.910 | 0.852-0.967 | 0.003* |
| Stigma | 0.960 | 0.933-0.985 | 0.002* |

COR = Crude odds ratio; CI = confidence interval; *p<0.05 indicates statistical significance

Several mechanisms may explain this association. First, male TB patients may possess greater authority and influence within family structures, enabling them to effectively encourage or mandate screening participation among their contacts.[12] Second, contacts may perceive greater urgency or seriousness when the index case is male, particularly if he is the primary breadwinner, leading to increased motivation for screening participation.[13] Third, male patients may have better access to information and resources, including healthcare navigation support, which they can share with their contacts.[14]

This finding contrasts with some studies from other settings that have reported no significant association between index case gender and contact screening attendance.[15] However, cultural and contextual factors likely play important roles in shaping these relationships, highlighting the importance of conducting locally relevant research to inform program development. The implications of this finding suggest that TB programs may need to provide additional support and targeted interventions for contacts of female TB patients to improve screening attendance rates.

**Table V: Multivariate Logistic Regression Analysis of Factors Associated with Non-Attendance at Initial TB Screening**

| Variables | AOR | 95% CI | p-value |
|---|---|---|---|
| Index Sex | | | |
| Male | 0.300 | 0.194-0.470 | <0.001* |
| Female | | | |
| Index Form of TB | | | |
| Extrapulmonary TB | 0.090 | 0.050-0.179 | <0.001* |
| Pulmonary TB | | | |
| TB Contact Education | | | |
| Secondary Education | 1.860 | 1.080-3.209 | 0.025* |
| Primary Education | 0.840 | 0.411-1.732 | 0.643 |
| No Formal Education | | | |
| Relationships | | | |
| Sibling/1stCousin/Grandfather/Grandchildren | 0.620 | 0.333-1.142 | 0.124 |
| Father/Mother/Child/Aunt/Uncle | 0.760 | 0.459-1.68 | 0.297 |
| Spouse | 0.380 | 0.131-1.112 | 0.078 |
| No Family Relationship | | | |
| Attitude | 0.880 | 0.818-0.952 | 0.001* |
| Stigma | 0.970 | 0.938-1.002 | 0.069 |

AOR = adjusted odds ratio; CI = confidence interval; *p < 0.05 indicates statistical significance.
Reference categories: Female (Index sex), Pulmonary TB (Index form of TB), No formal education (TB contact education), No family relationship (Relationships).

**Form of Tuberculosis and Risk Perception**

The association between index case TB form and contact screening attendance is an important finding but should be interpreted with caution. Contacts of extrapulmonary TB (EPTB) index cases were less likely to be non-attenders compared to those of pulmonary TB (PTB) index cases. However, the proportion of EPTB cases in this study was relatively small (17.3%), which may affect the stability of the estimates and limit the generalisability of this finding.

Differences in perceived risk and understanding of TB transmission may partly explain this observation. Pulmonary TB is widely recognised as the more infectious form of TB due to airborne transmission through respiratory droplets.16 This awareness may influence how contacts perceive their susceptibility and the urgency of seeking screening.[17-18]

The finding that contacts of EPTB index cases were more likely to attend screening is somewhat counterintuitive, as lower perceived susceptibility would typically reduce health-seeking behaviour according to the Health Belief Model.[19] One possible explanation is that stigma associated with pulmonary TB, which is commonly perceived as infectious, may lead to concealment of the disease and reduced engagement with health services. In contrast, EPTB may be perceived as less stigmatising, potentially facilitating greater acceptance of screening.[17,20] Nevertheless, this interpretation should be approached cautiously given the relatively small number of EPTB cases.

However, as stigma was measured after the screening outcome, the temporal relationship cannot be established. It is possible that interactions with the healthcare system during screening may have influenced participants' perception or awareness of stigma.

**Education and Structural Barriers**

The relationship between education level and screening attendance was not linear. While secondary education was associated with higher odds of non-attendance, primary education did not show a significant association. This may reflect a balance between basic literacy, which facilitates understanding of health information, and competing demands such as employment and time constraints among individuals with higher education levels.[21]

The distinction between secondary and upper secondary education reflects the structure of the Malaysian education system, where upper secondary corresponds to pre-university level (e.g., matriculation, STPM, A-Level), which is often associated with different socioeconomic status, employment patterns, and time commitments compared to general secondary education. This differentiation allows for a more nuanced understanding of how educational attainment influences screening behaviour.

Structural barriers, including work commitments and limited time availability, may further contribute to non-attendance. Evidence from Sabah indicates that logistical challenges can significantly affect TB contact screening participation,8 particularly among working individuals who may find it difficult to attend scheduled appointments.

These findings highlight the need for tailored health education and flexible service delivery approaches that account for varying education levels and structural constraints. TB programmes should consider strategies such as extended clinic hours, workplace-friendly screening options, and targeted communication to improve attendance among higher-risk groups.

**Relationship Dynamics and Family Support**

Although not statistically significant, the finding that spouses had 61.8% lower odds of non-attendance compared to other relationship types provides insights into the role of family dynamics and social support in healthcare utilization. Spousal relationships are characterized by unique features,

including shared living spaces, intimate physical contact, emotional support, and mutual care responsibilities, which may enhance motivation for screening participation.[22]

The non-significant nature of this association may reflect the relatively small number of spousal contacts in the study or the heterogeneity within this relationship category. However, the magnitude of the effect suggests that relationship type may be clinically meaningful even if not statistically significant in this sample size.[23]

Understanding relationship dynamics is important for TB program implementation, as different types of contacts may require different engagement strategies. Spousal contacts may be more easily reached and motivated through direct communication with index cases, while more distant contacts may require additional outreach efforts.[8]

**Health System and Program Implications**

The findings of this study have important implications for TB control programme design and implementation in Malaysia and similar settings. Identifying specific factors associated with non-attendance allows for the development of targeted interventions tailored to the needs of different contact groups. Contacts of female TB index patients, who demonstrated higher non-attendance, may benefit from enhanced outreach strategies, including more frequent follow-up, flexible appointment scheduling, and involvement of family members or community leaders to support screening participation. These approaches should be culturally sensitive and aligned with local social structures to promote equitable access to healthcare services.[24]

While differences in screening attendance were observed according to the form of TB, these findings should be interpreted cautiously due to the relatively small proportion of extrapulmonary TB cases in this study. As such, programmatic recommendations should primarily focus on more robust and modifiable factors influencing screening attendance, including knowledge, attitudes, and structural barriers. Interventions such as pre-screening counselling, peer support, and clear communication regarding screening procedures may help alleviate concerns and improve attendance.[25-26]

Interventions aimed at improving attitudes towards TB represent a particularly promising strategy, given the strong association observed in this study. These should be evidence-based, culturally appropriate, and delivered through multiple channels to maximise reach and effectiveness.[27] Community health workers, peer educators, and mass media platforms may play key roles in promoting positive health-seeking behaviours and increasing screening uptake.[28]

**Strengths and Limitations**

This study has several methodological strengths, including the case-control design, which allows efficient identification of factors associated with non-attendance, the use of validated instruments to assess knowledge, attitudes, and stigma, and the inclusion of participants from all subdistricts within Kudat District, enhancing the representativeness of the study population.

However, several limitations should be considered. First, knowledge, attitudes, and stigma were measured at a single point in time after the outcome had occurred. As such, the temporal relationship between these psychosocial factors and screening attendance cannot be clearly established, raising the possibility of reverse causality. Individuals who attended screening may have subsequently developed greater awareness or more positive attitudes through interaction with healthcare services.

Second, the relatively short study duration (approximately four months) may limit the ability to capture temporal variations in screening behaviour and may affect the generalisability of the findings.

Third, selection bias may be present, as only participants who consented to participate were included in the study. Individuals who declined participation may differ systematically in their health-seeking behaviour and attitudes towards TB, potentially influencing the observed associations.

Recall bias is also possible, as participants' responses regarding knowledge, attitudes, and stigma may have been influenced by their screening attendance status. In addition, social desirability bias may have affected responses, particularly for sensitive topics such as stigma and attitudes towards TB.

Although a validated instrument was used, the attitude domain demonstrated relatively low internal consistency in this study, which may be attributed to the limited number of items and the multidimensional nature of attitudes towards TB.

Finally, the study was conducted in a single district in Sabah, which may limit the generalisability of the findings to other regions of Malaysia or different settings. However, the diversity within Kudat District, including multiple ethnic communities and varying socioeconomic conditions, strengthens the internal validity of the study.

## CONCLUSION

This study demonstrates that multiple factors influence TB contact screening attendance in Kudat, Sabah, with significant implications for public health program development. The identification of index case sex and TB form, contact education level, and attitudes as significant predictors of attendance provides evidence for targeted intervention development. The complex relationships observed, including the counterintuitive association between secondary education and higher non-attendance, highlight the importance of context-specific research and culturally appropriate program design.

Public health interventions should prioritize addressing modifiable factors such as attitudes through evidence-based educational programs while considering non-modifiable characteristics for risk stratification and targeted outreach efforts. The development of comprehensive approaches that address both individual-level factors and structural barriers

may improve TB contact screening effectiveness and contribute to better TB control outcomes.

The findings contribute to the growing evidence base on TB contact screening challenges and provide a foundation for program improvement efforts in Malaysia and similar settings. Continued research and program evaluation will be essential for optimizing TB control strategies and achieving the goals of the End TB Strategy.

**Recommendations for Future Research**

Qualitative or mixed-method studies are recommended to further explore the underlying reasons for non-attendance, including individual, social, and health system-related barriers. Such evidence would support the development of targeted and context-specific interventions to improve TB contact screening uptake.

## ACKNOWLEDGEMENTS

The authors acknowledge the Sabah State Health Department, the Kudat District TB Unit, Universiti Malaysia Sabah, and all study participants for their cooperation and support in this research. Appreciation is extended to the TB healthcare workers in Kudat District.

The authors also thank Dr Abdul Marsudi Bin Abdul Manah, Dr Mischelle Goroh, Dr Eric Tan Chee How, and Dr Roddy Teo, for their valuable guidance and contributions.

## CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this study.

## FUNDING

This research did not receive any external funding.

## REFERENCES

1. World Health Organization. Global tuberculosis report 2025. Geneva: World Health Organization; 2025. [cited Apr 2026]. Available from: https://www.who.int/publications/i/item/9789240116924
2. Goroh MMD, Rajahram GS, Avoi R, van den Boogaard CHA, William T, Ralph AP, et al. Epidemiology of tuberculosis in Sabah, Malaysia, 2012-2018. Infect Dis Poverty 2020; 9: 119.
3. Centers for Disease Control and Prevention. Self-Study Modules on Tuberculosis. Module 8: Contact Investigations for Tuberculosis. Atlanta (GA): Centers for Disease Control and Prevention; 2014. [cited Apr 2026]. Available from: https://www.cdc.gov/tb/media/pdfs/Self_Study_Module_8_Contact_Investigations_for_Tuberculosis.pdf
4. Kigozi G, Engelbrecht M, Heunis C, Janse van Rensburg A. Household contact non-attendance of clinical evaluation for tuberculosis: a pilot study in a high burden district in South Africa. BMC Infect Dis 2018; 18: 106.
5. MacLellan J, Wallace K, Vacchelli E, Roe J, Davidson R, Abubakar I, et al. A multi-perspective service evaluation exploring tuberculosis contact screening attendance among adults at a North London hospital. J Public Health (Oxf) 2016; 38(3): e362-7
6. Rea E, Huard J, Lee R. Chapter 11: Tuberculosis contact investigation and outbreak management. Can J Respir Crit Care Sleep Med 2022; 6(S1): 167-83.
7. Loh SY, Zakaria R, Mohamad N. Knowledge, attitude, and stigma on tuberculosis and the associated factors for attitude among tuberculosis contacts in Malaysia. Medeni Med J 2023; 38: 45-53.
8. Goroh MMD, van den Boogaard CHA, Ibrahim MY, Tha NQ, Robinson F, Lukman K, et al. Factors affecting continued participation in tuberculosis contact investigation in a low-income, high-burden setting. Trop Med Infect Dis 2020; 5(3): 124.
9. Zakaria R, Wan Mohd Zahiruddin WM, Nik Husain NR, Wan Nor Arifin WN, Idris NA, Mohd Zain N, et al. Development and validation of the knowledge, attitude, practice and stigma questionnaire on tuberculosis among younger population in Kelantan, Malaysia. Malays J Public Health Med 2023; 23(3): 64-75.
10. Bursac Z, Gauss CH, Williams DK, Hosmer DW. Purposeful selection of variables in logistic regression. Source Code Biol Med 2008; 3: 17.
11. Kerkhoff AD, Mwamba C, Pry JM, Kagujje M, Nyangu S, Mateyo K, et al. A mixed methods study on men's and women's tuberculosis care journeys in Lusaka, Zambia: implications for gender-tailored tuberculosis health promotion and case finding strategies. PLoS Glob Public Health 2023; 3(6): e0001372.
12. Horton KC, MacPherson P, Houben RMGJ, White RG, Corbett EL. Sex differences in tuberculosis burden and notifications in low- and middle-income countries: a systematic review and meta-analysis. PLoS Med 2016; 13(9): e1002119.
13. Muttamba W, Omongot S, Najjingo I, Nuwarinda R, Buregyeya E, Otmani del Barrio M, et al. Using intersectional gender analysis to identify challenges in tuberculosis care at four health care facilities in Uganda. Infect Dis Poverty 2024; 13: 2.
14. Boah M, Kpordoxah MR, Adokiya MN. Self-reported gender differentials in the knowledge of tuberculosis transmission and curative possibility using national representative data in Ghana. PLoS One 2021; 16(7): e0254499.
15. Nair D, Rajshekhar N, Klinton JS, Watson B, Velayutham B, Tripathy JP, et al. Household contact screening and yield of tuberculosis cases: a clinic-based study in Chennai, South India. PLoS One 2016; 11(9): e0162090.
16. Nardell EA. Transmission and institutional infection control of tuberculosis. Cold Spring Harb Perspect Med. 2016;6(1):a018192.
17. Olsen JA, Chen G, Lamu AN. The relative importance of education and health behaviour for health and wellbeing. BMC Public Health 2023; 23: 1981.
18. Naga Mamo A, Furi Gilo R, Fikadu Tesema A, Fetene Worku N, Teshome Kene A, Legas Abgara A. Household contact tuberculosis screening adherence and associated factors among pulmonary tuberculosis patients on follow-up at health facilities in Shashamane Town, Southeast Ethiopia. Patient Prefer Adherence 2023; 17: 1867-79.
19. Latif AS. The importance of understanding social and cultural norms in delivering quality health care: a personal experience commentary. Trop Med Infect Dis 2020; 5(2): 22.
20. Kılıç A, Zhou X, Moon Y, Hamada H, Duong T, Layton C, et al. A systematic review exploring the role of tuberculosis stigma on test and treatment uptake for tuberculosis infection. BMC Public Health 2025; 25: 628.
21. El-Zayat A, Namnkani SA, Alshareef NA, Mustafa MM, Eimanagha NS, Algarni GA. Cyberchondria and its association with smartphone addiction and electronic health literacy among a Saudi population. Saudi J Med Med Sci. 2023; 11(2): 162-8.
22. Kamila KA, Liow JJK, Giam F, Lim ZL, Ho PJ, Mei YY, et al. Spousal perceptions and their role in promoting breast cancer screening: a focus group study. BMJ Open 2025; 15: e086340
23. Altman DG, Bland JM. Absence of evidence is not evidence of absence. BMJ 1995; 311: 485.
24. Handtke O, Schilgen B, Mösko M. Culturally competent healthcare: a scoping review of strategies implemented in healthcare organizations and a model of culturally competent healthcare provision. PLoS One 2019; 14(7): e0219971.

25. Aitambayeva N, Aringazina A, Nazarova L, Faizullina K, Bapayeva M, Narymbayeva N, et al. A systematic review of tuberculosis stigma reduction interventions. Healthcare (Basel) 2025; 13: 1846.
26. Hayward SE, Nosiuyile V, Vanqa N, Makanda G, Tisile P, Ngwatyu L, et al. "As a patient I do not belong to the clinic, I belong to the community": co-developing multi-level, person-centred tuberculosis stigma interventions in Cape Town, South Africa. BMC Glob Public Health 2024; 2: 55.
27. Doré A, Rebitschek FG, Morello K, Stierstädter E, Thiemann KJ, Kubiak T. A systematic review and meta-analysis of the effects of entertainment-education interventions on persuasive health outcomes. Sci Rep 2025; 15: 27939.
28. Topping KJ. Peer education and peer counselling for health and well-being: a review of reviews. Int J Environ Res Public Health 2022; 19(10): 6064.

# The impact of lymphovascular space invasion on recurrence and survival rate among women with stage I endometrioid endometrial cancer

**Wadeea Gherbal, MD[1], Yin Ping Wong, MD[2], Tan Geok Chin, PhD[2], Su Ee Phon, MD[3], Nirmala Chandralega Kampan, PhD[4]**

[1]Obstetrics and Gynecology Department, Gynae-oncology Unit, Hospital Canselor Tuanku Muhriz (HCTM), Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia, [2]Department of Pathology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia, [3]Hospital Pantai Cheras, Kuala Lumpur, Malaysia, [4]Pantai Hospital Kuala Lumpur, Malaysia

## ABSTRACT

**Introduction: Endometrial cancer is the most common gynecologic malignancy in developed countries, with rising incidence worldwide. While early stage disease generally carries a favorable prognosis, recurrence remains a significant clinical concern. Among the histopathological features, lymphovascular space invasion (LVSI) has emerged as a critical prognostic factor, reflecting tumor aggressiveness and potential for metastatic spread. LVSI is associated with increased risk of recurrence, distant metastasis, and reduced survival, even in patients with otherwise low risk disease. Understanding the role of LVSI in endometrial cancer is essential for refining risk stratification, guiding adjuvant therapy decisions, and improving patient outcomes. Our study to evaluate the impact of lymphovascular space invasion (LVSI) on treatment outcomes, recurrence, and survival in patients with stage I endometrioid endometrial cancer.**

**Materials and Methods: A retrospective cohort study was conducted at the Hospital Canselor Tuanku Muhriz (HCTM) Gynecologic Oncology Clinic, with ethical approval from Universiti Kebangsaan Malaysia. Patients with stage I endometrial carcinoma, classified according to the International Federation of Gynecology and Obstetrics (FIGO) 2018, and confirmed on hysterectomy specimens were included. Demographic clinicopathological, and treatment data were collected. LVSI was defined as the presence of tumor cells within endothelial lined spaces. Overall survival (OS) was the primary endpoint. Statistical analyses were performed using SPSS version 26, employing chi square, t tests, and Kaplan–Meier estimates, with significance set at $p < 0.05$.**

**Results: Of 180 patients, 163 had endometrioid carcinoma; 114 were included in the final analysis (mean age 58 years; 79.8% postmenopausal). LVSI was present in 14.2% of cases and was associated with higher grade and deeper myometrial invasion. Recurrence occurred in 8.5% overall, with 18.8% in LVSI positive and 4.1% in LVSI negative patients. The 2 year disease free survival (DFS) rate was 93.4% (80.8% LVSI positive vs 99% LVSI negative). The 5 year DFS rate was 91.1% (73.4% LVSI positive vs 94% LVSI negative). The OS rate was 97.3% (87.5% LVSI positive vs 99% LVSI negative). Distant metastasis predicted 2 year DFS, whereas LVSI positivity independently predicted reduced 5 year OS. At 5 years, the DFS rate was 91.1% (SE = 0.031), while the OS rate was 97.3% (SE = 0.013). The similarity between DFS and OS reflects the low number of recurrence and death events, indicating favorable prognosis and effective disease control. Median survival was not reached.**

**Conclusion: LVSI was associated with higher recurrence and poorer survival in patients with Stage I endometrioid endometrial carcinoma, independently predicting 5-year survival, supporting its role in risk stratification and treatment planning.**

**KEYWORDS:**
*Endometrial carcinoma; carcinoma, endometrioid; recurrence; survival rate; prognosis*

## INTRODUCTION

Endometrial cancer (EC) is the fifteenth most common malignancy worldwide and the sixth most common malignancy in women.[1] According to the International Agency for Research on Cancer (IARC), approximately 420,368 new cases of EC were diagnosed, and approximately 97,273 deaths were attributed to the disease in 2022.[1]

In Malaysia, EC ranks higher than global rates, being the fifth most common cancer in the country. According to IARC, approximately 1503 new cases of EC and 458 deaths were reported in Malaysia in 2022.[1] According to the Malaysian National Cancer Registry, the lifetime risk for uterine malignancy is one in 127 for all females, and 48.6% of cases are diagnosed at stage I.[2] The most significant risk factors associated with EC development are those that increase long-term exposure to unopposed estrogen (e.g., obesity and exogenous estrogen).[3]

Generally, patients with EC have a relatively favorable outcome.[4] Most patients present with International Federation of Gynecology and Obstetrics (FIGO) stage I

*This article was accepted: 24 June 2026*
*Corresponding Author: Wadeea Gherbal*
*Email: Wadeeaa1980@hotmail.com*

endometrioid cancers and do not have lymph node metastases at surgical staging. Despite uterine-limited disease on final pathology, 10–20% of these cancers recur.[5-7] Relapse usually occurs within 24 months of diagnosis.[5-7] Many studies report that young women with endometrial carcinoma tend to have a prognostically favorable histological type, such as endometrioid-type tumor, well-differentiated tumor grading, early staging, less myometrial involvement, and absence of lymphovascular stromal invasion.[4,7-9] This reflects the relatively good prognosis of EC when detected early or at a younger age.

The incidence is highest in the 55-69 age group, and an increased rate is seen in most age groups in 2017-2021.[2] Clinicopathological factors such as older age, deep myometrial invasion, grade 3 disease, and lymphovascular space invasion (LVSI) have predictive value for tumor recurrence and worse survival.[4]

LVSI is present in approximately 15% of early-stage ECs and is considered a potential adverse prognostic factor in EC. Researchers have found that patients with LVSI positivity show a higher rate of lymph node metastasis (LNM), are more likely to have local or distal relapses, and usually have shorter overall survival (OS).[10-17]

The Cancer Genome Atlas (TCGA) publication in 2013 decoded endometrial cancer into four expanded subtypes as they have their characteristics, molecular features, and prognosis.[1]

POLE ultra-mutated is characterized by a strong association with mutations in the exonuclease domain of polymerase-ε *(POLE)*, a group of tumours with a good prognosis that could exclude the necessity of adjuvant treatment.[2] Microsatellite instability (MSI) hypermutated is characterized by a loss of DNA mismatch repair proteins (MLH1, MSH2, MSH6, and PMS2). (3)Copy-number high, with *TP53* mutations, is usually associated with unfavourable results/poor prognosis, and (4) copy-number low with microsatellite stability and intermediate prognosis.[18-20]

The information brought by the molecular biology of EC may be relevant as a tool for predictive assessment and in the definition of therapeutic strategies, and the new FIGO 2023 document supports its incorporation in its staging system, despite controversies.[21] According to the new FIGO staging, in cases of anatomical stage I–II, the detection of a *POLE* mutation currently results in a decrease in the FIGO stage.[21] At the same time, abnormal p53 leads to increased staging, yielding escalation or de-escalation of adjuvant treatment. Furthermore, in cases of advanced disease, molecular types and their associations with hormonal expression, loss of expression of repair enzymes, and overexpression of HER2 are also valuable for choosing therapies. Several studies, including Gynecology Oncology Group (GOG) 99 and the Post-Operative Radiation Therapy in Endometrial Carcinoma (PORTEC) one and two randomized trials, found that patients with early-stage EC and LVSI treated with external beam radiation therapy (EBRT) had a decreased risk of pelvic recurrence without significant improvement in OS.[7,11,22-23] Based on these findings, Bosse et al. recommended the consideration of adjuvant EBRT in patients with early-stage EC and substantial LVSI, especially in the presence of additional risk factors.[11] The American National Comprehensive Cancer Network (NCCN) guideline, the American College of Obstetricians and Gynecologists/ Society of Gynecologic Oncology (ACOG/SGO) guideline, the European Society for Medical Oncology (ESMO), the European Society of Gynecological Oncology (ESGO), the European Society of Radiotherapy and Oncology (ESTRO) guideline, and the International Federation of Gynecology and Obstetrics (FIGO) for EC all consider LVSI and molecular classification as a risk factor and recommend LVSI-positive early-stage patients to receive adjuvant therapy after surgery.[9,24-25] Nevertheless, in recent years, some studies from different countries have shown negative results regarding the prognostic role of LVSI.[26-30] This reflects the ongoing debate on LVSI as a predictor of EC prognosis and the efficacy of adjuvant therapy in such cases. We aimed to explore the impact of LVSI on recurrence and survival rates in EC stage I patients in Malaysia.

## MATERIALS AND METHODS

This retrospective cohort study was conducted at the Gynecologic Oncology Clinic of Hospital Canselor Tuanku Muhriz (HCTM), a tertiary referral centre in Malaysia. Ethical approval was obtained from the Research Ethics Committee of the National University of Malaysia (RECUKM), and the study adhered to the principles of the Declaration of Helsinki.

All patients diagnosed with endometrial carcinoma and managed at HCTM between January 2002-December 2024 were reviewed. The study population was restricted to women with Stage I disease, classified according to FIGO 2018 staging system. Staging was confirmed by the final histopathological examination of the hysterectomy specimens following total abdominal hysterectomy with bilateral salpingo-oophorectomy and omental biopsy. Pelvic and para aortic lymphadenectomy was performed in most cases based on the surgeon's discretion and intraoperative findings. Patients with incomplete records, synchronous malignancies, or prior neoadjuvant therapy were excluded from the study.

Clinical and pathological data were extracted from electronic medical records and pathological reports. The demographic variables included age at diagnosis, ethnicity, menopausal status, parity, and comorbidities (e.g., hypertension and diabetes mellitus). Tumour characteristics included histological grade, tumour size, depth of myometrial invasion, presence of LVSI, and involvement of the lower uterine segment. Adjuvant treatment modalities (brachytherapy, external beam radiotherapy, or chemotherapy) were determined by the multidisciplinary team on stage, histologic grade, LVSI, and patient age. External beam radiotherapy (EBRT) was administered to high risk patients at a total dose of 45 Gy in 25 fractions over 5 weeks, with concurrent weekly cisplatin (40 mg/m$^2$) as a radiosensitizer, followed by high dose rate (HDR) brachytherapy at 5.5 Gy in 2 fractions. Vaginal vault brachytherapy was prescribed for intermediate risk patients at 21 Gy to 5 mm depth in 3 fractions over 2–3 weeks. Patients in the observation group did not receive adjuvant

therapy. These treatment strategies were applied in accordance with the Royal College of Radiologists (RCR) recommendations, ensuring alignment with contemporary standards of care.

LVSI was defined as the presence of viable tumour cells within endothelial lined lymphatic or vascular spaces beyond the main tumour mass, as identified on haematoxylin and eosin–stained sections. A general pathologist reviewed the histopathological slides. In keeping with the retrospective design of the study, LVSI status was recorded as either present or absent, without further subcategorization of extent or severity. The primary endpoint was OS, which was measured from the date of surgery to death from any cause. Patients alive at the last follow-up were censored on that date. The secondary endpoints included recurrence patterns and disease-free survival at 2 and 5 years (DFS), where available. All analyses were performed using the Statistical Package for the Social Sciences (SPSS) Statistics version 26 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as means ± standard deviations or medians with interquartile ranges, depending on the distribution, and compared using independent t-tests or Mann–Whitney U tests, as appropriate. Categorical variables were expressed as frequencies and percentages, and group differences were assessed using the chi-square or Fisher's exact tests. Survival probabilities at two and five years were estimated using the Kaplan–Meier method, and differences between strata were evaluated using the log-rank test. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated to estimate the hazard of recurrence. Univariate analysis used to estimate hazard ratios (HRs) for each factor separately to identify independent predictors of survival, with variables significant at $p<0.05$. Cox regression analysis for variables meeting the selection threshold ($p<0.05$) was entered into further evaluation. For each factor, hazard ratios (HRs) with 95% confidence intervals (CIs) were reported. Statistical significance was defined as $p<0.05$.

## RESULTS

A total of 180 patients with Stage I endometrial carcinoma were reviewed. Of these 163 (90.6%) with endometrioid carcinoma identified, 114 fulfilled the predefined inclusion criteria and were included in the final analysis, while the remaining 49 were excluded. The mean age at diagnosis was 58.1 years (Standard Deviation (SD)=10.14), and the majority were postmenopausal (79.8%). The most common comorbidities were hypertension (14.9%), diabetes mellitus (2.6%), and dyslipidaemia (6.1%). The details of the study parameters are presented in Table I.

Within the cohort, 54.4% were classified as Stage IA, 40.4% as Stage IB, and 5.3% as Stage IC, according to FIGO 2018 criteria. Histological grading revealed 61.4% of tumours were Grade I, 29.4% Grade II, and 8.8% Grade III. LVSI was identified in 14% of the cases. Table II presented the details of study parameters in both LVSI-negative and LVSI-positive groups

Among LVSI positive patients, 68.8% received adjuvant therapy and 31.3% were managed with observation alone. In contrast, among LVSI negative patients, 19.4% received adjuvant therapy and 80% were managed conservatively. The decision regarding the modalities of adjuvant therapy was determined by a multidisciplinary team, based on the stage, histological grade, LVSI and the patient age.

Recurrence was radiologically and histologically confirmed. Overall, 7.9% of the patients experienced disease recurrence. Recurrence was significantly more frequent in LVSI-positive cases (18.8%) than in LVSI-negative cases (4.1%). The sites of recurrence included distant metastasis (n=5; 2 LVSI-positive, 3 LVSI-negative), locoregional recurrence (n=2; 1 LVSI-positive, 1 LVSI-negative), and abdominal recurrence (n=; 1 1 LVSI-negative).

For the entire cohort, the mean time to recurrence was 58.2 months (95% CI, 56.7–59.8). Kaplan–Meier analysis showed that the median time to recurrence was not reached in either subgroup, as fewer than 50% of patients experienced recurrence. The mean time to recurrence was 59.2 months (95% CI: 58.2–60.3) for LVSI negative patients and 52.2 months (95% CI: 41.0–58.7) for LVSI positive patients. These findings indicate that recurrence occurred earlier and more frequently in LVSI positive patients compared to LVSI negative patients.

The median disease free survival (DFS) was not reached, as fewer than 50% of patients experienced recurrence or death during follow up. Patients lost to follow up were censored at their last disease free visit, contributing survival information up to that point. The estimated 2 year DFS rate for the entire cohort was 93.4% (95% CI, 92.9–99.9), with a mean DFS of 23.8 months (95% CI, 23.5–24.1). At 5 years, the estimated DFS rate was 91.1% (95% CI, 85.4–96.8), with a mean DFS of 57.9 months (95% CI, 56.2–59.6), as derived from the Kaplan–Meier survival function. Subgroup analysis revealed that patients with LVSI negative tumours had superior outcomes, with 2 year and 5 year DFS rates of 99% and 94%, respectively, whereas LVSI positive patients demonstrated poorer survival, with corresponding DFS rates of 80.8% and 73.4%. Univariate Cox proportional hazards regression demonstrated that LVSI was significantly associated with Disease free survival. The hazard ratio was 6.439 (95% CI: 1.721–24.082), indicating that patients with LVSI positive tumours had more than a six fold increased risk of recurrence and death compared to those without LVSI. These findings are illustrated in Figure 1.

Overall survival outcomes were similarly favourable. For the cohort of 114 patients, survival remained stable, with 2 year and 5 year OS rates of 97.3% (95% CI, 94.2–100.0). Stratified by LVSI status, the 2 year and 5 year OS was 99% in LVSI negative patients compared to 87.5% (95% CI, 69.1–100.0) in LVSI positive patients, with only three deaths occurred within the first 2 years, and no additional events were observed thereafter. However, because some patients were lost to follow up, it cannot be confirmed with certainty that these were the only deaths within the study cohort. These findings are illustrated in Figure 1. These findings highlight LVSI as an adverse prognostic factor for long term survival.

**Table I: Baseline Characteristics of Stage I Endometrial Carcinoma Patients**

| Parameter | Frequency | Percentage % |
|---|---|---|
| Histological subtypes | | |
| Endometrioid | 163 | 90.60% |
| Serous | 5 | 2.80% |
| Mixed | 2 | 1.10% |
| Carcinosarcoma | 5 | 2.80% |
| Mucinous | 2 | 1.10% |
| Clear | 1 | 0.60% |
| Not documented | 2 | 1.10% |
| Ethnicity | | |
| Malay | 63 | 55.30% |
| Chinese | 38 | 33.30% |
| Indian | 9 | 7.90% |
| Other | 4 | 3.50% |
| Menopausal Status | | |
| Perimenopause | 23 | 20.2% |
| Post menopause | 91 | 79.8% |
| Tumour Stage | | |
| STAGE1A | 62 | 54.40% |
| STAGE1B | 46 | 40.40% |
| STAGE1C | 6 | 5.30% |
| Tumour Grade | | |
| Grade I | 70 | 61.40% |
| Grade II | 34 | 29.40% |
| Grade III | 10 | 8.80% |

Survival rates stratified by LVSI status and adjuvant therapy demonstrated that LVSI positive patients without adjuvant therapy had lower survival compared to LVSI negative patients (80% vs. 99%, p<0.004). With brachytherapy alone, 5 year survival was 80% in LVSI positive versus 100% in LVSI negative patients (p=0.031). EBRT plus brachytherapy (100% vs 100%, p=0.44) were comparable between groups. In contrast, concurrent chemoradiotherapy was associated with poorer survival in both LVSI positive and LVSI negative patients (50% each, p=0.05) The details of the comparison of various adjuvant therapies according to LVSI status are presented in Table III.

Univariate analysis identified several clinicopathological variables with significant impact on OS. Patients with hypertension and dyslipidaemia had markedly poorer outcomes (non survivors 28.6% vs survivors 71.4%, p<0.001). Stage IB disease was associated with reduced survival (p=0.035), while Grade 1 tumours were linked to favourable prognosis (100% survival, p=0.025). Depth of invasion was significant, with invasion <50% showing 100% survival (p=0.011) compared to invasion >50% (90.9% survival, p=0.006). LVSI positivity was also associated with adverse outcomes (87.5% survival vs 12.5% non survivors, p=0.006). Treatment modality influenced survival, with concurrent chemoradiotherapy (CCRT) showing poorer outcomes (50% survival, p<0.001). Recurrence (p=0.001) and distant metastasis (p<0.001) were strongly associated Table IV presents the factors significantly impacting OS rates in the univariate analysis.

## DISCUSSION

This retrospective cohort study evaluated the prognostic significance of LVSI in patients with Stage I endometrioid endometrial carcinoma. Our findings demonstrate that LVSI is significantly associated with increased recurrence and reduced survival, underscoring its role as a key prognostic factor in early-stage disease.

The LVSI-positive rate of 14% in our cohort is consistent with previously reported ranges (8.3–32.8%).[11,27-31] Dai et al. for example, reported a rate of 12.16% [31], while Tortorella et al. observed higher frequencies in certain subgroups.[32] Variability across studies likely reflects differences in LVSI definition, pathologic assessment, and patient selection criteria, highlighting the need for standardized reporting of these parameters.

The overall recurrence rate in our study was 8.5%, but recurrence was disproportionately higher among LVSI-positive patients (18.8%) compared to LVSI-negative patients (4.1%). This aligns with the findings of Ureyen et al. who identified LVSI as an independent predictor of recurrence,[34] and Restaino et al. who demonstrated its association with both recurrence and distant metastasis.[32]

LVSI was also significantly associated with decreased survival rates. LVSI-positive patients had poorer outcomes. Kaplan–Meier analysis confirmed these differences, with statistically significant reductions in both Disease-free survival ($\chi^2$=10.388, p<0.001) and OS ($\chi^2$=7.441, p=0.006). These findings are consistent with those of Qin et al. (2023), whose meta-analysis demonstrated that LVSI is a strong predictor of recurrence (OR=2.79), reduced OS (HR=5.19), and reduced recurrence-free survival (HR=5.26). Similarly, Tortorella et al. reported a reduction in 5 year OS from 99.5% to 70.6% and in DFS from 93.6% to 56.5% among LVSI-positive patients.[32] Ureyen et al. also noted a decline in DFS from 96.8% to 80.1%.[34] In contrast, Askandar et al. and Dai et al. did not find LVSI to be an independent prognostic factor in multivariate analyses, suggesting that sample size, adjuvant therapy practices, and confounding variables may explain discrepancies across studies.[31,35]

**Table II: Study parameters in the LVSI-negative and LVSI-positive groups**

| Parameter | LVSI-negative n (%) | LVSI-positive n (%) | p-value |
|---|---|---|---|
| Mean age ± SD | 58.28 ± 9.917 | 56.30 ± 11.649 | 0.50 |
| Mean Parity | 2.47 ± 1.949 | 2.38 ± 2.062 | 0.98 |
| Menopausal status | | | 0.60 |
| Post menopause | 79(80.6%) | 12(75%) | |
| Perimenopause | 19(19.4%) | 4(25%) | |
| Comorbidity | | | |
| Diabetes mellitus | 3(3.1 %) | 0(0%) | 0.48 |
| Hypertension | 16(16.3%) | 1(6.3%) | 0.29 |
| Dyslipidaemia | 5(5.1%) | 1(6.3%) | 0.98 |
| Hypertension and diabetes mellitus | 16(16.3%) | 5(31.3%) | 0.15 |
| Diabetes mellitus and Dyslipidaemia | 8 (8.2%) | 2(12.5%) | 0.57 |
| Diabetes mellitus, hypertension and Dyslipidaemia | 14(14.3%) | 1(6.3%) | 0.38 |
| Myometrial invasion | | | |
| < 50% | 69(70.4%) | 7(43.4%) | 0 .061 |
| > 50% | 25(25.5%) | 9(56.3%) | 0.022 |
| Absence of myometrial invasion | 4(4.1%) | 0 (0%) | |
| No adjuvant therapy | 79(80.6%) | 5(31.3%) | <0.001 |
| Adjuvant therapy | 19(19.4%) | 11(68.8%) | <0.001 |
| Vaginal brachytherapy | 13(13.3%) | 5(31.3%) | |
| Vaginal brachytherapy and EBRT | 4(4.1%) | 4(25%) | 0.010 |
| CCRT | 2(2%) | 2(12.5%) | |
| Stage | | | 0.007 |
| IA | 59(60.2%) | 3(18.8%) | 0.002 |
| IB | 34(34.7%) | 12(75%) | 0.002 |
| IC | 5(5.1%) | 1(6.3%) | 0.890 |
| Grade | | | |
| I | 62(63.3%) | 8(50%) | 0.312 |
| II | 28(28.6%) | 6(37.5%) | 0.469 |
| III | 8(8.2%) | 2(12.5%) | 0.570 |
| Lymphadenectomy | | | 0.7 |
| No Lymphadenectomy | 30(30.6%) | 6(37.5%) | |
| Pelvic Lymphadenectomy | 68(69.4%) | 10(62.5%) | |
| Recurrence | 5(4.1%) | 3(18.8%) | 0.002 |
| Recurrence site | | | |
| Locoregional | 1(1%) | 1(6.3%) | 0.79 |
| Abdominal | 1(1%) | 0(0%) | 0.72 |
| Distant | 3(3.1%) | 2(12.5%) | 0.05 |
| Mean time to Recurrence (Months) | 59.2 months | 52.2 months | 0.006 |
| 2-year Disease Free Survival | 99% | 80.8% | <0.001 |
| 5-year Disease Free Survival | 94% | 73.4% | 0.006 |
| Overall survival | 97(99%) | 14 (87.5%) | 0.005 |

LVSI, lymphovascular space invasion. EBRT, external beam radiotherapy. CCRT, concurrent chemoradiotherapy. SD: standard deviation. Statistical significance was set at p<0.05.

**Table III: Survival rates based on adjuvant therapies in LVSI-negative and LVSI-positive groups**

| Parameter | LVSI-positive | LVSI-negative | p-value |
|---|---|---|---|
| No adjuvant | 5(80%) | 79(98.8%) | 0.04 |
| Brachytherapy | 4(80%) | 12(100%) | 0.32 |
| EBRT+ Brachytherapy | 4(100%) | 5(100%) | 0.44 |
| CCRT | 2(50%) | 2(50%) | 0.05 |

LVSI, lymphovascular space invasion; EBRT, external beam radiotherapy. CCRT, concurrent chemoradiotherapy Statistical significance was set at p<0.05.

**Table IV: Factors with significant impact on OS rate in univariate analysis**

| Parameter | Non-survivors | Survivors | p-value |
|---|---|---|---|
| Hypertension and dyslipidaemia | 2(28.6%) | 5(71.4%) | <0.001 |
| Stage IB | 3(6.5%) | 43(93.5%) | 0.035 |
| Grade 1 | 0(0%) | 70(100%) | 0.025 |
| Invasion<50% | 0(0%) | 77(100%) | 0.011 |
| Invasion>50% | 3(9.1%) | 30.(90.9%) | 0.006 |
| Positive LVSI | 2(12.5%) | 14(87.5%) | 0.006 |
| CCRT | 2(50%) | 2(50%) | <0.001 |
| Recurrence | 2(20%) | 8(80%) | 0.001 |
| Distant metastasis | 2(40%) | 3(60%) | <0.001 |

LVSI, lymphovascular space invasion; EBRT, external beam radiotherapy. CCRT, concurrent chemoradiotherapy. Statistical significance was set at p<0.05.

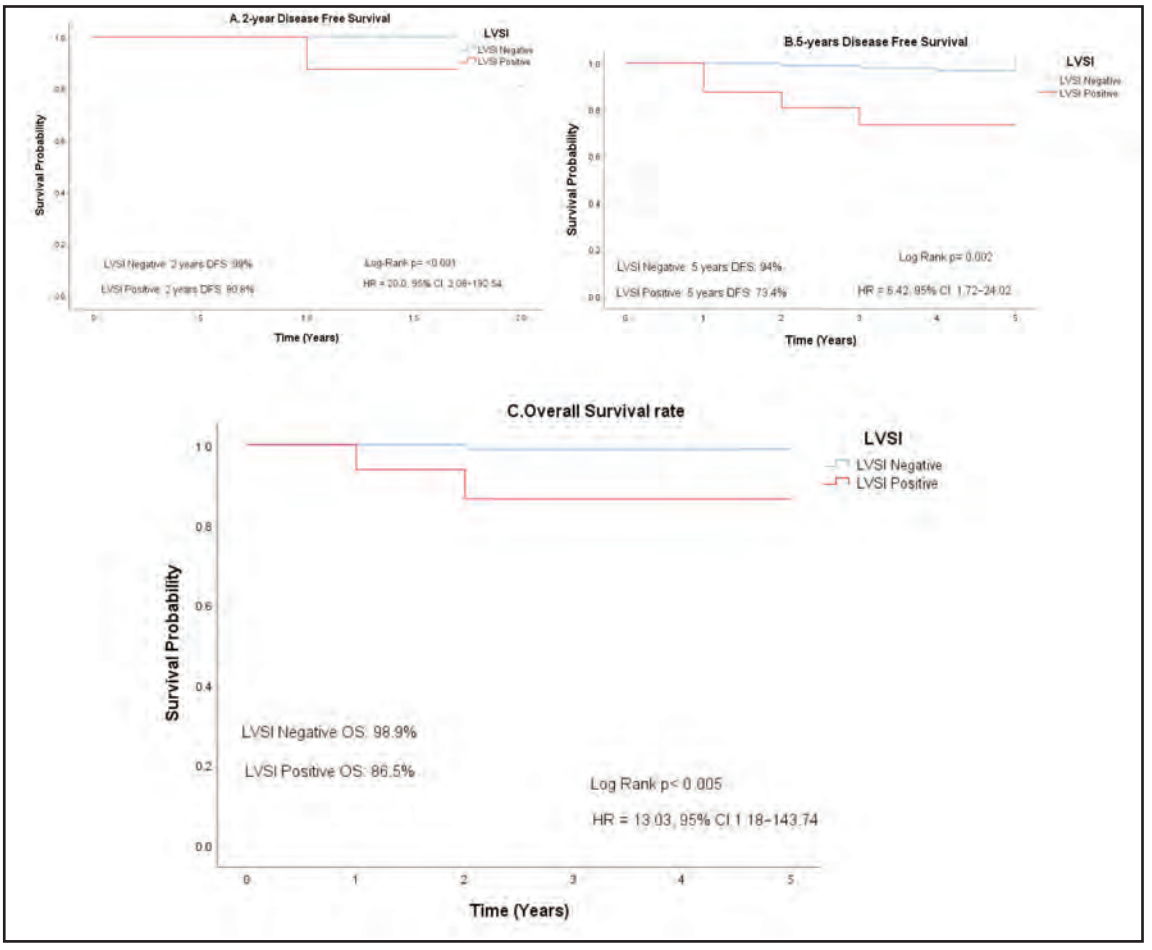



**Fig. 1:** A two-year disease-free survival; B, five-year disease-free survival; C, overall survival. DFS, disease-free survival; OS, overall survival; LVSI, lymphovascular space invasion

In our cohort, LVSI correlated with a higher deeper myometrial invasion, and greater use of adjuvant chemotherapy (68.8% vs. 19.4% in LVSI-negative cases). These associations are consistent with prior reports linking LVSI to aggressive pathological features.[32] Despite the more frequent use of chemotherapy in LVSI-positive patients, recurrence rates did not differ significantly between the treated and untreated subgroups ($p>0.05$). This may reflect the limited sample size and event numbers, but it also raises questions about the adequacy of current adjuvant strategies in mitigating LVSI-related risk. The lack of survival benefit in the multivariate analysis suggests that LVSI may identify a biologically aggressive subset of tumours that are less responsive to conventional therapies.

Although OS was defined as time from surgery to death from any cause, the available follow-up and number of death events limited the precision of longer-term estimates; therefore, survival results are presented primarily as 5-year OS estimates. Additionally, molecular staining (e.g., POLE, p53-abnormal, MMRd) was not consistently available, precluding the evaluation of its prognostic role.

The findings of this study contribute to the growing body of evidence supporting LVSI as a clinically relevant prognostic marker. Nevertheless, limitations such as the retrospective design, single centre setting, modest sample size, and incomplete survival timing data must be acknowledged. These constraints underscore the need for validation in larger, prospective, multicentre studies with standardized pathological evaluation of LVSI. Importantly, future research should integrate molecular classification systems (The Cancer Genome Atlas / Proactive Molecular Risk Classifier for Endometrial Cancer or TCGA/ProMisE groups) in accordance with the ESGO/ESTRO/ESP 2023 recommendations, which emphasize the combined use of histopathological features and molecular profiles to refine risk stratification and guide individualized therapy. In clinical practice, LVSI positivity should also influence nodal assessment strategies: sentinel lymph node (SLN) mapping remains the preferred approach in apparent early stage endometrial cancer, but LVSI strengthens the rationale for performing nodal staging even in otherwise low risk cases. Incorporating LVSI status into decision making, alongside molecular classification, provides a more comprehensive framework for individualized management and ensures alignment with contemporary international standards.

## CONCLUSION

This study demonstrates that LVSI is a significant and independent prognostic factor for Stage I endometrioid endometrial carcinoma. Its presence was strongly associated with increased recurrence, distant metastasis, and reduced OS, underscoring LVSI as a marker of aggressive tumour biology, even in early-stage disease. Importantly, LVSI correlated with adverse pathological features, such as deeper myometrial invasion, reinforcing its role as a surrogate indicator of poor prognosis.

From a clinical perspective, incorporating LVSI status into postoperative risk stratification provides an opportunity to refine the management strategies. Patients with LVSI-positive tumours may benefit from closer surveillance schedules and consideration of adjuvant therapy, whereas patients with LVSI-negative tumours could potentially avoid overtreatment. However, the lack of consistent survival benefit from chemotherapy in our cohort highlights the need for more targeted therapeutic approaches. LVSI may identify a biologically distinct subset of tumours that require novel systemic or combined modality treatments that go beyond conventional regimens.

In summary, LVSI should be recognized as a key determinant of outcome in Stage I endometrioid endometrial carcinoma. Its integration into risk stratification models with molecular classification system has the potential to optimize individualized management, improve prognostic accuracy, and guide future research on tailored adjuvant therapy strategies for early-stage EC.

## CONFLICT OF INTEREST

All authors declare no financial or non-financial conflict of interest.

## FUNDING

This research did not receive any special grant from funding agencies in the public, commercial, or not-for-profit sectors.

## ETHICAL APPROVAL

This study was conducted in accordance with the Helsinki Declaration and was approved by Research Ethics Committee of the National University of Malaysia (IRB: JEP-2025-328).

## DATA AVAILABILITY STATEMENT

Data is available upon request.

## REFERENCES

1. International Agency for Research on Cancer (IARC), World Health Organization. Global cancer statistics 2022: GLOBOCAN. [cited Jul 2026]. Available from: https://gco.iarc.who.int/media/globocan/factsheets/populations/900-world-fact-sheet.pdf
2. Ministry Ministry of Health. Summary of the Malaysia National Cancer Registry Report 2017–2021. Putrajaya (Malaysia): Ministry of Health; 2023 [cited Jul 2026]. Available from: https://repository.nih.gov.my/entities/publication/11eb07b4-c510-4e2f-ad46-38bdbee6cbbc
3. Feinberg J, Albright B, Black J, Lu L, Passarelli R, Gysler S, et al. Ten-year comparison study of type 1 and 2 endometrial cancers: risk factors and outcomes. Gynecol Obstet Invest 2019; 84(3): 290-7
4. Brooks RA, Fleming GF, Lastra RR, Lee NK, Moroney JW, Son CH, et al. Current recommendations, and recent progress in endometrial cancer. CA Cancer J Clin 2019; 69: 258-79.
5. Briet JM, Hollema H, Reesink N, Aalders JG, Mourits MJ, Ten Hoor KA, et al. Lymphvascular space involvement: an independent prognostic factor in endometrial cancer. Gynecol Oncol 2005; 96(3): 799-804.
6. Simpkins F, Yamada SD, Powell MA, Gibb RK, Kurnit KC, Mutch DG, et al. Patterns of recurrence in stage I endometrioid endometrial adenocarcinoma with lymphovascular space invasion. Int J Gynecol Cancer 2013; 23(1): 98-104.
7. Keys HM, Roberts JA, Brunetto VL, Zaino RJ, Spirtos NM, Bloss JD, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate-risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 2004; 92(3): 744-51.
8. Kuhn TM, Dhanani S, Ahmad S. An overview of endometrial cancer with novel therapeutic strategies. Curr Oncol 2023; 30(9): 7904-19.
9. American College of Obstetricians and Gynecologists. Practice Bulletin No. 149: Endometrial cancer. Obstet Gynecol 2015; 125: 1006-26.
10. Cohn DE, Horowitz N, Mutch D, Fowle JM, Rader JS, Herzog TJ. Should the presence of lymphovascular space involvement be used to assign patients to adjuvant therapy following hysterectomy for unstaged endometrial cancer? Gynecol Oncol 2002; 87(3): 243-6.
11. Bosse T, Peters EEM, Creutzberg CL, Nout RA, Jürgenliemk-Schulz IM, Jobsen JJ, et al. Substantial lymph-vascular space invasion is a significant risk factor for recurrence in endometrial cancer: a pooled analysis of PORTEC 1 and 2 trials. Eur J Cancer 2015; 51(13): 1742-50.
12. Weinberg LE, Kunos CA, Zanotti KM, Larkins-Pettigrew M, Parker C, Rose PG. Lymphovascular space invasion is an isolated poor prognostic factor for recurrence and survival among women with intermediate- to high-risk early-stage endometrioid endometrial cancer. Int J Gynecol Cancer 2013; 23(8): 1438-45.
13. Jorge S, Hou JY, Tergas AI, Burke WM, Huang Y, Wright JD, et al. Magnitude of risk for nodal metastasis associated with lymphovascular space invasion for endometrial cancer. Gynecol Oncol. 2016;140(3):418-23.
14. Creasman WT, Ali S, Mutch D, Miller DS, Powell MA, Fader AN, et al. Surgical-pathological findings in type 1 and 2 endometrial cancer: an NRG Oncology/Gynecologic Oncology Group study on GOG-210 protocol. Gynecol Oncol 2017; 145(3): 346-54.
15. Dos Reis R, Burzawa JK, Tsunoda A, Yuan Y, Hernandez MA, Ramirez PT, et al. Lymphovascular space invasion portends poor prognosis in low-risk endometrial cancer. Int J Gynecol Cancer 2015; 25(7): 1293-9.
16. Bendifallah S, Perrin M, Ouldamer L, Borie C, Canlorbe G, Ballester M, et al. Honing the classification of high-risk endometrial cancer with inclusion of lymphovascular space invasion. Surg Oncol 2017; 26(1): 9-15.
17. Taşkin S, Sükür YE, Varlı B, Tuncer ZS, Atalay MA, Ortaç F, et al. Nomogram with potential clinical use to predict lymph node metastasis in endometrial cancer patients diagnosed incidentally by postoperative pathological assessment. Arch Gynecol Obstet 2017; 296(4): 719-27.
18. American Cancer Society. 5-year relative survival rates for endometrial cancer [Internet]. Atlanta (GA): American Cancer Society; 2023 [cited 2026 Jun 30]. Available from: https://www.cancer.org/cancer/types/endometrial-cancer/detection-diagnosis-staging/survival-rates.html
19. Marnitz S, Walter T, Markiefka B, Brucker SY, Buderath P, Mallmann P. A modern approach to endometrial carcinoma: will molecular classification improve precision medicine in the future? Cancers (Basel) 2020; 12(9): 2577.

20. Murali R, Soslow RA, Weigelt B. Classification of endometrial carcinoma: more than two types. Lancet Oncol 2014; 15(7): e268-78.
21. McCluggage WG, Bosse T, Gilks CB, Parra-Herran C, Köbel M, Singh N, et al. FIGO 2023 endometrial cancer staging: too much, too soon? Int J Gynecol Cancer 2023; 34(Suppl 1): ijgc-2023-004981.
22. Creutzberg CL, van Putten W, Koper PCM, Lybeert MLM, Jobsen JJ, Wárlám-Rodenhuis CC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage I endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Lancet 2000; 355(9213): 1404-11.
23. Sadozye AH, Harrand RL, Reed NS. Lymphovascular space invasion as a risk factor in early endometrial cancer. Curr Oncol Rep 2016; 18(4): 24.
24. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: uterine neoplasms. Version 3 [Internet]. Fort Washington (PA): National Comprehensive Cancer Network; 2019 [cited 2019 Mar 17]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf.
25. Colombo N, Creutzberg C, Amant F, Bosse T, González-Martín A, Ledermann J, et al. ESMO–ESGO–ESTRO consensus conference on endometrial cancer: diagnosis, treatment and follow-up. Ann Oncol 2016; 27(1): 16-41.
26. Neal SA, Graybill WS, Garrett-Mayer E, Rossi EC, Boggess JF, Creasman WT, et al. Lymph-vascular space invasion in uterine corpus cancer: what is its prognostic significance in the absence of lymph node metastases? Gynecol Oncol 2016; 142(2): 278-83.
27. Therasakvichya S, Kuljarusnont S, Petsuksiri J, Jaishuen A, Chotikawattanapanit O, Lertkhachonsuk R, et al. Clinical outcomes of stage I endometrial carcinoma patients treated with surgery alone: Siriraj Hospital experiences. J Gynecol Oncol 2016; 27(5): e48.
28. Han KH, Kim HS, Lee M, Kim T, Song YS. Prognostic factors for tumor recurrence in endometrioid endometrial cancer stages IA and IB. Medicine (Baltimore) 2017; 96(21): e6976.
29. Sasada S, Yunokawa M, Takehara Y, Tamura K, Noda S, Kawabata T, et al. Baseline risk of recurrence in stage I–II endometrial carcinoma. J Gynecol Oncol 2018; 29(1): e9.
30. Ozkan N, Meydanli MM, Sarı ME, Gungor T, Yuce K, Ayhan A, et al. Factors associated with survival after relapse in patients with low-risk endometrial cancer treated with surgery alone. J Gynecol Oncol 2017; 28(5): e65.
31. Dai Y, Dong Y, Cheng Y, Hou H, Wang J, Wang Z, et al. Prognostic significance of lymphovascular space invasion in patients with endometrioid endometrial cancer: a retrospective study from a single center. J Gynecol Oncol 2019; 31(3): e27.
32. Tortorella L, Restaino S, Zannoni GF, Vizzielli G, Chiantera V, Gallotta V, et al. Substantial lymph-vascular space invasion (LVSI) as predictor of distant relapse and poor prognosis in low-risk early-stage endometrial cancer. J Gynecol Oncol 2021; 32(2): e11.
33. Qin ZJ, Wang YS, Chen YL, Zhang Y, Han L. Evaluation of prognostic significance of lymphovascular space invasion in early stage endometrial cancer: a systematic review and meta-analysis. Front Oncol 2024; 13: 1286221.
34. Ureyen I, Karalok A, Turkmen O, Kimyon G, Reis Akdas Y, Akyol A, et al. Factors predicting recurrence in patients with stage IA endometrioid endometrial cancer: what is the importance of LVSI? Gynecol Oncol.2020; 301: 737-44.
35. Askandar B, Ariyanto TB, Yuliati I, Sandhika W. The role of lymph vascular space invasion towards disease free survival and overall survival in high risk endometrial cancer endometrioid type patients. Syst Rev Pharm 2020; 11(5): 176-80. ISSN:0976 2779.

# Antenatal Hepatitis B screening in pregnancy: Prevention of mother-to-child transmission strategy in Kedah, Malaysia

**Nor Sarina Ismail, MD[1], Tan Wei Leong, DrPH[1], Mohd Azri Mohd Suan, MSc (Epid and Biostats)[2], Shahrul Aiman Soelar, MSc (Data Analysis)[2], Rahimah Ab Razak, MD[3]**

[1]Communicable Disease Control (CDC) Unit, Kedah State Health Department, Ministry of Health Malaysia, [2]Clinical Research Centre (CRC), Hospital Sultanah Bahiyah, Alor Setar, Kedah, Malaysia, [3]Communicable Disease Control (CDC) Unit, Kuala Muda District Health Office, Kedah, Malaysia

## ABSTRACT

**Introduction: Hepatitis B virus remains a major global public health concern, with mother-to-child transmission contributing substantially to chronic infection, cirrhosis and hepatocellular carcinoma. In 2019, the Ministry of Health Malaysia initiated pilot universal antenatal hepatitis B screening in four selected states, namely Kedah, Pahang, Terengganu and Sabah, to strengthen prevention of mother-to-child transmission (PMTCT). This study reviewed the implementation of the PMTCT hepatitis B pilot project in Kedah by evaluating the transmission rate of HBV to infants, antenatal screening coverage of HBV and the prevalence of hepatitis B among pregnant mothers.**

**Materials and Methods: A cross-sectional review of secondary data was conducted using programme registers from 17 participating health clinics in Kedah. Data were extracted and analysed. The key outcomes were antenatal screening coverage, maternal HBsAg prevalence and mother-to-child transmission rate.**

**Results: A total of 54,682 antenatal attendees were screened for HBV during the study period, giving an overall screening coverage of 95.8%. Maternal HBsAg prevalence was 0.16%, with 92 confirmed HBsAg-positive mothers. Of these, 91 were referred for further assessment and 83 received antiviral therapy during pregnancy. Among exposed infants with documented follow-up, no HBsAg-positive cases were detected, resulting in a mother-to-child transmission rate of 0%.**

**Conclusion: Overall, the mother-to-child transmission rate of the pilot project in Kedah was satisfactory at 0% among antenatal mothers who were treated and completed the follow-up plan. In addition, the prevalence of HBV among antenatal mothers was relatively low at 0.16%, with high HBV screening coverage of 95.8% among antenatal attendees.**

**KEYWORDS:**
*Hepatitis B; mother-to-child transmission; antenatal screening; prevention cascade; Malaysia*

## INTRODUCTION

Hepatitis B virus (HBV) remains a formidable global health challenge, with an estimated 240 million people living with chronic infection and over 780,000 deaths occurring annually from related complications such as cirrhosis and liver cancer.[1] Mother-to-child transmission (MTCT) is one of the primary modes of transmission, accounting for 30–50% of all chronic cases worldwide.[2] The risk of an infant acquiring chronic infection is exceptionally high, ranging from 70% to 90% if the mother is positive for both Hepatitis B surface antigen (HBsAg) and hepatitis B e-antigen (HBeAg), and between 10% and 40% for infants born to HBeAg-negative mothers.[2] In response, the World Health Organization (WHO) has established clear recommendations for preventing vertical transmission.[3] These include the universal administration of the Hepatitis B vaccine birth dose within 24 hours of delivery, completion of the full vaccine series, and the use of Hepatitis B immunoglobulin (HBIG) for infants born to highly infectious mothers.[3] These interventions are cornerstones of the WHO global strategy to reduce the MTCT rate below 2.0% and eventually eliminate MTCT of HBV by 2030.

Globally, universal infant Hepatitis B vaccination has achieved significant success in controlling HBV, with the prevalence of Hepatitis B among the paediatric population currently estimated at 0.6%. In Malaysia, the Ministry of Health implemented the universal infant Hepatitis B vaccination programme in 1989, with the aim of achieving a Hepatitis B prevalence of less than 0.1% among the paediatric population. In relation to this, persistent challenges in preventing MTCT must be proactively addressed, particularly in ensuring timely administration of the birth dose vaccine, maintaining a consistent and accessible supply of HBIG, and guaranteeing comprehensive follow-up for all exposed infants.[4]

To address these implementation gaps and align national efforts with WHO hepatitis elimination targets, the Ministry of Health, Malaysia has initiated a pilot project for universal antenatal HBV screening since 2019 in the states of Kedah, Pahang, Terengganu and Sabah.[4] This initiative was designed to test and refine a comprehensive prevention of mother-to-child transmission (PMTCT) strategy within the existing public health infrastructure. The primary objective for this study was the mother-to-child transmission rate of HBV in the state of Kedah, Malaysia. Secondary objectives were including antenatal screening coverage, maternal HBsAg prevalence, and the timeliness and completion rates of key interventions along the PMTCT.

*This article was accepted: 01 July 2026*
*Corresponding Author: Nor Sarina Ismail*
*Email: drnorsarina@moh.gov.my*

**Table I: Antenatal hepatitis B screening coverage and maternal HBsAg prevalence in Kedah, 2019–2025 (January-June)**

| Year(s) | Total Antenatal Attendees | Number Screened (RDT) | Screening Coverage (%) | Number Confirmed HBsAg Positive (EIA) | Maternal HBsAg Prevalence (%) |
|---|---|---|---|---|---|
| 2019 | 4, 970 | 4, 653 | 93.62 | 20 | 0.40 |
| 2020 | 7, 851 | 7, 851 | 100.00 | 15 | 0.19 |
| 2021 | 11, 698 | 10, 784 | 92.19 | 8 | 0.07 |
| 2022 | 11, 523 | 11, 523 | 100.00 | 19 | 0.16 |
| 2023 | 6, 259 | 6, 259 | 100.00 | 10 | 0.16 |
| 2024 | 10, 110 | 8, 929 | 88.32 | 11 | 0.11 |
| 2025 (January-June) | 4, 691 | 4, 683 | 99.83 | 9 | 0.19 |
| Total | 57, 102 | 54, 682 | 95.76 | 92 | 0.16 |

RDT, Rapid Diagnostic Test
EIA, Enzyme Immunoassay
HBsAg, Hepatitis B surface antigen

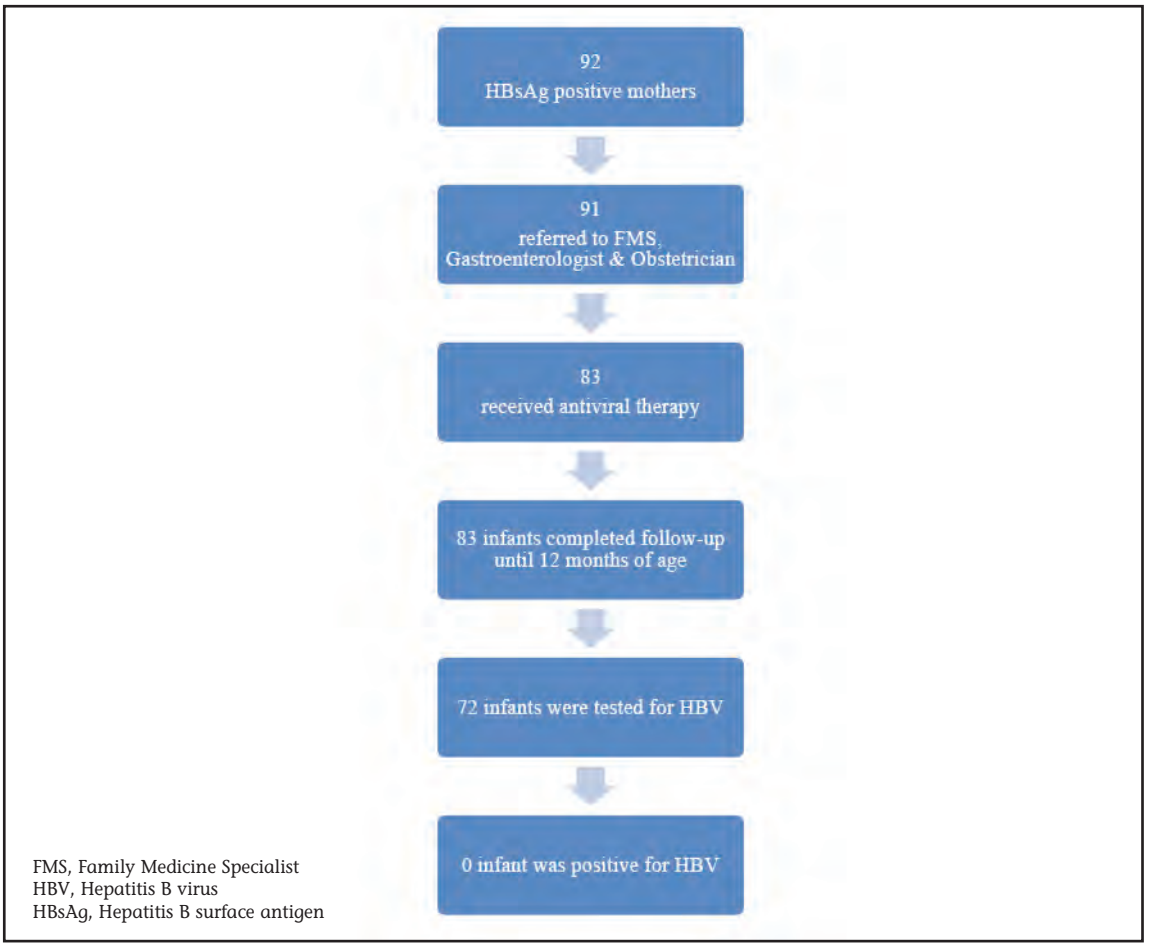



**Fig. 1:** Progression of care for PMTCT of HBV in Kedah, January 2019–June 2025

## MATERIALS AND METHODS

This cross-sectional study utilized secondary data extracted from the existing program registry created by the Communicable Disease Control (CDC) for this pilot project. The selected health clinics of the pilot project were determined by the CDC Unit of Kedah State Health Department, representing every district in Kedah state. The inclusion criteria were all pregnant women who attended antenatal care at the 17 participating government health clinics in Kedah between 1st January 2019 and 30th June 2025. Exclusion criteria were post-natal mothers who were transferred in from other non-participating health clinics.

The variables included in this registry are HBV screening status, HBV screening outcome, referral to specialist care, treatment of antiviral therapy, administration of immunoglobulin and HBV status of their infant. Under PMTCT, the HBV screening was done using rapid diagnostic test kit and subsequently laboratory confirmed by enzyme immunoassay to detect hepatitis B markers such as HBsAg.

All data were analysed using R software.[4] The analysis focused on descriptive -statistics to characterize the program cascade. Key performance indicators were calculated as proportions with 95% confidence intervals to quantify program performance against established targets. PMTCT cascade refers to the sequential steps in the prevention of mother-to-child transmission program, beginning from antenatal attendance and maternal HBV screening, followed by identification of HBsAg-reactive mothers, referral for further assessment, initiation of antiviral therapy when indicated, delivery planning, infant administration of timely hepatitis B birth dose and HBIG, and completion of infant follow-up testing to determine infection status. The cascade is used to evaluate program coverage, continuity of care and gaps at each stage of service delivery.

## RESULTS

Overall, in the PMTCT pilot program between 1st January 2019 and 30th June 2025, 54,682 from a total of 57, 102 antenatal attendees were screened (95.76%). Although the six-year average coverage remained high, annual fluctuations were observed, with a notable decline to 88.32% in 2024. The annual screening coverage and detailed year by-year performance are summarized in Table I. The prevalence of confirmed HBsAg among pregnant women was 0.16%, with a total of 92 mothers confirmed positive via EIA in this cohort.

This figure shows the progression of care among confirmed HBsAg-positive mothers and their exposed infants, including referral for further assessment, infant testing and follow-up, receipt of antiviral therapy during pregnancy, and mother-to-child transmission outcome.

Between January 2019 and June 2025, among the 92 confirmed HBsAg-positive mothers, 91 (98.9%) were successfully referred. Of these, 83 received antiviral therapy during pregnancy. Among the 83 exposed infants, complete follow-up was conducted, and definitive serological outcomes were available for 72 infants, all of whom tested non-reactive for HBsAg. None of the infants were tested positive, resulting in an MTCT rate of 0%.

## DISCUSSION

This study demonstrated a high antenatal HBV screening coverage in Kedah, with an overall coverage of 95.76%. There was a decline in the antenatal HBV screening in 2024. This decline was partly attributed to the transition of program management between different units. The change of program managers would require a smooth transition in term of the database maintenance as well as the training is required to ascertain the competency of the new managers. On top of that, we noticed that there was also a change of implementers at health clinic level and hence their comprehension of the program was important to sustain the continuous implementation of the screening among the antenatal attendees. The lack of understanding of the PMTCT would end up high rate of none screening among the attendees.

In this study, the maternal HBV prevalence was 0.16%. These findings stand in contrast to broader regional data; for instance, an 11.8% HBsAg positivity rate was reported among pregnant women in Northern Uganda.[5] Furthermore, while a pooled prevalence of 6.8% was found across Africa[6], regions in Southern China saw a decline from 14.5% in 2015 to 8.19% in 2020.[7] On a global scale, it is estimated that 71.4 million women of childbearing age were living with chronic HBV in 2021.[8] In short, the prevalence of HBV among antenatal mothers in Kedah was relatively low compared to various studies worldwide and this could be attributed to mandatory inclusion of Hepatitis B vaccination in Malaysian National Immunization Program in 1989.

As for the MTCT rate in Kedah, the low MTCT rate is certainly consistent with outcomes reported in settings with strong prevention programs. For instance, the MTCT rate has been reduced to 0.44%–0.60% through Triple Elimination initiatives and mandated antiviral prophylaxis for mothers with high viral loads in Shandong China.[9] Similarly, in low-endemic settings such as England, maternal HBV prevalence has been reported at approximately 0.5%–0.7%, with achievements exceeding WHO 2030 targets, supported by high screening coverage and timely birth-dose vaccination.[10] In Malaysia, published data on hepatitis B prevalence among antenatal mothers remain limited. A weighted analysis in Ipoh, Perak reported a prevalence of 1.35%, with 23.1% of HBsAg-positive pregnant women requiring antiviral prophylaxis due to high viral loads.[11] The findings from Kedah therefore highlight the effectiveness of a screen-and-treat model within the PMTCT pathway.

Although the MTCT rate in the pilot project was 0%, there were limitations and challenges in the progression of care. For instance, the attrition rate at every stage of progression of care was relatively prominent. In relation to this, there was one antenatal mother who were not referred to specialist for consultation and the reason was mainly due to refusal from patient. To overcome this, a proper and comprehensive counselling was warranted to inform the mother on the risk of vertical transmission to her newborn. On top of that, treatment uptake was only 91.2% which could have risk the vertical transmission to the newborn. This gap warrants a future exploration of the underlying causes of none treatment among the 8.8% antenatal mothers.

In term of the progression of care, the PMTCT shows high referral rate (98.9%) and treatment uptake (91.2%). On top of that, all of the mothers who received the antiviral therapy had 100.0% of follow up for their infants up-till 12 months of age. However, there were approximately 86.7% of the infants underwent the serological testing for HBV. Out of the 72 infants, the MTCT rate was 0%. Another gap detected in the pilot project was the attrition of infants follow up until 12 months whereby there were 11 infants who did not complete the 12 months follow up and hence no serological test was done to assess the transmission rate. To overcome this, a robust tracing system spanning the health clinics and paediatrics department is crucial to reduce attrition rate and hence to reduce transmission rate of HBV.

The limitations of this study include the data completeness as the main source of data was secondary. In addition, variables available in the database was also limited as the data collection concentrated in monitoring the program flow and planning of the program. Hence, there was specific documentations on the underlying reasons causing the attrition among the antenatal mothers and the infants during the progression of care for PMTCT.

## CONCLUSION

Overall, the MTCT rate of the pilot project in Kedah was satisfactory at 0% among all the antenatal mothers who were treated and completed the follow up plan. On top of that, the prevalence of HBV among the antenatal mothers was relatively low at 0.16% with a relatively high HBV screening (95.8%) among the antenatal attendees. These robust findings emphasize on the importance of PMTCT in preventing vertical transmission of HBV and in line with the goal set by WHO in reducing the MTCT rate below 2.0%.

## ACKNOWLEDGMENTS

The authors like to thank all participants of this study.

## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

## FUNDING

This stduy received no funding.

## REFERENCES

1. GBD 2015 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016; 388(10053): 1603-58.
2. Gentile I, Borgia G. Vertical transmission of hepatitis B virus: challenges and solutions. Int J Womens Health 2014; 6: 605-11.
3. World Health Organization. Guidelines for the prevention, diagnosis and treatment of chronic hepatitis B infection. Geneva: World Health Organization; 2024.
4. Ministry of Health Malaysia. Guideline on Prevention of Mother-to-Child Transmission of Hepatitis B, 1st Edition. Putrajaya: Ministry of Health Malaysia; 2025.
5. Bayo P, Ochola E, Oleo C, Mwaka AD. High prevalence of hepatitis B virus infection among pregnant women attending antenatal care: a cross-sectional study in two hospitals in northern Uganda. BMJ Open 2014; 4(11): e005889.
6. Larebo YM, Anshebo AA, Abdo RA, Behera SK, Gopalan N. Prevalence of hepatitis B virus infection among pregnant women in Africa: A systematic review and meta-analysis. PLoS One 2024; 19(7): e0305838.
7. Shan S, Zhao X, Jia J. Comprehensive approach to controlling chronic hepatitis B in China. Clin Mol Hepatol 2024; 30(2): 135-45.
8. Yang S, Zhong L, Huang L, Lin S, Li Y. Global burden and trends of viral hepatitis among women of childbearing age from 1990 to 2021. Front Microbiol 2025; 16: 1553129.
9. Meng X, Zhang W, Yan B, Feng Y, Lu J, Zhang L. Progress toward elimination mother-to-child transmission of HBV in Shandong Province, China: Coverage trend in hepatitis B vaccination and HBIG administration, 2017–2024. Hum Vaccin Immunother 2025; 21(1): 2554029.
10. UK Health Security Agency. Hepatitis B in England: 2025 report. London: UK Health Security Agency; 2025.
11. Hoo C, WZ WA, Omar H, Tan S. Prevention of mother-to-child transmission of hepatitis B virus: An observation of routine practice in a tertiary liver centre before and after the introduction of the global health sector strategy on viral hepatitis. Med J Malaysia 2023; 78(2): 234-40.

# Assessment of acceptability, appropriateness, and feasibility of the mindfulness and well-being toolkit for depression in Malaysian primary care clinics: A cross-sectional study

**Asma' Khalil[1], Zahir Izuan Azhar[1], Chen Xin Wee[1], Norley Shuib[2]**

[1]Department of Public Health Medicine, Faculty of Medicine, Universiti Teknologi MARA, Sungai Buloh Campus, Selangor, [2]Department of Psychiatry, Faculty of Medicine, Universiti Teknologi MARA, Sungai Buloh Campus, Selangor

## ABSTRACT

**Introduction: Depression is a major contributor to disability worldwide, and mild to moderate depressive symptoms are frequently managed in primary care, where time and specialist access are constrained. The Mindfulness and Well-being Toolkit (Mind-WELL Kit) was developed to support primary care providers in delivering brief, structured mindfulness-based support for depression, but its implementation potential requires evaluation.**

**Materials and Methods: A cross-sectional online survey was conducted among providers from a systematic sample of primary health care clinics in Selangor. Participants received the Mind-WELL Kit in portable document format (PDF) and were given approximately two weeks to review it before completing the acceptability of intervention measure (AIM), intervention appropriateness measure (IAM), and feasibility of intervention measure (FIM), along with a single-item overall satisfaction rating (1–5). Pearson correlation, independent-samples t-test, and one-way ANOVA were used to examine differences by participant characteristics.**

**Results: A total of 151 healthcare providers participated in the study, with a mean (standard deviation, SD) age of 37.83 (5.67) years, and 80.8% were female. Participants reported favourable perceptions of the Mind-WELL Kit, with mean (SD) scores of 4.13 (0.55) for AIM, 4.07 (0.59) for IAM, and 3.96 (0.61) for FIM. Scores did not differ significantly according to age, gender, ethnicity, job category, duration of service, or clinic type (p>0.05). Overall satisfaction was high, with a mean (SD) score of 4.21 (0.78), and 84.8% of participants rated the toolkit 4 or 5 out of 5.**

**Conclusions: The Mind-WELL Kit showed promising perceived implementation potential, with high acceptability and appropriateness, favourable feasibility, and strong overall satisfaction among primary care providers.**

**KEYWORDS:**
*Depression; mindfulness; implementation outcomes; primary care; AIM IAM FIM*

## INTRODUCTION

Depression remains one of the leading causes of disability worldwide and continues to impose substantial social and economic consequences across health systems.[1-2] Although pharmacological and psychotherapeutic treatments are well established, many individuals with mild to moderate depressive symptoms are treated in primary care settings. In these settings, short consultation times, limited access to mental health specialists, and uneven psychosocial resources often constrain the depth and continuity of care. In Malaysia, national data show a notable rise in depressive symptoms over the past decade, underscoring the need for practical, scalable interventions that can be delivered effectively within primary care.[2] The central issue is no longer whether effective interventions exist, but whether they can be integrated into routine clinical workflows in ways that are both sustainable and contextually appropriate.

Strengthening mental health services in primary healthcare requires more than a single standardized solution. Instead, it calls for integrated, biopsychosocial approaches that combine medical management with accessible psychological support. Embedding basic mental health care within primary care services facilitates early detection, continuity of follow-up, reduced stigma, and potentially lower long-term healthcare and social costs.[3] However, primary care providers often manage high patient volumes within limited consultation periods. Under such conditions, the introduction of any additional psychosocial component must align with workflow demands, provider confidence, and perceived clinical value.[4-5] Cultural relevance and contextual compatibility further shape provider engagement and sustained implementation. Without a systematic evaluation of these implementation factors, the transition from a validated manual to a routine clinical tool remains uncertain. Within this broader framework, structured psychosocial tools that are brief, adaptable, and feasible for non-specialist providers are particularly valuable.

Mindfulness-based interventions (MBIs) have emerged as one such evidence-supported approach. A growing body of systematic reviews and randomized controlled trials demonstrates that structured MBIs reduce depressive symptoms and help prevent relapse across diverse populations.[5-6] Beyond symptom reduction, mindfulness has been shown to strengthen emotional regulation and foster autonomous motivation through the satisfaction of basic psychological needs, as described in Self-Determination Theory.[7-9] These theoretical and empirical foundations

*This article was accepted: 01 July 2026*
*Corresponding Author: Zahir Izuan Azhar*
*Email: drzahir@uitm.edu.my*

support incorporating brief, structured mindfulness practices into primary care encounters, particularly when delivered in ways that align with patients' intrinsic motivation and everyday experiences.

In response to service gaps at the primary care level, we developed and validated the mindfulness and well-being toolkit (Mind-WELL Kit), an adapted mindfulness-based toolkit designed for practical delivery within Malaysian primary care settings. The toolkit was created through a theory-driven, multi-stage process grounded in self-determination theory and refined using a modified Delphi method with multidisciplinary experts.[10] Content and face validation demonstrated strong relevance, clarity, and usability, indicating that the toolkit was conceptually sound and contextually suited for Malaysian primary care settings. The Mind-WELL Kit was developed for use by primary healthcare providers involved in the assessment and management of patients with mild-to-moderate depression, including family medicine specialists, medical officers, assistant medical officers, nurses, and counsellors. The toolkit comprises two main components: a provider-focused manual that enhances mental health literacy, communication skills, and patient engagement strategies, and a collection of structured mindfulness exercises designed for use during routine clinical encounters. To facilitate integration into busy practice settings, the mindfulness activities were intentionally designed to be brief, flexible, and easily incorporated into existing consultations, including mental health screening, counselling sessions, chronic disease follow-up, and mental health reviews. Importantly, the toolkit functions as an adjunct to standard clinical management rather than a stand-alone intervention.

Despite encouraging validation findings, strong validation indices alone do not ensure successful uptake in everyday practice. Implementation science highlights the importance of examining outcomes such as acceptability, appropriateness, and feasibility when determining whether an intervention can be sustained in real-world settings.[11] Acceptability refers to the perception among implementation stakeholders that a particular treatment, service, practice, or innovation is agreeable, palatable, or satisfactory. Appropriateness involves the perceived fit, relevance, or compatibility of the innovation or evidence-based practice within a specific practice setting, for a provider or a consumer. It also encompasses the perceived fit of the innovation in addressing a particular issue or problem. Feasibility is defined as the extent to which a new treatment or innovation can be successfully utilized or implemented within a given agency or setting.[12] Even theoretically robust and clinically effective interventions may fail if these practical dimensions are not adequately addressed.

Therefore, the present study builds on earlier development and validation work by examining the acceptability, appropriateness, and feasibility of the Mind-WELL Kit among primary healthcare providers.[10] By focusing on these implementation outcomes, the study adds early insight into how well the toolkit fits real-world primary care settings and helps indicate whether larger effectiveness studies are needed.

## MATERIALS AND METHODS

### Study Design

A cross-sectional study was conducted in the fourth quarter of 2025. It involved the primary healthcare providers working in selected health clinics in Selangor, Malaysia. They included family medicine specialists, medical officers, counsellors, assistant medical officers, staff nurses, community nurses, and others. The sampling frame comprised all primary health care clinics in Selangor (N=85). Clinics were first organised by district, then selected using systematic random sampling with an interval of five. Every fifth clinic on the district-based list was selected until the required number of clinics was reached. Using this approach, 20 primary care clinics were selected.

### Participant Recruitment

Healthcare personnel were eligible if they met at least one of the following conditions within the selected clinics: (i) were involved in the clinic's mental health programme, (ii) were assigned to the dedicated Non-Communicable Disease (NCD) unit, and (iii) were involved in mental health screening activities in the outpatient department. Individuals were excluded if they did not consent or were on extended leave during the study period. A site investigator was appointed at each selected clinic to facilitate participant recruitment. Eligible healthcare personnel were identified according to the predefined eligibility criteria and invited to participate voluntarily. Given the variability in staffing structures and service arrangements across clinics, site investigators recruited eligible personnel based on availability during the study period. Therefore, the total number of healthcare personnel approached was not systematically recorded.

The required sample size was estimated using a single-mean formula, $n=\left(\frac{z\sigma}{\Delta}\right)$, where z is the critical value for the chosen confidence level, $\sigma$ is the standard deviation, and $\Delta$ is the desired precision around the population mean. Using a 95% confidence level (z=1.96) with a precision of 1, the estimated sample sizes were 34 for acceptability based on a standard deviation of 2.96, 118 for appropriateness based on a standard deviation of 5.55, and 64 for feasibility based on a standard deviation of 4.07, using estimates reported by Chung et al. (2022).[13] Since appropriateness produced the largest required sample size, and after adjusting for a 20% non-response rate, the minimum required sample size for this study was 148 participants.

### Data Collection

The selected site investigators distributed an electronic copy of the Mind-WELL Kit to the eligible participants, who were given two weeks to review. Subsequently, a Google Form containing the consent form, the link to assess the toolkit, and the questionnaires was distributed. Participant characteristics (age, gender, ethnicity, occupation, duration of service, and clinic type) and three validated implementation outcome measures (AIM, IAM, and FIM) were collected. No personal identifiers were collected to protect participants' privacy and confidentiality.

### Study Instrument

Acceptability, appropriateness, and feasibility were assessed using the AIM, IAM, and FIM questionnaires. They are

**Table I: Participants' Demographics (N=151)**

| Characteristics | Mean (SD)/ n (%) |
|---|---|
| Mean age, mean (SD) | 37.8 (5.67) |
| Sex | |
| Male, n (%) | 29 (19.2) |
| Female, n (%) | 122 (80.8) |
| Ethnicity | |
| Malay, n (%) | 121 (80.1) |
| Chinese, n (%) | 4 (2.7) |
| Indian, n (%) | 18 (11.9) |
| Others, n (%) | 8 (5.3) |
| Designation | |
| Family Medicine Specialist, n (%) | 15 (9.9) |
| Medical Officer, n (%) | 66 (43.7) |
| Counsellor, n (%) | 2 (1.3) |
| Assistant Medical Officer, n (%) | 16 (10.6) |
| Staff Nurse, n (%) | 28 (18.5) |
| Community Nurse, n (%) | 7 (4.6) |
| Others, n (%) | 17 (11.3) |
| Duration of Service | |
| Less than 5 years, n (%) | 11 (7.3) |
| 5-10 years, n (%) | 38 (25.2) |
| 10-15 years, n (%) | 63 (41.7) |
| More than 15 years, n (%) | 39 (25.8) |
| Clinic Type | |
| Type I | 23 (15.2) |
| Type II | 10 (6.6) |
| Type III | 94 (62.3) |
| Type IV | 22 (14.6) |
| Type V | 2 (1.3) |

Note. Values are presented as mean (SD) for continuous variables and n (%) for categorical variables. Percentages may not total 100% due to rounding.

**Table II: Item-level Responses to the AIM, IAM, and FIM Measures for the Mind-WELL Kit (N=151)**

| Question | 5 | 4<br>n (%) | 3<br>n (%) | 2<br>n (%) | 1<br>n (%) | Mean<br>n (%) | 95% CI<br>(SD) | Min-Max |
|---|---|---|---|---|---|---|---|---|
| **AIM** | | | | | | | | |
| The Mind-WELL Kit meets my approval. | 39 (25.8) | 96 (63.6) | 12 (7.9) | 3 (2.0) | 1 (0.7) | 4.13 (0.55) | 4.04–4.22 | 2.00–5.00 |
| The Mind-WELL Kit is appealing to me. | 39 (25.8) | 100 (66.2) | 11 (7.3) | 1 (0.7) | 0 (0) | | | |
| I like the Mind-WELL Kit. | 32 (21.2) | 107 (70.9) | 9 (6.0) | 3 (2.0) | 0 (0) | | | |
| I welcome the Mind-WELL Kit | 37 (24.5) | 99 (65.6) | 11 (7.3) | 4 (2.7) | 0 (0) | | | |
| **IAM** | | | | | | | | |
| The Mind-WELL Kit seems fitting. | 32 (21.2) | 99 (65.6) | 16 (10.6) | 3 (2.0) | 1 (0.7) | 4.07 (0.59) | 3.98–4.17 | 2.00–5.00 |
| The Mind-WELL Kit seems suitable. | 34 (22.5) | 97 (64.2) | 15 (9.9) | 3 (3.3) | 0 (0) | | | |
| The Mind-WELL Kit seems applicable. | 35 (23.2) | 101 (66.9) | 13 (8.6) | 2 (1.3) | 0 (0) | | | |
| The Mind-WELL Kit seems like a good match. | 30 (19.9) | 103 (68.2) | 15 (9.9) | 3 (1.9) | 0 (0) | | | |
| **FIM** | | | | | | | | |
| The Mind-WELL Kit seems implementable. | 27 (17.9) | 98 (64.9) | 22 (14.6) | 3 (2.0) | 1 (0.7) | 3.96 (0.61) | 3.86–4.06 | 1.25–5.00 |
| The Mind-WELL Kit seems possible. | 25 (16.6) | 100 (66.2) | 22 (14.6) | 3 (2.0) | 1 (0.7) | | | |
| The Mind-WELL Kit seems doable. | 24 (15.9) | 106 (70.2) | 17 (11.3) | 3 (2.0) | 1 (0.7) | | | |
| The Mind-WELL Kit seems easy to use. | 21 (13.9) | 104 (68.9) | 21 (13.9) | 4 (2.7) | 1 (0.7) | | | |

Note. Response options were rated on a 5-point Likert scale: 1 = completely disagree, 2 = disagree, 3 = neither agree nor disagree, 4 = agree, and 5 = completely agree. Mean (SD) and 95% confidence intervals are shown for the overall AIM, IAM, and FIM construct mean scores, each calculated as the average of four items, with possible increments of 0.25. AIM = Acceptability of Intervention Measure; IAM = Intervention Appropriateness Measure; FIM = Feasibility of Intervention Measure. Percentages may not total 100% due to rounding.

**Table III: AIM, IAM, and FIM Scores by Participant Characteristics (N=151)**

| Factor | n Mean (SD) | AIM | 95% CI | p-value Mean (SD) | IAM | 95% CI | p-value Mean (SD) | FIM | 95% CI | p-value |
|---|---|---|---|---|---|---|---|---|---|---|
| Age | 151 | | | 0.803[a] | | | 0.837[a] | | | 0.954[a] |
| Gender | | | | | | | | | | |
| Male | 29 | 4.09 (0.68) | 3.83-4.35 | 0.626[b] | 4.06 (0.72) | 3.78-4.34 | 0.913[b] | 3.96 (0.70) | 3.69-4.22 | 0.961[b] |
| Female | 122 | 4.14 (0.51) | 4.05-4.23 | | 4.07 (0.56) | 3.97-4.18 | | 3.96 (0.59) | 3.86-4.07 | |
| Ethnicity | | | | | | | | | | |
| Malay | 121 | 4.15 (0.53) | 4.05-4.24 | 0.204[c] | 4.08 (0.58) | 3.98-4.19 | 0.728c | 3.98 (0.61) | 3.87-4.09 | 0.580[c] |
| Chinese | 4 | 4.56 (0.52) | 3.74-5.38 | | 4.31 (0.47) | 3.56-5.07 | | 4.25 (0.54) | 3.39-5.11 | |
| Indian | 18 | 3.99 (0.63) | 3.68-4.29 | | 3.97 (0.72) | 3.62-4.33 | | 3.82 (0.69) | 3.47-4.17 | |
| Bumiputera Sabah/ Sarawak | 8 | 3.97 (0.63) | 3.44-4.50 | | 4.00 (0.67) | 3.44-4.56 | | 3.91 (0.59) | 3.41-4.41 | |
| Job Category | | | | | | | | | | |
| Family Medicine Specialist | 15 | 4.00 (0.65) | 3.64-4.36 | 0.413[c] | 4.00 (0.68) | 3.62-4.38 | 0.219[c] | 3.80 (0.96) | 3.27-4.33 | 0.517[c] |
| Medical Officer | 66 | 4.20 (0.57) | 4.06-4.34 | | 4.14 (0.64) | 3.98-4.29 | | 3.96 (0.66) | 3.80-4.12 | |
| Assistant Medical Officer | 16 | 4.00 (0.51) | 3.73-4.27 | | 3.91 (0.63) | 3.57-4.24 | | 3.91 (0.53) | 3.62-4.19 | |
| Staff Nurse | 28 | 4.16 (0.37) | 4.02-4.30 | | 4.13 (0.36) | 3.88-4.28 | | 4.00 (0.34) | 3.87-4.13 | |
| Counsellor | 2 | 5.0 | | | 5.0 | | | 5.0 | | |
| Community Nurse | 7 | 4.13 (0.35) | 3.83-4.42 | | 4.19 (0.37) | 3.88-4.50 | | 4.19 (0.37) | 3.88-4.50 | |
| Others | 17 | 4.01 (0.67) | 3.67-4.36 | | 3.82 (0.65) | 3.49-4.16 | | 3.93 (0.56) | 3.64-4.22 | |
| Duration of Service | | | | | | | | | | |
| < 5 years | 11 | 4.18 (0.48) | 3.86-4.50 | 0.497[c] | 4.09 (0.50) | 3.75-4.43 | 0.874c | 4.07 (0.53) | 3.72-4.42 | 0.849[c] |
| 5 - 10 years | 38 | 4.09 (0.56) | 3.90-4.27 | | 4.07 (0.56) | 3.89-4.26 | | 3.95 (0.57) | 3.76-4.13 | |
| 10- 15 years | 63 | 4.20 (0.65) | 4.04-4.37 | | 4.11 (0.71) | 3.93-4.29 | | 3.99 (0.74) | 3.80-4.17 | |
| >15 years | 39 | 4.04 (0.33) | 3.94-4.15 | | 4.01 (0.43) | 3.87-4.15 | | 3.90 (0.46) | 3.86-4.06 | |
| Clinic Type | | | | | | | | | | |
| Type I | 23 | 4.32 (0.49) | 4.10-4.53 | 0.108[c] | 4.22 (0.51) | 4.00-4.44 | 0.261[c] | 4.13 (0.58) | 3.88-4.38 | 0.246[c] |
| Type II | 10 | 4.35 (0.58) | 3.84-4.66 | | 4.13 (0.52) | 3.76-4.49 | | 3.94 (0.64) | 3.47-4.38 | |
| Type III | 94 | 4.04 (0.57) | 3.92-4.16 | | 3.99 (0.63) | 3.86-4.12 | | 3.88 (0.64) | 3.75-4.01 | |
| Type IV | 22 | 4.28 (0.43) | 4.09-4.48 | | 4.25 (0.52) | 4.02-4.48 | | 4.15 (0.5) | 3.93-4.37 | |
| Type V | 2 | 4.0 (0) | 4.00-4.00 | | 4.0 (0) | 4.00-4.00 | | 4.0 (0) | 4.00-4.00 | |

Note. Values are the mean (SD). p-values are two-tailed. a Pearson correlation (age with AIM/ IAM/ FIM scores). b Independent-samples t-test (gender). c One-way ANOVA (ethnicity, job category, duration of service, clinic type). A p-value < 0.05 was considered statistically significant. Estimates for subgroups with small sample sizes (n < 5) are not reported for standard deviation and 95% confidence intervals due to statistical instability and limited precision.

**Table IV: Overall Satisfaction Rating with the Mind-WELL Kit (N=151)**

| Overall Satisfaction | n | % |
|---|---|---|
| 1 | 2 | 1.3 |
| 2 | 0 | 0 |
| 3 | 21 | 13.9 |
| 4 | 69 | 45.7 |
| 5 | 59 | 39.1 |
| Total | 151 | 100 |

Note. Ratings were recorded on a 5-point scale (1 = very dissatisfied to 5 = very satisfied).
Percentages are based on valid responses, with no missing data.

available in English and have established psychometric properties. Prior validation reported good structural validity using confirmatory factor analysis (CFI=0.96; RMSEA=0.08; factor loadings=0.75–0.89), strong internal consistency (Cronbach's alpha=0.85–0.91), and acceptable test–retest reliability (0.73–0.88). Each construct contains four items, rated on a 5-point Likert scale (1=completely disagree to 5=completely agree). Higher scores indicate more favourable perceptions of acceptability, appropriateness, or feasibility. In addition to AIM, IAM, and FIM, an overall satisfaction item was included. Participants rated their overall satisfaction with the Mind-WELL Kit on a 5-point scale (1=very dissatisfied to 5=very satisfied).

### Statistical Analysis

Descriptive statistics were used to summarise participant characteristics and implementation outcome scores. Mean scores for the AIM, IAM, and FIM were calculated in accordance with the instrument's scoring guidance. For each construct, item responses were summed and divided by four to generate a mean score ranging from 1 to 5, with higher scores indicating more favourable perceptions. Associations between age and implementation outcomes (AIM, IAM, FIM) were examined using Pearson's correlation coefficient. Differences in mean scores by gender were assessed using independent-samples t-tests. Comparisons across categorical variables with more than two groups (ethnicity, job category, duration of service, and clinic type) were conducted using one-way analysis of variance (ANOVA). A two-sided p-value of $<0.05$ was considered statistically significant. Where appropriate, subgroup-specific mean scores and 95% confidence intervals were reported to support descriptive interpretation. These subgroup analyses were exploratory in nature and were not intended to test formal equivalence between groups. All analyses were performed using IBM SPSS Statistics for Windows, Version 30.0.

Participants were nested within 20 primary care clinics; however, clustering at the clinic level was not explicitly accounted for in the analysis. As such, standard errors and confidence intervals may be slightly underestimated due to potential intra-clinic correlation. Given the primarily descriptive and exploratory nature of the analyses, this limitation is unlikely to meaningfully affect the overall interpretation of the findings.

### Ethical Approval

Ethical approval for this study was obtained from the Universiti Teknologi MARA (UiTM) Research Ethics Committee (FREC), approval reference number: REC/09/2024 (PG/MR/473), and the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia (NMRR ID-24-04045-JF5 (IIR)). Permission to conduct the study within the selected primary health care clinics was obtained from the relevant authorities prior to data collection.

## RESULTS

### Participants' Characteristics

A total of 151 primary healthcare providers participated in the study (Table I). Participants were aged between 25 and 58 years, with a mean (SD) age of 37.8 (5.67) years, and most participants were female (80.8%, n=122). The sample was predominantly Malay (80.1%, n=121), followed by Indian (11.9%, n=18), with smaller proportions of Chinese (2.7%, n=4) and Bumiputera Sabah/ Sarawak (5.3%, n=8).

In terms of professional designation, the largest group comprised medical officers (43.7%, n=66), followed by staff nurses (18.5%, n = 28) and assistant medical officers (10.6%, n=16). Family medicine specialists represented 9.9% (n=15). Smaller proportions included community nurses (4.6%, n=7), counsellors (1.3%, n=2), and other job categories (11.3%, n=17). Most participants reported substantial clinical experience, with approximately 41.7% (n=63) having 10–15 years of service, while 25.8% (n=39) had more than 15 years.

Among the 151 participants, most worked in Type III clinics (n=94, 62.3%), followed by Type I (n=23, 15.2%), Type IV (n=22, 14.6%), Type II (n=10, 6.6%), and Type V (n=2, 1.3%). Clinic type (Klinik Kesihatan, KK) was defined according to the MOH Malaysia classification based on the average daily patient attendance. In this classification, clinics are categorized as Type I (>800 patients per day), Type II (500–800 patients per day), Type III (300–500 patients per day), Type IV (150–300 patients per day), and Type V (100–150 patients per day).[14]

Overall, participants reported favourable perceptions of the Mind-WELL Kit across all three implementation outcomes. Acceptability had the highest mean score (AIM: 4.13, SD=0.55), followed by appropriateness (IAM: 4.07, SD=0.59) and feasibility (FIM: 3.96, SD=0.61). Feasibility was slightly lower than the other two domains, although all mean scores remained high. Item-level responses showed a consistently positive pattern across the AIM, IAM, and FIM measures, with most participants selecting "agree" or "completely agree" for all items (Table II). Feasibility items showed slightly greater variability than acceptability and appropriateness items.

As shown in Table III, AIM, IAM, and FIM scores were broadly similar across participant characteristics. No statistically

significant differences were observed by age, gender, ethnicity, job category, duration of service, or clinic type (all p>0.05). Although no statistically significant differences were observed across participant subgroups, several categories contained small numbers of participants (e.g., counsellors, Chinese participants, and Type V clinics). Therefore, subgroup findings should be interpreted cautiously as these analyses may have been underpowered to detect meaningful differences.

Overall satisfaction with the Mind-WELL Kit was high, with a mean (SD) rating of 4.21 (0.78), and most participants reported ratings of 4 or 5 (84.8%) (Table IV). Additional analyses showed no statistically significant associations between overall satisfaction and participant characteristics, including age, gender, ethnicity, job category, duration of service, and clinic type (p>0.05).

## DISCUSSION

This study examined how primary healthcare providers viewed the Mind-WELL Kit in terms of acceptability, appropriateness, and feasibility for managing patients with mild-to-moderate depression in routine primary care. Three main findings stand out. First, providers reported high acceptability and appropriateness, with mean scores above 4.0. Second, feasibility was also rated positively but was the lowest of the three domains, with a wider observed range (1.25–5.00), suggesting greater variability in perceived ease of implementation than in perceived fit or appeal. Third, perceptions were remarkably consistent across participant characteristics, as AIM, IAM, and FIM did not differ by age, gender, ethnicity, job category, service duration, or clinic type. The high overall satisfaction rating (mean 4.21; 84.8% rating 4–5) converged with the domain scores, reinforcing the interpretation that providers generally endorsed the toolkit as both desirable and usable.

High acceptability and appropriateness scores suggest that providers not only valued the toolkit but also perceived it as suitable for primary care realities. In implementation science terms, acceptability and appropriateness are often regarded as early "leading indicators" of an innovation's likelihood of adoption and sustained use, even before effectiveness outcomes are tested.[15] The consistency of favourable item-level endorsement, with most responses clustering in "agree" and "completely agree," aligns with broader implementation outcomes research showing that stakeholder-perceived fit and satisfaction frequently precede uptake decisions and influence subsequent engagement.[16] In the Malaysian setting, these findings are plausible given the growing public health burden of depression. National Health and Morbidity Survey (NHMS) 2023 estimated that about 1 million Malaysians aged 16 years and above had depression, and that the number had doubled since 2019, reinforcing the need for scalable psychosocial supports that can be integrated into routine care.[17] The relatively high AIM, IAM, and FIM scores in the present study are broadly consistent with other mental health implementation studies using the same measures. DeVylder et al. found mean acceptability, appropriateness, and feasibility scores of 4.3, 4.4, and 4.4, respectively, for the COVID Coach mobile mental health app among frontline healthcare workers.[18] In rural Guatemala, de la Garza Iga et al. likewise reported high mean scores for acceptability, appropriateness, and feasibility, equivalent to approximately 4.7, 4.7, and 4.5 on a 5-point scale.[19] Taken together, these findings suggest that the Mind-WELL Kit achieved similarly favourable perceived implementation ratings among primary healthcare providers.

Although perceived feasibility remained favourable, it was lower than acceptability and appropriateness, and this is understandable in the Malaysian primary care context. Implementation theory distinguishes these constructs, with feasibility focusing specifically on whether an intervention can be successfully used in a particular setting, rather than simply whether it is liked or seen as relevant.[12,16] In Malaysian clinics, such caution is plausible because adding new activities often occurs within busy services. Malaysian implementation research has shown that new activities in public clinics are often constrained by human resources, clinic infrastructure, and the need to adapt workflows locally.[20] Local workforce studies further show substantial strain among providers, including high levels of personal and work-related burnout in Selangor primary care clinics and greater work-related stress among Malaysian primary care doctors as job demands increase.[21-22] The slightly lower feasibility score may therefore reflect realistic concern about implementation within busy clinic workflows rather than doubt about the value of the Mind-WELL Kit itself. This interpretation is also compatible with implementation research emphasising the need to measure implementation outcomes carefully in behavioural health settings, where context strongly shapes what is practically deliverable.[15]

The absence of statistically significant differences by provider characteristics further suggests that perceptions of the Mind-WELL Kit were broadly shared across professional roles and levels of experience. This is encouraging because implementation in primary care is inherently multidisciplinary, and uptake is more likely to be sustained when new practices are acceptable across professional groups rather than supported by a single cadre.[23] At the same time, these findings should be interpreted with caution. Some subgroups in the present study, such as counsellors and Chinese participants, were very small, which limits statistical power and increases uncertainty around subgroup-specific estimates. As a result, the absence of significant differences is better understood as indicating no clear evidence of systematic variation in perceptions within this sample, rather than definitive evidence that perceptions are identical across all clinic settings.[24] Similarly, implementation scores did not differ significantly across clinic types, suggesting that the Mind-WELL Kit was viewed positively across different levels of Malaysian public primary care. This is notable because clinic type in Malaysia generally reflects differences in patient load and service demand, and such organisational factors often shape how easily new interventions can be incorporated into routine practice.[20]

The favourable implementation profile of the Mind-WELL Kit is important because the usefulness of MBIs depends not only on their clinical effectiveness, but also on whether they can be integrated into routine care. MBIs have shown benefit in

reducing depressive symptoms and supporting relapse prevention, although the magnitude of effect varies across delivery formats and implementation contexts.[25] More recent evidence continues to support MBIs as scalable options within stepped-care models, including for individuals who do not respond adequately to first-line treatment.[5,26] Against this background, the high AIM, IAM, and FIM scores in the present study suggest that the Mind-WELL Kit was perceived by Malaysian primary healthcare providers as a useful, relevant, and potentially implementable resource. These findings add to the current body of knowledge by providing early implementation evidence for a mindfulness-based support guide in Malaysian primary care, a setting where scalable mental health resources are needed. In practice, this supports the potential role of the Mind-WELL Kit as an accessible adjunct to primary mental healthcare, while future studies should evaluate actual uptake, delivery under routine service conditions, and effectiveness for patients.

**Implications for practice and next research steps**

These findings justify moving beyond perception-based evaluation toward early-phase implementation testing. A sensible next step is a pilot that embeds the toolkit into routine workflows and evaluates: (1) adoption and reach, (2) fidelity and adaptations, (3) time burden and workflow impact, and (4) patient-level proximal outcomes. Mixed-method designs would be particularly useful because feasibility barriers often emerge in qualitative detail even when quantitative feasibility scores are "high." In parallel, the slightly lower feasibility and the "easy to use" item pattern suggest that implementation supports may be needed, such as brief orientation sessions, scripts for short consultations, and integration into documentation prompts.

## LIMITATIONS

Several limitations should be considered when interpreting these findings. First, the study relied on self-reported responses, which may be influenced by social desirability or positive expectation bias. This risk was partly reduced by administering the survey online, which may have encouraged more candid responses by allowing participants to complete it privately rather than in front of the research team. However, because participants had not yet implemented the toolkit under routine service conditions, ratings, particularly for feasibility, may still have been more optimistic than would be observed during actual use. Second, selection bias may also have influenced the findings. Participation was voluntary, and healthcare personnel with a greater interest in mental health care, implementation initiatives, or professional development may have been more likely to participate. Similarly, the online format may have preferentially attracted individuals who were more comfortable with digital platforms or more engaged in psychosocial aspects of care. Together, these factors may have contributed to more positive perceptions than those that might be observed across the broader primary healthcare workforce.

Lastly, the sample was demographically skewed, with a predominance of female and Malay participants, and several subgroups were small. This limits the stability of subgroup comparisons and reduces confidence in interpreting differences across categories such as ethnicity or job category. In addition, the analysis did not account for potential clustering of responses within clinics. Healthcare personnel working in the same clinic are likely to share similar organisational environments, workplace cultures, and exposure to mental health programmes, which may result in correlated responses. Failure to adjust for such clustering could have led to underestimated standard errors and overly narrow confidence intervals. However, because the primary objective of the study was descriptive, to estimate overall perceptions of the Mind-WELL Kit rather than to examine complex multilevel relationships, the effect of this limitation on the principal findings is likely to be modest. Despite these limitations, the study provides valuable preliminary evidence that the Mind-WELL Kit was perceived positively by Malaysian primary healthcare providers.

## CONCLUSION

In a context where the depression burden is rising and primary care capacity is stretched, the Mind-WELL Kit was perceived positively by Malaysian primary healthcare providers, demonstrating high levels of acceptability, appropriateness, and feasibility. These findings provide preliminary evidence of its implementation potential and support further evaluation in real-world clinical settings. The slight feasibility gap relative to acceptability or appropriateness is not a weakness; it is an actionable cue about where implementation support should focus. Taken together, the results warrant progression to real-world pilot implementation and, if workflow integration proves workable, to larger effectiveness and scale-up studies in Malaysia.

## CONFLICT OF INTEREST

The authors declare no competing interests.

## FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## REFERENCES

1. Simon G, Moise N, Mohr D. Management of depression in adults: A review. JAMA 2024; 332(2): 141-52.
2. World Health Organization. Depressive disorder (depression) fact sheet. Geneva: World Health Organization; 2025. [cited March 2026] Accessed from:https://www.who.int/news-room/fact-sheets/detail/depression.
3. Abdulla SAA, Mohammed AM, Mansaray MA, Al-Kuwari MG. Evaluation of primary care mental health integration and screening of anxiety and depression symptoms in Qatar from 2018 to 2023. Sci Rep 2026; 16: 56.
4. Sherman MD, Miller LW, Keuler M, Trump L, Mandrich M. Managing behavioral health issues in primary care: Six five-minute tools. Family Practice Management. Fram Pract Manag. 2017; 24(2): 30-6.
5. Strauss C, Evans A, Jones R, Williams JMG. Clinical effectiveness and cost-effectiveness of mindfulness-based cognitive therapy self-help compared with cognitive behavioural therapy self-help for adults with mild to moderate depression (LIGHTMind trial): A randomized controlled trial. JAMA Psychiatry 2023; 80(4): 344-54.

6. Kaiser T, Sokolova A, Anderssonz G. The effectiveness of mindfulness-based cognitive therapy intervention for depression in adults: A systematic review of randomized controlled trials. Current Psychology. 2025. Advance online publication.
7. Donald JN, Ryan RM, Vella-Brodrick DA. Mindfulness and its association with varied types of motivation: A systematic review and meta-analysis using self-determination theory. Personality and Social Psychology Bulletin. 2020; 46(7): 1121-38.
8. Ryan RM, Deci EL. Self-determination theory and the facilitation of intrinsic motivation, social development, and well-being. American Psychologist, 2000; 55(1): 6878.
9. Ryan RM, Donald JN, Bradshaw EL. Mindfulness and motivation: Implications for self-determination theory. In K. W. Brown, J. D. Creswell, & R. M. Ryan (Eds.), Handbook of mindfulness: Theory, research, and practice (2nd ed.). New York: Guilford Press; 2021; 271-88.
10. Khalil A, Azhar ZI, Chen XW, Shuib N. Development and validation of a mindfulness toolkit: A manual on managing patients with mild-moderate depression for primary healthcare providers. Asian Journal of Psychiatry. AJSP 2025; Volume 114, 2025; 104743.
11. Geng EH, Peiris D, Kruk ME. Implementation science: Relevance in the real world without sacrificing rigor. PLoS Med 2017; 14(4): e1002288.
12. Proctor E, Silmere H, Raghavan R, et al. Outcomes for implementation research: Conceptual distinctions, measurement challenges, and research agenda. Administration and Policy in Mental Health and Mental Health Services Research 2011; 38: 65–76.
13. Chung OS, Johnson AM, Dowling NL, Robinson T, Ng, CH, Yücel M, Segrave RA. Are Australian Mental Health Services Ready for Therapeutic Virtual Reality? An Investigation of Knowledge, Attitudes, Implementation Barriers and Enablers. Frontiers in Psychiatry 2022; 13: 792663.
14. Ministry of Health. Klasifikasi klinik kesihatan. Putrajaya: Kementerian Kesihatan Malaysia; 2019. [cited March 2026] Accessed from:https://hq.moh.gov.my/bpkk/index.php/klasifikasi-klinik-kesihatan.
15. Mettert K, Lewis C, Dorsey C, Halko H, Weiner B. Measuring implementation outcomes: An updated systematic review of measures' psychometric properties. Implementation research and practice. 2020; 1: 2633489520936644.
16. Proctor EK, Bunger AC, Lengnick-Hall R, Gerke DR, Martin JK, Phillips RJ, Swanson JC. Ten years of implementation outcomes research: a scoping review. Implementation science. 2023; IS, 18(1): 31.
17. Ministry of Health. National Health and Morbidity Survey (NHMS) 2023 (NMRR-22 00545-XAC). Non-communicable diseases and healthcare demand: Key findings 2024. [cited February 2026] Accessed from:https://iku.nih.gov.my/images/nhms2023/report-nhms-2023.pdf.
18. DeVylder EK, Breda KL, Pietrzak RH. Implementation of a self-help mobile mental health app in COVID-19 frontline health care workers: A quality improvement project. Archives of Psychiatric Nursing 2023; 47: 35-37.
19. de la Garza Iga FJ, Mejía Alvarez M, Cockroft JD, Rabin J, Cordón A, Elias Rodas DM, et al. Using the Project ECHO™ model to teach mental health topics in rural Guatemala: An implementation science-guided evaluation. International Journal of Social Psychiatry 2023; 69(8): 2031-41.
20. Low LL, Rahim FIAB, Hamzah NAR, Ismail MS. Process evaluation of enhancing primary health care for non-communicable disease management in Malaysia: Uncovering the fidelity & feasibility elements. PLOS ONE 2021; 16(1): e0245125.
21. Ching SM, Cheong AT, Yee A, Thurasamy R, Lim PY, Irmi Ismail Zarina I, et al. Prevalence and factors associated with burnout among healthcare providers in Malaysia: A web-based cross-sectional study. Irish Journal of Medical Science 2024; 193: 851-63.
22. Shahrudin, M. S., Nik-Nasir, N. M., & Mohamed-Yassin, M.-S. Work-related stress and its associated factors among primary care doctors in Malaysia during the COVID-19 pandemic. BMC Primary Care 2025; 26: 4.
23. Bates SM, Lin J, Allen LN, Wright M, Kidd M. Can multidisciplinary teams improve the quality of primary care? A scoping review. eClinicalMedicine 2025; 88: 103497.
24. Wang X, Piantadosi S, Le-Rademacher J, & Mandrekar SJ. Statistical considerations for subgroup analyses. Journal of Thoracic Oncology 2021; 16(5): 811-23.
25. Tseng HW, Chou FH, Chen CH, Chang YP. Effects of mindfulness-based cognitive therapy on major depressive disorder with multiple episodes: a systematic review and meta-analysis. International Journal of Environmental Research and Public Health. 2023; 20(2), 1555.
26. Barnhofer T, Dunn BD, Strauss C, Ruths FA, Barrett B, Ryan M, et al. Mindfulness-based cognitive therapy versus treatment as usual after non-remission with NHS Talking Therapies high-intensity psychological therapy for depression: a UK-based clinical effectiveness and cost-effectiveness randomised controlled, superiority trial. The Lancet Psychiatry 2025; 12(6): 433-46.

# Exploring the integration of Islamic practice in a tertiary shariah-compliant hospital: A qualitative study

**Nazri Mohd Yusof, MMed (Ortho)[1], Sanisah Saidi, PhD[2], Muhammad Anas Mahmood, Master Health Science[3], Sarah Shakina Suhaimey, BSNs[4], Asma' Anuar, MBBS[5], Aasim Padela, MD[6]**

[1]Department of Orthopaedic, Traumatology and Rehabilitation, Kulliyyah of Medicine, International Islamic University of Malaysia, Kuantan, Pahang, [2]Department of Medical Surgical Nursing, Kulliyyah of Nursing, International Islamic University Malaysia, Kuantan, Pahang, [3]Kulliyyah of Medicine, International Islamic University of Malaysia, Kuantan, Pahang, [4]Kulliyyah of Nursing, International Islamic University Malaysia, Kuantan, Pahang, [5]Hospital Sultanah Nur Zahirah, Kuala Terengganu, Terengganu, [6]Department of Emergency Medicine, Medical College of Wisconsin, Milwaukee, United States of America

## ABSTRACT

**Introduction: *Shariah*-compliant and *ibadah*-friendly hospitals have been established in the Malaysian healthcare system for nearly two decades to support the religious needs of Muslim patients. In parallel, the Islamic input in the medical program curriculum has been designed to train healthcare professionals, particularly doctors, to integrate Islamic principles into their medical expertise, as they are expected to incorporate Islamic values into their daily practice. However, the practice of doctors with this Islamic integrated medical curriculum has not been thoroughly investigated. Thus, to what extent they embodied the Islamic values within their practice and the challenges they faced in realising this is not known. Therefore, this study aimed to explore the experiences of doctors and patients related to the integration of Islamic principles within Shariah-compliant hospital services.**

**Materials and Methods: A single-site qualitative case study design was employed, recruiting 20 doctors and 18 adult patients receiving treatment in the Orthopaedic wards and clinic of a Shariah-compliant teaching hospital. In addition, 19 relevant documents have been sampled and included. The study was conducted using multiple data collection methods including individual in-depth interviews, non-participant observations and document analysis between June 2023 and February 2024. The data analysis was done according to framework technique facilitated by NVivo software version 5.**

**Results: Four key themes emerged: (1) fulfilling religious and spiritual needs through clinical interactions and services; (2) practising therapeutic communication guided by Islamic values such as compassion, honesty, and patience; (3) upholding privacy, dignity, and autonomy in patient care; and (4) the importance of an effective training program and a sustainable working environment. Doctors expressed varying levels of confidence and consistency in applying Islamic principles, often influenced by personal understanding, workload, and institutional support. Patients generally appreciated the effort to integrate religious values but noted inconsistencies in delivery and expectations.**

**Conclusion: This study highlights both the perceptions and actual practices of doctors in integrating Islamic principles into their clinical roles, as well as how patients perceive and respond to such efforts. While both groups value the integration of Islamic values, variations in interpretation and practice reveal gaps between the intended Shariah-compliant model and its implementation on the ground.**

**KEYWORDS:**
*Medical practice management; religion and medicine; islam; qualitative research*

## INTRODUCTION

Attending to the religious and spiritual needs, particularly within the hospital setting, is critical for patient-centred and holistic care delivery. It yields substantial benefits, including improved psychological well-being, enhanced patient satisfaction, and better overall health outcomes.[1] With a 63.5% Muslim population, the Malaysian healthcare system has started to focus on supporting Muslim patients by facilitating patients performing their ritual prayers and by providing *halal* medications through the *ibadah*-friendly hospital initiative.[2] However, focusing solely on these two aspects didn't fulfil the role of an Islamic healthcare, which is comprehensive and holistic.[3] In response to this shortcoming, a *shariah*-based quality management standard system (MS 1900:2014) was developed by the Standard and Industrial Research Institute of Malaysia (SIRIM) for hospitals that have achieved the benchmark.[4] The Malaysian ministry of health also recognised Islamic medical practice as one of the designated forms of traditional and complementary medicine under the Traditional and Complementary Medicine Act, 2016. Islamic medical practice utilises supplications from the Quran and *hadith* (recorded sayings, actions and silent approval of the Prophet Muhammad (peace be upon him)), in its treatment.

Despite the growing emphasis on Islamic holistic healthcare, these initiatives have predominantly involved the hospital's supporting staff and collaboration with religious authorities, rather than directly engaging doctors, who are the core healthcare service providers. While the infrastructure and supportive services for shariah-compliant healthcare may be in place, the direct clinical application of Islamic medical practice by the primary caregivers, the doctors, remains an area that has not been adequately addressed.

*This article was accepted: 02 July 2026*
*Corresponding Author: Nazri Mohd Yusof*
*Email: nazriyusof@iium.edu.my*

In parallel, Islamic values have been integrated into the medical curriculum for undergraduate students in several medical faculties in Malaysia, such as the International Islamic University Malaysia (IIUM) and Islamic Science University Malaysia (USIM).[5] However, the extent to which these Islamic values have been truly integrated and consistently practised in the daily work of doctors remains unclear. This raises a crucial question: if doctors are being trained in these values, why are they not the primary focus of implementation initiatives? The lack of clarity regarding the actual integration and daily practice of Islamic values by doctors represents a critical unaddressed area in the current healthcare landscape. This study aimed to explore the perception of doctors and their implementation of Islamic practice in daily activities in the shariah-compliant hospital. This study also explores the challenges faced by doctors in providing Islamic medical care in their daily practice.

## MATERIALS AND METHODS

### Study Design

A qualitative case study design was employed to explore experiences, perspectives and challenges of doctors in integrating Islamic principles in their medical practices and views and experiences of the patients receiving service and treatment from them.[6]

### Study setting

This study was conducted at the department of orthopaedics, traumatology and rehabilitation, in a tertiary teaching hospital on the east coast of west Malaysia. This hospital has been certified as a *shariah*-compliant hospital by the Malaysian Quality Management System (MS 1900:2014), indicating that the hospital adheres to Islamic principles and law in its management and service delivery. The data collection sites include orthopaedic clinics, orthopaedic wards and operating theatres.

The hospital was selected because it offers a distinctive context as it is the only shariah-compliant hospital on the east coast of Malaysia, and it is affiliated with a medical faculty that has implemented an Islamic-integrated medical curriculum. This combination creates a practice environment where clinical care and Islamic principles are closely connected. Examining this setting allows for a deeper understanding of how these values shape everyday healthcare practices.

The orthopaedics, traumatology and rehabilitation department was chosen because it represents one of the most active and multidisciplinary areas within the hospital. It manages a broad range of cases across clinics, wards, and operating theatres, offering opportunities to observe practice at different stages of the patient journey. The dynamic workflow and high degree of teamwork provide a rich environment for exploring how practice unfolds in a real clinical setting.

### Sampling and recruitment

Potential participants were identified using purposive sampling. The healthcare professionals, including medical officers, postgraduate trainees, specialists, and consultants responsible for providing medical services and teaching at the orthopaedic, traumatology and rehabilitation department, were invited to participate. Additionally, patients aged 18 years old and above, able to communicate in English or Malay, and receiving treatment at the orthopaedic department during the data collection period, were recruited.

Participant recruitment was guided by a maximum variation sampling strategy to ensure representation across a wide range of characteristics, including profession, years of experience, clinical roles, age and treatment received. Fifty eligible individuals (25 participants from each group) were invited; however, a total of 20 healthcare professionals and 18 patients agreed to participate. The sampling plan initially aimed for approximately twenty participants in each group, with flexibility to adjust based on the richness of the data and the point at which saturation was reached. Data saturation was achieved when no new themes or insights emerged from successive interviews and this occurred after 15 interviews with healthcare professionals and 12 interviews with patients. Additional interviews were conducted to confirm saturation and ensure robustness.

Informed consent was obtained after participants were briefed on the study's purpose, procedures, risks, and their rights, including voluntary participation and withdrawal without penalty. The participant information sheet and consent form were provided in Malay or English, depending on the participant's preference.

Documents related to the implementation of Islamic practice in the clinical setting within the case study sites, including the standard operating procedures of the hospital, content and report of Islamic integrated medical course, shariah-compliant policy at the hospital and relevant patients' or doctors' reports were retrieved.

### Ethical consideration

The study was approved by the Kulliyyah of Medicine Research Committee and the IIUM Research Ethics Committee (IREC 2022-112), as well as the Institutional Review Board of the respective hospital.

### Data collection

The data were collected through multiple methods, including in-depth, semi-structured individual interviews, non-participant observation, and analysis of relevant documents related to the implementation of Islamic practice at the case study site. The use of multiple data sources and units of analysis, a process known as triangulation, was a deliberate methodological strength. This approach allowed for cross-validation of findings and was instrumental in identifying discrepancies between what was stated in interviews, what was observed in practice, and what was prescribed in official documents. This systematic comparison directly contributed to uncovering the knowledge-practice divide central to the research questions.

Individual interviews with doctors and patients were conducted at a time and date convenient to each participant. Most interviews took place in clinic rooms, ward areas, or

**Table I: Demographics of healthcare professionals' participants**

| Participants' ID | Position | Age | Gender | Race | Religion |
|---|---|---|---|---|---|
| HCP 1 | PG Student | 33 | Male | Malay | Islam |
| HCP 2 | MO Service | 30 | Female | Malay | Islam |
| HCP 3 | Specialist | 53 | Male | Malay | Islam |
| HCP 4 | PG Student | 33 | Male | Chinese | Atheist |
| HCP 5 | PG Student | 33 | Male | Chinese | Buddhist |
| HCP 6 | PG Student | 33 | Male | Malay | Islam |
| HCP 7 | MO Service | 31 | Male | Malay | Islam |
| HCP 8 | Specialist | 43 | Female | Malay | Islam |
| HCP 9 | Specialist | 41 | Male | Malay | Islam |
| HCP 10 | Specialist | 55 | Male | Malay | Islam |
| HCP 11 | Specialist | 42 | Male | Malay | Islam |
| HCP 12 | Specialist | 35 | Male | Chinese | Buddhist |
| HCP 13 | PG Student | 32 | Male | Malay | Islam |
| HCP 14 | MO Service | 31 | Male | Malay | Islam |
| HCP 15 | Specialist | 53 | Male | Malay | Islam |
| HCP 16 | PG Student | 33 | Male | Malay | Islam |
| HCP 17 | Specialist | 54 | Male | Malay | Islam |
| HCP 18 | PG Student | 33 | Male | Malay | Islam |
| HCP 19 | Specialist | 53 | Male | Malay | Islam |
| HCP 20 | Specialist | 52 | Male | Malay | Islam |

Abbreviations: HCP = Healthcare Provider, PG = Postgraduate, MO = Medical Officer

**Table II: Demographics of patient participants**

| Participants' ID | Age | Gender | Race | Occupation |
|---|---|---|---|---|
| PT 1 | 20 | Female | Malay | Student |
| PT 2 | 50 | Female | Malay | Housewife |
| PT 3 | 21 | Male | Malay | Student |
| PT 4 | 58 | Male | Malay | Pensioner |
| PT 5 | 75 | Female | Malay | Pensioner |
| PT 6 | 41 | Female | Malay | Private Sector |
| PT 7 | 47 | Male | Malay | Civil Servant |
| PT 8 | 45 | Female | Malay | Housewife |
| PT 9 | 24 | Male | Indian | Civil Servant |
| PT 10 | 25 | Male | Malay | Unemployed |
| PT 11 | 49 | Female | Malay | Housewife |
| PT 12 | 28 | Female | Malay | Civil Servant |
| PT 13 | 33 | Female | Malay | Private Sector |
| PT 14 | 23 | Female | Malay | Student |
| PT 15 | 35 | Male | Malay | Private Sector |
| PT 16 | 31 | Female | Malay | Teacher |
| PT 17 | 25 | Female | Malay | Freelancer |
| PT 18 | 44 | Female | Malay | Housewife |

Abbreviations: PT = Patient

other secluded spaces to minimise interruptions. Each interview lasted approximately 30–40 minutes and was audio-recorded with participants' consent. A semi-structured topic guide, developed from the literature and the study's research questions, was used to ensure consistency while allowing participants to express their views freely.

Immediately after each interview, the recording was replayed to check for completeness, and the interview was transcribed verbatim within 24–48 hours. Transcripts were produced in the language used by participants to preserve meaning and nuance. For data presentation, transcripts in languages other than English were later translated during the analysis phase. Following translation, the research team conducted peer checking to ensure that the original meaning and intent of participants' accounts were maintained

With participants' consent, non-participant observations were carried out during consultation sessions in the wards and clinics, as well as during procedures in the operating theatre. Both general and focused observations were guided by an observation schedule. Field notes were taken by the primary researchers throughout these sessions to capture interactions, behaviours, and contextual features relevant to the study. To reduce the potential for researcher bias, the field notes were subsequently reviewed by the first and second authors, who examined the observations for consistency, clarity, and alignment with the study objectives. This process helped ensure that the observational data were interpreted in a balanced and credible manner

**Reflexivity/role of researchers**

Data collections were primarily conducted by the third author and fourth author (MA & SS). Prior to the data collection a thorough discussion has been done with the

research team to identify the pre-conceived ideas that could influence the data collection and data analysis process. The prior experience and ideas possessed by the primary researchers related to the phenomena being studied was listed out (bracketed) prior to the commencement of the study. With the limited experience and the position of both primary researchers on the settings and phenomena being studied, it could be anticipated that, the influenced of the researchers in the data collection and analysis could be minimised. Furthermore, the preconceived ideas that being listed earlier has been revisited during the data analysis to ensure the findings generated are grounded from the data.

**Data Analysis**

Data were analysed using Framework Analysis, supported by NVivo for data management. Several researchers were involved to enhance the credibility of the analysis. Transcripts were first transcribed by two researchers and independently checked for accuracy by two others. During familiarisation and initial coding, two researchers coded the transcripts separately, and their codes were then compared and discussed to develop a shared, agreed-upon analytical framework. This framework guided the charting and interpretation stages, with regular team discussions used to review theme development, resolve differences, and ensure consistency across the dataset. Although member checking was not feasible due to participants' clinical demands, the use of multiple coders, cross-checking of codes, and peer debriefing supported the trustworthiness of the findings. Data saturation was reached when no new insights were identified after 15 interviews with healthcare professionals and 12 with patients and later interviews confirmed the stability of the themes.

## RESULTS

Data collection was done between June 2023 and February 2024. Twenty healthcare professionals and 18 patients were interviewed about their perception and experience of Islamic practice in medical care. A total of 18 observations were conducted throughout the data collection process. Nineteen documents pertinent to the implementation of the Islamic practice in the medical care at the case study site have been included as data sources.

The demographic characteristics of the healthcare professionals and patients who participated in the study are presented in Table I and Table II, respectively. The inclusion of healthcare professionals from diverse positions (Post-graduate (PG) student, medical officer (MO) service, specialist), races, religions (Islam, Atheist, Buddhist), genders, and ages provides a rich context for interpreting the findings, particularly concerning how IMP is understood and practised across different professional and personal backgrounds. Similarly, the patient demographics offer insights into the experiences of recipients of care from varied age groups, genders, races, and occupations.

***Emergent Themes***

Thematic analysis from interviews, observations, and document analysis revealed four major themes related to the integration of Islamic practice in clinical care. These include: (1) Fulfilling religious and spiritual needs, (2) Practising therapeutic communication (3) Respecting patient privacy, dignity, and autonomy (4) Importance of an effective training program and sustainable working environment. Direct quotations from participants are identified by codes: HP refers to Healthcare Professionals (doctors), and PT refers to Patients.

***Fulfilling Religious and Spiritual Needs***

All participating healthcare professionals demonstrated an understanding that Islamic medical practice extends to assisting patients with their daily prayers, including knowledge of methods for performing ablution and prayer when patients are physically unable to do so normally.

> *"Knows how the patient can pray as he is able… for example, when on cast, how he takes ablution." (HCP 2*)

It is also about reminding the patient about their religious obligation.

> *"during the morning round (you greet your patient) how are you uncle? Have you pray ? have you had you breakfast " (HCP 8)*
>
> *"Before starting the operation, the doctor who performed the surgery recited a prayer. When the Chinese doctor wanted to insert the epidural, he also asked me to recite a prayer. Even though he was a non-Muslim. He respected me as a Muslim patient." (PT 5)*

From the interviews, it is evident that the healthcare professionals, including non-Muslim doctors, were aware of the need to fulfil religious and spiritual needs. However, a notable observation was that some patients did not receive such spiritual guidance from their doctors:

> *"The patient has a cast on his leg and is hanging due to a broken leg. The doctor asked him how his leg was and called the nurse who was in the ward to assist him in doing a procedure. Then, the doctor trimmed the cast and left the patient. No further explanation or interaction was made after that." (Observation field note – August 2023)*

While *ibadah* education is stipulated in the shariah-compliant hospital guidelines and is part of *Fiqh* Ibadah training and clinical student syllabi, and the *shariah*-compliant department produces Islamic Spiritual Care (INSPIRE) guidelines and organises courses, direct observation in the wards revealed that doctors primarily focused on clinical management and did not regularly discuss ibadah-related issues with patients. This clear discrepancy between healthcare professionals' professed understanding of spiritual support and their inconsistent application in practice highlights a significant gap between theoretical knowledge and its practical implementation. It suggests that merely possessing the knowledge is insufficient without the practical tools, time, or institutional reinforcement to consistently apply it in a busy clinical environment.

***Providing therapeutic communication***

Doctors widely recognised the importance of a strong doctor-patient relationship fostered through effective communication:

> *"We greet Muslims with salam and non-Muslims with good morning… even if they complain, we stay calm." (HCP 7)*
>
> *" its not just telling the patient how to pray during illness,….it*

*more of how you treat your patients and how to make them at ease ….,the way you talk to them, the way you address them " (HCP 8)*

Doctors emphasised that beyond reminding patients about prayer, effective practice involves how one treats patients, makes them feel at ease, and communicates with them. Giving the Islamic greeting "salam" and keeping patients informed during procedures were noted to enhance patient comfort and satisfaction. One patient shared:

*"At first, the doctor greeted me with Assalamualaikum (peace be upon you). Then, he asked for my permission and explained he would mark the leg for surgery." (PT 10)*

*"The doctor asked me to sabar (be patient) and be strong... They told me that this is a test from Allah SWT. InshaAllah, (God willing) if we are patient... Allah SWT will give us more." (PT 10)*

The reassurance and clear explanations provided by doctors play a critical role in easing these concerns. PT 10, for instance, felt calmer after the doctor confidently explained the procedure. The doctor's use of *"InshaAllah"* also offered spiritual reassurance, helping the patient feel at peace with the uncertainties.

During the observation in the operating theatre, good communication was established before any procedure was done on the patient:

*"During a preoperative round, the doctor greets the patient and her husband. He explores, identifies, and attends to the patient's concerns about the surgery. He explains the procedure and the rehabilitation protocol to ease and comfort the patient."* (Observation field notes – March 2024)

Hospital guidelines mandate staff to practice good manners *(adab)* and etiquette, including using polite language and avoiding sensitive statements related to religion or race. Communication skills are also taught in *Fiqh Ibadah* and spiritual care workshops. Observations in the ward confirmed that doctors consistently communicated with patients during examinations to minimise discomfort and expressed gratitude for patient cooperation.

***Respecting Privacy, Dignity, and Autonomy***

All doctors expressed strong awareness of the importance of preserving patients' modesty , particularly for female patients, by limiting unnecessary exposure while ensuring quality clinical evaluation:

*"Unnecessary exposure of patients should be limited… their dignity should be protected and respected." (HCP 5)*

*"Getting a chaperone to examine a female patient is not just Islamic practice. It is a normal practice in general medical practice" (HCP 4)*

This concern was echoed by PTs:

*"He covered my aurah (intimate part of bodies that should be covered) and only exposed my leg. Before checking, he closed the curtain for privacy." (PT 10)*

Observation in the male ward shows that the healthcare professional indeed practices respecting privacy, dignity, and autonomy:

*"Then, I observed another male doctor in the ward greeting a patient on a bed with his chaperone. It is noted that the patient consistently smiles. As the doctor begins to inspect the patient, the nurse beside him covers the unnecessary parts of the patient to be inspected. The patient appears to be comfortable with the doctor and nurse. After that, the nurse closed the curtain to begin the inspection."* (Observation field note – August 2023)

Respect for religious autonomy was also emphasised in cases involving non-halal treatments:

*"For medications that contain porcine DNA, we need to get consent." (HCP 7)*

*"Patient's choices can be influenced by their healthcare, their culture, could be from their upbringing, their religion. Doesn't matter what it is, as long as when it comes to (patient) choice, I respect it nonetheless." (HCP 5)*

Patients also prefer halal medication. They put their trust in the doctors if the use of non-halal medication is indicated.

*"If possible, I want medication with halal sources. But I'm not sure what kind of law it is. But for me, I'm okay with non-halal medication because there may be no other medicine to treat. If there is only that, as long as it is not harmful, I can accept it. We also follow the doctor's recommendation only" (PT 10)*

Hospital guidelines exist for general consent regarding aurah exposure, different gender interactions, and the use of non-halal medication. Observations corroborated these practices, with doctors greeting patients with a chaperone, nurses covering unnecessary body parts during examinations, and curtains being closed for patient privacy.

**Importance of an effective training program and a sustainable working environment**

While all participants had been exposed to various Islamic programs, whether as postgraduate students, service medical officers, or lecturers, the effectiveness of these programs was questioned:

*"We have lectures and case write-ups… but what you practice in clinic or OT depends on individuals." (HCP 8)*

*"Undergraduates have modules… for postgraduates, we don't have yet." (HCP 8)*

Many programs were delivered as online lectures and group presentations, with a notable lack of hands-on application in the ward setting. Furthermore, there was no formal assessment of participants' knowledge or practical application of Islamic practice in daily medical care. This indicates a disconnect between theoretical exposure and practical competency, hindering the translation of knowledge into consistent clinical practice.

The understanding and integration of Islamic medical practice were found to be influenced by doctors' prior educational backgrounds. Some healthcare professionals, particularly those whose primary and secondary education did not focus on Islamic values, expressed a need to learn these principles. There was also a perception among some that religious and spiritual matters were less important than physical health problems, leading to their occasional omission during ward rounds. A concerning trend noted was the discontinuation of compulsory Diploma in Islamic

Studies programs for lecturers, which previously ensured a foundational understanding of Islamic values:

*"The difficulty is our basic education wasn't grounded in Islamic values. We need to learn." (HCP 10)*

A major impediment to the sustainability of Islamic practice was the busy hospital environment. Many doctors were unable to participate in organised courses due to heavy workloads with time constraints, including operations, on-calls, clinics, and ward duties:

*"We want everyone to join, but with OT and on-calls, it's hard to get everyone involved." (HCP 7)*

This time pressure meant that even when doctors remembered to advise patients on spiritual matters, the busy schedule often led to them forgetting or prioritising other clinical tasks:

*"Sometimes we forget to advise patients… depends on the individual." (HCP 1)*

This hectic environment is not merely a challenge but a fundamental root cause that exacerbates other issues, such as ineffective training and the knowledge-practice gap. It creates a systemic barrier where time pressures consistently override the integration of spiritual care, despite doctors' awareness of its importance. This suggests that solutions must address not just what is taught, but how it can be realistically integrated into a high-pressure clinical setting

## DISCUSSION

The findings of this qualitative study offer a different perspective on how Islamic values are integrated into daily clinical routines within a shariah-compliant hospital. The qualitative approach allowed for an in-depth exploration of the implementation of Islamic practice, providing rich contextual detail. A notable strength of this research is its diverse study population, which includes doctors and patients from various religious backgrounds, experiences, and levels of expertise. This diversity yielded perspectives on the integration of Islamic practice that extend beyond a singular viewpoint. Furthermore, the inclusion of patients, as the direct recipients of care, provided invaluable feedback on the tangible impact of Islamic integration on their healthcare experience.

To our knowledge, this is among the first qualitative studies that focus on the integration of Islamic principles among the doctors in a shariah-compliant hospital. In Indonesia, the integration of Islamic values into medical practice is primarily introduced during undergraduate education. Elements such as the doctors' ethical code, competence in the *fiqh* (Islamic rulings) related to illness, observance of aurah and gender-specific services, provision of spiritual care, and ensuring halal medication are incorporated within the shariah hospital standard issued by the National Sharia Council and the Indonesian Ulema Council (Dewan Syariah Nasional – Majelis Ulama Indonesia, DSN-MUI). Nevertheless, these aspects are only addressed briefly.[7] Another study conducted focused on the organisational structure of a hospital that practices Islamic medical services, which was explored through in-depth interviews with top management personnel.[8] In Iran, studies on spiritual care among nurses have shown that the quality of spiritual care work is moderate because nurses often lack sufficient training and frequently feel unqualified to provide spiritual care.[9] Similarly, a qualitative study in a maternity unit in the north west of England among the midwives, nurses, support workers, and sonographers found that their understanding of the needs of the Muslim patients was inadequate and emphasised the need for a further training program that would help them to provide quality patient-specific care.[10] A survey on the religious perception among doctors in a tertiary hospital in Saudi Arabia found that most doctors believe that religion has a positive influence on health; however, half of them never ask about their patients' religious issues.[11]

The study underscored the centrality of holistic care in applying Islamic principles within daily clinical practice. This model addresses not only the physical dimensions of illness but also the psychological, social, and spiritual well-being of patients. Islamic spiritual care—comparable to chaplaincy services in western contexts was found to play a vital role by providing emotional support, religious guidance, and prayer. However, the research revealed a notable gap between healthcare professionals' theoretical understanding and their practical application of Islamic practices in hospital settings.[12] Although many practitioners possess sound knowledge of these principles, they seldom educate patients about religious concessions or rukhsah during illness. This disconnect is largely attributed to the fast-paced, high-pressure nature of clinical environments, where medical treatment tends to take precedence over spiritual care.[13]

The study also pointed out other challenges, including a lack of effective training programs and high turnover of doctors. Although a program to integrate Islamic principles into the medical curriculum has existed for decades, its application is not always visible in practice, especially among postgraduate students. The study suggests that to overcome these issues, medical teachers should take the lead in integrating Islamic practices into clinical sessions. By acting as role models, they can demonstrate how to apply these principles in real-life medical scenarios, which the study suggests is more effective than formal lectures alone.

Many values central to medical professionalism such as respect for patient autonomy, preservation of dignity, and compassionate care closely resonate with Islamic principles. The key distinction, however, lies in the foundation: Islamic values are rooted in faith and reliance upon Allah, the Creator.[14-15] This spiritual grounding is reflected in everyday practices, including expressions such as Insha'Allah (God willing) and Assalamu'alaikum (peace be upon you), the recitation of supplication or Bismillah (in the name of Allah) before performing medical procedures, and the preference for halal-certified medications.

Although the aims and objectives of the study have been fulfilled, several limitations can be noted. The unit analysis of this study focuses only on orthopaedic doctors as a case study. In a Shariah-compliant hospital, other stakeholders such as patients, nurses, medical assistants, Shariah compliance officers, clerks, and administration make the hospital function as a whole.

All stakeholders must be included to explore the extent of perspectives and the holistic practice of Islamic medical care. Furthermore, this study focuses only on a tertiary public university hospital. In Malaysia, other shariah-compliant hospitals, such as An-Nur Specialist Hospital and Hospital Universiti Sains Malaysia (USM) have also been accredited by a shariah-based quality managementsystem accreditation and standard, MS 1900:2014, by SIRIM Berhad. Different hospitals may have different governance and curricula when implementing Islamic medical practices. Thus, these differences shaped how healthcare professionals practice Islamic values in their daily clinical routine.

This study adopts an exploratory approach to examine the lived realities and operational dynamics within a Shariah-compliant hospital setting. The preliminary insights generated herein underscore the need for subsequent empirical investigations aimed at informing key stakeholders and facilitating the development of a robust framework and evidence-based guidelines for the effective implementation of Shariah-compliant healthcare institutions.

## CONCLUSION

The successful implementation of Islamic practice in medical care hinges on four essential elements: fulfilling religious and spiritual needs, practising therapeutic communication, respecting patient privacy, dignity, and autonomy, and the importance of an effective training program and a sustainable working environment. This study identified a significant gap between Islamic knowledge and the actual practice of doctors within the shariah-compliant hospital. The findings underscore that the success of ibadah-friendly and shariah-compliant hospital programs in the orthopaedic department is not merely a clinical or educational issue but fundamentally a governance and strategic alignment challenge. Therefore, a critical need exists for robust, collaborative efforts between the university and the hospital to ensure the successful and sustainable integration of Islamic practice. This collaboration is crucial for translating theoretical knowledge into consistent clinical practice, fostering effective role models, and embedding Islamic practice as a core institutional value. The insights derived from this research contribute significantly to understanding the complexities of Islamic practice in medical care and provide a foundation for future policy and practice improvements in Shariah-compliant healthcare settings.

## ACKNOWLEDGEMENTS

This research has been funded by a grant from the Malaysian Ministry of Higher Education, Fundamental Research Grant Scheme (FRGS/1/2021/SS02/UIAM/01/1).

## CONFLICT OF INTEREST

The authors declare that they have no competing interests.

## REFERENCES

1. Jamaludin MA, Kartika B, Ramli A, Hamzah H. Muslim-friendly hospital services framework. Halal J 2019; 3: 11-24.
2. Mas'ud I, Abd Halim S, Mohamad Shafi S, Ramli NA, Awang MZ, Subhan IA. What is ibadah friendly hospital? J Br Islam Med Assoc. 2021; 7(3): 1-8.
3. Mahmood MA, Mohd Yusof N, Saidi S, Che Ahmad A. The integration of Islamic values in daily clinical practice among healthcare professionals: a scoping review. IIUM Med J Malaysia 2023; 22(3): 33-40.
4. Shariff SM, Rahman ARA. Shari'ah compliant hospital; from concept to reality: A Malaysian experience. Bangladesh J Med Sci 2016; 15(1): 1-4.
5. Ariff O. Islamic input in medical program: a realization of a holistic medical education. J Educ Soc Sci 2016; 4: 147=53.
6. Yin RK 2018. Case study research and applications. 6th ed. California: SAGE Publications.
7. Ismail SA, Hamid B, Sulistiadi W, Sagiran. Journey to Shariah hospital: an Indonesian experience. Int J Hum Health Sci 2018; 2(2): 55-64.
8. Dewi A, Hidayah N, Astuti RJ, Listiowati E. Implementation of Islamic values in Indonesia's hospital. In: International Conference on Hospital Administration (ICHA). 2019.
9. Tirgari B, Iranmanesh S, Cheraghi MA, Arefi A. Meaning of spiritual care: Iranian nurses' experiences. Holist Nurs Pract 2013; 27(4): 199-206.
10. Hassan SM, Leavey C, Rooney JS, Puthussery S. A qualitative study of healthcare professionals' experiences of providing maternity care for Muslim women in the UK. BMC Pregnancy Childbirth 2020; 20(1): 400.
11. Al-Yousefi NA. Observations of Muslim physicians regarding the influence of religion on health and their clinical approach. J Relig Health 2012; 51(2): 269-80.
12. Hairulisa NA, Wan Mamat WH, Mohamad Shariff N, Jaafar SNI, Che Ahmad A, Salah M. Challenges in providing spiritual care among healthcare workers: a qualitative study. IIUM Med J Malaysia 2025; 24(1): 78-84.
13. Burkhart L, Bretschneider A, Gerc S, Desmond ME. Spiritual Care in Nursing Practice in Veteran Health Care. Glob Qual Nurs Res. 2019;6:1-9
14. Taib F. Ihsan in medicine – the key to ethical conduct for Muslim medical professionals. Malays J Med Health Sci 2024; 20(6): 1-2.
15. Woodman A, Albar MA, Chamsa-Pasha H. Introduction to Islamic medical ethics. J Br Islam Med Assoc 2019; 2(1): 1-5.

ORIGINAL ARTICLE

# Determinants of oral health-related quality of life among undergraduate university students: A cross-sectional study

**Nurhidayah Zahrulsham, MDPH, Norkhafizah Saddki, MCommMed (Oral Health), Khuzaimah Kamarazaman, DrDPH**

School of Dental Sciences, Universiti Sains Malaysia, Health Campus, Kubang Kerian, Kelantan, Malaysia

**ABSTRACT**

**Introduction: Young adulthood is a critical period for establishing lifelong health behaviours, yet oral health is often neglected. This study investigated factors associated with oral health-related quality of life (OHRQoL) among Malaysian university students.**

**Materials and Methods: A cross-sectional survey was conducted among 395 undergraduate students aged 18 to 25 years. Data were collected using a structured questionnaire assessing sociodemographic characteristics, perceived oral health status, oral healthcare seeking behaviour, and OHRQoL via the short Malay version of the Oral Health Impact Profile (S-OHIP(M)). Multiple linear regression was used to identify predictors of OHRQoL.**

**Results: The prevalence of OHRQoL impact was 41.0%, with a mean S-OHIP(M) score of 9.15 (SD=6.39). Significant predictors of poorer OHRQoL included having at least one oral health problem, dissatisfaction with oral health status, and visiting the dentist due to an oral health issue. Dental and medical students reported significantly better OHRQoL compared to health sciences students. Oral health care seeking behaviour, although generally favourable, was not significantly associated with OHRQoL.**

**Conclusion: OHRQoL among young adults is influenced by both subjective perceptions and behavioural patterns. Promoting routine dental visits and enhancing oral health awareness may improve quality of life outcomes. These findings inform strategies for preventive care and service delivery targeting young adult populations.**

**KEYWORDS:**
*Oral health; quality of life; students; health behaviour; Malaysia*

## INTRODUCTION

Young adulthood marks a pivotal life stage characterised by rapid personal, social, and professional development. This transitional period from adolescence to full adulthood is often accompanied by significant milestones such as pursuing higher education, entering the workforce, and living independently. While these experiences foster growth, they also introduce challenges to maintaining overall health.[1] Despite being in their physical prime, young adults are particularly vulnerable to adopting unhealthy behaviours, including poor dietary habits, irregular sleep patterns, and sedentary lifestyles, which contribute to the early onset of chronic conditions such as obesity, hypertension, and type 2 diabetes.[2] Oral health is especially neglected during this phase, as many young adults underestimate the importance of preventive care.[3] Financial constraints, logistical barriers, and competing priorities often result in irregular dental visits and poor oral hygiene practices.[4,5]

Oral health issues are increasingly prevalent among young adults. Dental caries remains high, driven by frequent consumption of sugary and acidic foods and inconsistent oral hygiene practices.[6] Early-onset periodontitis is also rising and often goes undetected due to subtle symptoms.[7] Stress-related behaviours like bruxism are common, contributing to tooth wear, jaw pain, and temporomandibular joint disorders.[8] Pericoronitis, often associated with the eruption of third molars that may become impacted or partially erupt, commonly affects young adults aged 21 to 25.[9] Tooth sensitivity, often resulting from enamel erosion due to acidic diets, aggressive brushing, use of abrasive toothpaste, and bruxism, is frequently observed and can interfere with daily activities.[10] Additionally, malocclusion, a condition frequently seen in young adults, can significantly impact dental aesthetics and is associated with reduced self-perception and impaired social interactions.[11]

Oral health is a vital aspect of overall well-being, influencing not only physical function but also psychological and social dimensions of life. Studies show that young adults with visible dental issues often experience embarrassment, reduced willingness to smile, and avoidance of social interactions, factors that can limit daily activities, personal relationships, and professional opportunities.[12-15] Chronic oral pain or discomfort may further disrupt concentration, sleep quality, and dietary habits.[16-17] Moreover, poor oral health in young adults has been linked to lower levels of life satisfaction and diminished self-esteem.[12]

In this context, oral health-related quality of life (OHRQoL) has emerged as a valuable, multidimensional measure that captures the subjective impact of oral health on daily functioning and overall life satisfaction.[18] OHRQoL is shaped by a complex interplay of physical, psychological, functional, and social factors.[19] For young adults, these influences are particularly dynamic due to lifestyle transitions, evolving self-identity, and shifting health behaviours.[1] Understanding how young adults perceive their

*This article was accepted: 03 July 2026*
*Corresponding Author: Norkhafizah Saddki*
*Email: fizah@usm.my*

oral health and utilise oral health services is essential for developing effective public health strategies. This manuscript aimed to explore these interconnected factors, offering insights into the barriers and motivators that influence OHRQoL in this population. The findings are intended to guide policymakers, educators, and healthcare providers in creating targeted initiatives that promote preventive care, improve service accessibility, and ultimately enhance the oral health and overall quality of life of young adults.

## MATERIALS AND METHODS

### Study design and study population

This cross-sectional study was conducted between May and June 2023 among undergraduate students aged 18 to 25 years old at the Universiti Sains Malaysia Health Campus. The Health Campus comprises three academic schools: the School of Health Sciences (PPSK), the School of Medical Sciences (PPSP), and the School of Dental Sciences (PPSG). While the PPSP and the PPSG each offers only one undergraduate programme, the Doctor of Medicine programme and the Doctor of Dental Surgery programme, respectively, the PPSK offers 10 undergraduate health sciences programmes including audiology, biomedicine, dietetic, environmental and occupational health, exercise & sport science, forensic science, medical radiation, nursing, nutrition and speech pathology.

During the study period, undergraduate enrolment varied across the schools. The PPSP had over 700 students, while the PPSG enrolled around 250. The PPSK had the highest number of students, with slightly more than 1,000 enrolled during the study period. These figures include international students, primarily from middle eastern countries such as Iran, Saudi Arabia, and Egypt, as well as from China. In this study, only Malaysian students were included. Students with chronic systemic medical conditions or psychiatric disorder were excluded due to the potential confounding effects of these conditions on oral health outcomes.

The required sample size was calculated using a single proportion formula, based on an estimated prevalence of 35.7%, the proportion of Malaysian university students who had visited a dentist within the past year.[20] With a precision level of 0.05 and a 95% confidence interval, the minimum required sample size was determined to be 380. To account for a potential 10% non-response rate, the final target sample size was set at 420. Ethical approval for this study was obtained from the Universiti Sains Malaysia Human Research Ethics Committee (USM/JEPeM/KK/23010092).

### Research Tool

A structured, self-administered questionnaire was employed to collect data on the variables of interest, which included sociodemographic characteristics, perceived oral health status, oral healthcare seeking behaviour and utilisation, and OHRQoL. The questionnaire was divided into four sections. The first section captured sociodemographic information through seven items, including sex, ethnic group, degree programme, and monthly household income. The household income was also classified based on Malaysia's 2023 household income classification system as follows: Bottom 40% (B40) for income less than Malaysian Ringgit (MYR) 4,851, middle 40% (M40) for income between MYR 4,851 and MYR 10,970, and top 20% (T20) for income exceeding MYR 10,970.

The second section assessed perceived oral health status and included four items: perceived general oral health status, presence of oral health problems, perceived oral symptoms, and satisfaction with current oral health status. The third section focused on oral healthcare seeking behaviour and utilisation using five items: response behaviour when having oral health problem, perceived ability to access dental care when needed, the time elapsed since last dental visit, the primary reason for that visit, whether it was for a routine check-up or due to a specific oral health issue. If the visit was prompted by a problem, respondents were asked to identify the oral health problem from a predefined list.

The final section comprised the short Malay version of the Oral Health Impact Profile (S-OHIP(M)), a validated instrument used to assess the perceived impact of oral health on quality of life.[21] The S-OHIP(M) consists of 14 items grouped into seven domains, with two items per domain. Respondents rated the frequency of each impact experienced over the past year using a 5-point Likert scale ranging from 0 (never) to 4 (very often). The total S-OHIP(M) score, ranging from 0 to 56, was calculated by summing the responses to all items, with higher scores indicating greater severity of impact and poorer OHRQoL. Additionally, the prevalence of impact was determined by identifying the proportion of respondents who reported experiencing at least one item 'fairly often' or 'very often'.

### Data collection

Name lists of undergraduate students enrolled in the 2022/2023 academic session were obtained from the respective academic offices of each school. A non-proportionate stratified random sampling technique was employed. This approach was chosen to obtain an equal number of participants from each school, ensuring adequate representation across all academic years and programmes. It also secured sufficient sample sizes from smaller schools, particularly the PPSG, and enabled meaningful comparisons across academic disciplines despite differences in population size. To minimise the risk of selection bias during recruitment, simple random sampling was used to select 140 students within each school, yielding the predetermined sample size of 420.

The list of selected names was provided to the respective class representatives, who facilitated the distribution and return of questionnaires. An information sheet outlining the study objectives, eligibility, procedures, and other relevant details was provided to the students, and those who consented to participate were required to sign an informed consent form prior to completing the questionnaire. Data collection was conducted in small groups before or after scheduled teaching and learning sessions, when the entire class was already assembled. None of the investigators were present during the data collection sessions, ensuring that participation remained voluntary and free from any potential coercion. Completed questionnaires were collected by the class

**Table I: Sociodemographic profile of respondents (n=395)**

| Variable | Frequency (%) |
|---|---|
| Sex | |
| Male | 86 (21.8) |
| Female | 309 (78.2) |
| Ethnic group | |
| Malay | 301 (76.2) |
| Chinese | 50 (12.7) |
| Indian | 31 (7.8) |
| Others | 13 (3.3) |
| Degree programme | |
| Health Sciences | 134 (33.9) |
| Dentistry | 134 (33.9) |
| Medicine | 127 (32.2) |
| Monthly household income category (MYR) | |
| T20 (> 10,970) | 69 (17.5) |
| M40 (4,851 –10,970) | 147 (37.2) |
| B40 (< 4,851) | 179 (45.3) |

MYR: Malaysian Ringgit

**Table II: Perceived oral health status (n=395)**

| Variable | Frequency (%) |
|---|---|
| Perceived general oral health status | |
| Very good | 49 (12.4) |
| Good | 232 (58.7) |
| Fair | 110 (27.9) |
| Poor | 4 (1.0) |
| Very poor | 0 (0.0) |
| Presence of oral health problems | |
| No | 179 (45.3) |
| Yes | 216 (54.7) |
| Perceived oral symptoms (n= 216)* | |
| Toothache | 22 (5.6) |
| Sensitive teeth | 110 (27.8) |
| Cavitated tooth | 81 (20.5) |
| Gum pain | 13 (3.3) |
| Bleeding gum | 62 (15.7) |
| Swollen gum | 16 (4.1) |
| Bad breath | 27 (6.8) |
| Abscess gum | 1 (0.3) |
| Loose tooth | 4 (1.0) |
| Oral ulcer | 63 (15.9) |
| Other | 0 (0.0) |
| Satisfaction with current oral health status | |
| Very satisfied | 43 (10.9) |
| Satisfied | 205 (51.9) |
| Fair | 135 (34.2) |
| Dissatisfied | 12 (3.0) |
| Very dissatisfied | 0 (0.0) |

*Respondents can choose more than one answer

representatives and subsequently submitted to the principal investigator.

**Statistical analysis**

Data analysis was conducted using IBM SPSS Statistics version 26.0. The dataset, initially compiled in Microsoft Excel via responses collected through Google Forms, was imported into SPSS for further processing. Prior to analysis, data cleaning procedures were carried out to ensure accuracy and consistency. Descriptive statistics were used to summarise respondents' demographic characteristics and oral health knowledge. Categorical variables were reported as frequencies and percentages, while continuous variables were expressed as means and standard deviations (SD) for normally distributed data, or as medians and interquartile ranges (IQR) for skewed distributions.

To identify factors associated with respondents' OHRQoL, linear regression analyses were performed. Initially, simple linear regression was used to assess the relationship between S-OHIP(M) score and each of the following independent variables: sex, ethnicity, degree programme, monthly household income, perceived oral health status, presence of oral health problems, satisfaction with current oral health, response behaviour to oral health issues, ability to access dental care when needed, timing of the last dental visit, and the primary reason for that visit.

**Table III: Oral healthcare seeking behaviour and utilisation (n=395)**

| Variable | Frequency (%) |
|---|---|
| Oral health problem response behaviour | |
| Immediately seek oral health care | 335 (84.8) |
| Delay in seek oral health care | 60 (15.2) |
| Ability to go to dental clinic if needed | |
| Very easy | 145 (36.7) |
| Easy | 215 (54.4) |
| Difficult | 33 (8.4) |
| Very difficult | 2 (0.5) |
| Last dental visit | |
| Within the past 1 year | 259 (65.6) |
| 1 – 2 years ago | 60 (15.2) |
| >2 years ago | 76 (19.2) |
| Main reason for the last dental visit | |
| Regular dental check-up | 218 (55.2) |
| Having oral health problem | 177 (44.8) |
| Oral health problem during last dental visit (n=177)* | |
| Toothache | 68 (17.2) |
| Sensitive teeth | 19 (4.8) |
| Cavitated tooth | 83 (21.0) |
| Gum pain | 7 (1.8) |
| Bleeding gum | 4 (1.0) |
| Swollen gum | 10 (2.5) |
| Abscess gum | 3 (0.8) |
| Bad breath | 0 (0.0) |
| Loose tooth | 11 (2.8) |
| Oral ulcer | 6 (1.5) |
| Other | 1 (0.3) |

*Respondents can choose more than one answer

**Table IV: Prevalence and severity of oral impact (n=395)**

| S-OHIP(M) domain and item | Prevalence of impact (%) | Mean S-OHIP(M) score (SD) |
|---|---|---|
| Functional limitation | | |
| Difficulty chewing any foods | 8 (2.0) | 0.5 (0.77) |
| Problems caused bad breath | 13 (3.3) | 0.6 (0.82) |
| Physical Pain | | |
| Discomfort eating any food | 14 (3.5) | 0.7 (0.86) |
| Ulcers in mouth | 39 (9.9) | 1.2 (0.99) |
| Psychological Discomfort | | |
| Discomfort due to food getting stuck | 108 (27.3) | 1.9 (1.07) |
| Felt shy | 44 (11.1) | 1.0 (1.10) |
| Physical disability | | |
| Avoided eating certain foods | 13 (3.3) | 0.6 (0.84) |
| Avoided smiling | 18 (4.6) | 0.6 (0.94) |
| Psychological Disability | | |
| Sleep been disturbed | 5 (1.3) | 0.3 (0.62) |
| Concentration been disturbed | 4 (1.0) | 0.4 (0.68) |
| Social disability | | |
| Avoided going out | 2 (0.5) | 0.1 (0.41) |
| Problems in carrying out daily activities | 2 (0.5) | 0.2 (0.46) |
| Handicap | | |
| Had to spend a lot of money | 10 (2.5) | 0.5 (0.75) |
| Felt less confident | 27 (6.8) | 0.8 (1.00) |

SD: Standard deviation

Subsequently, multiple linear regression analysis was conducted using forward selection, backward elimination, and stepwise selection methods to construct a preliminary main-effects model. Variables that were statistically significant were further examined for potential two-way interactions and multicollinearity, assessed using the likelihood ratio (LR) test and the Variance Inflation Factor (VIF), respectively. Residual plots were generated to evaluate the assumptions of linearity, normality, and homoscedasticity. Outliers were identified based on standardised residuals exceeding ±3.0. The final regression model is presented with adjusted regression coefficients, 95% confidence intervals (CI), t-statistics, and p-values. A significance level of 0.05 was used throughout the analysis.

## RESULTS

A total of 395 undergraduate students completed the questionnaire, giving a response rate of 94.1%. The sociodemographic characteristics of the respondents are

**Table V: Factors associated with OHRQoL (n=395)**

| Variable | Simple Linear Regression | | Multiple Linear Regression | | |
|---|---|---|---|---|---|
| | Crude b (95% CI) | p-value | Adjusted b (95% CI) | t-statistics | p-value |
| Sex | | | | | |
| Male * | | | | | |
| Female | 0.96 (-0.57, 2.50) | 0.217 | – | – | – |
| Ethnic group | | | | | |
| Malay * | | | | | |
| Others | -1.29 (-2.77, 0.20) | 0.089 | – | – | – |
| Degree programme | | | | | |
| Health Sciences * | | | | | |
| Dentistry | -1.59 (-2.92, -0.27) | 0.019 | -2.60 (-3.96, -1.23) | -3.74 | <0.001 |
| Medicine | -2.30 (-3.73, -1.06) | <0.001 | -2.79 (-4.18, -1.40) | -3.94 | <0.001 |
| Monthly household income category (MYR) | | | | | |
| T20 (> 10,970) * | | | | | |
| M40 (4,851 –10,970) | 1.00 (-0.26, 2.27) | 0.120 | – | – | – |
| B40 (< 4,851) | -0.42 (-1.73, 0.89) | 0.527 | – | – | – |
| Perceived general oral health status | | | | | |
| Very good/Good * | | | | | |
| Fair/Poor/Very poor | 4.06 (2.72, 5.40) | <0.001 | – | – | – |
| Presence of oral health problems | | | | | |
| No * | | | | | |
| Yes | 4.25 (2.05, 5.45) | <0.001 | 2.47 (1.26, 3.67) | 4.03 | <0.001 |
| Satisfaction with current oral health status | | | | | |
| Very satisfied/Satisfied * | | | | | |
| Fair/Dissatisfied/Very dissatisfied | 4.56 (3.33, 5.79) | <0.001 | 2.79 (1.56, 4.03) | 4.45 | <0.001 |
| Oral health problem response behaviour | | | | | |
| Immediately seek oral health care * | | | | | |
| Delay in seek oral health care | 3.62 (1.89, 5.34) | <0.001 | – | – | – |
| Ability to go to dental clinic if needed | | | | | |
| Very easy/Easy * | | | | | |
| Difficult/Very difficult | 2.13 (-0.09, 4.34) | 0.060 | – | – | – |
| Last dental visit | | | | | |
| Within the past 1 year * | | | | | |
| >1 year ago | 0.17 (-1.17, 1.50) | 0.808 | – | – | – |
| Main reason for the last dental visit | | | | | |
| Regular dental check-up * | | | | | |
| Having oral health problem | 3.65 (2.43, 4.87) | <0.001 | 2.45 (1.31, 3.59) | 4.23 | <0.001 |

b: Regression coefficient, CI: Confidence interval, MYR: Malaysian Ringgit
* Reference category

shown in Table I. Most were Malay (76.2%) and female (78.2%). About half (45.3%) came from B40 households, based on the Malaysian household income classification at the time of data collection.

Table II presents the respondents' perceptions of their oral health status. Most respondents rated their oral health as either good (58.7%) or very good (12.4%), with none reporting it as very poor. More than half of the respondents (54.7%) reported experiencing at least one oral health problem. The commonly reported problem was sensitive teeth (27.8%), followed by cavitated teeth (20.5%). Other frequently mentioned problems included oral ulcers (15.9%) and bleeding gums (15.7%). Despite the prevalence of oral health problems, most respondents were satisfied (51.9%) or very satisfied (10.9%) with their current oral health status.

Most respondents (84.8%) claimed that they would seek oral health care immediately when having an oral health problem. Most also reported that accessing a dental clinic was either easy (54.4%) or very easy (36.7%). More than half (65.6%) visited a dentist within the past year. The primary reason for the most recent dental visit among 55.2% of respondents was a routine dental check-up. The remainder visited the dentist due to oral health problems, most commonly for cavitated teeth (21.0%) and toothache (17.2%). These findings are presented in Table III.

The S-OHIP(M) demonstrated good internal consistency in the present sample (Cronbach's alpha=0.822). The prevalence of impact caused by oral health problems over the past 12 months was 41.0%. The severity scores ranged from 0 to 30, with a mean score of 9.15 (SD=6.39). Table IV presents the prevalence and mean severity scores for each S-OHIP(M) item. The most frequently reported impact was psychological discomfort due to food getting stuck (27.3%). Other common impacts were feeling shy because of oral health problems (11.1%) and physical pain from oral ulcers (9.9%). In terms of mean item scores, discomfort due to food getting stuck had the highest score, followed by oral ulcers and feelings of shyness due to oral health problems.

Table V displays the results of the simple and multiple linear regression analyses examining factors associated with the students' OHRQoL. In the univariable analysis, dental students had significantly lower mean S-OHIP(M) scores compared to health sciences students (p=0.019), as did medical students (p<0.001). Students with at least one oral

health problem also had significantly higher mean scores than those without (p<0.001). Additionally, higher S-OHIP(M) scores were also observed among students who were fairly dissatisfied, dissatisfied, or very dissatisfied with their current oral health status (p<0.001), and among those whose last dental visit was due to an oral health problem (p<0.001).

In the multivariable analysis, having at least one oral health problem, dissatisfaction with current oral health status, and visiting the dentist due to an oral health issue remained significant predictors of higher mean S-OHIP(M) scores. Conversely, being a dental or medical student was associated with lower mean S-OHIP(M) scores. These findings suggest that OHRQoL was significantly better among dental and medical students compared to health sciences students, and poorer among those with oral health problems, dissatisfaction with their oral health, or problem-driven dental visits. The final model accounted for 24.0% of the variance in S-OHIP(M) scores (Adjusted $R^2$=0.240). No significant two-way interactions were found, multicollinearity was not detected, and all model assumptions were met with no outliers identified.

## DISCUSSION

OHRQoL is a multidimensional construct that reflects the impact of oral health conditions on daily functioning, psychological well-being, and social interactions.[18] The findings of this study underscore a substantial burden of oral health problems among young adults, with 41.0% of respondents reporting impacts on their OHRQoL over the past 12 months, and a mean S-OHIP(M) score of 9.15 (SD=6.39). These results align with global trends but also reveal notable differences when compared to similar studies using the same measurement tool. For instance, Lu et al.[22] reported a slightly higher prevalence of OHRQoL impacts (50.6%) among young adults in Hong Kong, but with a lower mean OHIP-14 score of 6.3 (SD=5.8), suggesting less severe impacts despite greater frequency. Similarly, a study among medical and dental undergraduate students in Russia found that 53.6% were impacted by their oral health conditions, with a mean OHIP-14 score of 4.63 (SD=4.90).[12] In contrast, a study among undergraduate students at Jouf University, Northern Border University, and King Saud University in Saudi Arabia, most of whom were enrolled in non-health-related programmes, reported a much higher mean OHIP-14 score of 24.69 (SD=5.2), indicating more severe impacts.[14] Across these studies, the most frequently reported and severe impacts were related to physical pain and psychological discomfort, highlighting a predominantly functional source of distress rather than aesthetic concerns, which are often assumed to be more relevant in this age group sensitive to appearance and social acceptance.

Numerous studies have explored the factors influencing OHRQoL among young adults, identifying a range of associated determinants. These include sociodemographic characteristics, clinical indicators, sign and symptoms, self-perceived oral health status, and behavioural factors such as dental attendance patterns.[6,12-15,22] Recent evidence indicates that OHRQoL among young and middle-aged adults is shaped more profoundly by subjective perceptions and lifestyle behaviours, such as self-rated oral health, dental self-care, and socioeconomic context than by clinical indicators alone.[23] In the present study, we examined the role of oral health care seeking behaviour, a factor that, to the best of our knowledge, has not been previously investigated in relation to OHRQoL among young adults.

Oral health care seeking behaviour refers to the actions individuals take in response to perceived oral health issues, based on the belief that professional assessment or treatment is needed.[24] It reflects the way oral health services are accessed and utilised. Young adulthood is a critical time to establish and sustain favourable preventive oral healthcare, including oral health seeking behaviour, which may influence subsequent oral health outcomes and well-being.[1] In the current study, a substantial proportion of the respondents (84.8%) reported seeking oral health care promptly when experiencing problems, and only 15.2% delayed having dental check-ups or treatment when having dental problems. This positive finding indicates that the respondents have good oral health awareness, probably because they were students in health sciences programmes and were future healthcare professionals. Furthermore, the availability of on-campus dental services likely facilitated access to care, as reflected in most students reporting that accessing a dental clinic was either easy or very easy. However, despite this favourable behaviour, our analysis revealed that oral health care seeking behaviour was not significantly associated with OHRQoL. This finding suggests that while timely care-seeking may reflect awareness and access, it does not necessarily translate into improved perceived outcomes. It is possible that the nature of the dental visits, often reactive rather than preventive, limits their impact on overall well-being. This underscores the need to promote not only access and responsiveness but also preventive engagement with oral health services to achieve meaningful improvements in OHRQoL.

Regular dental check-ups play a vital role in maintaining oral health and facilitating preventive care. In the absence of reliable evidence regarding the optimum frequency of dental examinations, there is consensus that recall intervals should be determined according to an individual's assessed risk of oral disease.[25] Additionally, while current evidence indicates that recall intervals of up to 24 months may not adversely affect oral health outcomes,[26] many health authorities, including the Ministry of Health Malaysia, advocate for at least once-a-year dental check-ups as a baseline recommendation. In the current study, most respondents (80.8%) reported having had a dental visit within the past one to two years, suggesting a relatively high level of engagement with oral health services. However, the fact that nearly half (44.8%) were symptomatic dental attendee who sought care only in response to oral health problems, most commonly cavitated teeth (21.0%) and toothache (17.2%). This pattern of problem-driven behaviour is often linked to delayed utilisation of services until symptoms significantly interfere with daily functioning, reflecting a reactive rather than proactive pattern of oral health care seeking. Such individuals typically exhibit irregular dental attendance, which contributes to the progression of oral diseases and often results in more advanced clinical presentations at the time of consultation,[27] and potentially poorer OHRQoL.[28]

Within the public health domain, symptomatic dental attendees represent a critical target for interventions designed to promote timely, routine engagement with oral health services, ultimately supporting healthier behaviours and improved long-term outcomes. Our findings further reinforce this priority by demonstrating that students whose last dental visit was prompted by an oral health problem reported significantly poorer OHRQoL. This pattern is consistent with broader evidence showing that problem-driven dental visits are associated with low OHRQOL.[23,29] A systematic review of longitudinal studies further supports that regular dental attendance is associated with better oral health outcomes, including less dental caries experience, fewer missing teeth, and improved OHRQoL, whereas symptomatic visits often reflect delayed care and a greater burden of oral disease.[27] Therefore, promoting routine dental visits, especially among young adults, may therefore serve as a key strategy in mitigating the severity of oral health impacts and improving overall OHRQoL.

More than half of the respondents in this study reported experiencing at least one oral health problem. Despite this, the majority perceived their oral health status as good or very good and expressed satisfaction with their current condition. This apparent disconnect between clinical symptoms and self-perceived oral health highlights the complex and subjective nature of OHRQoL. It suggests that individuals may normalise or downplay certain oral health issues, particularly when they do not cause significant pain or interfere with daily activities, allowing them to maintain a positive self-assessment. Moreover, as shown by Costa et al.,[30] subjective evaluations of oral health among young adults are influenced not only by physical symptoms but also by broader factors such as socioeconomic status, access to and experiences with dental care, and aesthetic concerns, elements that reflect underlying issues of health literacy, service utilisation, and personal expectations. Notably, our findings also revealed that the presence of oral health problems and dissatisfaction with oral health status were significantly associated with greater severity of impact on OHRQoL, indicating that even when overall perceptions remain positive, specific issues can contribute meaningfully to functional and psychological burdens. In agreement, a study conducted among Russia undergraduate students by Drachev et al.[12] reported that dissatisfaction with the condition of the teeth and mouth was significantly associated with lower OHRQoL.

In this study, dental and medical students demonstrated significantly lower mean S-OHIP(M) scores, indicating better OHRQoL compared to students enrolled in other health sciences disciplines. This finding may be attributed to their comparatively higher levels of oral health knowledge and awareness, which exert a positive influence on health-related behaviours and attitudes. Gardner et al.[31] reported that students with better oral health knowledge were significantly less likely to experience OHRQoL impacts such as speech difficulties, sleep disturbances, and diminished social participation. This protective effect of oral health knowledge among dental and medical students was also evident in a study by Mahanta et al.[32] Their regular exposure to clinical environments and familiarity with healthcare settings may reduce dental anxiety and foster more positive attitudes toward dental care. Moreover, as future healthcare professionals, dental and medical students may feel a stronger sense of responsibility toward maintaining personal health, including oral health. Collectively, these factors may contribute to the reduced functional and psychological burdens related to oral health, resulting in better overall OHRQoL among these students as observed in our study. At the same time, this body of evidence underscores the importance of implementing oral health promotion initiatives targeted at students from non-medical and non-dental disciplines. Such programmes should aim to strengthen oral health literacy, enhance awareness of preventive practices, promote routine dental screenings, and facilitate access to dental care. Addressing these disparities would not only improve OHRQoL among students in other academic programmes but also contribute to fostering a broader culture of preventive oral health within the university setting.

This study offers several notable strengths. It addresses a critical gap by exploring OHRQoL among young adults in Malaysia, a population often underrepresented in oral health research. The use of the validated (S-OHIP(M)) ensures robust measurement across multiple domains of OHRQoL. By including students from diverse health-related disciplines, the study enhances internal diversity and relevance within the university context. Moreover, the incorporation of oral health care seeking behaviour as a variable adds a novel behavioural dimension to the analysis. However, certain limitations should be acknowledged. The cross-sectional design restricts causal interpretations between oral health factors and OHRQoL outcomes. Reliance on self-reported data introduces potential recall and social desirability biases, particularly regarding dental attendance and perceived oral health status. The exclusion of non-Malaysian students may limit the generalisability of findings to international populations in similar academic settings. Additionally, conducting the study within a single institution may constrain external validity beyond the university environment. Future studies should consider recruiting participants from a wider range of educational, occupational, and socioeconomic backgrounds, including non healthcare related young adults, to enhance sample representativeness and strengthen external validity.

## CONCLUSION

This study highlights a substantial burden of oral health problems among young Malaysian adults, with nearly half reporting impacts on their quality of life. Key predictors of poorer OHRQoL included the presence of oral health problems, dissatisfaction with oral health status, and problem-driven dental visits. Conversely, students in dental and medical programmes exhibited better OHRQoL, likely due to greater oral health awareness and engagement. While most respondents demonstrated favourable care-seeking behaviour, its lack of association with OHRQoL underscores the need to promote preventive dental visits over reactive ones. These findings support targeted interventions to enhance oral health literacy, encourage routine dental care, and improve service accessibility for young adults.

## ACKNOWLEDGEMENTS

The authors gratefully acknowledge the Director General of Health Malaysia for granting permission to publish this article. We also extend our sincere appreciation to the undergraduate students of Universiti Sains Malaysia from the School of Dental Sciences, School of Medical Sciences, and School of Health Sciences for their valuable participation in this research. Artificial intelligence (AI) tools were used to refine the language, improve grammar, and enhance sentence clarity. No AI tools were used to generate, analyse, or interpret any part of the study content.

## REFERENCES

1. Rod NH, Davies M, de Vries TR, Kreshpaj B, Drews H, Nguyen TL, et al. Young adulthood: a transitional period with lifelong implications for health and wellbeing. BMC Glob Public Health 2025; 3(1): 25.
2. Alosaimi N, Sherar LB, Griffiths P, Pearson N. Clustering of diet, physical activity and sedentary behaviour and related physical and mental health outcomes: a systematic review. BMC Public Health 2023; 23(1): 1572.
3. Yamamoto T, Seguchi M, Mori Y, Ejiri H, Tanaka M, Kozai H, et al. Investigation of oral health awareness and associated factors among Japanese university students: Analyzing behaviors influencing lifelong oral health promotion. Healthcare (Basel) 2025; 13(12): 1370.
4. Vaishampayan P, Beniwal JS, Wilk P, McLean S, Jessani A. Unmet oral health needs and barriers to dental services among socially marginalized youth: a scoping review. Front Oral Health 2025; 6: 1521753.
5. Hadler-Olsen E, Bondø T, Bergli LM, Schmalfuss A, Nermo H. Oral health and use of dental services in early adulthood and changes from adolescence - Fit Futures, a longitudinal cohort study. BMC Oral Health 2025; 25(1): 852.
6. Hagman J, Wide U, Werner H, Hakeberg M. Oral health and oral health behavior in young adults with caries disease. BDJ Open 2021; 7(1): 28.
7. Wang Y, Zhuo L, Yang S, Dong C, Shu P. Burden of periodontal diseases in young adults. Sci Rep 2025; 15(1): 6653.
8. Melo G, Duarte J, Pauletto P, Porporatti AL, Stuginski-Barbosa J, Winocur E, et al. Bruxism: An umbrella review of systematic reviews. J Oral Rehabil 2019; 46(7): 666-90.
9. Wehr C, Cruz G, Young S, Fakhouri WD. An insight into acute pericoronitis and the need for an evidence-based standard of care. Dent J (Basel) 2019; 7(3): 88.
10. Favaro Zeola L, Soares PV, Cunha-Cruz J. Prevalence of dentin hypersensitivity: Systematic review and meta-analysis. J Dent 2019; 81: 1-6.
11. Choi SH, Kim BI, Cha JY, Hwang CJ. Impact of malocclusion and common oral diseases on oral health-related quality of life in young adults. Am J Orthod Dentofacial Orthop 2015; 147(5): 587-95.
12. Drachev SN, Brenn T, Trovik TA. Oral health-related quality of life in young adults: A survey of Russian undergraduate students. Int J Environ Res Public Health 2018; 15(4): 719.
13. Sun L, Wong HM, McGrath CPJ. The factors that influence oral health-related quality of life in young adults. Health Qual Life Outcomes 2018; 16(1): 187.
14. Thirunavukkarasu A, Alotaibi AM, Al-Hazmi AH, ALruwaili BF, Alomair MA, Alshaman WH, et al. Assessment of oral health-related quality of life and its associated factors among the young adults of Saudi Arabia: A multicenter study. Biomed Res Int 2022; 2022: 5945518.
15. Yamane-Takeuchi M, Ekuni D, Mizutani S, Kataoka K, Taniguchi-Tabata A, Azuma T, et al. Associations among oral health-related quality of life, subjective symptoms, clinical status, and self-rated oral health in Japanese university students: a cross-sectional study. BMC Oral Health 2016; 16(1): 127.
16. Belli V. Sleep disorders and orofacial pain: Is there an interplay? J Contemp Dent Pract 2023; 24(6): 349-50.
17. Sigurðsson K, Andersen BV, Bendixen KH, Baad-Hansen L. Are orofacial pain and xerostomia associated with differences in diet, sensory perception, appetite and enjoyment of eating?-An explorative study. J Oral Rehabil 2024; 51(4): 703-11.
18. Sischo L, Broder HL. Oral health-related quality of life: what, why, how, and future implications. J Dent Res 2011; 90(11): 1264-70.
19. Spanemberg JC, Cardoso JA, Slob EMGB, López-López J. Quality of life related to oral health and its impact in adults. J Stomatol Oral Maxillofac Surg 2019; 120(3): 234-9.
20. Peltzer K, Pengpid S. Dental health status and oral health behavior among university students from five ASEAN countries. Nagoya J Med Sci 2017; 79(2): 123-33.
21. Saub R, Locker D, Allison P. Derivation and validation of the short version of the Malaysian Oral Health Impact Profile. Community Dent Oral Epidemiol 2005; 33(5): 378-83.
22. Lu HX, Wong MCM, Lo ECM, McGrath C. Oral health related quality of life among young adults. Appl Res Qual Life 2015; 10(37-47).
23. Hong CL, Thomson WM, Broadbent JM. Oral health-related quality of life from young adulthood to mid-life. Healthcare (Basel) 2023; 11(4): 515.
24. Gilliland MJ, Phillips MM, Raczynski JM, Smith DE, Cornell CE, Bittner V. Health-Care-Seeking Behaviors. In: Raczynski JM, DiClemente RJ, editors. Handbook of Health Promotion and Disease Prevention The Springer Series in Behavioral Psychophysiology and Medicine. Boston, MA: Springer; 1999.
25. Levine R, Stillman-Lowe C. The scientific basis of oral health education. 8th ed. Switzerland AG: Springer Nature; 2019.
26. Fee P, Riley P, Worthington H, Clarkson J, Boyers D, Beirne P. Recall intervals for oral health in primary care patients. Cochrane Database Syst Rev 2020; 10(10): CD004346.
27. Mohd Khairuddin AN, Bogale B, Kang J, Gallagher JE. Impact of dental visiting patterns on oral health: A systematic review of longitudinal studies. BDJ Open 2024; 10(1): 18.
28. Yactayo-Alburquerque MT, Alen-Méndez ML, Azañedo D, Comandé D, Hernández-Vásquez A. Impact of oral diseases on oral health-related quality of life: A systematic review of studies conducted in Latin America and the Caribbean. PLoS One 2021; 16(6): e0252578.
29. Gaewkhiew P, Bernabé E, Gallagher JE, Klass C, Delgado-Angulo EK. Oral impacts on quality of life and problem-oriented attendance among South East London adults. Health Qual Life Outcomes 2017; 15(1): 82.
30. Costa LBA, Cunha RO, Leite ICG. Self-perceived oral health among Brazilian university students: a cross-sectional study. Braz Oral Res 2024; 38: e058.
31. Gardner J, Huang B, Ip RHL. Oral health knowledge is associated with oral health-related quality of life: a survey of first-year undergraduate students enrolled in an American university. BMC Oral Health 2023; 23(1): 961.
32. Mahanta SK, Humagain M, Prajapati D, Paudial B, Upadhyay P. Oral health knowledge, attitude, and practice among medical and non-medical students at a tertiary hospital. J Nepal Dent Assoc 2021; 21(32): 29-33.

ORIGINAL ARTICLE

# Comparing failure rate and complications between Seldinger and conventional chest drainage techniques in pneumothorax: A retrospective cohort study

**Shan Kai Ing, MD[1], Yih Hoong Lee, MD[1], Jeffrey Soon Yit Lee, MD[2], Nga Hung Ngu, MD[1]**

[1]Division of Respiratory Medicine, Department of Medicine, Sibu General Hospital, Sibu, Sarawak, Malaysia, [2]Clinical Research Center, Sibu Hospital, Sibu, Sarawak, Malaysia

## ABSTRACT

**Introduction: Chest drainage remains an important intervention for pneumothorax when conservative or ambulatory management is not suitable. Although chest drain techniques have been widely studied, contemporary real-world data from Southeast Asia remain limited, particularly in populations with a high burden of secondary pneumothorax related to infectious lung disease.**

**Materials and Methods: We conducted a retrospective cohort study of adult pneumothorax patients who underwent intercostal chest drain insertion at Sibu Hospital, Sarawak, Malaysia, between January 2021 and February 2024. Patients were managed with either conventional trocar chest tubes or Seldinger wire-guided drains. The primary outcome was chest drain–related complications. Secondary outcomes included chest drain duration, hospital length of stay, persistent air leak (PAL >5 days) and mortality. Continuous variables were analysed using independent t-tests and categorical variables using chi-square or Fisher's exact tests. Multivariate logistic regression was performed to identify predictors of subcutaneous emphysema, and multiple linear regression was used to evaluate factors associated with chest drain duration.**

**Results: A total of 123 patients were included (86 conventional and 37 Seldinger). Subcutaneous emphysema occurred significantly less frequently in the Seldinger group (5.4% vs 55.8%, p<0.001). Mean chest drain duration was shorter in the Seldinger group (8.86 ± 7.10 vs 10.34 ± 11.96 days, p=0.032). Differences in insertion failure (0% vs 8.1%, p=0.074), tube dislodgement (2.7% vs 11.6%, p=0.112), persistent air leak >5 days (67.6% vs 54.7%, p=0.182) and mortality (10.8% vs 15.1%, p=0.518) were not statistically significant. Multivariate logistic regression identified conventional chest drainage as an independent predictor of subcutaneous emphysema (OR 27.6, 95% CI 5.24–145.94; p<0.001). Multiple linear regression demonstrated that conventional drainage, non-tension pneumothorax, smoking and persistent air leak were independently associated with longer chest drain duration.**

**Conclusion: In this retrospective cohort, the Seldinger technique was associated with lower complication rates and shorter drainage duration compared with conventional chest drainage. Prospective multicentre studies are required to confirm these findings.**

**KEYWORDS:**
*Pneumothorax; chest tubes; thoracostomy; seldinger technique; subcutaneous emphysema; treatment outcome*

## INTRODUCTION

Pneumothorax occurs when air accumulates in the pleural space and impairs lung expansion, resulting in varying degrees of respiratory compromise. Management strategies depend on symptom severity, pneumothorax size and underlying lung disease, with chest drainage remaining an important intervention for patients who are symptomatic or unsuitable for conservative management. Contemporary guidance, including the 2023 British Thoracic Society (BTS) pleural disease guideline, supports conservative or ambulatory approaches in selected patients while recommending chest drainage for those who are symptomatic or at higher risk.[1]

Conventional trocar-based chest drain insertion has long been widely practiced but may be associated with greater tissue trauma and procedure-related complications.[2] The Seldinger technique allows placement of a small-bore catheter using a guidewire and is increasingly used as a less invasive alternative.[3] Previous studies have demonstrated comparable effectiveness between small-bore and large-bore chest drains in pneumothorax management, although real-world comparative data remain limited, particularly in Southeast Asia.[2-3]

In Malaysia and other parts of Asia, secondary pneumothorax related to infectious lung diseases such as tuberculosis remains common, and the optimal drainage approach in such populations is less well described.[4] Given these considerations, we conducted a retrospective cohort study to compare complications and clinical outcomes between conventional and Seldinger chest drainage techniques in a Malaysian secondary referral hospital.

## MATERIALS AND METHODS

### Study Design and Setting

This retrospective cohort study was conducted at Sibu Hospital, Sarawak, Malaysia, a secondary referral centre serving a population of approximately 760,000 people. Adult patients aged 18 years and above with radiologically confirmed pneumothorax who underwent intercostal chest

*This article was accepted: 03 July 2026*
*Corresponding Author: Ing Shan Kai*
*Email: shankai1992@gmail.com*

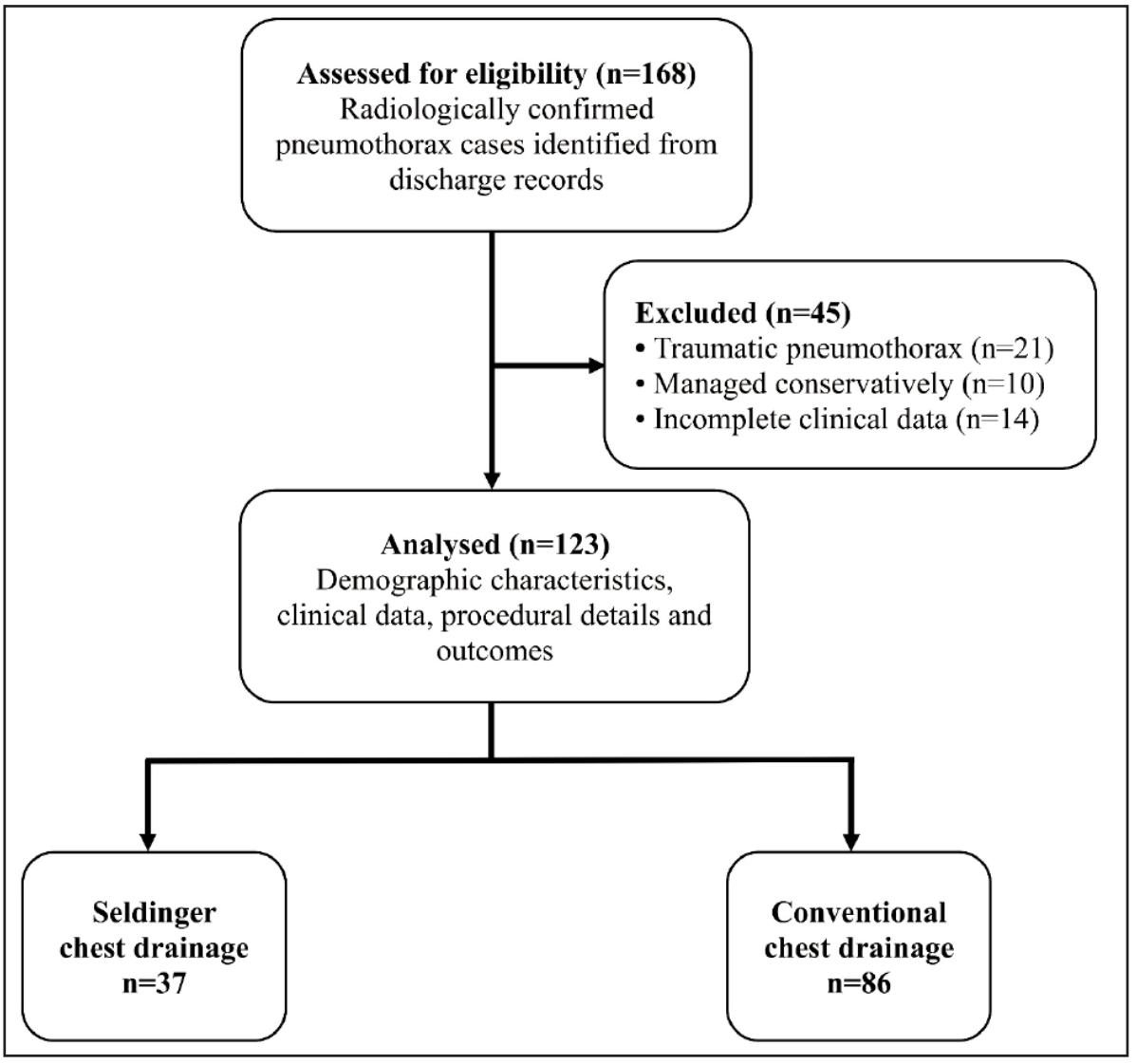



**Fig. 1:** Flow diagram of patient selection and analysis

drain insertion between January 2021 and February 2024 were included. Patients were identified through electronic discharge records using the keyword "pneumothorax" and verified using individual medical records. Consecutive sampling was applied. Patients with traumatic pneumothorax, those managed conservatively without drainage and those with incomplete clinical data were excluded. The process of patient selection is illustrated in Figure 1.

**Chest Drain Insertion Procedures**

Chest drainage was performed using either conventional trocar-based chest tubes (16–36 Fr) or wire-guided Seldinger chest drains (Rocket Medical plc, Watford, United Kingdom; 12 Fr and 18 Fr kits). The choice of technique was determined by the availability of Seldinger chest drains, operator preference and clinical judgement. Procedures were performed under local anaesthesia using sterile techniques in the emergency department, medical wards or intensive care unit as appropriate. Operator experience was not standardised, and procedures were performed by clinicians of varying seniority as part of routine clinical practice.

**Definitions and Outcomes**

The primary outcome was chest drain–related complications, defined as clinical subcutaneous emphysema, tube dislodgement, failed insertion, local infection or haematoma, haemothorax, tube malfunction, organ injury and mortality attributable to chest drainage. Failed insertion was defined as inability to successfully place a functioning chest drain requiring reinsertion or alternative technique. Intention-to-treat analysis was done, where any crossover was retained in the initial group during analysis.

Secondary outcomes included chest drain duration (days), hospital length of stay (days), persistent air leak (PAL >5 days) and mortality. Subcutaneous emphysema and other complications were confirmed based on clinical documentation and radiographic findings recorded in patient charts.

**Table I: Baseline demographic and clinical characteristics of patients undergoing chest drainage for pneumothorax**

| Parameters | Total (n=123) | Seldinger group (n=37) | Conventional group (n=86) | p-value |
|---|---|---|---|---|
| Gender, n (%) | | | | |
| Male | 82 (66.7) | 21 (56.8) | 61 (70.9) | 0.119† |
| Female | 41 (33.3) | 16 (43.2) | 25 (29.1) | |
| Smoker, n (%) | 76 (61.8) | 20 (54.1) | 56 (65.1) | 0.243† |
| History of pneumothorax, n (%) | 13 (10.6) | 4 (10.8) | 9 (10.5) | 0.953† |
| Tension pneumothorax, n (%) | 26 (21.1) | 6 (16.2) | 20 (23.3) | 0.382† |
| Comorbidities, n (%) | | | | |
| Hypertension | 47 (38.2) | 15 (40.5) | 32 (37.2) | 0.728† |
| Diabetes mellitus | 27 (22.0) | 11 (29.7) | 16 (18.6) | 0.180† |
| Dyslipidaemia | 32 (26.0) | 8 (21.6) | 24 (27.9) | 0.464† |
| CKD/ESRF | 4 (3.3) | 3 (8.1) | 1 (1.2) | 0.079‡ |
| Autoimmune disease | 6 (4.9) | 3 (8.1) | 3 (3.5) | 0.358‡ |
| Thyroid disease | 3 (2.4) | 0 (0) | 3 (3.5) | 0.550‡ |
| COPD/asthma | 16 (13.0) | 3 (8.1) | 13 (15.1) | 0.296† |
| Stroke | 1 (0.8) | 1 (2.7) | 0 (0) | 0.304‡ |
| IHD/heart failure | 2 (1.6) | 1 (2.7) | 1 (1.2) | 0.538‡ |
| Gout | 4 (3.3) | 1 (2.7) | 3 (3.5) | 1.000‡ |
| RVD | 3 (2.4) | 2 (5.4) | 1 (1.2) | 0.206‡ |
| Aetiology, n (%) | | | | |
| Primary spontaneous | 6 (4.9) | 1 (2.7) | 5 (5.8) | 0.668‡ |
| Active tuberculosis | 43 (35.0) | 16 (43.2) | 27 (31.4) | 0.218† |
| Old tuberculosis | 10 (8.1) | 4 (10.8) | 6 (7.0) | 0.496‡ |
| Pneumonia | 27 (22.0) | 5 (13.5) | 22 (25.6) | 0.139† |
| Malignancy | 5 (4.1) | 3 (8.1) | 2 (2.3) | 0.151‡ |
| Emphysema/bullous | 13 (10.6) | 2 (5.4) | 11 (12.8) | 0.206‡ |
| Iatrogenic | 17 (13.8) | 6 (16.2) | 11 (12.8) | 0.622† |
| Catamenial | 1 (0.8) | 0 (0) | 1 (1.2) | 1.000‡ |
| ILD | 1 (0.8) | 0 (0) | 1 (1.2) | 1.000‡ |

Data are presented as n (%), or mean (SD). *, statistically significant. † , Pearson chi-squared; ‡ , Fisher's exact test. CKD, chronic kidney disease; ESRF, end stage renal failure; COPD, chronic obstructive pulmonary disease; IHD, ischemic heart disease; RVD, retroviral disease; ILD, interstitial lung disease.

**Table II: Clinical outcomes and procedure-related complications**

| Parameters | Total (n=123) | Seldinger group (n=37) | Conventional group (n=86) | p-value |
|---|---|---|---|---|
| Subcutaneous emphysema, n (%) | 50 (40.7) | 2 (5.4) | 48 (55.8) | <0.001*,† |
| Chest drain duration (days) | 9.87 (10.63) | 8.86 (7.10) | 10.34 (11.96) | 0.032*,§ |
| Hospital length of stay (days) | 16.46 (15.12) | 15.54 (12.60) | 16.84 (16.26) | 0.648§ |
| Persistent air leak >5 days, n (%) | 72 (58.5) | 25 (67.6) | 47 (54.7) | 0.182† |
| Insertion failure, n (%) | 7 (5.7) | 0 (0) | 7 (8.1) | 0.074‡ |
| Tube dislodgement, n (%) | 11 (8.9) | 1 (2.7) | 10 (11.6) | 0.112‡ |
| Local infection/haematoma, n (%) | 6 (4.9) | 1 (2.7) | 5 (5.8) | 0.670‡ |
| Haemothorax, n (%) | 4 (3.3) | 1 (2.7) | 3 (3.5) | 1.000‡ |
| Mortality, n (%) | 17 (13.8) | 4 (10.8) | 13 (15.1) | 0.518† |

Data are presented as n (%), or mean (SD). * , statistically significant. † , Pearson chi-squared; ‡ , Fisher's exact test; § , Independent samples t-test.

**Table III: Multivariate logistic regression analysis for predictors of subcutaneous emphysema**

| Variables | Adjusted OR | 95% CI | p-value |
|---|---|---|---|
| Conventional chest drainage (vs Seldinger) | 27.60 | 5.24–145.94 | <0.001* |
| Smoking (smoker vs non-smoker) | 1.42 | 0.63–3.19 | 0.397 |
| Tension pneumothorax (yes vs no) | 0.88 | 0.31–2.51 | 0.811 |
| Chest drain duration (per day increase) | 1.02 | 0.98–1.06 | 0.331 |
| Underlying aetiologies† | — | — | NS |

Model adjusted for smoking status, tension pneumothorax, chest drain duration, hospital length of stay and underlying aetiologies. Nagelkerke $R^2 = 0.62$. * , statistically significant. † , Included primary spontaneous, active tuberculosis, old tuberculosis, pneumonia, malignancy, emphysema/bullous lung disease, iatrogenic, catamenial, and interstitial lung disease. NS = not significant.

**Table IV: Multiple linear regression analysis for predictors of chest drain duration**

| Variables | Adjusted β coefficient | 95% CI | p-value |
|---|---|---|---|
| Conventional chest drainage (vs Seldinger) | 1.68 | 1.45–1.94 | <0.001* |
| Non-tension pneumothorax (vs tension) | 1.21 | 1.03–1.43 | 0.021* |
| Smoking (smoker vs non-smoker) | 1.17 | 1.02–1.35 | 0.028* |
| Persistent air leak >5 days (yes vs no) | 1.52 | 1.29–1.78 | <0.001* |
| Underlying aetiologies† | — | — | NS |

Model adjusted for pneumothorax type, smoking status, persistent air leak and underlying aetiologies. $R^2 = 0.41$; adjusted $R^2 = 0.38$. * , statistically significant. † , Included primary spontaneous, active tuberculosis, old tuberculosis, pneumonia, malignancy, emphysema/bullous lung disease, iatrogenic, catamenial, and interstitial lung disease. NS = not significant.

### Data Collection

Data were extracted using a standardised case record form and included demographic characteristics, smoking status, pneumothorax type (primary vs secondary; tension vs non-tension), underlying aetiology (including tuberculosis, pneumonia, emphysema/bullous lung disease and iatrogenic causes), procedural details and clinical outcomes. No patient identifiers such as names, initials or hospital numbers were recorded.

### Sample Size

The sample size was estimated based on the expected difference in complication rates between conventional and small-bore chest drainage techniques reported in previous studies. Prior comparative studies have demonstrated complication rates ranging from approximately 45%–60% with conventional large-bore chest tubes and 10%–20% with small-bore or Seldinger drains in pneumothorax management.[2,3] Assuming a conservative absolute difference in complication rates of 35% between groups, with a two-sided α of 0.05 and statistical power of 80%, the minimum required sample size was calculated to be 102 patients, comprising 68 in the conventional group and 34 in the Seldinger group. The unequal group sizes reflect routine clinical practice during the study period, in which conventional trocar-based drainage remained more commonly performed owing to greater operator familiarity and earlier adoption, whereas the Seldinger technique was introduced later and used less frequently.

### Statistical Analysis

Statistical analysis was performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean and standard deviation (SD) and compared using independent t-tests. Categorical variables were presented as frequencies and percentages and analysed using chi-square or Fisher's exact tests as appropriate. Additionally, we performed exploratory binary logistic regression to identify independent predictors of subcutaneous emphysema. Multiple linear regression was used to evaluate factors associated with chest drain duration. Variables included in multivariate models were selected based on clinical relevance and univariate analysis results. A two-sided p-value <0.05 was considered statistically significant.

### Ethical Considerations

This study was approved by the Medical Research and Ethics Committee, Ministry of Health, Malaysia (NMRR ID-24-01329-54S (IIR) dated June 27, 2024). The requirement for informed consent was waived due to the retrospective study design.

## RESULTS

During the study period, 168 patients with radiologically confirmed pneumothorax were screened. After exclusion of patients with traumatic pneumothorax (n=21), those managed conservatively without drainage (n=10) and those with incomplete clinical data (n=14), a total of 123 patients were included in the final analysis. Of these, 37 underwent Seldinger chest drainage and 86 underwent conventional chest drainage. Three failed conventional insertions were subsequently salvaged using Seldinger drains but were analysed within the conventional group according to intention-to-treat principles.

The overall mean (SD) age was 49.7 (17.1) years old, with no significant difference between the conventional and Seldinger groups (p=0.376). There were no significant differences in gender distribution, clinical characteristics or underlying aetiology between the two groups, as summarised in Table I.

Clinical outcomes and procedure-related complications are summarised in Table II. Subcutaneous emphysema was significantly more frequent in the conventional drainage group. Although other complications were also more common with conventional drainage, these differences did not reach statistical significance. Chest drain duration was shorter in the Seldinger group, while hospital length of stay was comparable between groups. There were likewise no significant differences in persistent air leak or in-hospital mortality.

Multivariate logistic regression analysis demonstrated that conventional chest drainage remained an independent predictor of subcutaneous emphysema after adjustment for potential confounders, including smoking status, tension pneumothorax, chest drain duration and underlying aetiologies (Table III).

Multiple linear regression analysis identified several independent predictors of chest drain duration. Conventional chest drainage was independently associated with longer drainage duration. In addition, non-tension pneumothorax, smoking status and persistent air leak lasting more than five days were independently associated with prolonged chest drainage (Table IV).

Subgroup analyses comparing pneumothorax types and tube sizes did not demonstrate statistically significant differences in all outcomes. These analyses were exploratory and limited by the smaller number of patients in the Seldinger group.

## DISCUSSION

This study shows that the Seldinger technique for chest drainage in pneumothorax is associated with lower rates of subcutaneous emphysema and shorter drainage duration compared with conventional trocar-based drainage in routine clinical practice. These findings remained consistent after multivariate adjustment and highlight the potential procedural advantages of wire-guided small-bore chest drains in contemporary pneumothorax management.

The lower incidence of subcutaneous emphysema observed with the Seldinger technique is biologically plausible. Guidewire-assisted insertion typically requires a smaller incision and less blunt dissection than conventional trocar techniques, which may reduce tissue disruption and air leakage along the insertion tract. Previous comparative studies have similarly reported favourable safety profiles with small-bore chest drains and comparable effectiveness to larger chest tubes in pneumothorax management.[1-3] These findings support the continued shift toward minimally invasive drainage approaches in selected patients.

The shorter chest drain duration observed in the Seldinger group may reflect improved tube positioning, reduced insertion-related trauma and fewer complications requiring prolonged drainage. Earlier studies have reported similar findings, suggesting that small-bore catheters achieve comparable clinical success while potentially improving patient comfort and reducing healthcare utilisation.[2,4] Contemporary international guidance, including the 2023 British Thoracic Society pleural disease guideline, also supports minimally invasive drainage strategies when intervention is required.[5] In many resource-limited settings where ambulatory pneumothorax devices are not widely available, wire-guided small-bore chest drains may represent a practical alternative.

In addition to procedural factors, patient-related variables influenced drainage duration. Smoking was independently associated with longer chest drainage, which is consistent with prior studies demonstrating delayed pleural healing and increased risk of persistent air leak among smokers.[6] Persistent air leak itself was also strongly associated with prolonged drainage, which is expected given its central role in determining chest tube removal timing.

Interestingly, non-tension pneumothorax was associated with longer drainage duration in our cohort. This may reflect differences in underlying pathology rather than severity at presentation, as secondary pneumothorax, particularly tuberculosis-related disease was common in our population and often requires longer drainage due to structural lung damage and bronchopleural fistula formation.[7] Taken together, these findings reinforce the importance of minimally invasive chest drainage strategies in contemporary practice and highlight the multifactorial determinants of drainage duration beyond procedural technique alone.

An important epidemiological observation in our cohort was the predominance of secondary pneumothorax, with active tuberculosis representing the most frequent underlying condition. This differs from many western cohorts in which primary spontaneous pneumothorax predominates and underscores the importance of evaluating pneumothorax management strategies in diverse clinical settings.[7,8] Our findings therefore contribute regionally relevant data that may better reflect practice patterns in southeast Asia.

Other outcomes, including insertion failure, tube dislodgement, persistent air leak and mortality, did not differ significantly between groups and should not be overinterpreted. Subgroup analyses comparing pneumothorax types and tube sizes were exploratory and likely underpowered given the smaller Seldinger cohort.

Despite the potential advantages of the Seldinger technique, several procedure-related risks have been described in previous studies. Guidewire-assisted catheter insertion may be associated with complications such as guidewire kinking or loss, catheter malposition, inadequate drainage due to small catheter diameter and rare visceral injury during insertion. Previous reports evaluating small-bore catheter drainage have also noted occasional tube blockage, kinking and the need for repositioning or reinsertion in a minority of cases.[2-4] However, in the present study, we did not observe any major guidewire-related complications or procedure-related organ injury among patients managed with the Seldinger technique. These findings suggest that, when performed using appropriate technique and operator experience, Seldinger chest drainage may have a favourable safety profile in routine clinical practice. Nevertheless, prospective randomised controlled trials would be required to more definitively evaluate the comparative safety and clinical effectiveness of Seldinger technique.

Several limitations should be considered when interpreting the findings of this study. First, the retrospective design introduces potential selection bias and residual confounding, and is subject to incomplete or inconsistently documented data. Second, the unequal group sizes reflect real-world practice patterns but may reduce statistical precision, particularly for subgroup analyses. Third, the multivariable analyses were exploratory in nature and not powered to establish causal relationships.

Despite these limitations, this study provides contemporary real-world data from a Southeast Asian population with a high prevalence of secondary pneumothorax. These findings demonstrate the feasibility and safety of minimally invasive chest drainage techniques in routine clinical practice. Prospective multicentre randomised controlled trials would further clarify the role of the Seldinger technique in pneumothorax management.

## CONCLUSION

The Seldinger technique for chest drainage in pneumothorax has lower rates of subcutaneous emphysema and shorter chest drain duration compared with conventional trocar-based drainage. These findings support wire-guided small-bore chest drains as a safe and effective alternative in routine clinical settings.

## ACKNOWLEDGEMENTS

The authors would like to thank the Director General of Health Malaysia for permission to publish this study.

## CONFLICT OF INTEREST

The authors declare that they have no competing interests.

## FUNDING

The authors declare that no funding was received for this study.

## ETHICAL APPROVAL

This study was approved by the Medical Research and Ethics Committee, Ministry of Health Malaysia (NMRR ID-24-01329-54S (IIR) dated June 27, 2024). The requirement for informed consent was waived due to the retrospective study design and use of anonymised medical record data.

## REFERENCES

1. Laws D, Neville E, Duffy J. BTS guidelines for the insertion of a chest drain. Thorax 2003; 58(Suppl II): ii53-59.
2. Ayed AK, Chandrasekaran C, Sukumar M. Tube thoracostomy for spontaneous pneumothorax: small-bore vs large-bore chest tubes. Ann Thorac Surg 2006; 82: 986-9.
3. Ho KK, Ong MEH, Koh MS, Wong E. A randomized controlled trial comparing small-bore and conventional chest drains in pneumothorax. Respirology 2011; 16: 550-5.
4. Tsai WK, Chen W, Lee JC, Cheng WE, Chen CH, Hsu WH, et al. Pigtail catheter vs large-bore chest tube for management of pneumothorax. Am J Emerg Med 2006; 24: 795-800.
5. MacDuff A, Arnold A, Harvey J. Management of spontaneous pneumothorax: British Thoracic Society pleural disease guideline 2023. Thorax 2023; 78(Suppl 1): i1-42.
6. Baumann MH, Strange C. Treatment of spontaneous pneumothorax: a review. Chest 1997; 112: 789–804.
7. Porcel JM. Tuberculous pneumothorax: epidemiology and management. Respiration 2010; 79: 321-7.
8. Light RW. Pneumothorax. In: Pleural diseases. 7th ed. Philadelphia: Wolters Kluwer; 2022.

ORIGINAL ARTICLE

# Ethnicity-specific polygenic risk score for predicting coronary heart disease mortality in Malaysian patients with type 2 diabetes

**Khairul Anwar Zarkasi, PhD[1,2], Nor Azian Abdul Murad, PhD[1], Noraidatulakma Abdullah, PhD[1], Nurul Ain Mhd Yusuf, MSc[1], Nazihah Abd Jalal, BSc[1], Norliza Ismail, BSc[1], Mohd Arman Kamaruddin, MSc[1], Norfazilah Ahmad, PhD[3], Rahman Jamal, PhD[1]**

[1]UKM Medical Molecular Biology Institute, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia, [2]Biochemistry Unit, Preclinical Department, Faculty of Medicine and Defence Health, Universiti Pertahanan Nasional Malaysia, Kuala Lumpur, Malaysia, [3]Department of Public Health Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia

## ABSTRACT

**Introduction: Polygenic risk scores (PRS) are used to aggregate single-nucleotide polymorphisms (SNPs) effects across the genome to estimate an individual's risk of coronary heart disease (CHD). However, most PRS models were developed mainly in Caucasian populations, limiting their applicability to Malaysia's diverse populations. This study aimed to develop a PRS to predict CHD mortality among individuals with type 2 diabetes (T2D) in The Malaysian Cohort (TMC).**

**Materials and Methods: In Phase 1, 224 CHD-death cases and 625 controls were genotyped using Illumina's Infinium Asian Screening Array, followed by genetic imputation. From the genome-wide association analysis, 56 SNPs were identified at suggestive genome-wide significance ($P < 5 \times 10^{-5}$), with 15 SNPs selected to construct the PRS. In Phase 2, 806 T2D participants without known CHD at baseline were followed until death.**

**Results: The PRS distinguished cases from controls across all ethnicities, with an area under the receiver operating characteristic curve (AUC) indicating good discriminative ability. At 0.85 cut-off score, the PRS achieved 64.7% sensitivity and 73.1% specificity. Those in the high-PRS category had significantly shorter mean survival than those in the low-risk group: observed among Malays (6.60 vs 8.92 years), Chinese (6.20 vs 8.66 years), and Indians (7.21 vs 8.60 years). After adjusting for covariates, high-PRS individuals had increased CHD mortality risk, with hazard ratios of 3.23 (Malays), 9.59 (Chinese), and 9.65 (Indians) (all $p<0.05$).**

**Conclusion: This study demonstrates the utility of a population-specific PRS in predicting CHD mortality among Malaysian T2D patients, supporting its potential role in precision medicine and long-term risk stratification.**

**KEYWORDS:**
*Coronary heart disease; polygenic risk score; single nucleotide polymorphism; type 2 diabetes mellitus*

## INTRODUCTION

Coronary heart disease (CHD) remains a leading cause of morbidity and mortality worldwide. According to the World Health Organization, CHD accounted for approximately 9.1 million deaths globally in 2021, representing 13% of total mortality.[1] CHD results from the progressive accumulation of atherosclerotic plaque in the coronary arteries, ultimately impairing myocardial tissue perfusion and oxygenation. Type 2 diabetes mellitus (T2D), particularly when poorly controlled, accelerates atherosclerosis and substantially increases the risk of CHD-related mortality.

In Malaysia, T2D poses a growing public health concern, with a national prevalence of 18.3%, which is significantly higher than the global (10.5%), Southeast Asian (8.7%) and Western Pacific (11.9%) averages.[2-3] T2D is strongly associated with both microvascular and macrovascular complications, including CHD. The high prevalence of T2D suggests that Malaysians face an elevated risk of developing CHD, with CHD-related mortality being among the most severe outcomes. Data from the National Heart Association of Malaysia reported a 12% increase in patients requiring percutaneous coronary intervention between 2017 to 2020,[4] coinciding with a rise in CHD-related deaths from 13.9% to 16.1% during the same period.[5]

While traditional risk factors such as age, male sex, smoking, alcohol use, physical inactivity, obesity, dyslipidemia, hypertension, and family history are well established,[6-8] genetic predisposition has emerged as a significant contributor to disease risk. Genome-wide association studies (GWAS) have identified 202 single nucleotide polymorphisms (SNPs) across 109 genomic loci significantly associated with CHD ($P < 5 \times 10^{-8}$).[9] Notably, several SNPs have shown strong associations with CHD risk specifically in T2D patients, including rs10911021 *(GLUL)* ($P = 2.0 \times 10^{-8}$), rs74617384 *(LPA)* ($P = 3.2 \times 10^{-12}$), and rs10811652 (9p21) ($P = 6.0 \times 10^{-11}$).[10,11]

These findings have facilitated the development of polygenic risk scores (PRS), which quantify an individual's genetic risk by summing the effects of multiple risk alleles across the genome. PRS have been shown to predict CHD risk in several large cohorts, including the Framingham Offspring Study

*This article was accepted: 14 July 2026*
*Corresponding Author: Rahman Jamal*
*Email: rahmanj@hctm.ukm.edu.my*

and the Second Northwick Park Heart Study.[12-13] However, the performance and transferability of PRS are often limited by population-specific genetic architectures. Most existing PRS are derived from cohorts of European ancestry, reducing their applicability in other ethnic groups.1[4] Consequently, the number and selection of SNPs included in PRS models vary widely, from dozens to millions, depending on the population and study design.

Despite the growing body of research on PRS for CHD, few studies have focused on multiethnic Southeast Asians populations such as Malaysia's. Therefore, the present study aimed to develop and evaluate a population-specific PRS for predicting CHD mortality in T2D individuals enrolled in The Malaysian Cohort (TMC) project.

## MATERIALS AND METHODS

*Ethics statement*

This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Universiti Kebangsaan Malaysia (UKM) Research Ethics Committee (Reference no.: UKM PPI/111/8/JEP-2020-473). Written informed consent was obtained from all participants during their initial recruitment into TMC.

*Study design and study population*

This study was conducted in two phases. Phase 1 involved a case-control design comprising 224 individuals with type 2 diabetes mellitus (T2D), who died from coronary heart disease (CHD) (T2D+CHD group) and 625 T2D participants who died from non-CHD deaths (T2D group). All participants were identified from The Malaysian Cohort (TMC) project database, recruited between April 2006 and September 2012 from various regions nationwide.[15] Participants with a baseline fasting plasma glucose (FPG) of > 7.5 mmol/L (or 126 mg/dL) and those with established disease history were classified as having T2D.[16]

Causes of death were determined from death certificates obtained from the National Registration Department of Malaysia. CHD was defined as death due to acute coronary syndrome (ACS), unstable angina, ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), or coronary atherosclerosis. Individuals with other forms of diabetes mellitus (e.g., type 1 diabetes mellitus, gestational diabetes mellitus, and maturity-onset diabetes in the young) and those who died from other cardiovascular diseases (e.g., cerebrovascular disease, peripheral artery disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis, and pulmonary embolism) were excluded.

Whole blood samples from participants were retrieved from the TMC Biobank for DNA extraction and genotyping. Findings from genetic analysis in phase 1 were used to develop a polygenic risk score (PRS) for CHD death in individuals with T2D. In phase 2, a retrospective cohort study was conducted among 806 T2D participants who were free from CHD at baseline. The aim was to evaluate the ability of the PRS to predict future CHD-related mortality.

*DNA extraction, genotyping, and quality control*

Genomic DNA was extracted and purified from whole blood samples using the QIAsymphony automated system (Qiagen, Hilden, Germany). DNA quantification was performed using the Qubit dsDNA BR Assay Kit (Thermo Fischer Scientific, Massachusetts, USA). All DNA samples were normalised to a concentration of 50 ng/µL before further analyses.

Genotyping was conducted using the Infinium Asian Screening Array (ASA)-24 v1.0 Beadchip (Illumina Inc., California, USA), which includes 653,893 SNPs tailored for the East and Southeast Asian populations, including Chinese, Japanese, Korean, Vietnamese, Mongolian, and Malay ethnicities. Initial genotype calling was performed using GenomeStudio software v2.0.5 (Illumina). Quality control of individual genotypes was based on the following criteria: (i) p10GC ≥ 0.38, (ii) call rate ≥ 95%, and (iii) concordance between clinical and genotypic sex. Among all samples, 88,267 SNPs were monomorphic, and 565,626 SNPs were polymorphic.

Genotype data that passed quality control were exported using the PLINK Input Report Plug-in v2.1.4 (Illumina) and uploaded into the Michigan Imputation Server (University of Michigan, USA) for genotype imputation using the following parameters: (i) Imputation software: Minimac4 v1.7.1, (ii) Reference panel: GenomeAsia Pilot (GAsP), (iii) Assembly: GRCh37/hg19, (iv) R2 filter: Off, (v) Phasing: Eagle v2.4 (phased output), (vi) Population: ASN (Asian), and (vii) Mode: Quality control and imputation.

Further quality control was performed using PLINK software v1.90.[17] SNPs were excluded if they met any of the following criteria: minor allele frequency < 0.01, genotype call rate < 95%, significant deviation from the Hardy-Weinberg equilibrium ($P < 1.0 \times 10^{-5}$), excess heterozygosity (± 8 standard deviations [SD] from the mean), discordance between clinical and genotypic sex, or evidence of cryptic relatedness (identity-by-descent [IBD] proportion > 0.1875, corresponding to mid-point between second and third-degree relatives).

Population stratification was assessed via principal component analysis (PCA), comparing study participants to references samples from the Singaporean Genome Variation Project (SGVP). Individuals who did not cluster within ± 6 SD from the mean of their ancestral group along the first two principal components were excluded.

*Clinical data*

Clinical data were obtained from the TMC Biobank database and included sociodemographic variables (e.g., sex, ethnicity, marital status, education level, employment status, residential area), lifestyle and family history (i.e., smoking status, alcohol intake, use of antihypertensive medications, known case of CHD and family history of CHD), age at TMC recruitment and age of death. Biophysical and laboratory parameters were also included: systolic (SBP) and diastolic blood pressures (DBP), body mass index (BMI), waist circumference, waist-hip ratio, fasting blood glucose (FBG), glycated hemoglobin (HbA1c), total cholesterol, triglycerides, LDL-C, and HDL-C. Participants with FBG > 7.0 mmol/L

and/or $HbA_{1c} \geq 7.0\%$ were categorised as having uncontrolled T2D.[18]

*Statistical analysis*
Statistical analyses of clinical data were performed using IBM SPSS Statistics version 26 (IBM Corporations, New York, USA) and R version 4.3.0 software (The R Foundation for Statistical Computing) within the RStudio environment (version 2023.06.1 build 524; Posit Software, Massachusetts, USA). Continuous data were expressed as mean ± SD, and comparisons between the cases and controls were made using independent t-tests. Categorical variables were summarised as frequencies and percentages (n, %) and compared with the chi-square ($\chi^2$) test or Fisher's exact test, as appropriate. Statistical significance was defined as a two-sided p-value < 0.05.

Genomic data analysis was performed using PLINK software. The association between individual SNP and CHD-related mortality was tested using the "--assoc" command, which applies a chi-square test. After adjusting for genomic inflation ($\lambda_{GC}$), SNPs with $P < 5.0 \times 10^{-5}$ (suggestive genome-wide significance) and directly genotyped on the ASA beadchip were selected for polygenic risk score (PRS) development. Logistic regression was applied to estimate the β-value (log-odds) for each SNP, which were then used as weights in the PRS calculation. PRS scores were computed using the "--score" command in PLINK.

In Phase 1, the discriminatory performance of the PRS in classifying CHD death among individuals with T2D was tested using the area under the receiver operating characteristic curve (AUC). Calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test. In phase 2, participants were stratified into low- and high-risk groups based on a predetermined PRS cut-off. The predictive utility of the PRS for future CHD-related mortality was assessed using the Kaplan-Meier survival analysis and Cox proportional hazards regression. Covariates were included in the Cox model to control potential confounding factors.

## RESULTS

A total of 849 participants (224 cases, 625 controls) were included in Phase 1 of the study after quality control procedures, comprising 224 CHD death cases and 625 non-CHD death controls. Ethnic composition included 528 Malays (133 cases, 395 controls), 105 Chinese (21 cases, 84 controls), and 216 Indians (70 cases, 146 controls). Principal component analysis (PCA) demonstrated clear separation of the three ethnic groups, each clustering closely with their respective SGVP counterparts, indicating adequate population structure control (figure not shown). Initial genotyping using the Infinium ASA beadchip yielded 653,893 SNPs. After imputation and post-imputation quality control, the final dataset comprised 959,119 high-quality SNPs for association analysis.

*Genome-wide associations with CHD death in T2D*
Quantile-quantile (Q-Q) analysis indicated no significant inflation in test statistics, suggesting minimal population stratification or confounding, with a genomic inflation factor (λGC) of 0.99 (figure not shown). Among the ~1 million SNPs analysed, rs6765857 (located within the ZBTB38 gene) exhibited the strongest association with CHD death among participants with T2D (OR = 2.81, 95% CI = 1.90–4.17, $P = 7.18 \times 10^{-7}$), followed by rs57987238 in KLF3 (OR = 6.59, 95% CI = 2.98–14.60, $P = 7.74 \times 10^{-7}$). The risk allele for both variants was G, with minor allele frequencies (MAFs) of 0.066 for rs6765857 and 0.018 for rs57987238. Both SNPs were located within intronic regions of their respective genes.

These results corresponded to the prominent peaks observed on the Manhattan plot, particularly on chromosomes 3 and 4 (figure not shown). A total of 56 SNPs met suggestive genome-wide significance ($P < 5.0 \times 10^{-5}$), although none reached the conventional genome-wide significance threshold ($P < 5.0 \times 10^{-8}$) (data not shown). These SNPs were mapped to 23 loci, distributed as follows: 43 in intronic regions, seven intergenic, four upstream, one downstream, and one in the 3' untranslated region. MAFs for the 56 SNPs ranged between 0.010 to 0.383.

*Discriminative performance of the polygenic risk score (PRS)*
Fifteen lead SNPs were selected from the list of 56 suggestive variants to construct a polygenic risk score (PRS), using their logistic regression β-coefficients as weights (Table I). All selected SNPs were directly genotyped from the ASA chip and represented distinct genetic loci. SNPs with a positive β-values were associated with increased risk of CHD death, whereas negative β-values indicated protective effects. The largest positive β-value was observed for rs71505297 in the *RXRA* gene (β = 2.00) suggesting a strong risk-enhancing effect. Conversely, the most negative β-value was identified for rs10751517 in *HMCN2* (β = –0.95), indicating a potential protective role.

Type 2 diabetic participants who died from CHD had significantly higher mean PRS values compared to those who died from non-CHD causes. This trend was observed both in terms of the overall cohort and within each ethnic group (Figure 1). Discrimination analysis using the AUC demonstrated that PRS could significantly distinguish CHD-related deaths from non-CHD deaths among T2D participants across all ethnicities. The AUC was 0.792 for Malays ($p<0.001$), 0.744 for Chinese ($p=0.001$), 0.792 for Indians ($p<0.001$), and 0.762 for the overall sample ($p<0.001$), indicating strong discriminative ability. Calibration of the PRS using the Hosmer-Lemeshow goodness-of-fit test showed good agreement between observed and expected CHD death frequencies within each ethnicity and the overall sample ($p>0.05$). A clear increasing trend in CHD death prevalence was observed across PRS deciles, supporting the PRS's gradational predictive value (figure not shown).[19]

*Baseline characteristics of the retrospective cohort study*
Based on the AUC analysis, a PRS cut-off score of 0.85 was selected for risk stratification, yielding 64.7% sensitivity and 73.1% specificity. While the moderate sensitivity and specificity suggest some limitations in individual-level prediction, the PRS may still hold value in identifying population-level risk trends and guiding targeted interventions.

**Table I: Selected lead single nucleotide polymorphisms for polygenic risk score**

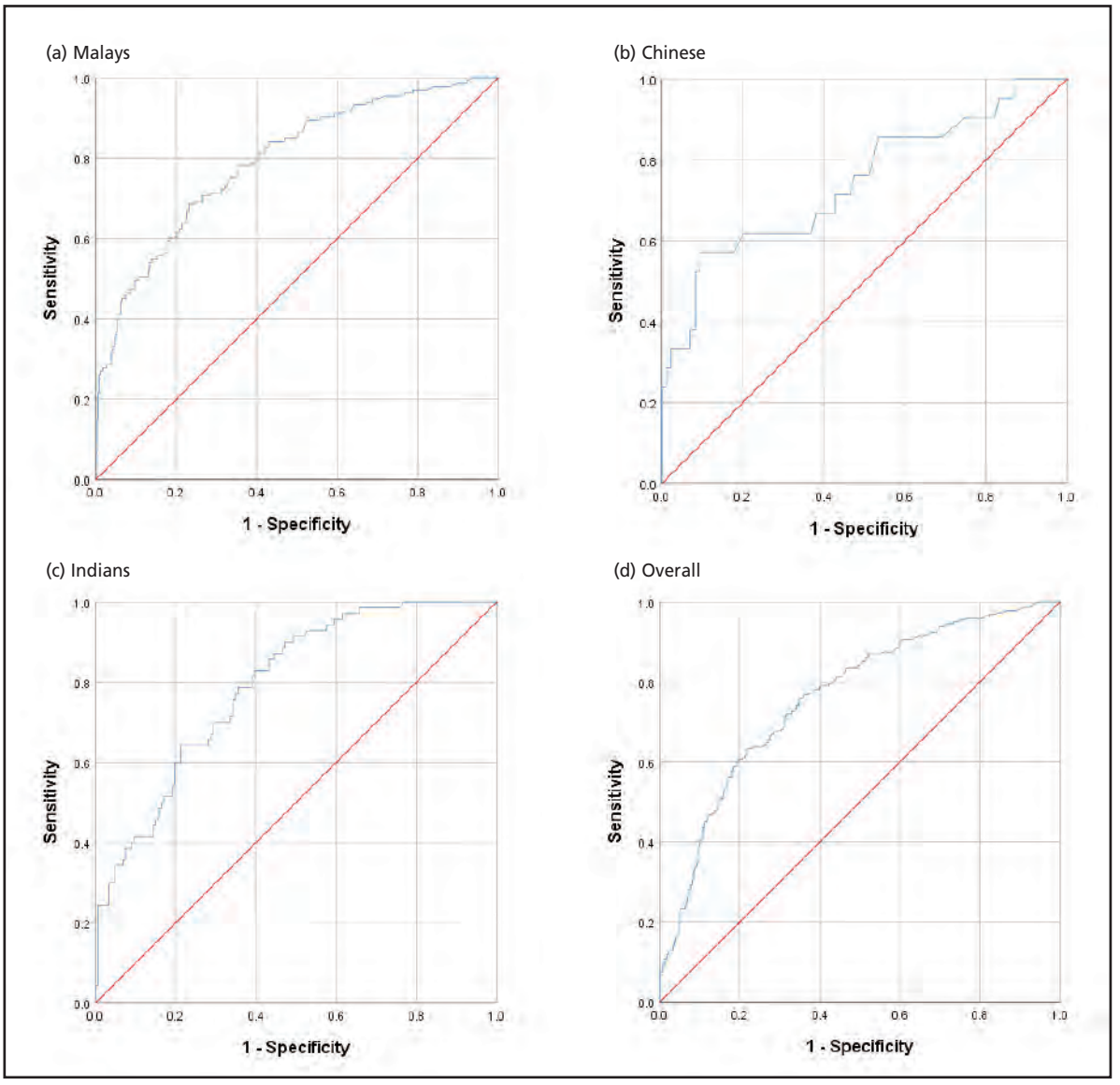
| Chr | SNP | A1 | A2 | Mapped gene | Variant | β |
|---|---|---|---|---|---|---|
| 1 | rs483202 | G | A | GRHL3 | Intronic | 0.56 |
| 1 | rs10910660 | C | T | PCNX2 | Intronic | 0.53 |
| 1 | rs6692683 | A | G | EPHB2 | Intronic | 0.46 |
| 2 | rs807608 | C | T | - | Intergenic | –0.85 |
| 3 | rs6795197 | A | C | ZBTB38 | Intronic | 0.88 |
| 4 | rs35887929 | C | T | UGT2B10 | Intronic | 1.24 |
| 4 | rs10008290 | G | A | LOC105377356 | Intronic | 1.15 |
| 5 | rs6888803 | C | T | LOC105377700 | Intronic | –0.75 |
| 6 | rs34836069 | A | G | POLR1C | Intronic | 0.52 |
| 7 | rs2867567 | A | G | CALN1 | Intronic | –0.48 |
| 9 | rs10751517 | C | T | HMCN2 | Intronic | –0.95 |
| 9 | rs71505297 | T | C | RXRA | Intronic | 2.00 |
| 19 | rs56166910 | G | A | HAS1 | Intronic | –0.49 |
| 19 | rs1865062 | A | G | MLLT1 | Intronic | 1.49 |
| 20 | rs6102788 | A | G | PTPRT | Intronic | –0.59 |

Abbreviations: A1 (minor allele), A2 (major allele), Chr (chromosome), SNP (single nucleotide polymorphism).

**Table II: The baseline characteristics of the participants with type 2 diabetes mellitus in the retrospective cohort study were based on their polygenic risk categories**

| Characteristic | High-risk (PRS ≥ 0.85) | Low-risk (PRS < 0.85) | p-value |
|---|---|---|---|
| Age at recruitment (years) | 55.22 ± 6.27 | 56.49 ± 6.01 | 0.005* |
| Sex | | | |
| Female | 94 (29.7%) | 223 (70.3%) | 0.001* |
| Male | 200 (40.9%) | 289 (59.1%) | |
| Ethnicity | | | |
| Malay | 117 (23.2%) | 387 (76.8%) | < 0.001* |
| Chinese | 11 (10.9%) | 90 (89.1%) | |
| Indian | 166 (82.6%) | 35 (17.4%) | |
| Marital status | | | |
| Married | 266 (36.7%) | 458 (63.3%) | 0.891 |
| Single | 5 (35.7%) | 9 (64.3%) | |
| Divorced/widowed | 23 (33.8%) | 45 (66.2%) | |
| Education level | | | |
| Primary | 153 (33.7%) | 301 (66.3%) | 0.102 |
| Secondary | 128 (41.0%) | 184 (59.0%) | |
| Tertiary | 13 (32.5%) | 27 (67.5%) | |
| Working status | | | |
| Not working | 146 (34.8%) | 274 (65.2%) | 0.292 |
| Working | 148 (38.3%) | 238 (61.7%) | |
| Residency | | | |
| Rural | 103 (27.1%) | 277 (72.9%) | < 0.001* |
| Urban | 191 (44.8%) | 235 (55.2%) | |
| Smoking status | | | |
| Not/past smoker | 220 (35.4%) | 401 (64.6%) | 0.257 |
| Active smoker | 74 (40.0%) | 111 (60.0%) | |
| Alcohol intake | | | |
| No | 255 (34.2%) | 491 (65.8%) | < 0.001* |
| Yes | 39 (65.0%) | 21 (35.0%) | |
| Diabetes duration | | | |
| ≤ 5 years | 153 (33.3%) | 306 (66.7%) | 0.033* |
| > 5 years | 141 (40.6%) | 206 (59.4%) | |
| Family history of CHD | | | |
| No | 90 (30.1%) | 209 (69.9%) | 0.004* |
| Yes | 204 (40.2%) | 303 (59.8%) | |
| SBP (mmHg) | 139.03 ± 21.92 | 144.69 ± 24.82 | 0.001* |
| DBP (mmHg) | 80.56 ± 11.49 | 80.93 ± 12.59 | 0.674 |
| Body mass index (kg/m²) | 26.70 ± 4.43 | 27.20 ± 4.86 | 0.151 |
| Waist circumference (cm) | 91.98 ± 11.41 | 91.42 ± 11.26 | 0.497 |
| Waist-hip ratio | 0.94 ± 0.07 | 0.93 ± 0.07 | 0.047* |
| Total cholesterol (mmol/L) | 5.79 ± 1.35 | 6.13 ± 1.51 | 0.001* |
| Triglyceride (mmol/L) | 2.14 ± 1.33 | 2.32 ± 2.19 | 0.147 |
| LDL-C (mmol/L) | 3.66 ± 1.21 | 3.86 ± 1.26 | 0.025* |
| HDL-C (mmol/L) | 1.15 ± 0.31 | 1.23 ± 0.38 | 0.002* |
| FBG (mmol/L) | 10.48 ± 4.42 | 10.05 ± 4.08 | 0.169 |
| HbA1c (%) | 9.10 ± 2.33 | 8.98 ± 2.50 | 0.508 |

Data are presented as frequency (percentage) and mean ± standard deviation (SD) for categorical and continuous variables. *Significant difference between high and low PRS groups at P < 0.05. Abbreviations: CHD (coronary heart disease), DBP (diastolic blood pressure), FBG (fasting blood glucose), HbA1c (glycated hemoglobin), HDL-C (high-density lipoprotein cholesterol), LDL-C (low-density lipoprotein cholesterol), SBP (systolic blood pressure).

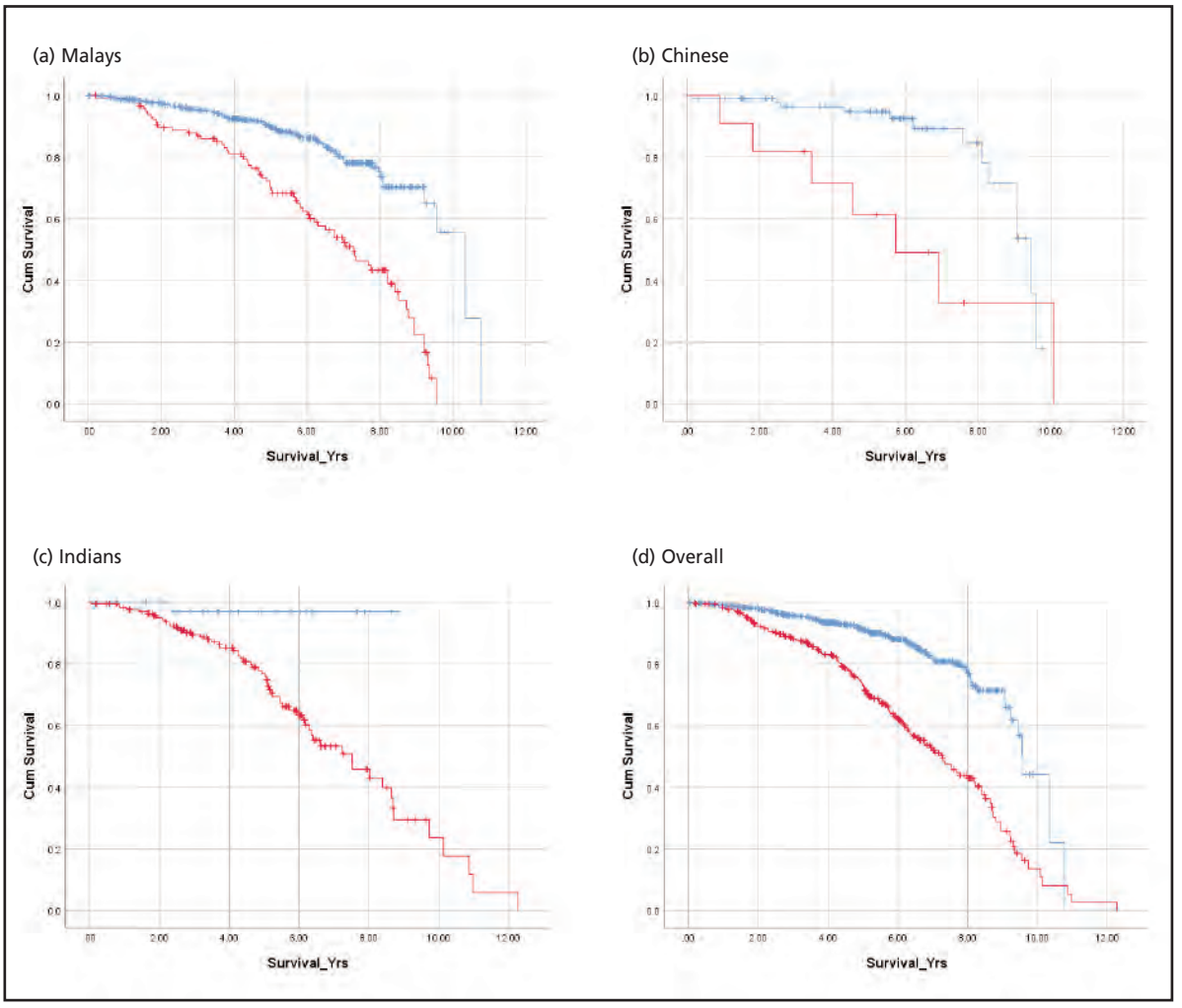



| Ethnicity | PRS | | | p-value |
|---|---|---|---|---|
| | T2D+CHD | T2D | AUC | |
| Malay | 0.85 ± 0.04 | 0.82 ± 0.03 | 0.792 | < 0.001* |
| Chinese | 0.84 ± 0.04 | 0.81 ± 0.02 | 0.744 | 0.001* |
| Indian | 0.94 ± 0.05 | 0.88 ± 0.04 | 0.792 | < 0.001* |
| Overall | 0.88 ± 0.06 | 0.83 ± 0.04 | 0.762 | < 0.001* |

**Fig. 1:** Discrimination analysis shows the area under the receiver operating characteristic curve and the mean values of polygenic risk score among (a) Malays, (b) Chinese, (c) Indians, and (d) Overall subjects

*Significant results at p<0.05. Legends: Blue line (PRS), red line (reference). Abbreviations: AUC (area under receiver operating characteristic curve), CHD (coronary heart disease), PRS (polygenic risk score), T2D (type 2 diabetes)

To test its clinical utility, a retrospective cohort of 806 T2D participants without prior CHD at baseline was analysed. Participants were stratified into high-risk (PRS≥0.85) and low-risk (PRS<0.85) groups. The high-risk group was significantly younger (55.22 vs 56.49 years, p=0.005), comprised more males (40.9 vs 29.7%, p=0.001), and had a higher proportion of Indian ethnicity (82.6%) compared to Malays (23.2%) and Chinese (10.9%) (p<0.001). Urban residency was also more prevalent in the high-risk group (44.8 vs 27.1%, p<0.001) (Table II). Additionally, the high-risk group had higher prevalence of alcohol consumption (65.0 vs 35.4%, p<0.001), longer diabetes duration (> 5 years: 40.6 vs 33.3%, p=0.033), and greater family history of CHD (40.2 vs 30.1%, p=0.004). Biophysically, the high-risk individuals had lower systolic blood pressure (139.03 vs 144.69 mmHg, p=0.001), higher waist-hip ratio (0.94 vs 0.93, p=0.047), and more favourable lipid profiles, with lower serum total cholesterol (5.79 vs 6.13 mmol/L, p=0.001), LDL-C (3.66 vs 3.86 mmol/L, p=0.025), except for HDL-C (1.15 vs. 1.23 mmol/L, p=0.002).




| Ethnicity | Mean survival years (95% CI) | | p-value |
|---|---|---|---|
| | High risk PRS | Low risk PRS | |
| Malays | 6.60 (6.08–7.11) | 8.92 (8.50–9.35) | < 0.001* |
| Chinese | 6.20 (3.98–8.41) | 8.66 (8.15–9.16) | 0.011* |
| Indians | 7.21 (6.54–7.88) | 8.60 (8.21–8.99) | 0.001* |
| Overall | 6.88 (6.47–7.29) | 8.88 (8.52–9.25) | < 0.001* |

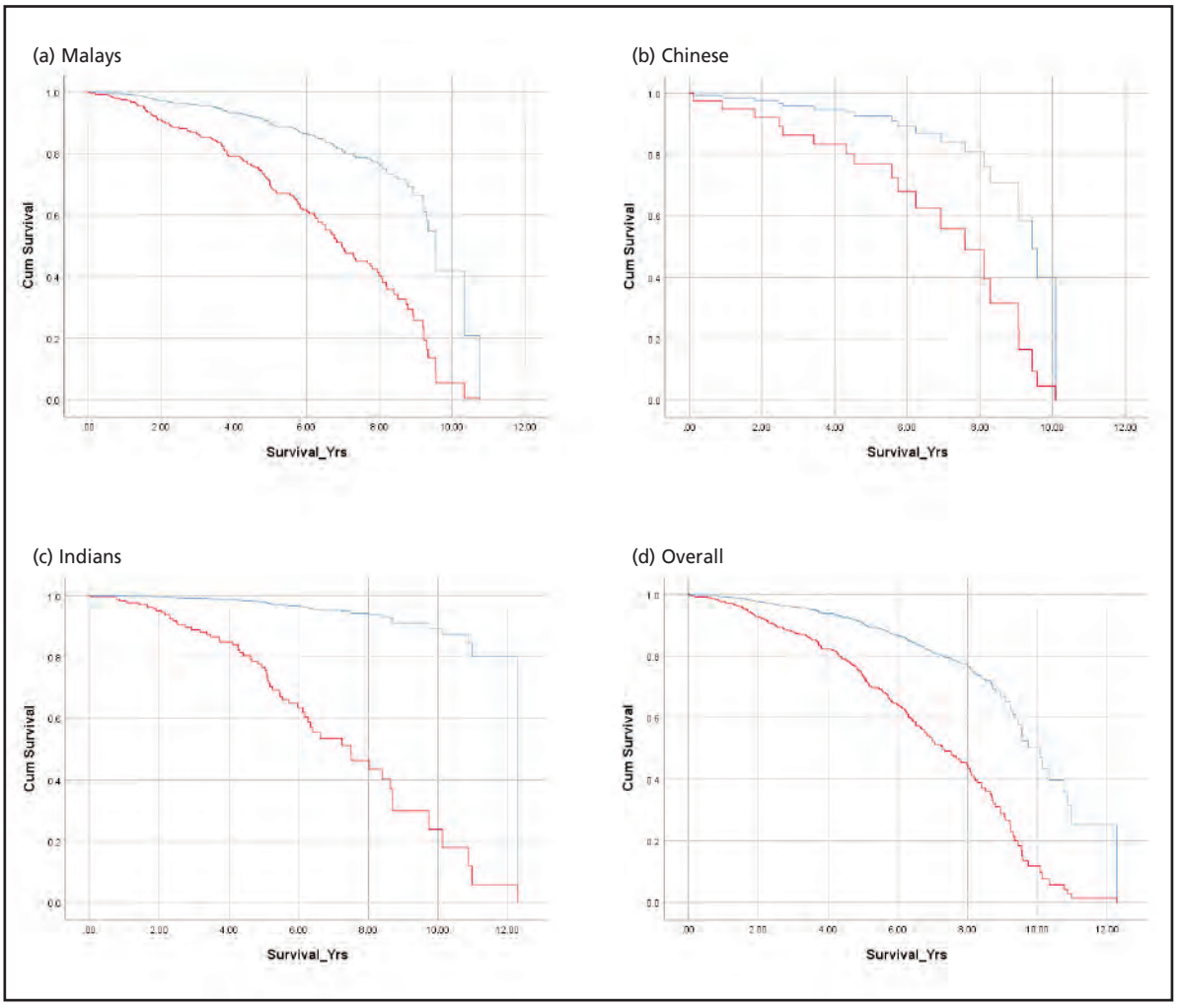
**Fig. 2:** Kaplan-Meier survival analysis results for the prediction of future CHD death by polygenic risk score among T2D TMC participants in the retrospective cohort study among (a) Malays, (b) Chinese, (c) Indians, and (d) Overall subjects

*Significant results at p<0.05. Abbreviations: CHD (coronary heart disease), CI (confidence interval), Cum Survival (cumulative survival), PRS (polygenic risk score), Survival (survival years). Legends: Blue line (low-risk PRS), red line (high-risk PRS)

*Validation of PRS in predicting future CHD death*

The predictive utility of the PRS cut-off (≥0.85) for future CHD death among T2D individuals was validated in the retrospective cohort study using Kaplan-Meier (KM) survival analysis and Cox proportional hazards analysis with covariate adjustments. Kaplan-Meier analysis demonstrated significant shorter mean survival durations among high-risk participants across all ethnic groups: Malays (6.60 vs 8.92 years), Chinese (6.20 vs 8.66 years), and Indians (7.21 vs 8.60 years), all with p<0.05 (Figure 2). In the overall samples, high-risk individuals also had significantly reduced survival (6.88 vs 8.88 years, p<0.001).

Cox regression analysis further confirmed that high-risk individuals (PRS ≥ 0.85) had significantly increased hazards of CHD death. After adjusting for relevant covariates (age, sex, ethnicity, urban/rural residence, alcohol consumption, diabetes duration, family history of CHD, systolic blood pressure, waist-hip ratio, total cholesterol, LDL-C, and HDL-C), the adjusted hazard rations were: Malays: HR=3.23 (p<0.001); Chinese: HR=9.59 (p=0.005); Indians: HR=9.65 (p=0.027); Overall sample: HR=3.51 (p<0.001) (Figure 3). These findings underscore the PRS's robust predictive capacity for CHD mortality risk across ethnic groups in the Malaysian T2D population.




| Ethnicity | Ref.: Low-risk PRS (< 0.85) | | | | | p-value |
|---|---|---|---|---|---|---|
| | β | SE | Wald | df | HR (95% CI) | |
| Malays | 1.17 | 0.19 | 36.57 | 1 | 3.23 (2.21–4.73) | < 0.001* |
| Chinese | 2.26 | 0.81 | 7.80 | 1 | 9.59 (1.96–46.90) | 0.005* |
| Indians | 2.27 | 1.02 | 4.91 | 1 | 9.65 (1.30–71.66) | 0.027* |
| Overall | 1.26 | 0.17 | 54.22 | 1 | 3.51 (2.52–4.91) | < 0.001* |

**Fig. 3:** Cox regression analysis results for the prediction of future CHD death by polygenic risk score among T2D TMC participants in the retrospective cohort study among (a) Malays, (b) Chinese, (c) Indians, and (d) Overall subjects

Regression was performed with covariate adjustment (i.e., age at recruitment, gender, ethnicity, residency, alcohol intake, diabetes duration, family history of CHD, SBP, WHR, total cholesterol, LDL-C, and HDL-C). *Significant results at p<0.05. Abbreviations: CHD (coronary heart disease), CI (confidence interval), Cum Survival (cumulative survival), HR (hazard ratio), PRS (polygenic risk score), Survival_Yrs (survival years). Legends: Blue line (low-risk PRS), red line (high-risk PRS).

## DISCUSSION

From the 56 SNPs identified with suggestive genome-wide significance in Phase 1 of this study, the strongest association with CHD death among the T2D participants in the TMC was observed for rs6765857, located in the intron of the *ZBTB38* gene (OR=2.81, P = 7.18 × $10^{-7}$). This imputed variant has a minor allele frequency of 0.0066. Interestingly, another variant within the same gene that was directly genotyped on the array, rs6795197, also ranked among the top five SNPs most strongly associated with CHD death in our cohort.

The *ZBTB38* gene encodes a zinc finger and BTB domain-containing protein known to regulate gene transcription through binding to methylated CpG dinucleotides.20 Functional studies suggest that *ZBTB38* modulates the expression of approximately 2,000 target genes, and some of these genes have been reported to associate with T2D and CHD, including angiopoietin-like 4 *(ANGPTL4)*, feline sarcoma proto-oncogene *(FES)*, dan serpin family A member 1 *(SERPINA1)*, which are involved in lipid metabolism, vascular function, and inflammation, respectively.[21–25] A pleiotropic GWAS analysis has also identified the 3q23 locus (harboring *ZBTB38*) as a shared genetic susceptibility region for both prostate cancer and T2DM.[22]

Further supporting its relevance, the DHS-MIND study involving 506 Caucasians in The United States, demonstrated that rs6765857 and rs6795197 were significantly associated with serum levels of advanced glycation end-products (AGE) levels,[26] which are known to accumulate in hyperglycaemic conditions and contribute to vascular inflammation and atherogenesis via pathways involving IL-6, IL-8, VCAM1, and ICAM-1.[27–30] These mechanistic insights suggest a plausible biological role for ZBTB38 variants in mediating CHD risk among T2D individuals.

In the context of genome-wide association studies (GWAS), the *ZBTB38* is associated with multiple metabolic traits including body fat percentage,[31] fasting blood glucose,[32] and glycated haemoglobin (HbA1c) levels.[33] Interestingly, despite strong trans-ethnic associations with T2D, genome-wide significance was observed only among Caucasians ($p=1.10 \times 10^{-14}$) and not among Asian populations ($p=3.90 \times 10^{-1}$),[34] underscoring the importance of population-specific genetic studies.

In the current study, a 15-SNP PRS was developed using lead variants with suggestive significance. This PRS demonstrated good discriminative ability (AUC=0.762 for the overall population), with performance consistent across Malay, Chinese and Indian subgroups. Apart from rs6795197 *(ZBTB38)*, other SNPs comprised rs483202 *(GRHL3)*, rs10910660 *(PCNX2)*, rs6692683 *(EPHB2)*, rs807608 (intergenic), rs35887929 *(UGT2B10)*, rs10008290 *(LOC105377356)*, rs6888803 *(LOC105377700)*, rs34836069 *(POLR1C)*, rs2867567 *(CALN1)*, rs10751517 *(HMCN2)*, rs71505297 *(RXRA)*, rs56166910 *(HAS1)*, rs1865062 *(MLLT1)*, and rs6102788 (PTPRT). Many of the SNPs' association with CHD death had not been reported before. However, rs35887929 *(UGT2B10)* has been linked to nicotine metabolism,[35] and rs71505297 *(RXRA)* to levels of azelaic acid levels, a fatty acid with potential anti-atherosclerotic effects,[36-37]

Using a PRS cut-off score of ≥0.85, sensitivity and specificity were 64.7% and 73.1% respectively. While these values indicate moderate diagnostic performance, they remain clinically useful in stratifying patients into high- and low-risk categories for CHD death, particularly in a resource-limited setting where early risk identification can guide preventive strategies. However, the modest sensitivity suggests that a proportion of at-risk individuals may not be identified using this PRS alone, highlighting the need for integration with traditional risk factors in future predictive models. The CARDIoGRAMplusC4D consortium, reported that PRS is usually associated with traditional cardiovascular risk factors, including elevated triglyceride, LDL-C, glucose, and HbA1c, with decreased HDL-C levels.[38]

Importantly, participants in the high-risk PRS group exhibited characteristics not typically associated with higher CHD risk: lower SBP, total cholesterol, and LDL-C levels. This suggests that the PRS may capture genetic risk that operates independently of conventional cardiometabolic markers, possibly through alternative pathways such as inflammation, oxidative stress, or endothelial dysfunction. Despite these differences, locally developed PRS in the present study was able to predict future CHD deaths, similar to prior findings among 401,471 Caucasians in Canada.39 Although using a different set of SNPs, the PRS can predict the incidence of myocardial infarction and all-cause mortality with a remarkable p-value.[39]

It is worth noting that the Cox regression analysis yielded remarkably high hazard ratios for the Chinese (HR=9.59) and Indian (HR = 9.65) subgroups compared to Malays (HR=3.23), accompanied by wide 95% confidence intervals. These observations are direct consequences of smaller subgroup sample sizes and uneven sample distribution within risk categories in Phase 2, such as the small number of Chinese individuals in the high-risk group (n=11) and Indian individuals in the low-risk group (n=35). While the wide confidence intervals imply that the numerical magnitude of these hazard ratios must be interpreted with caution, the persistent statistical significance ($p<0.05$) across all adjusted subgroups underscores a robust and genuine genetic predisposition to accelerated CHD mortality in these populations.

Despite the encouraging findings, this study has several limitations. First, the sample size, although adequate for initial GWAS discovery, was relatively small by global GWAS standards, limiting the detection of SNPs reaching conventional genome-wide significance ($P < 5 \times 10^{-8}$). The selection of lead variants based on a suggestive threshold ($P < 5 \times 10^{-5}$) demands a cautious interpretation regarding individual SNP effects, as it carries an inherently higher risk of type I error. However, this strategy was adopted to capture population-specific genetic variations that would otherwise be ignored. Besides, the risk of false-positive was substantially mitigated by the robust predictive performance of the 15-SNP PRS in the Phase 2 of the study. Second, the use of the Illumina Asian Screening Array, which lacks comprehensive South-Asian genomic content, may have affected variant detection among Indian participants. This limitation was mitigated through imputation using the GenomeAsia Pilot reference panel, which incorporates genetic data from diverse Asian populations.

Nevertheless, this study also has notable strengths. It is the first to identify *ZBTB38* as a top candidate gene associated with CHD death among Malaysian individuals with T2D, and it introduces a population-specific PRS with predictive validity in a multi-ethnic Asian cohort. These findings provide a foundation for the development of precision medicine tools aimed at improving cardiovascular risk stratification and management among T2D patients in Malaysia and potentially other Asian populations.

## CONCLUSION

This study identified 56 SNPs with suggestive genome-wide significance for CHD death among T2D participants in the TMC, with rs6765857 in *ZBTB38* emerging as the strongest genetic signal. A 15-SNP PRS demonstrated potential clinical utility in predicting CHD death risk in this population, independent of traditional cardiovascular risk factors. The findings support the integration of PRS into precision medicine approaches for secondary prevention of CHD among individuals with T2D, particularly in multi-ethnic

Southeast Asian populations. Future studies with larger sample sizes and prospective validation are warranted to confirm these associations and enhance PRS performance.

## ACKNOWLEDGEMENTS

This research was supported by the UKM Medical Molecular Biology Institute (UMBI), Universiti Kebangsaan Malaysia (UKM), through grant number PDE48 for The Malaysian Cohort (TMC) project. The publication fee was funded by the Research Management Centre, Universiti Pertahanan Nasional Malaysia (UPNM). The authors extend their sincere gratitude to the postgraduate students, staff, and academic personnel of UMBI, UKM, as well as staff of TMC, particularly Ts. Muhiddin Ishak, Mdm. Zam Zureena Mohd Rani, and Mr. Mohd Ridhwan Abd Razak for valuable assistance and support, both direct and indirect, throughout the course of this research.

## CONFLICTS OF INTEREST

The authors declare no conflict of interest.

## REFERENCES

1. World Health Organization. The Top 10 Causes of Death. [cited April 2025] Accessed from: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death.
2. National Institute of Health, Shah Alam, Selangor, Malaysia. 2020. National Health and Morbidity Survey 2019: Technical Report – Volume I: NCDs – Non-Communicable Diseases: Risk Factors and other Health Problems.
3. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract 2022; 183: 109119.
4. National Heart Association of Malaysia, Kuala Lumpur, Malaysia. 2023. Annual Report of the NCVD-PCI Registry, Year 2019–2020.
5. Department of Statistics Malaysia. Statistics on Causes of Death, Malaysia, 2023. [cited April 2025] Accessed from: https://www.dosm.gov.my/portal-main/release-content/statistics-on-causes-of-death-malaysia-2023.
6. Dendup T, Feng X, Clingan S, Astell-Burt T. Environmental risk factors for developing type 2 diabetes mellitus: A systematic review. Int J Environ Res Public Health 2018; 15(1): 78.
7. Malakar AK, Choudhury D, Halder B, Paul P, Uddin A, Chakraborty S. A review on coronary artery disease, its risk factors, and therapeutics. J Cell Physiol 2019; 234(10): 16812–23.
8. Ab Zayin AA, Zainol Z, Nohuddin PNE, Mohamed H. Peramalan risiko diabetes menggunakan aplikasi MyDiabeticRisk. Zulfaqar J Def Sci Eng Technol 2023; 6(2): 1-12.
9. McPherson R, Tybjaerg-Hansen A. Genetics of coronary artery disease. Circ Res 2016; 118(4): 564-78.
10. Qi L, Qi Q, Prudente S, Mendonca C, Andreozzi F, di Pietro N, et al. Association between a genetic variant related to glutamic acid metabolism and coronary heart disease in individuals with type 2 diabetes. JAMA 2013; 310(8): 821-8.
11. Fall T, Gustafsson S, Orho-Melander M, Ingelsson E. Genome-wide association study of coronary artery disease among individuals with diabetes: The UK Biobank. Diabetologia 2018; 61(10): 2174-9.
12. Thanassoulis G, Peloso GM, Pencina MJ, Hoffmann U, Fox CS, Cupples LA, et al. A genetic risk score is associated with incident cardiovascular disease and coronary artery calcium. Circ Cardiovasc Genet 2012; 5(1): 113-21.
13. Beaney KE, Cooper JA, Ullah Shahid S, Ahmed W, Qamar R, Drenos F, et al. Clinical utility of a coronary heart disease risk prediction gene score in UK healthy middle aged men and in the Pakistani population. PLoS One 2015; 10(7): 1-13.
14. Lambert SA, Gil L, Jupp S, Ritchie SC, Xu Y, Buniello A, et al. The Polygenic Score Catalog as an open database for reproducibility and systematic evaluation. Nat Genet 2021; 53(4): 420-5.
15. Jamal R, Syed Zakaria SZ, Kamaruddin MA, Abd Jalal N, Ismail N, Mohd Kamil N, et al. Cohort profile: The Malaysian Cohort (TMC) project: A prospective study of non-communicable diseases in a multi-ethnic population. Int J Epidemiol 2015; 44(2): 423-31.
16. Abdullah N, Abdul Murad NA, Attia J, Oldmeadow C, Mohd Haniff EA, Syafruddin SE, et al. Characterizing the genetic risk for type 2 diabetes in a Malaysian multi-ethnic cohort. Diabet Med 2015; 32(10): 1377-84.
17. Chang CC, Chow CC, Tellier LC, Vattikuti S, Purcell SM, Lee JJ. Second-generation PLINK: Rising to the challenge of larger and richer datasets. Gigascience 2015; 4: 7.
18. Ministry of Health Malaysia, Putrajaya, Malaysia. 2020. Clinical Practice Guidelines: Management of Type 2 Diabetes Mellitus, 6th Edition.
19. Schulz C, Padmanabhan S. Methods to assess genetic risk prediction. In: Touyz RM, Schiffrin EL, Editors. Hypertension: Methods in molecular biology, vol. 1527. Humana Press; 2017: 27-40.
20. Stelzer G, Rosen N, Plaschkes I, Zimmerman S, Twik M, Fishilevich S, et al. The GeneCards Suite: From gene data mining to disease genome sequence analyses. Curr Protoc Bioinformatics 2016; 54: 1.30.1-33.
21. Ding G, Lu W, Zhang Q, Li K, Zhou H, Wang F, et al. ZBTB38 suppresses prostate cancer cell proliferation and migration via directly promoting DKK1 expression. Cell Death Dis 2021; 12(11): 998.
22. Ray D, Chatterjee N. A powerful method for pleiotropic analysis under composite null hypothesis identifies novel shared loci between type 2 diabetes and prostate cancer. PLoS Genet 2020; 16(12): e1009218.
23. Yang Q, Yin RX, Cao XL, Huang F, Zhou YJ, Chen WX. ANGPTL4 variants and their haplotypes are associated with serum lipid levels, the risk of coronary artery disease and ischemic stroke and atorvastatin cholesterol-lowering responses. Nutr Metab 2018; 15(1): 70.
24. Yang X, Yang W, McVey DG, Zhao G, Hu J, Poston RN, et al. FURIN expression in vascular endothelial cells is modulated by a coronary artery disease-associated genetic variant and influences monocyte transendothelial migration. J Am Heart Assoc 2020; 9(4): e014333.
25. Liu G, Liao W, Lv X, Huang L, He M, Li L. A potential coagulation-related diagnostic model associated with immune infiltration for acute myocardial infarction. Genes Immun 2024; 25(6): 471–82.
26. Adams JN, Raffield LM, Martelle SE, Freedman BI, Langefeld CD, Carr JJ, et al. Genetic analysis of advanced glycation end products in the DHS MIND study. Gene 2016; 584(2): 173-9.
27. Hashim Z, Zarina S. Advanced glycation end products in diabetic and non-diabetic human subjects suffering from cataract. AGE 2011; 33(3): 377-84.
28. Kilhovd BK, Berg TJ, Birkeland KI, Thorsby P, Hanssen KF. Serum levels of advanced glycation end products are increased in patients with type 2 diabetes and coronary heart disease. Diabetes Care 1999; 22(9): 1543-8.
29. Kanehisa M, Goto S. KEGG: Kyoto Encyclopedia of Genes and Genomes. Nucleic Acids Res 2000; 28(1): 27-30.
30. Libby P, Ridker PM, Hansson GK. Progress and challenges in translating the biology of atherosclerosis. Nature 2011; 473(7347): 317-25.
31. Harris BHL, Di Giovannantonio M, Zhang P, Harris DA, Lord SR, Allen NE, et al. New role of fat-free mass in cancer risk linked with genetic predisposition. Sci Rep 2024; 14(1): 7270.

32. Chen J, Spracklen CN, Marenne G, Varshney A, Corbin LJ, Luan J, et al. The trans-ancestral genomic architecture of glycemic traits. Nat Genet 2021; 53(6): 840-60.
33. Sakaue S, Kanai M, Tanigawa Y, Karjalainen J, Kurki M, Koshiba S, et al. A cross-population atlas of genetic associations for 220 human phenotypes. Nat Genet 2021; 53(10): 1415-24.
34. Vujkovic M, Keaton JM, Lynch JA, Miller DR, Zhou J, Tcheandjieu C, et al. Discovery of 318 new risk loci for type 2 diabetes and related vascular outcomes among 1.4 million participants in a multi-ancestry meta-analysis. Nat Genet 2020; 52(7): 680-91.
35. Perez-Paramo YX, Watson CJW, Chen G, Thomas CE, Adams-Haduch J, Wang R, et al. Impact of genetic variants in the nicotine metabolism pathway on nicotine metabolite levels in smokers. Cancer Epidemiol Biomarkers Prev 2023; 32(1): 54-65.
36. Al-Khelaifi F, Diboun I, Donati F, Botrè F, Abraham D, Hingorani A, et al. Metabolic GWAS of elite athletes reveals novel genetically-influenced metabolites associated with athletic performance. Sci Rep 2019; 9(1): 19889.
37. Litvinov D, Selvarajan K, Garelnabi M, Brophy L, Parthasarathy S. Anti-atherosclerotic actions of azelaic acid, an end product of linoleic acid peroxidation, in mice. Atherosclerosis 2010; 209(2): 449-54.
38. Dennis JK, Sealock JM, Straub P, Lee YH, Hucks D, Actkins K, et al. Clinical laboratory test-wide association scan of polygenic scores identifies biomarkers of complex disease. Genome Med 2021; 13(1): 6.
39. Manikpurage HD, Eslami A, Perrot N, Li Z, Couture C, Mathieu P, et al. Polygenic risk score for coronary artery disease improves the prediction of early-onset myocardial infarction and mortality in men. Circ Genomic Precis Med 2021; 14(6): e003452.

ORIGINAL ARTICLE

# Ear, nose and throat foreign bodies: A cross sectional study on incidence, clinical factors and dimensions

**Hardip Singh Gendeh, Dr ORL-HNS (UKM)[1-3], Goh Bee See, MS ORL-HNS (UKM)[1,3]**

[1]Department of Otorhinolaryngology, Head and Neck Surgery, Universiti Kebangsaan Malaysia, Cheras, Kuala Lumpur, Malaysia, [2]Allergic Unit, Orl-HNS Clinic, Hospital Canselor Tuanku Muhriz, Universiti Kebangsaan Malaysia, Cheras, Kuala Lumpur, Malaysia, [3]ORL-HNS Unit, Department of Pediatric Surgery, Hospital Tunku Ampuan Besar Tuanku Aisyah Rohani (TABTAR), Hospital Pakar Kanak-Kanak Universiti Kebangsaan Malaysia, Cheras, Kuala Lumpur, Malaysia

## ABSTRACT

**Introduction: Ear, nose and throat (ENT) foreign body (FB) is common problem with significant morbidity and mortality. They are classified into organic or inorganic. Aerodigestive FBs are responsible for suffocation and death up to three years old with a 10% mortality up to 14 years old in Europe. Malaysia lacks local data that quantifies FB in dimensions to predict its risk. The study objectives were to determine the incidence of ENT FBs (paediatric and adult) in a Malaysian tertiary referral center; to determine the association between the FB types and factors contributing to its occurrence (largest dimension, volume, witnessed); to determine the treatment required; and association between hand dominance with ENT FBs.**

**Materials and Methods: Prospective data of all children (<18 years old) and adults (≥18 years old) seen by the ENT physicians presenting with ENT foreign body were included over 12 months at Hospital Canselor Tuanku Muhriz (HCTM) from 1st February 2017 to 31st January 2018. All cases are seen by an ENT doctor (specialist and/or medical officer) during on-call, in hospital and outpatient's referrals. FB dislodged in the lower airways (trachea, bronchus and bronchiole) and upper gastrointestinal (GI) tract (oesophagus) were included. Exclusion criteria were FB dislodged in non-ENT orifices such as the stomach and beyond with no other ENT FBs. Bias was reduced by a proforma after obtaining an informed consent and taking the average of three measurements of FB dimensions.**

**Results: The incidence of ENT FB within HCTM was 3.5% (overall), 1.9% (organic), 1.6% (inorganic); 1.65% (children) and 1.85% (adults). Children have a mean age of 5.34 and adults 49.35 years. Among the patient factors; children FB are often inorganic (73.95%; plastic, metal, graphite), males predominant (56.5%), unwitnessed (66.67%), witnessed incidents were by adults (69.5%) at home (91.3%). Adult FB are often organic (77.1%; fish bone, cotton, tick), male to female ratio 1.4:1; not associated with occupation. Mackerel followed by red snapper and tilapia were common fish bones ingested. Common locations of FB among children and adults were throat (35.3%), ear (32.03%) and nose (26.14%). Less than one fifth required hospitalization due to aerodigestive FBs with 6 (72.7%) of hospitalised patients suffering complications of hypoxic brain injury, lung collapse, pneumonia, esophageal perforation and lacerations. Fifty-seven (37.25%) patients (adults predominant) required endoscopic removal under general or local anaesthesia. The side of ear and nose FB to hand dominance was significant (p<0.05).**

**Conclusion: ENT FB are more common in the ear and nose in children; not witnessed, located in the oropharynx and occurred at home and during playtime. Organic FB and fish bones were common among adults in the Malaysian population. Aerodigestive FBs are associated with hospitalization, complications, requiring antibiotics and endoscopic intervention.**

**KEYWORDS:**
*Choking; adult; children; aspiration; epidemiology*

## INTRODUCTION

Foreign body (FB) within ear, nose and throat (ENT) is a common presentation to outpatient and inpatient units with significant morbidity and mortality among children and adults. Chiun et al (1) reported that there were a whopping 1084 cases of FB with 825 outpatients and 259 inpatients over a five-year span at the Sarawak General Hospital.[1]

Shaariyah et al (2) reported seventy cases of FB requiring endoscopic intervention in the upper gastrointestinal tract at a tertiary centre in Kuala Lumpur, Malaysia over 9.5 years; an average of seven per annum.[2] FB among children is often more common compared to adults with a majority of less than five years old.[1] A 10-year data of ingested FBs in the United States showed children (90.5%) with the mean age of three were more suscepible to FB ingestion than adults.[3]

Although ear and nose FB often results in local symptoms, aerodigestive FB carry the highest liability in suffocation and death up to three years old with a 10% mortality from 50 000 incidents up to 14 years of age in the European Union (EU).[4] Europe has seen an advancement with the European registry of foreign body registries i.e. Susy safe project, a multinational pan-European systematic study accessible to the public for accurate data collection and appraisal. It acts as a surveillance system and risk profiles non- food related FB.[5]

ENT FB presents in a plethora of size, shape, consistency and material. They can be divided into organic or inorganic. Food objects are more common than non-food objects, while

*This article was accepted: 14 July 2026*
*Corresponding Author: Hardip Gendeh*
*Email: hardip88@hotmail.com*

causative factor among children is the lack of supervision.[5] In Korea, ENT FB incidence among children were commoner in the throat (59.2%), followed by nose (33.4%) and ear (7.4%).[6] A hallmark finding from Susy safe would be the discovery of elliptical FB being common in the younger age groups.[5] FB are peculiar to the orifices they are foundered. Studies from EU and Asia (India, Thailand, Malaysia) concur that spherical objects such as pearls, marbles and coins are predominant in the throat owing to their larger diameter that prevents insertion into the nose and ears. Seeds, nuts and beads are common in ears and nose.[1,5,7-8] Malaysia lacks local data that quantifies FB in dimensions. In a nutshell, FB ingestion are preventable and is of paramount importance.

It is hypothesized that the risk ENT FB are inorganic and more common in the ear and nose among children; while organic FBs are commoner among adults. The general objective of this research study is firstly to determine the incidence of ENT FBs (paediatric and adult) in a tertiary center in Malaysia; secondly to determine the association between the type of FB and factors contributing to its occurrence (largest dimension, volume, witnessed); thirdly to determine the treatment required (inpatient, outpatient, surgical intervention, antibiotics and analgesia) and association between hand dominance with ENT FBs.

## MATERIALS AND METHODS

*Study Design*

This was a prospective cross-sectional observational study on ENT FB among children and adults presenting as an inpatient and outpatient to the Department of otorhinolaryngology, head and neck surgery at Hospital Canselor Tuanku Muhriz (HCTM), Universiti Kebangsaan Malaysia (UKM); a tertiary centre in Kuala Lumpur, Malaysia. The study period from a selected population of patients with ENT FB was over 12 months from 1st of February 2017 to 31st January 2018. The study was approved by the research ethics committee of the faculty of medicine UKM (FF-2017-060). The STROBE recommendations for observational studies were adhered to.[9]

*Bias*

A proforma was prepared and details of patients (and guardians) were recorded during consultation to reduce potential bias after obtaining an informed consent. A standardised ruler on the proforma was used to measure FB dimensions. Three measurements were taken for every dimension. Missing data within the proforma was filled up via telephone call or on outpatient follow-up. The departmental census was checked to ensure FB cases were not missed.

*Participants*

Inclusion criteria involved all children below eighteen years (<18) which falls into the paediatric population of Malaysia.10 Adults are patients with ages eighteen and above (≥18). All cases are seen by an ENT doctor (specialist and/or medical officer) either via on-call referrals, in hospital referrals or outpatients. This included FB dislodged in the lower airways (trachea, bronchus and bronchiole) and upper gastrointestinal (GI) tract (oesophagus). Exclusion criteria included FB dislodged in non-ENT orifices such as the stomach and beyond with no other ENT FBs.

*Outcome Measures*

Organic FBs are defined as objects derived from parts of organs of living (or previously lived) organisms such as animals, plants or fungi. Inorganic FBs are derived from non-living products such as metals or plastic. They were common in the ear and nose.

The incidence of ENT foreign body was calculated using the following formula

$$\text{Incidence of FB: } \frac{(A + B + C)}{\text{Total number of new ENT cases during the period}}$$

whereby A: number of ear FB; B: number of nose FB; C: number of throat FB

The Statistical Package for the Social Sciences (SPSS) version 19 (SPSS Inc., Chicago Illinois) was used for statistical analyses and calculations. Depending on their sample size distribution, the difference between two categorical groups were analyzed using Chi-square test for large sample size whereas Fisher Exact test for smaller sample size. For scale variables, all the variables were assumed on normality assumption or equality of continuous probability distribution. Noting with the normality assumption, the difference between two groups categorical with scale variable was analyzed using respective parametric statistical test, Independent Sample T test. The difference between more than two groups, categorical with scale variable was analysed using Analysis of Variance (ANOVA) test. All significance analysis was considered 95% confidence level or 5% level of statistical significance.

## RESULTS

*Incidence and epidemiology of FBs*

The total outpatients and on-call referrals to ENT was 4374 patients. ENT FB seen during the same period was 153 patients. Therefore, the incidence of FB was 3.5%. A total of 82 (53.6%) patients had organic foreign body within the ENT region. They are more common within the throat. Majority of the organic FB were fish bones (47) followed by cotton (12) and tick (4). Mackerel (14) was the most popular fish bone organic foreign body among the adults, followed by red snapper (8) and tilapia (6). Seventy-one (46.4%) patients had in organic FB within the ENT region. Majority of non-organic FB were derived from manufactured plastic material (34) followed by metal (8) and graphite (3). Results were summarised in Table I. Incidence of organic FB was 1.9% and inorganic FB was 1.6%.

Incidence of ENT FB among children was 1.65% and adults was 1.85%. The mean age was 5.34 and 49.35 years for children and adults respectively. Children less than 5 years-old was one third at 48 (31.3%) (Table IIa). These age groups tend to have FBs in the nose (64.58%) followed by ear (27.08%) and throat (6.25%). Children between 5 and less than 18 have the most FB in the ear (72%). Both young and older adults have experienced throat FBs followed by ear (Table IIb). Among all children, 8 (11.6%) were disabled with

**Table I: Types of Organic and Inorganic FB**

| | Organic (n, %) 82 (53.6%) | In-Organic (n, %) 71 (46.4%) |
|---|---|---|
| Type of FB | | |
| Fish bone | 47 (57.3%) | - |
| Cotton | 12 (14.6%) | - |
| Tick | 4 (4.9%) | - |
| Plastic | - | 34 (47.9) |
| Metal | - | 8 (11.3%) |
| Graphite | - | 3 (42.3%) |
| Others | 19 (23.1%) | 26 (36.6%) |
| Fish Bones (Malay Name) | | |
| Cod | 1 (2.1%) | - |
| Catfish | 1 (2.1%) | - |
| Mackerel | 14 (29.8%) | - |
| Pegasius (Patin) | 2 (4.3%) | - |
| Pomphret (Bawal) | 2 (4.3%) | - |
| Red Snapper | 8 (17.0%) | - |
| Sardines | 2 (4.3%) | - |
| Scad (Selar) | 4 (8.5%) | - |
| Seabass (Kurau) | 1 (2.1%) | - |
| Snakehead (Haruan) | 1 (2.1%) | - |
| Threadfin (Terisik) | 1 (2.1%) | - |
| Tilapia | 6 (12.8%) | - |
| Tolishad (Terubok) | 1 (2.1%) | - |
| Torpedo Scad (Cencaru) | 3 (6.4%) | - |

**Table II: Percentage of FB in accordance to gender and age and FB location in accordance to age**

a. Percentage of FB in accordance to gender and age

| | Female | | Male | | Total | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| ≤ 5 years | 23 | 35.94 | 25 | 28.09 | 48 | 31.37 |
| 6 - 18 years | 9 | 14.06 | 16 | 17.98 | 25 | 16.34 |
| 19 - 55 years | 25 | 39.06 | 24 | 26.97 | 49 | 32.03 |
| > 55 years | 7 | 10.94 | 24 | 26.97 | 31 | 20.26 |
| Total | 64 | 100.00 | 89 | 100.00 | 153 | 100.00 |

p-value is 0.058 which is insignificant (p <0.05)

b. Percentage of FB location in accordance to age

| | <5 years | | 5- 18 years | | 19 - 55 years | | > 55 years | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % | N | % |
| Bronchus | 0 | 0.00% | 0 | 0.00% | 1 | 2.04% | 0 | 0.00% | 1 | 0.65% |
| Ear | 13 | 27.08% | 18 | 72.00% | 10 | 20.41% | 8 | 25.81% | 49 | 32.03% |
| Eophagus | 1 | 2.08% | 0 | 0.00% | 2 | 4.08% | 6 | 19.35% | 9 | 5.88% |
| Nose | 31 | 64.58% | 4 | 16.00% | 5 | 10.20% | 0 | 0.00% | 40 | 26.14% |
| Throat | 3 | 6.25% | 3 | 12.00% | 31 | 32.28% | 17 | 54.84% | 54 | 35.30% |

**Table III: Mean volume of FB according the age and site**

| | FB Location | | | | |
|---|---|---|---|---|---|
| Age range (years) | Trachea/ Bronchus ($mm^3$) | Ear ($mm^3$) | Oesophagus ($mm^3$) | Nose ($mm^3$) | Throat ($mm^3$) |
| <5 0 | 49.68 | 570.2 | 261.77 | 171.53 | |
| 5 to <12 | 0 | 29.43 | 0 | 120.95 | 36.91 |
| 12 to <18 | 0 | 39.8 | 0 | 0 | 20.42 |
| ≥18 | 502.65 | 211.03 | 6644.59 | 56.78 | 242.45 |

**Table IV: FB treated as outpatients**

| | Age Group | | p-value |
|---|---|---|---|
| | child (<18 years ) Count (%) | adult (≥18 years) Count (%) | |
| No of Patients | 61 (86.9%) | 69 (83.1%) | |
| Antibiotics | | | |
| yes | 12 (19.67%) | 22 (31.88%) | 0.400 |
| no | 49 (80.33) | 47 (68.11%) | |
| Antibiotic Name (route) | | | |
| Co-amoxiclav (oral) | 6 (50%) | 15 (71.4%) | 0.585 |
| Cefuroxime (oral) | 0 (0%) | 1 (4.76%) | |
| Maxitrol (ear drops) | 1 (8.33%) | 0 (0%) | |
| Ofloxacin (ear drops) | 2 (16.67%) | 3 (14.29%) | |
| Sofradex (ear drops) | 3 (25%) | 2 (9.52%) | |
| Analgesia | | | |
| yes | 10 (16.39%) | 24 (34.78%) | *0.013 |
| no | 51 (83.61%) | 45 (65.22%) | |
| Medical/ Sick Leave | | | |
| yes | 1 (1.63%) | 3 (4.34%) | 0.623 |
| no | 60 (98.37%) | 66 (95.66%) | |

*p-value <0.05 is considered significant

five had cognitive impairment such as autism, attention deficit hyperactivity disorder (ADHD) and speech disorder. Three were of a physical impairment with one adult having significant visual deficit and two children with significant hearing deficits. Among the children 18 (26.1%) had organic ENT FB while 51 (73.95) had inorganic ENT FB. 8 (11.6%) were hospitalised and 61 (88.4%) treated as outpatient.

In the adult group, only 3 (3.6%) were disabled. Among the adults, organic FB amounted to 64 (77.1%) and inorganic 19 (22.9%). 13 (15.7%) were hospitalised and 70 (84.3%) were treated as outpatients. Overall, the location with the most FB among children and adults are the throat (and base of tongue) at 35.3% followed by ear (32.03%) and nose (26.14%), see Figure 1a.

*Factors in relation to ENT FB*

The largest of the 3 measured dimensions and mean values were taken based on ages for ear, nose and throat respectively (Figure 1b). FB within the bronchus was only reported among adults with a mean of 12mm of the largest dimension. Ear FB were within 4 to 5.77mm among children and 7.97mm among adults. Oesophageal FB among children had the largest diameter of 22mm, almost half of that of adults at 38.94mm. Nasal FBs had a decreasing trend with age, contrary to throat FBs.

Nasal and throat FBs were comparable in volume with mean of 217.48mm3 and 220.18 $mm^3$ respectively. Ear FB volumes were almost half with mean of 101.93$mm^3$. However, throat FB volumes had a bigger standard deviation of 1341.59 indicating a larger spread. There was no significant difference between ear, nose and throat FB volumes. Ear and nose FB volumes for children became smaller with increasing age (Table III).

A third, 23 (33.3%) of FB incidents among children were witnessed. Parents were the highest witness at 13 (56.52%) followed by siblings 5 (7.2%) and caretakers 3 (4.3%). Sixteen (69.5%) among witnessed events were adults. Home (either parents or caretakers' property) had the highest occurrence of FB insertion at 91.3% followed by school at 4.3%. One child (1.4%) accidently ingested a FB while she was in a moving vehicle. More than half had FB incidents during their play time with 2 (2.9%) occurring when the child was asleep. Eleven (15.9%) of parents or carer were unsure of the child's activity during the FB incident.

The majority of adult associated FB occurred during or as a cause of eating with 63.9%. Eight (9.6%) occurred during ear cleaning with cotton buds and one gentleman (1.2%) had a stone into his ear while washing his car.

*Treatment*

Eight children (13.1%) and 14 adults (16.9%) from a total of 153 patients were hospitalized respectively as a direct cause of the FB incident. Seven (87.5%) children and all adults had FB in the aerodigestive tract. Among the hospitalised, 2(25%) children and 4 (28.6%) adults required either Intensive Care Unit (ICU) or High Dependency Unit (HDU) care. A total of 2 (25%) children and 3 (21.4%) adults required referral to other specialties (respiratory and cardiothoracic and upper gastrointestinal) surgery for tmultidisciplinary input. One child had a complication of hypoxic brain injury as a result of choking on soft food while being fed by his caretaker at a supine position. First aid had failed resulting in cerebral palsy and was discharged home in a dependent state. A total of 5 adults suffered from various complications ranging from lung collapse, laryngeal oedema, pneumonia, oesophageal perforation and oral ulcers/ laceration. No deaths were reported secondary to FB.

The remaining patients 61 (86.9%) and 69 (83.1%) of children and adults respectively were treated and managed as an outpatient (Table IV). Twelve (19.67%) children and 22 (31.88%) of adults were prescribed oral antibiotics to be completed at home. Co-amoxiclav was the highest prescribed oral antibiotics among 6 (50%) children and 15 (71.4%) adults. Ofloxacin (Tarivid) and Dexamethasone/ Framycethin/ Gramicidin (Sofradex) topical ear drops were

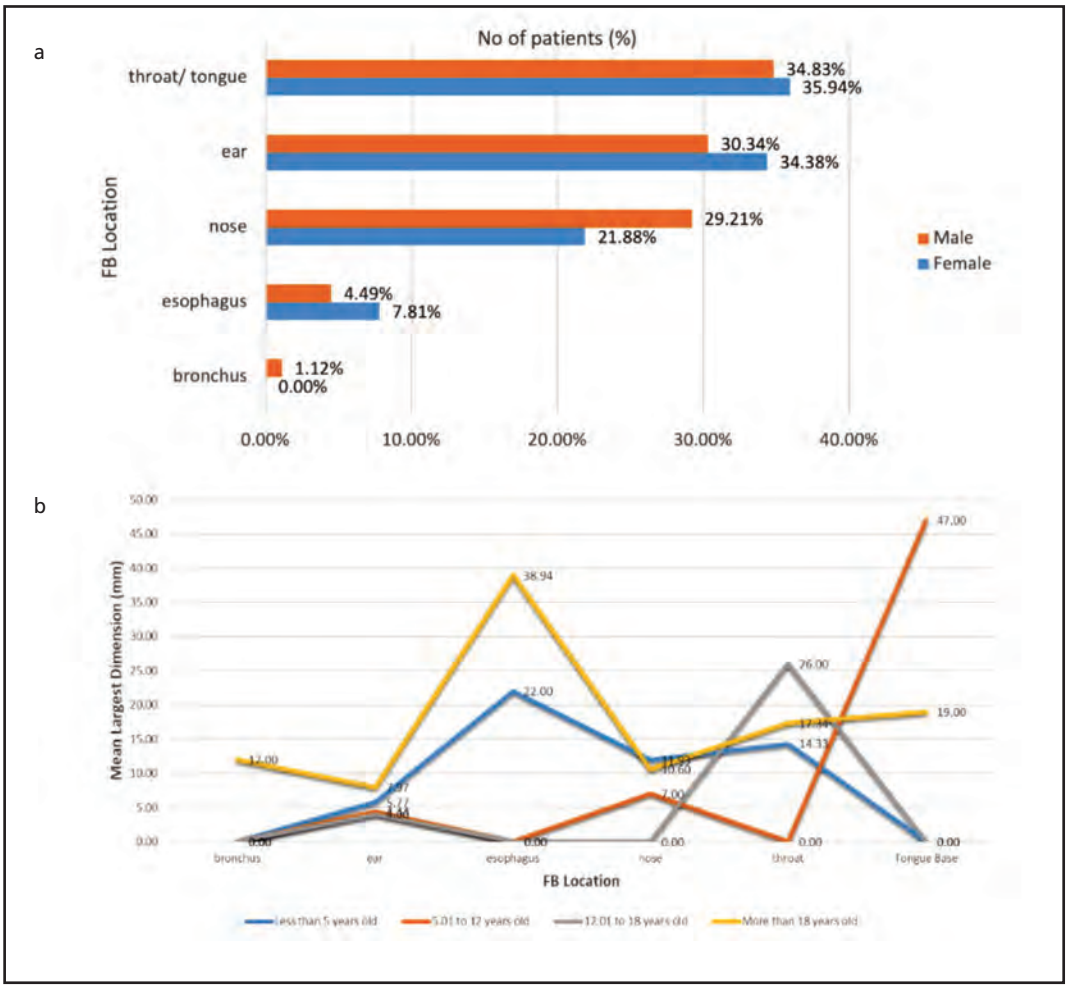



**Fig. 1:** a. FB location in association with gender; b. Mean largest dimension of FB in relation to age in the ear, nose, throat, oesophagus, bronchus and tongue.

prescribed among five children and adults respectively. Significantly more adults (34.78%) required analgesia compared to children (16.39%). Only one child and 3 (4.34%) adults required sick leave for the day due to their outpatient visit.

A total of 57 (37.25%) patients required endoscopic treatment either as an office-based procedure or in the operation theatre. For the endoscopic procedure, only three had a flexible endoscopy in the form of Flexible-Naso-Pharyngo-Laryngo-Scopy (FNPLS) without a working channel strictly used to visualise a FB. Two were for a fish bone removal and one was to visualised an ingested tobacco ball which subsequently required an upper gastroscopy. Majority of children, 55 (76.4%) did not have endoscopic treatment. This is in reversal to adults with 54 (66.7%) requiring endoscopic treatment which was significant.

Thirty-two (20.9%) patients had complications as a direct result of their FB. Ten were hospitalised and 22 managed as an out- patient. Common complications were bleeding (including epistaxis), inflammation, mucosal ulceration/laceration, aspiration and tissue necrosis. One in-patient required a tracheostomy for his laryngeal oedema and failure of extubation.

*Hand Dominance and the presence of ENT FB*

Majority of FB within the right ear or nose (94.34%) were from the right-hand dominant patients with only 5.66% being left hand dominant. On the other hand, FB within the left ear or nose were common also among right hand dominant patients at 78.26% compared to 21.7% from those with left hand dominance. The difference is statistically significant but does not correspond to site.

## DISCUSSION

This study provides the first comprehensive annual incidence rate for ENT FBs in a tertiary center in Peninsular Malaysia. ENT FBs are common in HCTM with an annual incidence of 3.5% (3 to 4 cases of FBs in every 100 ENT consultations). The incidences among children and adults are similar at 1.65% and 1.85%; comparable to the European incidence of 2%.[7] Organic and inorganic FBs for this study had no significant difference. Organic FBs often occur in the throat, esophagus, trachea and bronchus as it is often food placed into the mouth. The biggest contributors to inorganic FBs were the nose and ear. Children accounted for the highest rate of inorganic FBs into their aerodigestive tract. It is their innate and curious nature that provokes non-edible objects insertion into their ENT; having FBs in their mouth while playing and crying; and lacking adequate molars for chewing food.[11]

Adults had a higher incidence of organic FBs due to fish bones. Each Malaysian consumes on average 45-55kgs of fish annually, above the 20kg per capita of world average; with 33% consuming fish daily and 78% twice weekly.[11-12] Malaysian consumption is on par with her eastern neighbour, Japan (64.7kg/person/year).[11] Popular fishes were mackerel followed by seabass and grouper which is similar to our data.[11-12] However, there was little data and literature on the method of preparation (fried or steamed) as fried fish may have a lower incidence due to its crispier nature-allowing bones to be chewed easily compared to steamed preparation. Future work should compare the risks of fish bone FBs from stewed versus fried as it's a norm here for fish to be cooked as a whole with its bones intact rather than boneless fillets.[13]

Chevalier Jackson from US pioneered the modern-day FB study with 3200 objects between 1920 and 1932. The data derived from the Small Parts Test Fixture (SPTF) in the US in the 1970s to guide the industry. It is a cylinder with a superior diameter of 1.75 inches (44.45mm) representing the mouth opening and lower depth of 1.50—2.25 inches (38.1mm to 57.15mm) emulating the pharynx.[14-15] Similarly, across in Europe the Safety of Toys Specifications for Mechanical and Physical Properties has advised on a similar cylinder test to reduce the risk of choking in children less than 3 years old. Its dimensions were 31.7 mm on the superior diameter (largest opening of the anterior jaw in a child less than 3 years old) with a lower depth of 51.7mm and 25.4mm. Objects larger than the cylinder were deemed safe for children of ages 3 and above.[16] However, it is without its controversies. Milkovich et al (17) suggested for an open-bottom gauge with a 38.1mm diameter for non-spherical objects and 44.5mm for spherical objects as 23% of 93 incidents of aerodigestive FB failed to be detected by the existing cylinder test.[17] Asia or South East Asia have yet to have a similar guide for the industry to date. This UKM data showed that the mean largest dimension of throat and esophagus FB for children below 5 were 14.33 and 22mm, which were smaller than Chevalier's, the European data and Malkovich's data.

Aerodigestive FB have been shown to be common in children ages less than 4 years old. The Susy Safe registry looked into 16 878 FBs among children with a hallmark finding of ENT FB of the aerodigestive system are more common in ages less than 3 years old with oesophageal FB being more common in less than 1 years old.[5] In order to determine what length of object is suitable for children, we first must revisit the aerodigestive anatomy. A new-born vocal cord has a length of 2.5 – 3mm, increases in size until the age of 20 whereby the vocal cord length of an adult male is 17-21mm and female 11-15mm.[18-19] Therefore, the largest mean dimension of throat FB among children less than 5 years old was 14.3mm and adults was 17.34mm, too large to pass through the laryngeal inlet. The paediatric larynx is conical shape, matures with age with formation of ligaments from the age of 4 to take up a more cylindrical shape in adulthood. The paediatric epiglottis is softer and pliable, comes into contact with the tongue base as it sits higher within the neck.[20] This allows an easier excess of FB into the larynx and trachea.

On the other hand, the subglottis at approximately 4mm is the narrowest in the paediatric population compared to adults.[19] Therefore, to quantify the safe dimensions of aerodigestive FB based on the vocal cord length alone is inadequate as it continues to grow. Ideally, an object ought to be large enough to not bypass the oropharynx itself. Gag reflex will allow the child to cough and expel the object, preventing choking. Therefore, the cylindrical method of measuring a safe object is ideal for the industry for now. FB accidents among children occur when left alone without supervision. However, among the third with supervision, to our surprise, almost 70% were under direct adult supervision. There were two probabilities-either the adults were distracted with chores, or were not aware of the risk associated with FBs. Beads were one of the highest inorganic FB among children, probably due to its decorative presence on textiles and Malaysian traditional clothing.

Given that the majority of adult FB were organic in nature, it is of no surprise that adult FB were non-occupational hazards and occurred in the domestic setting. One patient swallowed a bottle cap and another an aluminium foil housing paracetamol tablets. Since homemakers, retirees and unemployed adults make up the largest numbers, like children, adult FB does have a susceptibility to occur at home. There was no significant change in incidence of ENT FBs during the COVID-19 pandemic lock-downs compared to pre-pandemic times indicating that home poses a significant risk.[21] Oesophageal FB among Malaysian and Asian adults were due to fish bones unlike the western world which was primarily due to meat products.[22-23] Oropharyngeal FB among adults were commoner among the younger age group as compared to oesophageal FB which was predominant in the older age group.[23] It is postulated that ageing related decadence of swallowing physiology is a contributing factor to the higher incidence of oesophageal FB among the older population.[23]

More adults required analgesia due to odynophagia caused by fish bone ingestion. Ear FB may be associated with otitis externa from external canal trauma or localised infection with *Pseudomonas aeruginosa, Staphylococcus aureus,* Hemophilus influenza that were sensitive to oflaxin and Framycethin/ Gramicidin (Sofradex) topical antibiotics.[24-26] Systemic co-amoxiclav is a Beta (β) Lactamase inhibitor consisting of amoxicillin, a β-lactam antibiotic, and potassium clavulanate is a broad-spectrum antibiotic for upper respiratory tract and infections from oral bacterial flora.[27] Metronidazole is occasionally added for aerodigestive FB for anaerobes cover. Esophageal mucosal penetration and perforation can occur in more than 50% of cases, therefore prophylactic antibiotics in such cases should be considered even in the absence of mediastinitis.[22,28]

Although less than half of overall patients required an endoscopic treatment (otoendoscopy, nasoendoscopy, laryngoscopy, tracheoscopy, bronchoscopy, oesophagoscopy), majority of adults required an endoscopic procedure. Adults presented with fish bone, if involving the lower segment of the oropharynx (inferior poles of tonsils and base of tongue), larygopharynx or oesophagus, often benefitted from laryngoscopy (diagnostic and therapeutic).

Right handedness has been said to be primitive to feeding to the human race as it has been shown that apes would always prefer to reach out for food with their right hands.[29-30] Hand dominance may be handy in predicting which nostril or ear to look into if a FB incident was not witnessed and when the child is unreliable for a history or decide on which hand to apply mittens on for recurrent offenders. However, this remains a postulation as the evidence behind this is scarce. This study and others have shown that motor laterality or hand dominance is not a predictor of the laterality of ENT FB insertion.[31]

Better education on the awareness and prevention of ENT FB among children is required. A multidisciplinary and multicenter audit on ENT FB should be conducted nationwide for a larger population based on data on the volume of aero digestive FB and risk of choking among children. This is to guide the local industry on responsible determination of safe ages for toys and food.[32] FBs removed by the paediatric and emergency specialties were not included as it was not a multidisciplinary study potentially underscoring the overall incidence. Volume calculations for FB may be inaccurate especially for fish bones which were assumed to be cylindrical for ease of measurements. Fish bones may take a conical or tapered cylinder shape which may overestimate its volume if assumed to be a cylinder.[33] A larger sample is required to explore hand dominance and laterality of ENT FBs.

## CONCLUSION

ENT FBs have a high overall incidence of 3.5% with children being 1.65% and adults 1.85%; commonly inorganic in children and organic (fish bone) among adults. FBs among children were not witnessed, located in the oropharynx and occurred at home and during playtime. FBs in adults were predominantly fish bones within the aerodigestive tract, non-occupational and associated with more pain requiring analgesia. Aerodigestive FBs were associated with hospitalization, complications, requiring antibiotics and endoscopic intervention. Hand dominance is not a reliable predictor for laterality of ear and nose FBs. This calls for a local regional policy for choking hazards for toys and food among children based on local data on FB dimensions and better public education as FB injuries are preventable.

## ACKNOWLEDGEMENTS

The authors would like to thank Mr Neoh Siang Gee for his expertise in the statistical analysis.

## FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## CONFLICT OF INTEREST

The authors declared that there are no direct or indirect financial interests or conflict of interest for disclosure.

## REFERENCES

1. Chiun KC, Tang IP, Tan TY, Jong DE. Review of ear, nose and throat foreign bodies in Sarawak General Hospital. A five year experience. Med J Malaysia 2012; 67(1): 17-20
2. Shaariyah MM, BS Goh. Retrospective Review of Surgical Management of Foreign Body Ingestion. Med J Malaysia 2009; 64(4): 307-10.
3. Lad H, Durant S, Yan K, Kaye R. Trends and Outcomes of Foreign-Body Ingestion: National Emergency Department Data Over a Decade. Laryngoscope 2026; 136(7): 2938- 46
4. RPA, Inedibles in Food Product Packaging Prepared for STOA, European Parliament, 2003 [Cited Feb 2026]. Available from: https://easac.eu/fileadmin/PDF_s/reports_statements/Review-1.pdf.
5. The Susy Safe Working Group. The Susy Safe project overview after the first four years of activity. Int J Pediatr Otorhinolaryngol 2012; 76(1):3-11.
6. Kwon B, Choi Y, Kim SK, Hong SJ, Kim YB, Hong SM. Ear, Nose, and Throat Foreign Bodies in Children: A Retrospective Study. Children (Basel) 2022; 49(1):63.
7. Gendeh BS, Gendeh HS, Purnima S, Comoretto RI, Gregori D, Gulati A. Inhaled Foreign Body Impaction: A Review of Literature in Malaysian Children. Indian J Pediatr 2019; 86(1):20-4.
8. Ray R, Dutta M, Mukherjee M. Foreign Body in Ear, Nose and Throat: Experience in a TertiaryHospital. Indian J Otolaryngol Head Neck Surg 2014; 66(1):13-6.
9. Cuschieri S. The STROBE guidelines. Saudi J Anaesth 2019;13(1):31-4.
10. Rovin JD, Rodgers BM. Pediatric Foreign Body Aspiration. Pediatr Rev 2000; 21(3); 86-90.
11. Fisheries country Profile: Malaysia 2025. Southeast Asian Fisheries Development Center. [Cited July 2026]. Available from: https://www.seafdec.org/fisheries-country-profile-malaysia/.
12. Ahmad NI, Wan Mahiyuddin WR, Tengku Mohamad TR, Ling CY, Daud SF, Che Hussein N et al. Fish consumption pattern among adults of different ethnics in Peninsular Malaysia. Food Nutr Res 2016; 60: 32697.
13. Shishido T, Suzuki J, Ikeda R, Kobayashi Y, Katori Y. Characteristics of fish-bone foreign bodies in the upper aero-digestive tract: The importance of identifying the species of fish. PLoS One 2021; 16(8): e0255947.
14. Reilly BK, Stool D, Chen X, Rider G, Stool SE, Reilly JS. Foreign body injury in children in the twentieth century: a modern comparison to the Jackson collection. Int J Pediatr Otorhinolaryngol 2003; 67(1): 171-4.
15. Reilly JS, Cook SP, Stool D, RiderG. Prevention and management of foreign body injuries in childhood. Pediatr Clin North Am 1996; 43(6): 1403-11.
16. International Organization for Standardization (ISO). ISO 8124-1:2022 Safety of Toys. Part 1: Safety Aspects Related to Mechanical and Physical Properties. [Cited July 2026]. Available from: https://www.iso.org/standard/80767.html.
17. Milkovich SM, Altkorn R, Chen X, Reilly JS, Stool D, Tao L et al. Development of the small parts cylinder: lessons learned. Laryngoscope 2008; 118(11): 2082-6.
18. Sapienza CM, Ruddy BH, Baker S. Laryngeal structure and function in the pediatric larynx: clinical applications. Lang Speech Hear Serv Sch 2004; 35(4): 299-307.
19. Hirano M, Kurita S, Nakashima T. Growth development and aging of the vocal folds. In: Bless DM, Abbs JH, Editors. Vocal fold physiology: Contemporary research and clinical issues. College-HillPress; 1983: 22-43.
20. Slyvian E. 1983. Paediatric Otorhinolaryngology. Volume 2. Philadelphia. WB Saunders.
21. Garg J, De Castro F, Puttasidiah P. Ear, Nose, and Throat Foreign Bodies in the Paediatric Population: Did the COVID-19 Lockdown Change Anything? Cureus. 2022; 14(8): e27892.
22. Kim HU. Oroesophageal Fish Bone Foreign Body. Clin Endosc 2016; 49(4): 318-26.

23. Kim JP, Kwon OJ, Shim HS, Kim RB, Kim JH, Woo SH. Analysis of Clinical Feature and Management of Fish Bone Ingestion of Upper Gastrointestinal Tract. Clin Exp Otorhinolaryngol 2015; 8(3): 261-7.
24. Khosravi Y, Ling LC, Loke MF, Shailendra S, Prepageran N, Vadivelu J. Determination of the biofilm formation capacity of bacterial pathogens associated with otorhinolaryngologic disease in the Malaysian population. Eur Arch Otorhinolaryngol 2014; 271(5): 1227-33.
25. Jayakar R, Sanders J, Jones E. A study of acute otitis externa at Wellington Hospital, 2007–2011. Australas Med J 2014; 7(10): 392-9.
26. Kullar P, Yates PD. Infections and foreign bodies in ENT. Surgery 2012; 30(11): 590-6.
27. Todd PA, Benfield P. Amoxicillin/clavulanic acid. An update of its antibacterial activity, pharmacokinetic properties and therapeutic use. Drugs 1990; 39(2): 264-307.
28. Kim HU, Song HJ. Clinical characteristics of an esophageal fish bone foreign body from Chromis notata. J Korean Med Sci 2012; 27(10): 1208–14.
29. MacNeilage PF, Rogers LJ, Vallortigara G. Origins of the Left & Right Brain. Sci Am 2009; 301(1): 60-7.
30. Hopkins WD, Cantalupo C. Handedness in chimpanzees (Pan troglodytes) is associated with asymmetries of the primary motor cortex but not with homologous language areas. Behav Neurosci. 2004;118(6):1176-83.
31. Peridis S, Athanasopoulos I, Salamoura M, Parpounas K, Koudoumnakis E, Economides J. Foreign bodies of the ear and nose in children and its correlation with right or left handed children. Int J Pediatr Otorhinolaryngol. 2009; 73(2): 205-8.
32. Gendeh HS, Gendeh BS. Perspective Chapter: Classification and Complications of Aerodigestive Button Batteries and Magnets. In: Gendeh BS, Editor. Updates on Foreign Body in ENT Practice. IntechOpen; 2024: 33-45.
33. Zwillinger D. 2011. CRC Standard Mathematical Tables and Formulae, 32nd Edition. CRC Press, Boca Raton.

ORIGINAL ARTICLE

# Interobserver and intra-observer agreement among radiographers in assessing the quality of chest radiograph

**Dwi Rochmayanti, MEng[1,2], Kusworo Adi, Dr.[2], Catur Edi Widodo, Dr.[2], Akhmad Haris Sulistiyadi, MKes[1], Siti Daryati, MSc[1]**

[1]Study Program of Information System, Postgraduate School, Diponegoro University, Semarang, Indonesia, [2]Department of Radiodiagnostic and Radiotherapy Technics, Poltekkes Kemenkes Semarang, Semarang, Indonesia

## ABSTRACT

**Introduction: Chest radiography is a commonly performed examination for screening, clinical assessment, and pre-intervention evaluation. Image quality plays an important role in supporting diagnostic interpretation. After image acquisition, radiographers decide whether the image should be accepted or repeated. Variation in these decisions may affect patient radiation exposure and radiology workflow. This study aimed to evaluate variation and agreement among radiographers in accepting or rejecting chest radiographs.**

**Materials and Methods: This cross-sectional study involved 91 certified radiographers in Indonesia. Thirty de-identified chest radiographs representing technical-quality categories were selected by an expert panel, and 12 duplicate images were added to assess intra-observer consistency. The resulting 42 images were presented in random order. The acceptance and rejection criteria were classified into 8 factors: accepted, artifact, blurring, mispositioning, incorrect body part, body part cut-off, exposure failure, and under/over exposure. Data were analysed using Cohen's kappa for duplicated image pairs and Fleiss' kappa for inter-observer agreement.**

**Results: There were radiographer's perception variations in accepting or rejecting X-ray chest images. Intra-observer agreement for duplicated image pairs ranged from κ=0.027 to κ=0.727, with a simple mean Cohen's kappa of κ=0.525, indicating moderate agreement. Overall inter-observer agreement across the 42 images was fair (Fleiss' κ=0.337). Category-specific Fleiss' kappa values were highest for artifact-related rejection (κ=0.474) and image acceptance (κ=0.436), and lowest for blurring (κ=0.068), exposure failure (κ=0.076), incorrect body part (κ=0.107), and incorrect positioning (κ=0.173).**

**Conclusion: Radiographers showed moderate intra-observer consistency but only fair inter-observer agreement when evaluating chest radiograph quality. The findings demonstrate variation in accepting or rejecting chest X-ray image. Collaboration between radiographers and radiologists is recommended to align evaluation standards.**

**KEYWORDS:**
*Chest radiography; observer variation; observer agreement; radiography quality assurance*

## INTRODUCTION

Chest radiography is commonly used to evaluate patient's condition in general, screening and pre-intervention assessments such as surgeries and other medical procedures.[1-2] High quality image that meets technical quality standards is required to provide accurate diagnostic value.[3] Patient movement, mispositioning, and image receptor-related artifacts can result in image rejection.[4] Repeated radiographic examinations lead to increased radiation exposure and additional economic costs.[2,5] To enhance image quality, radiographers have to adopt a proactive role, not only during image acquisition but throughout the entire imaging process.[6] Radiographers control the image acquisition process and the factors that determine final image quality. Therefore, radiographer-based strategies are essential to raise quality awareness, improve image outcomes, and reduce rejection rates.[7]

Diagnostic inaccuracies in radiology are estimated to occur in approximately 30% of image interpretations. Studies have shown that suboptimal image quality is correlated with false-positive and false-negative interpretations.[6] Quality assurance becomes a priority to improve client satisfaction and the sustainability of healthcare organizations8. An important aspect of radiology quality management is a systematic approach to ensuring high-quality imaging outcomes, emphasizing processes, protocols, and performance improvements. This approach includes minimizing image rejection and repetition. Radiologists and radiographers play a significant role in minimizing rejected image or repeated examination. However, subjectivity determines the justification for rejection or repetition. These decisions depend to the individual perception, leading to potential bias and inefficiencies due to inconsistent implementation.[2] As reported, image quality assessment is subjective and significantly varies among radiographers.[3] This study aimed to identify the perceptions profile for accepting or rejecting Chest X-ray images among radiographers.

## MATERIALS AND METHODS

*Study Design and Data Collection*

This cross-sectional observer-agreement study involved 91 certified radiographers from 53 accredited hospitals and 2 clinics in Indonesia that applied radiology quality-control programme. Fifty-five radiographers (60.4%) were from

*This article was accepted: 09 July 2026*
*Corresponding Author: Dwi Rochmayanti*
*Email: dwirochmayanti@poltekkes-smg.ac.id*

**Table I: Participant's characteristic**

| No | Characteristic | Specification | Number |
|---|---|---|---|
| 1 | Hospital | Full | 77 |
| | Accreditation Level | Main | 9 |
| | | Middle | 4 |
| | | Basic | 1 |
| 2 | Working Experience | ≤5 years | 13 |
| | | > 5 years | 78 |
| 3 | Certified | National Certification | 91 |
| 4 | Involved in QA/QC | Radiography | 91 |

QA= Quality Assurance; QC= Quality Control

**Table II: The acceptance and rejection criteria**

| No | Decision | Rejection Factor | Definition | Number of Images |
|---|---|---|---|---|
| 1 | Accepted | None | Anatomy of interest is visualized with correct position, adequate brightness and contrast within collimation area. The image is free from artifact and un-sharpness. | 5 |
| 2 | Rejected | Incorrect body-part | The body part being visualized is different to the requested body part. | 1 |
| 3 | Rejected | Body-part cut off | Anatomy of interest outside the collimation. | 9 |
| 4 | Rejected | Incorrect positioning | Incorrect patient position, anatomical part position, and under/ over rotation. | 13 |
| 5 | Rejected | Blurring | Un-sharpness due to patient, object movement, and/ or equipment. | 1 |
| 6 | Rejected | Artifact | Visualization undesirable objects or body parts, grid lines, and/ or equipment related defects. | 7 |
| 7 | Rejected | Under/over exposure | Excessive noise due to underexposure or excessive density due to over exposure that reduced contrast. | 5 |
| 8 | Rejected | Exposure failure | Blank or double exposed image. | 1 |

**Table III: Agreement classification**

| Category | Range |
|---|---|
| Poor | <0.00 |
| Slight | 0.00–0.20 |
| Fair0.21–0.40 | |
| Moderate | 0.41–0.60 |
| Substantial | 0.61–0.80 |
| Almost Perfect | >0.80 |

Note: According to Landis and Koch.[20]

**Table IV: Intra-observer consistency for duplicated image pairs**

| Image | Cohen's Kappa (κ) | Category |
|---|---|---|
| 1 – 2 | 0.355 | Fair |
| 3 – 4 | 0.592 | Moderate |
| 7 – 8 | 0.582 | Moderate |
| 9 – 10 | 0.637 | Substantial |
| 12 – 13 | 0.027 | Slight |
| 17 – 18 | 0.494 | Moderate |
| 22 – 23 | 0.498 | Moderate |
| 24 – 25 | 0.653 | Substantial |
| 29 – 30 | 0.518 | Moderate |
| 31 – 32 | 0.489 | Moderate |
| 36 – 37 | 0.727 | Substantial |
| 38 – 39 | 0.727 | Substantial |
| Average | 0,525 | Moderate |

Note: The average is a simple unweighted descriptive mean of the 12 duplicated image-pair kappa values and should not be interpreted as a pooled inferential estimate.

**Table V: Category-specific inter-observer agreement according to accept/reject decision**

| No | Decision | Factor | Fleiss' Kappa (κ) | Category |
|---|---|---|---|---|
| 1 | Accept | None | 0.436 | Moderate |
| 2 | Reject | Incorrect body-part | 0.107 | Slight |
| 3 | Reject | Body-part cut off | 0.363 | Fair |
| 4 | Reject | Incorrect positioning | 0.173 | Slight |
| 5 | Reject | Blurring | 0.068 | Slight |
| 6 | Reject | Artifact | 0.474 | Moderate |
| 7 | Reject | Under/over exposure | 0.204 | Fair |
| 8 | Reject | Exposure failure | 0.076 | Slight |

Note: Category-specific Fleiss' kappa values were calculated as separate one-versus-all binary classifications for each response category.

Central Java Province and 36 (39.6%) were from other regions. Seventy-eight observers (85.7%) had more than five years of work experiences, whereas 13 (14.3%) had five years of work experiences or less. All participants were certified radiographers; however, the survey did not collect exact years of experience, hospital type or level, prior formal training in reject/repeat analysis, or vendor-specific digital radiography experience. The participant's characteristic is described in Table I.

Thirty chest radiographs were purposively selected from a de-identified institutional digital radiography archive. The images were selected by an expert panel comprising two consultant radiologists, three senior quality-control radiographers, and three medical physicists to represent the predefined acceptance and rejection categories listed in Table II. Patient identifiers were removed before the survey. The expert panel assigned a reference technical-quality label to each image for dataset construction, but these labels were not used as a gold standard for accuracy analysis. Disagreements were resolved through consensus discussion. Pathological findings, when present, were not used as selection criteria or outcome variables; observers were instructed to evaluate technical image quality and reject/repeat factors rather than diagnostic findings. Twelve images were duplicated and mixed with the 30 initial images, resulting in 42 images presented to observers in random order. The acceptance and rejection criteria were classified into eight factors, as described in Table II.

*Data Analysis*

The validity of the survey instrument was assessed by the expert panel, yielding a validity index of 0.98. Cohen's kappa was used to assess intra-observer consistency for each duplicated image pair. Fleiss' kappa was used to assess overall inter-observer agreement across all observers and images. Category-specific Fleiss' kappa values were calculated as separate one-versus-all binary classifications for each response category. Agreement strength was interpreted according to the Landis and Koch classification.[20] The average Cohen's kappa reported in Table III is a simple unweighted descriptive mean across duplicated image pairs and was not treated as a pooled inferential estimate.

## RESULTS

Intra-observer agreement was assessed using Cohen's kappa for the 12 duplicated image pairs presented to the same observers. The kappa values ranged from 0.027 to 0.727, indicating varying levels of consistency across image pairs. Most duplicated image pairs showed moderate agreement, while four pairs showed substantial agreement, particularly image pairs 24-25, 9-10, 36-37, and 38-39. The lowest agreement was observed for image pair 12-13 (κ=0.027), indicating slight agreement. The simple unweighted mean Cohen's kappa across the 12 pairs was κ=0.525, which was interpreted descriptively as moderate agreement.

Overall inter-observer agreement across all 42 images was assessed using Fleiss' kappa. The overall value was κ=0.337, indicating fair agreement among the 91 observers. This result reflects agreement in image acceptance or rejection classifications, not the diagnostic accuracy or correctness of the decisions.

Category-specific inter-observer agreement varied according to the response category. The highest Fleiss' kappa values were found for artifact-related rejection (κ=0.474) and image acceptance (κ=0.436), both indicating moderate agreement. Lower agreement was observed for body-part cut-off (κ=0.363) and under/over exposure (κ=0.204), both categorized as fair agreement. The lowest agreement was observed for blurring (κ=0.068), exposure failure (κ=0.076), incorrect body part (κ=0.107), and incorrect positioning (κ=0.173), all categorized as slight agreement.

## DISCUSSION

Chest radiography is a routine examination, but the decision to accept or repeat an image has direct implications for patient exposure, workflow, and quality assurance. Reject or repeat analysis is therefore an important component of radiology quality management because it identifies not only the number of rejected or repeated images but also the technical factors contributing to rejection.

Radiographers are key personnel in radiology quality assurance. After image acquisition, they visually evaluate whether the examination should be accepted or repeated. Accepting a suboptimal image may reduce diagnostic value, while unnecessarily rejecting an acceptable image may expose the patient to avoidable repeat radiation.

***Interpretation of Consistency***

The numerical findings show that radiographers were more consistent with their own repeated assessments than with one another. The simple mean Cohen's kappa for duplicated pairs was moderate (κ=0.525), whereas the overall Fleiss' kappa across all images was fair (κ=0.337). These findings indicate variability in technical-quality judgement and agreement; they do not establish whether individual decisions were correct or incorrect against a gold standard. The category-specific results provide further practical insight. Agreement was higher for artifact-related rejection (κ=0.474) and image acceptance (κ=0.436), but substantially lower for blurring (κ=0.068), exposure failure (κ=0.076), incorrect body part (κ=0.107), and incorrect positioning (κ=0.173). This pattern suggests that more visually obvious findings may be recognized more consistently, whereas positioning, motion, and exposure-related decisions may require clearer operational criteria.

From a clinical quality perspective, inconsistent acceptance or rejection decisions can affect both patient safety and operational efficiency. Unnecessary rejection may lead to avoidable repeat exposure, whereas acceptance of technically suboptimal images may reduce the value of the radiographic examination. Therefore, improving the reliability of radiographic image-quality evaluation remains a practical priority for radiology departments.

***Link to Practice***

The factors with the lowest agreement in this study--incorrect body part, incorrect positioning, blurring, and exposure

failure--identify priority topics for radiographer training and quality assurance activities. Radiography education and continuing professional development programme may benefit from structured image-evaluation exercises, standardized reject/repeat criteria, peer-review sessions, and feedback mechanisms. These activities could reduce interpretive variability, particularly for positioning accuracy, motion blur, and exposure adequacy.

Hospital radiology departments should also consider structured reject/repeat analysis programme. Regular review of rejected images, group discussion, and consensus-building sessions may help align radiographers' perceptions and improve consistency in quality assessment. Standardized and field-relevant rejection categories are essential because users should be able to select clearly defined, actionable, and easily understood reasons for image rejection.[9] Department-wide rejection analysis can support process improvement and help reduce patient radiation doses.[10]

Joint discussions between radiographers and radiologists may also reduce subjectivity in borderline cases. Previous work has shown that radiologists and radiographers may differ in their decisions to keep or reject plain radiographic images, particularly for positioning errors.[11] Consensus discussion can therefore help harmonize acceptance parameters and improve confidence in reject/repeat decisions.[12-13] Rejected or repeated images should be systematically documented, analyzed for underlying causes, and followed by corrective action. The AAPM Task Group Report 305 provides guidance for standardizing vendor-neutral rejection categories, but each department should adapt these categories to its clinical workflow and equipment context.[9]

## LIMITATIONS

Several limitations should be considered when interpreting the findings. First, the study did not employ a definitive gold standard for image acceptance or rejection. Although the images were selected and labelled by an expert panel consisting of radiologists, senior radiographers, and medical physicists, observer judgments were compared with each other rather than with an absolute reference standard. Consequently, the study evaluates observer agreement and variation, not decision accuracy. Second, the participant questionnaire recorded region and broad work-experience category but did not collect exact years of experience, hospital type or level, prior formal training in reject/repeat analysis, or experience with specific digital radiography systems. These unmeasured characteristics may have contributed to variation and should be captured in future studies.

Third, although the study involved radiographers from multiple regions of Indonesia, most participants were from Central Java Province. The findings may therefore not fully represent all clinical settings, equipment standards, or training backgrounds across Indonesia. Fourth, viewing conditions and display devices were not standardized across participants. Differences in monitor resolution, ambient lighting, or image-display settings may have influenced observers' perceptions of image quality. Despite these limitations, the study provides useful evidence of variation in radiographers' agreement when evaluating chest radiograph quality in the Indonesian clinical context.

### *Future Directions*

The observed variability highlights an opportunity to develop automated image-quality assessment systems based on artificial intelligence (AI) and deep learning technologies. Such systems may support, rather than replace, radiographers' technical evaluation. AI-based image-quality assessment systems could assist radiographers by identifying common rejection factors such as positioning errors, exposure inadequacy, motion blur, and artifacts. These systems could provide real-time feedback during image acquisition and may help reduce repeat examinations and patient radiation exposure. AI-supported reject/repeat analysis has been reported to enhance technologist performance and image auditing.[12] Neural network approaches can also predict anatomical cut-off and motion-related errors in thoracic images, supporting radiographer and radiologist decision-making.[14-15]

Future AI research should use large annotated datasets that combine radiographers' perception profiles with expert-validated ground truth labels. This approach would help models learn from real-world clinical decisions while remaining anchored to objective technical-quality standards. Information systems can support radiology departments in maintaining quality standards and monitoring rejection patterns.[17] Imaging protocols should also be optimized during acquisition and post-processing to prevent repeat examinations and reduce unnecessary radiation exposure.[18]

Future studies should use multi-centre datasets with larger and more diverse samples to improve generalisability. Longitudinal studies are also needed to examine how radiographers' decisions change after structured training or quality-improvement interventions. A rigorous quality assurance programme remains fundamental to image quality. Routine acceptance testing, periodic inspections, maintenance evaluations, and annual assessments are needed to support patient safety and diagnostic value.[19] Combining standardized training, improved quality-assurance protocols, and AI-assisted image evaluation may lead to more consistent radiographic quality assessment and safer imaging practice.

## CONCLUSION

This study found moderate intra-observer consistency and fair inter-observer agreement among radiographers when assessing chest radiograph image quality. Agreement was higher for artifact-related rejection and image acceptance, but lower for blurring, exposure failure, incorrect body part, and incorrect positioning. The findings show variation in radiographers' agreement rather than decision accuracy against a gold standard. Collaboration between radiographers and radiologists, standardized reject/repeat criteria, structured training, and AI-assisted decision-support tools may help improve consistency in image-quality assessment.

## ACKNOWLEDGMENTS

We acknowledge the multi-years research fund, granted by Poltekkes Kemenkes Semarang in 2023-2024.

## CONFLICTS OF INTEREST

There are no conflicts of interest to declare.

## ETHICAL APPROVAL

This study was approved by Health Research Ethics Committee of Poltekkes Kemenkes Semarang. Approval Letter No. 0103/EA/KEPK/2024.

## REFERENCES

1. Wambersie A, DeLuca PM, Seltzer SM, editors. Image quality in chest radiography. ICRU Report 70. Bethesda, MD: International Commission on Radiation Units and Measurements; 2003.
2. Rochmayanti D, Adi K, Widodo CE. Repeat analysis program as a quality assurance system for radiology management: causal repeat and challenges. E3S Web Conf. 2023; 448.
3. Kjelle E, Chilanga C. The assessment of image quality and diagnostic value in X-ray images: a survey on radiographers' reasons for rejecting images. Insights Imaging. 2022; 13(1): 1-6.
4. Jones AK, Heintz P, Geiser W, Goldman L, Jerjian K, Martin M, et al. Ongoing quality control in digital radiography: Report of AAPM Imaging Physics Committee Task Group 151. Med Phys. 2015; 42(11): 6658-70.
5. Mesfin Z, Elias K, Melkamu B. Analysis and economic implication of X-ray film reject in Diagnostic Radiology Department of Jimma University Specialized Hospital, Southwest Ethiopia. Ethiop J Health Sci. 2017; 27(4): 421-6.
6. Reiner BI. Hidden costs of poor image quality: a radiologist's perspective. J Am Coll Radiol. 2014; 11(10): 974-8.
7. Tonks A, Jimenez Y, Gray F, Ekpo E. A stake in the game: can radiographer image interpretation improve X-ray quality? A scoping review. Radiography (Lond). 2024; 30(2): 641-50.
8. Papp J. Quality management in the imaging sciences. 6th ed. St Louis: Elsevier; 2019.
9. Little KJ, Reiser I, Apgar BK, Dalal P, Dave JK, Fisher R, et al. AAPM Task Group Report 305: guidance for standardization of vendor-neutral reject analysis in radiography. J Appl Clin Med Phys. 2023; 24(5): e13985.
10. DeMaio DN, Herrmann T, Noble LB, Orth D, Peterson P, Young J, et al. Best practices in digital radiography. Radiol Technol. 2019; 91(2): 198-201.
11. Kjelle E, Schanche AK, Hafskjold L. To keep or reject, that is the question: a survey on radiologists' and radiographers' assessments of plain radiography images. Radiography (Lond). 2021; 27(1): 115-9.
12. Hardy M, Harvey H. Artificial intelligence in diagnostic imaging: impact on the radiography profession. Br J Radiol. 2020; 93(1108): 20190840.
13. Varghese AP, Naik S, Andrabi ASH, Luharia A, Tivaskar S. Enhancing radiological diagnosis: a comprehensive review of image quality assessment and optimization strategies. Cureus. 2024; 16(6); 1-10
14. Whaley JS, Pressman BD, Wilson JR, Bravo L, Sehnert WJ, Foos DH. Investigation of the variability in the assessment of digital chest X-ray image quality. J Digit Imaging. 2013; 26(2): 217-26.
15. Moradi M, Siegel E, Kashyap S, Karargyris A, Wu JT, Saboury B, et al. Artificial intelligence for point-of-care radiograph quality assessment. 2019; 128.
16. Maes F, Robben D, Vandermeulen D, Suetens P. The role of medical image computing and machine learning in healthcare. In: Ranschaert ER, Morozov S, Algra PR, editors. Artificial intelligence in medical imaging. Cham: Springer; 2019. p. 9-23.
17. Minnigh TR, Gallet J. Maintaining quality control using a radiological digital X-ray dashboard. J Digit Imaging. 2009; 22(1): 84-8.
18. Krupinski EA, Williams MB, Andriole K, Strauss KJ, Applegate K, Wyatt M, et al. Digital radiography image quality: image processing and display. J Am Coll Radiol. 2007; 4(6): 389-400.
19. Mahesh M. Essential role of a medical physicist in the radiology department. Radiographics. 2018; 38(5): 1665-71.
20. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977; 33(1): 159-74.

# Determinants of self-care and psychosocial readiness among hypertensive patients: Implications for nursing in low-resource settings

**Ni Putu Ayu Ratna Dewi, M.Kep[1,2], Nursalam, PhD[1], Ni Luh Putu Inca Buntari Agustini, PhD[2], Ni Wayan Sri Wahyuni, M.Kep[3], Komang Ardidhana Nugraha Putra, M.Kep[2]**

[1]Faculty of Nursing, Universitas Airlangga, Surabaya, Indonesia, [2]Faculty of Health, Institute of Technology and Health Bali, Denpasar, Indonesia, [3]Faculty of Health, Universitas Triatma Mulya, Denpasar, Indonesia

**ABSTRACT**

**Introduction: Self-care behaviour, motivation, and self-efficacy represent related but distinct dimensions of hypertension self-management. Previous Indonesian studies have generally examined self-care behaviour as the primary outcome or treated motivation and self-efficacy as its explanatory factors. Evidence describing the outcome-specific associations of sociodemographic and clinical characteristics with these three domains remains limited. This study examined the associations of selected sociodemographic and clinical characteristics with self-care behaviour, motivation, and self-efficacy among adults with hypertension.**

**Materials and Methods: This analytical cross-sectional study included 120 adults with hypertension attending the Gianyar 1 Community Health Centre, Bali, Indonesia, between August and September 2024. Participants were selected from an eligible patient registry using simple random sampling. Self-care behaviour, motivation, and self-efficacy were measured using the validated Indonesian version of the High Blood Pressure Self-Care Profile. Bivariate comparisons were followed by three separate multiple linear regression models.**

**Results: The mean scores were 44.09 (95% confidence interval [CI] 42.44–45.74) for self-care behaviour, 44.64 (95% CI 42.56–46.72) for motivation, and 42.99 (95% CI 41.21–44.78) for self-efficacy. The self-care behaviour model was statistically significant ($R^2$=0.375; adjusted $R^2$=0.304; p<0.001). Higher self-care behaviour scores were observed among participants aged 41–50 years and private-sector employees, whereas lower scores were observed among participants with no formal schooling, junior high school education, and a hypertension duration of 1–5 years. The motivation model was also statistically significant but had lower explanatory value ($R^2$=0.186; adjusted $R^2$=0.094; p=0.028). Participants aged 41–50 years had higher motivation scores, whereas those with junior high school education had lower scores. The overall self-efficacy model was not statistically significant.**

**Conclusion: Associations were observed mainly for self-care behaviour and motivation, whereas the examined characteristics did not collectively explain self-efficacy. These findings support individualised assessment of behavioural, motivational, and confidence-related needs in primary care. Causal relationships cannot be inferred from this cross-sectional study.**

**KEYWORDS:**
*Hypertension; self care; self efficacy; motivation; self-management; primary health care; Indonesia*

## INTRODUCTION

Hypertension remains a major global health challenge and an important cause of preventable cardiovascular, cerebrovascular, and renal morbidity.[1] The burden has increasingly shifted towards low- and middle-income countries, where limitations in diagnosis, continuity of care, and long-term disease management continue to impede hypertension control.[2] In Indonesia, the prevalence of hypertension increased from 25.8% in 2013 to 34.1% in 2018 and was estimated at 30.8% in 2023.[3] Bali also carries a substantial burden, with 562,519 cases reported in 2022.[4] Although national programmes have expanded chronic disease services, effective control ultimately requires patients to perform recommended activities consistently outside healthcare encounters. These activities include taking medication as prescribed, reducing dietary sodium, engaging in regular physical activity, monitoring blood pressure, managing stress, and avoiding tobacco and excessive alcohol consumption.[5,6]

Hypertension self-management involves more than the performance of recommended behaviours. The High Blood Pressure Self-Care Profile distinguishes three related but conceptually different domains: self-care behaviour, motivation, and self-efficacy.[7,8] Self-care behaviour represents the extent to which recommended activities are performed. Motivation reflects the importance attributed to those activities and the willingness to maintain them, whereas self-efficacy represents confidence in one's ability to perform self-care under different circumstances.[9] For the purposes of this study, motivation and self-efficacy were treated as psychosocial dimensions of readiness for hypertension self-management. Examining these domains separately is clinically relevant because patients may recognise the importance of self-care but lack confidence in performing it, or may express confidence without consistently translating that confidence into behaviour.[10]

*This article was accepted: 25 July 2026*
*Corresponding Author: Ni Putu Ayu Ratna Dewi*
*Email: ayuratna622@gmail.com*

This study was conceptually informed by the Health Belief Model. The model proposes that engagement in health-related action is shaped by perceived susceptibility to a health threat, perceived severity of its consequences, perceived benefits of the recommended action, perceived barriers to performing it, cues to action, and self-efficacy.[11,12] Applied to hypertension, patients may be more willing to undertake self-care when they recognise their vulnerability to complications, understand the seriousness of uncontrolled blood pressure, perceive self-care as beneficial, consider its barriers manageable, receive appropriate prompts, and feel capable of performing the required activities. Motivation was not treated as a separate construct within the Health Belief Model. Instead, it was interpreted as a proximal state of readiness that may arise from patients' appraisal of health threats, expected benefits, perceived barriers, and cues to action. Because the present study did not directly measure all Health Belief Model constructs, the model was used to guide the selection of variables and interpretation of the relationships rather than to test the complete theoretical pathway. Recent studies have demonstrated the relevance of these beliefs to hypertension care, salt-reduction practices, lifestyle modification, and continuity of chronic disease care.[11–13]

Within this framework, age, sex, educational attainment, employment status, and duration of hypertension were considered personal and contextual modifying factors. Educational attainment may influence the interpretation of health information and understanding of the benefits of self-care, whereas employment may affect financial resources, daily routines, and perceived barriers.[14] Duration of hypertension may reflect accumulated experience with treatment, repeated exposure to health information, and previous opportunities to practise self-management.[2] Age and sex may also be associated with differences in functional capacity, social roles, perceived vulnerability, and healthcare experience.[15-16]

Previous Indonesian studies have contributed important evidence on hypertension self-care, but their analytical focus has differed from that of the present study. Sarfika et al. examined self-care behaviour according to participant characteristics but did not analyse motivation and self-efficacy as parallel outcomes.[14] More recently, Upoyo et al. measured self-care behaviour, motivation, and self-efficacy, but treated motivation and self-efficacy primarily as explanatory factors for self-care behaviour.[17] Consequently, it remains unclear whether sociodemographic and clinical characteristics demonstrate similar or distinct associations with behavioural performance, motivation, and self-efficacy when the three domains are treated as parallel continuous outcomes using the same validated instrument and predictor set.

Therefore, this study aimed to examine the associations of age, sex, educational attainment, employment status, and duration of hypertension with continuous self-care behaviour, motivation, and self-efficacy scores among adults receiving hypertension care at a community health centre in Bali, Indonesia. We hypothesised that these sociodemographic and clinical characteristics would be independently associated with the three outcomes, with outcome-specific patterns of association across the domains. The contribution of the present study therefore extends beyond providing evidence from a different geographical setting by examining three complementary domains of hypertension self-management as parallel continuous outcomes using the same instrument and predictor set.

## MATERIALS AND METHODS

*2.1 Design and Setting*

An analytical cross-sectional study was conducted between August and September 2024 at the Gianyar 1 Community Health Centre in Bali, Indonesia. The study examined sociodemographic and clinical factors associated with self-care behaviour, motivation, and self-efficacy among adults with hypertension. The study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for cross-sectional studies.

*2.2 Sample and Participants*

Following eligibility screening, 189 patients with hypertension met the predefined eligibility criteria and constituted the sampling frame in June 2024.

The target sample size was initially estimated from the finite eligible population using the formula $n=N/[1+N(e^2)]$, commonly referred to as the Slovin formula, with a 5% margin of error. With 189 eligible patients, the calculation yielded 128.35; an operational target of approximately 128 participants was established during the original study planning. This finite-population approach was selected because participants were to be randomly selected from a complete and finite patient registry.

Because this formula does not incorporate the anticipated effect size or the number of regression parameters, a sensitivity analysis was subsequently conducted for the achieved sample in accordance with contemporary recommendations for multiple regression sample-size assessment.[18] With 120 participants, 12 predictor parameters, a two-sided significance level of 0.05, and 80% power, the minimum detectable overall effect was Cohen's $f^2=0.159$, equivalent to an $R^2$ of approximately 0.137. The achieved sample was therefore capable of detecting approximately moderate overall regression effects, although smaller associations may not have been identified.

A total of 128 patients were selected from the eligible sampling frame using a computer-generated random-number list. Eight selected patients could not be contacted and therefore did not participate. Among the 120 patients who were successfully contacted, none declined participation. All 120 completed the study assessments and were included in the analysis, corresponding to a response rate of 93.8%.

Participants were eligible if they: (1) were older than 40 years; (2) had been diagnosed with primary hypertension for at least 12 months before recruitment; (3) were receiving antihypertensive treatment; and (4) were able to communicate in Indonesian or Balinese. Patients were excluded if they had severe hypertension at recruitment,

defined as systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥120 mmHg, or a severe medical condition that prevented participation or questionnaire completion, including end-stage renal disease, active malignancy, or decompensated heart failure.

*2.3 Instruments*

Data were collected using a demographic questionnaire and the Indonesian version of the High Blood Pressure Self-Care Profile.

1. The demographic questionnaire recorded age, sex, religion, educational attainment, employment status, and duration of hypertension.
2. The High Blood Pressure Self-Care Profile comprises three 20-item subscales measuring self-care behaviour, motivation, and self-efficacy.[7-8] Each item is scored on a four-point Likert scale ranging from 1 to 4. Item scores within each subscale are summed to produce a total score ranging from 20 to 80, with higher scores indicating better self-care behaviour, higher motivation, or greater self-efficacy. The Indonesian version has demonstrated satisfactory validity and internal consistency, with Cronbach's alpha coefficients exceeding 0.70 for the three subscales.[8]

The continuous total score for each subscale was used as the primary outcome in all bivariate and multivariable analyses. For supplementary descriptive presentation only, scores were classified as poor (<40), moderate (40–59), or good (≥60). These cut-off values were not established as validated clinical thresholds by either the original instrument developers or the Indonesian validation study. Therefore, the categories were used solely to describe the distribution of scores and were not used in hypothesis testing, variable selection, or multiple linear regression.

*2.4 Data Collection*

Data collection was conducted by trained research assistants using standardised procedures. All interviews were conducted in private consultation rooms at the health centre to protect confidentiality and facilitate questionnaire completion. The research assistants received training regarding participant communication, questionnaire administration, neutral probing, and data completeness checks. Completed forms were reviewed on the same day by a field supervisor. De-identified data were entered twice into a password-protected database, and discrepancies between the two entries were resolved by checking the original questionnaire.

*2.5 Data Analysis*

Categorical participant characteristics were summarised using frequencies and percentages. Continuous self-care behaviour, motivation, and self-efficacy scores were summarised using means, standard deviations, 95% confidence intervals for the means, medians, and interquartile ranges. The distributions of the three continuous outcome scores were examined using histograms, Q–Q plots, skewness, kurtosis, and the Shapiro–Wilk test. Bivariate comparisons were conducted using an independent-samples t test for sex and one-way analysis of variance for age, educational attainment, employment status, and duration of hypertension. An adjustment for unequal variances was applied when the homogeneity-of-variance assumption was not met. Each participant characteristic was examined separately in the bivariate analysis.

Three separate multiple linear regression models were constructed, with self-care behaviour, motivation, and self-efficacy entered as continuous dependent variables. Age, sex, educational attainment, employment status, and duration of hypertension were selected a priori based on the conceptual framework, clinical relevance, and previous evidence. All five variables were entered simultaneously into each model regardless of their bivariate p-values. Categorical predictors were represented using indicator variables. The comparison categories were age 61–70 years, male sex, diploma or bachelor's education, other employment, and a hypertension duration of 11–15 years. A positive unstandardised regression coefficient indicated a higher adjusted mean outcome score than the stated comparison category, whereas a negative coefficient indicated a lower adjusted mean score.

Multiple linear regression assumptions were assessed using residual-versus-predicted plots for linearity, the Breusch–Pagan test for homoscedasticity, variance inflation factors for multicollinearity, Cook's distance for influential observations, and the Shapiro–Wilk test for residual normality. Variance inflation factor values greater than 5 and Cook's distance values greater than 1 were considered potentially problematic. Regression results were reported as unstandardised regression coefficients (B), 95% confidence intervals, and p-values. Overall model performance was reported using $R^2$, adjusted $R^2$, and the model p-value. Statistical significance was defined as a two-sided p-value $<0.05$. Analyses were performed using IBM SPSS Statistics version 24. There were no missing values for the variables included in the analyses; therefore, all 120 participants were included in each model, and no missing-data imputation was required.

*2.6 Ethical Considerations*

Ethical approval was obtained from the Research Ethics Commission of ITEKES Bali (approval number 03.0233/KEPITEKES-BALI/VII/2024). All participants provided written informed consent before data collection. Participant information was de-identified, stored securely, and used exclusively for research purposes. Participation was voluntary, and participants could withdraw at any time without penalty or any effect on the healthcare services they received. The study was conducted in accordance with the Declaration of Helsinki.

## RESULTS

*3.1 Participant Characteristics*

Of the 128 patients selected through simple random sampling, eight could not be contacted and therefore did not participate. Among the 120 patients who were successfully contacted, none declined participation. All 120 participants completed the study assessments and were included in the analysis, resulting in a response rate of 93.8%. The mean age was 57.3 years (SD 8.5). More than half of the participants were female (53.3%), and the majority were Hindu (78.3%). Junior high school was the most frequently reported

**Table I: Sociodemographic and clinical characteristics of the participants (n = 120)**

| Characteristics | Frequency (f) | Percentage (%) |
|---|---|---|
| Age, years | | |
| 41-50 | 32 | 26.7 |
| 51-60 | 43 | 35.8 |
| 61-70 | 45 | 37.5 |
| Mean (SD) | 57.3 (8.5) | |
| Sex | | |
| Male | 56 | 46.7 |
| Female | 64 | 53.3 |
| Religion | | |
| Hinduism | 94 | 78.3 |
| Islam | 16 | 13.3 |
| Christianity | 10 | 8.3 |
| Education | | |
| No school | 25 | 20.8 |
| Elementary school | 26 | 21.7 |
| Junior high school | 27 | 22.5 |
| Senior high school | 26 | 21.7 |
| Diploma or bachelor's degree | 16 | 13.3 |
| Employment | | |
| Not employed | 41 | 34.2 |
| Private-sector employee | 38 | 31.7 |
| Civil servant | 9 | 7.5 |
| Other | 32 | 26.7 |
| Duration of hypertension, years | | |
| 1-5 | 39 | 32.5 |
| 6-10 | 65 | 54.2 |
| 11-15 | 16 | 13.3 |

**Table II: Distribution of self-care behaviour, motivation, and self-efficacy scores (n = 120)**

| Category | f | % | Mean (SD) | 95% CI of mean | Median (IQR) |
|---|---|---|---|---|---|
| Behaviour | | | | | |
| Poor | 43 | 35.8 | | | |
| Moderate | 70 | 58.3 | 4.09 (9.13) | 42.44–45.74 | 44.5 (37.0–51.0) |
| Good | 7 | 5.8 | | | |
| Motivation | | | | | |
| Poor | 39 | 32.5 | | | |
| Moderate | 63 | 52.5 | 44.64 (11.51) | 42.56–46.72 | 43.0 (33.0–51.0) |
| Good | 18 | 15.0 | | | |
| Self-Efficacy | | | | | |
| Poor | 51 | 42.5 | | | |
| Moderate | 60 | 50.0 | 42.99 (9.88) | 41.21–44.78 | 42.0 (33.0–51.0) |
| Good | 9 | 7.5 | | | |

Note: Higher scores indicate better self-care behaviour, motivation, or self-efficacy. Categories were defined as poor (<40), moderate (40–59), and good (≥60) and were used only for descriptive presentation. CI, confidence interval; IQR, interquartile range; SD, standard deviation.

educational category (22.5%), 34.2% were not employed, and 54.2% had lived with hypertension for 6–10 years (Table I).

*3.2 Distribution of self-care behaviour, motivation, and self-efficacy scores*

The mean self-care behaviour score was 44.09 (SD 9.13; 95% CI 42.44–45.74), with a median of 44.5 (IQR 37.0–51.0). The mean motivation score was 44.64 (SD 11.51; 95% CI 42.56–46.72), with a median of 43.0 (IQR 33.0–51.0). The mean self-efficacy score was 42.99 (SD 9.88; 95% CI 41.21–44.78), with a median of 42.0 (IQR 33.0–51.0) (Table II). Both mean-based and median-based summaries are presented because the raw score distributions showed some departure from normality. For supplementary descriptive presentation, 58.3% of participants were classified as having moderate self-care behaviour, 52.5% as having moderate motivation, and 50.0% as having moderate self-efficacy. These categories were used only to describe the score distributions and were not used in the bivariate or multivariable analyses.

*3.3 Bivariate analysis*

Self-care behaviour scores differed significantly according to age (p=0.043), educational attainment (p=0.002), employment status (p=0.003), and duration of hypertension (p=0.001). No significant difference in self-care behaviour scores was observed according to sex (p=0.709). Motivation scores differed significantly according to employment status (p=0.029), but not according to age, sex, educational attainment, or duration of hypertension. No statistically significant differences in self-efficacy scores were observed according to the participant characteristics examined (Table III).

**Table III: Bivariate associations of participant characteristics with self-care behaviour, motivation, and self-efficacy (n = 120)**

| Variable | Behaviour | | Motivation | | Self-efficacy | |
|---|---|---|---|---|---|---|
| | mean (SD) | p-value | mean (SD) | p-value | mean (SD) | p-value |
| Age group | | 0.043 | | 0.068 | | 0.393 |
| 41–50 years | 46.44 (9.88) | | 48.47 (11.65) | | 44.91 (11.03) | |
| 51–60 years | 45.09 (8.76) | | 44.28 (11.55) | | 43.00 (9.57) | |
| 61–70 years | 41.47 (8.45) | | 42.27 (10.89) | | 41.62 (9.28) | |
| Sex | 0.709 | | 0.255 | | 0.948 | |
| Female | 43.80 (8.74) | | 43.50 (10.02) | | 43.05 (9.76) | |
| Male | 44.43 (9.63) | | 45.95 (12.97) | | 42.93 (10.10) | |
| Education | | 0.002 | | 0.167 | | 0.228 |
| No school | 38.72 (9.88) | | 41.76 (13.33) | | 39.88 (9.73) | |
| Elementary school | 44.46 (8.61) | | 45.08 (10.57) | | 41.58 (9.42) | |
| Junior high school | 42.44 (6.61) | | 41.85 (8.19) | | 43.00 (9.05) | |
| Senior high school | 47.12 (9.21) | | 47.31 (10.76) | | 46.27 (10.82) | |
| Diploma or bachelor's degree | 49.75 (7.84) | | 48.81 (14.55) | | 44.81 (9.79) | |
| Employment | | 0.003 | | 0.029 | | 0.073 |
| Not employed | 41.98 (8.08) | | 41.59 (11.43) | | 42.20 (9.23) | |
| Private-sector employee | 48.32 (8.95) | | 48.95 (10.32) | | 45.34 (10.67) | |
| Civil servant | 48.22 (9.72) | | 47.00 (14.12) | | 47.89 (11.36) | |
| Other | 40.63 (8.40) | | 42.78 (10.99) | | 39.84 (8.41) | |
| Duration of hypertension | | 0.001 | | 0.317 | | 0.278 |
| 1–5 years | 39.54 (8.40) | | 42.64 (12.74) | | 40.95 (9.21) | |
| 6–10 years | 46.11 (7.64) | | 46.15 (10.31) | | 43.95 (9.38) | |
| 11–15 years | 47.00 (12.38) | | 43.38 (12.78) | | 44.06 (12.95) | |

Note: Values are presented as mean (SD). Bivariate comparisons were conducted using an independent-samples t test for sex and one-way analysis of variance for characteristics with three or more categories. An adjustment for unequal variances was applied when appropriate. Each characteristic was examined separately without adjustment for the other variables.

*3.4 Multivariable Analysis*

Three separate multiple linear regression models were constructed for self-care behaviour, motivation, and self-efficacy. The comparison categories were age 61–70 years, male sex, diploma or bachelor's education, other employment, and a hypertension duration of 11–15 years. A positive B coefficient indicates a higher adjusted mean score than the stated comparison category, whereas a negative B coefficient indicates a lower adjusted mean score.

*Self-care behaviour*

The self-care behaviour model was statistically significant ($R^2$=0.375; adjusted $R^2$=0.304; p<0.001). After adjustment for the other participant characteristics, participants aged 41–50 years had self-care behaviour scores that were, on average, 5.07 points higher than those aged 61–70 years (B=5.07; 95% CI 1.38–8.75; p=0.008). Participants with no formal schooling had scores that were 8.88 points lower than those with a diploma or bachelor's degree (B=–8.88; 95% CI –14.15 to –3.61; p=0.001), while those who had completed junior high school had scores that were 5.62 points lower (B=–5.62; 95% CI –10.85 to –0.39; p=0.035).

Private-sector employees had self-care behaviour scores that were 7.22 points higher than participants in the other-employment category (B=7.22; 95% CI 3.47–10.96; p<0.001). Participants who had lived with hypertension for 1–5 years had scores that were 5.61 points lower than those who had lived with hypertension for 11–15 years (B=–5.61; 95% CI –10.28 to –0.93; p=0.019). The remaining adjusted associations were not statistically significant (Table IV).

*Motivation*

The motivation model was statistically significant but explained a smaller proportion of the score variance ($R^2$=0.186; adjusted $R^2$=0.094; p=0.028). Participants aged 41–50 years had motivation scores that were, on average, 5.43 points higher than those aged 61–70 years (B=5.43; 95% CI 0.13–10.73; p=0.045). Participants who had completed junior high school had motivation scores that were 8.24 points lower than those with a diploma or bachelor's degree (B=–8.24; 95% CI –15.76 to –0.72; p=0.032). No other adjusted association with motivation was statistically significant (Table IV).

*Self-efficacy*

The overall self-efficacy model was not statistically significant ($R^2$=0.131; adjusted $R^2$=0.033; p=0.206). Private-sector employment showed a positive coefficient compared with other employment (B=5.49; 95% CI 0.71–10.26; p=0.025). However, because the overall model was not statistically significant, this category-specific estimate was considered exploratory and was not interpreted as a conclusive independent association (Table IV).

*Model assessment*

Variance inflation factor values ranged from 1.12 to 2.59, indicating no problematic multicollinearity. Visual examination of the residual-versus-predicted plots did not indicate material violations of linearity. The Breusch–Pagan tests were non-significant for the self-care behaviour ($\chi^2$=12.43; p=0.412), motivation ($\chi^2$=12.60; p=0.399), and self-efficacy models ($\chi^2$=15.30; p=0.226), indicating no evidence of heteroscedasticity. The maximum Cook's distance was 0.155 for self-care behaviour, 0.145 for motivation, and 0.070 for self-efficacy; all values were below the prespecified threshold of 1. Residual normality was acceptable for the self-care behaviour (Shapiro–Wilk W=0.987; p=0.292) and self-efficacy models (W=0.982; p=0.111). The motivation-model residuals showed some departure from normality (W=0.932; p<0.001); therefore, its category-specific estimates were interpreted cautiously.

**Table IV: Multiple linear regression of factors associated with continuous self-care behaviour, motivation, and self-efficacy scores (n = 120)**

| Outcome and predictor | Comparison | B | 95% CI | p-value |
|---|---|---|---|---|
| Self-care behaviour | Model: $R^2$=0.375; adjusted $R^2$=0.304; p<0.001 | | | |
| Age | 41–50 vs 61–70 years | 5.07 | 1.38 to 8.75 | 0.008 |
| | 51–60 vs 61–70 years | 2.76 | –0.59 to 6.11 | 0.105 |
| Sex | Female vs male | 0.97 | –1.95 to 3.89 | 0.513 |
| Educational attainment | No formal schooling vs diploma/bachelor's | –8.88 | –14.15 to –3.61 | 0.001 |
| | Elementary school vs diploma/bachelor's | –3.33 | –8.42 to 1.76 | 0.198 |
| | Junior high school vs diploma/bachelor's | –5.62 | –10.85 to –0.39 | 0.035 |
| | Senior high school vs diploma/bachelor's | –1.32 | –6.18 to 3.53 | 0.590 |
| Employment status | Not employed vs other | 1.88 | –1.96 to 5.72 | 0.334 |
| | Private-sector employee vs other | 7.22 | 3.47 to 10.96 | <0.001 |
| | Civil servant vs other | 2.89 | –3.39 to 9.17 | 0.364 |
| Duration of hypertension | 1–5 vs 11–15 years | –5.61 | –10.28 to –0.93 | 0.019 |
| | 6–10 vs 11–15 years | –1.29 | –5.74 to 3.17 | 0.568 |
| Motivation | Model: $R^2$=0.186; adjusted $R^2$=0.094; p=0.028 | | | |
| Age | 41–50 vs 61–70 years | 5.43 | 0.13 to 10.73 | 0.045 |
| | 51–60 vs 61–70 years | 1.06 | –3.75 to 5.88 | 0.663 |
| Sex | Female vs male | –0.67 | –4.87 to 3.53 | 0.753 |
| Educational attainment | No formal schooling vs diploma/bachelor's | –7.09 | –14.66 to 0.49 | 0.067 |
| | Elementary school vs diploma/bachelor's | –3.06 | –10.38 to 4.27 | 0.410 |
| | Junior high school vs diploma/bachelor's | –8.24 | –15.76 to –0.72 | 0.032 |
| | Senior high school vs diploma/bachelor's | –1.38 | –8.36 to 5.60 | 0.696 |
| Employment status | Not employed vs other | –1.28 | –6.80 to 4.25 | 0.648 |
| | Private-sector employee vs other | 5.17 | –0.21 to 10.55 | 0.060 |
| | Civil servant vs other | –0.79 | –9.82 to 8.24 | 0.863 |
| Duration of hypertension | 1–5 vs 11–15 years | 1.61 | –5.10 to 8.33 | 0.635 |
| | 6–10 vs 11–15 years | 3.71 | –2.69 to 10.12 | 0.253 |
| Self-efficacy | Model: $R^2$=0.131; adjusted $R^2$=0.033; p=0.206 | | | |
| Age | 41–50 vs 61–70 years | 3.37 | –1.33 to 8.07 | 0.158 |
| | 51–60 vs 61–70 years | 1.60 | –2.67 to 5.87 | 0.459 |
| Sex | Female vs male | 0.81 | –2.91 to 4.54 | 0.666 |
| Educational attainment | No formal schooling vs diploma/bachelor's | –3.20 | –9.93 to 3.52 | 0.347 |
| | Elementary school vs diploma/bachelor's | –1.34 | –7.83 to 5.15 | 0.683 |
| | Junior high school vs diploma/bachelor's | 0.15 | –6.52 to 6.82 | 0.964 |
| | Senior high school vs diploma/bachelor's | 2.39 | –3.81 to 8.58 | 0.446 |
| Employment status | Not employed vs other | 3.28 | –1.62 to 8.17 | 0.188 |
| | Private-sector employee vs other | 5.49 | 0.71 to 10.26 | 0.025 |
| | Civil servant vs other | 5.90 | –2.11 to 13.91 | 0.147 |
| Duration of hypertension | 1–5 vs 11–15 years | –2.55 | –8.51 to 3.41 | 0.398 |
| | 6–10 vs 11–15 years | –0.63 | –6.31 to 5.05 | 0.825 |

Note: B is the unstandardised regression coefficient. A positive B value indicates that the adjusted mean outcome score was higher than the stated comparison category, whereas a negative B value indicates that the adjusted mean score was lower. All predictors were entered simultaneously into each model. CI, confidence interval.

*3.5 Differences between bivariate and multivariable findings*

Some differences were observed between the bivariate and multivariable findings. For example, age and educational attainment were not significantly associated with motivation in the bivariate analysis, but specific age and educational comparisons became significant after adjustment. Conversely, employment status was associated with motivation in the bivariate analysis, but none of the individual employment comparisons remained significant in the adjusted model. These findings are not necessarily contradictory because the two analyses address different statistical questions. The bivariate analysis in Table III assessed the overall differences across all categories of each participant characteristic without accounting for the other variables. In contrast, the multiple linear regression in Table IV estimated specific category-to-comparison-category differences after adjustment for the other characteristics included in the model. Consequently, an association may become stronger or weaker after adjustment because of potential confounding and the use of a specific comparison category.

## DISCUSSION

This study examined age, sex, educational attainment, employment status, and duration of hypertension in relation to three parallel HBP-SCP outcomes. The hypotheses were partly supported because the selected characteristics showed different patterns of association across the three separately analysed outcomes. The models explained more variation in self-care behaviour than in motivation and little adjusted variation in self-efficacy. These patterns represent outcome-specific findings rather than a formal statistical comparison of coefficients across models. Behavioural performance, motivation, and confidence should therefore not be interpreted as interchangeable dimensions of hypertension self-management.

Within the Health Belief Model, age, educational attainment, employment status, and duration of hypertension can be understood as modifying factors that may shape patients' exposure to health information, perceived barriers, cues to action, and opportunities to perform self-care. However, perceived susceptibility, severity, benefits, barriers, and cues to action were not directly measured. The model therefore provided a framework for variable selection and interpretation but was not tested as a complete theoretical pathway. The relatively limited explanatory capacity of the motivation and self-efficacy models suggests that future studies should measure these core beliefs directly.

Participants aged 41–50 years had higher adjusted self-care behaviour and motivation scores than those aged 61–70 years, whereas participants aged 51–60 years did not differ significantly from the comparison category. The findings therefore do not demonstrate a consistent linear decline in self-management with age. Previous evidence regarding age has been mixed, and age-related differences may coexist with variation in functional condition, disease burden, social support, healthcare experience, and opportunities to perform self-care.[2,5,14] Because these factors were not directly measured, the mechanisms underlying the observed age associations remain uncertain.

Educational attainment was more clearly associated with self-care behaviour than with the other outcomes. Participants with no formal schooling and those who had completed junior high school had lower adjusted self-care behaviour scores than participants with a diploma or bachelor's degree. Junior high school education was also associated with lower motivation. However, elementary- and senior-high-school education did not differ significantly from the comparison category, and educational attainment was not independently associated with self-efficacy. The pattern was therefore not strictly graded. Previous Indonesian primary care research has similarly reported differences in hypertension self-care according to educational attainment, although the outcome definitions and analytical approaches differed.[19]

Formal education may reflect opportunities to access, understand, and apply health information, but it should not be considered equivalent to health literacy. Studies among adults with hypertension have linked health literacy with self-care behaviour and self-efficacy, while more recent evidence suggests that illness perception and self-efficacy may partly explain the relationship between health literacy and self-management.[20–22] Indonesian evidence has also identified motivation and self-efficacy as proximal correlates of self-care behaviour.[17] Because health literacy and illness perception were not measured in the present study, they remain plausible explanatory pathways rather than demonstrated mechanisms.

Private-sector employment was associated with higher self-care behaviour than the heterogeneous other-employment category, but not with motivation, and the overall self-efficacy model was not significant. Employment may reflect differences in financial resources, daily routines, workplace support, health information, or access to healthcare. Conversely, work responsibilities may limit the time available for self-care. Recent research has shown that employment and income may coexist with differences in health outcomes among patients with hypertension.[22] The adoption of home blood pressure monitoring may also depend on patient resources, knowledge, healthcare-provider support, and access to monitoring devices.[23] Income, working conditions, job flexibility, insurance coverage, and access to equipment were not measured in this study. The observed coefficient should therefore be interpreted as an association between employment categories rather than evidence that private-sector employment itself improves self-care.

Participants who had lived with hypertension for 1–5 years had lower self-care behaviour scores than those with a duration of 11–15 years, but duration was not associated with motivation or self-efficacy. Longer disease experience may provide repeated opportunities to receive counselling, become familiar with treatment requirements, and establish self-care routines. However, duration may also coexist with treatment burden, comorbidities, and changes in adherence. Reviews indicate that disease knowledge, medication-related factors, social support, and healthcare access interact in hypertension self-management, while Indonesian primary care data demonstrate substantial variation in medication adherence, lifestyle modification, and blood pressure control.[2,20] Evidence from rural Indonesia also suggests that education combined with continuing follow-up can support the maintenance of recommended dietary behaviour and blood pressure control.[23] Nevertheless, the cross-sectional design of the present study cannot establish whether longer duration improved self-care or whether participants with better self-care remained more consistently engaged with long-term services.

The non-significant self-efficacy model is also informative. The examined characteristics explained little adjusted variation in self-efficacy, suggesting that confidence in performing hypertension self-care may be more closely related to psychological, informational, and social factors than to demographic characteristics alone. Previous studies have linked self-efficacy and self-management with motivation, health literacy, illness perception, perceived social support, resilience, and empowerment.[17,21-22,24-25] These findings identify relevant constructs for future investigation but do not establish the mechanisms operating in the present sample. The positive private-sector coefficient should remain exploratory because the overall self-efficacy model was not statistically significant.

These findings support individualised nursing assessment rather than a specific intervention. Age, educational attainment, employment status, and hypertension duration may prompt assessment of treatment understanding, daily barriers, previous self-management experience, motivation, confidence, social support, and access to monitoring resources; however, these characteristics should not be used as deterministic labels. Future prospective studies should evaluate whether nurse-led support tailored to directly measured needs improves self-management and blood pressure outcomes.[23,27-29]

## STUDY LIMITATIONS

Several limitations should be considered. The cross-sectional design precludes temporal and causal inference, while the single-centre setting and exclusion of patients with severe hypertension may limit generalisability. Self-reported outcomes may have been affected by recall and social desirability bias. Although the response rate was high, eight selected patients could not be contacted; therefore, non-response bias cannot be excluded. Small numbers in several participant categories may have reduced the precision of category-specific estimates. Residual confounding remains possible because health literacy, medication adherence, household income, family and social support, blood pressure control, health insurance, comorbidities, treatment complexity, and access to healthcare were not measured. The motivation-model residuals departed from normality; therefore, its estimates should be interpreted cautiously. Finally, the descriptive score categories were not validated clinical thresholds.

## CONCLUSION

Age, educational attainment, employment status, and duration of hypertension were associated mainly with self-care behaviour, while age and educational attainment were also associated with motivation. The overall model for self-efficacy was not statistically significant. Because this was a single-centre cross-sectional study with potential residual confounding, the findings should not be interpreted causally. Multicentre prospective studies should directly assess health literacy, adherence, social support, income, comorbidities, insurance coverage, and access to care before evaluating nurse-led support tailored to patients' assessed needs.

## ACKNOWLEDGEMENTS

The authors thank all participants who contributed to this study and the staff of Gianyar 1 Community Health Centre, Bali, for their assistance during participant recruitment and data collection.

## CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest related to this study.

## FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## REFERENCES

1. World Health Organization. Hypertension. 2023 [cited Apr 2024]. Available from: https://www.who.int/news-room/fact-sheets/detail/hypertension
2. Konlan KD, Shin J. Determinants of self-care and home-based management of hypertension: an integrative review. Glob Heart 2023; 18(1): 16.
3. Health Development Policy Agency, Ministry of Health Republic of Indonesia. Indonesian Health Survey (SKI) 2023 in figures [in Indonesian]. Jakarta: Health Development Policy Agency; 2024.
4. Bali Provincial Health Office. Bali Province health profile 2022. Denpasar: Bali Provincial Health Office; 2022.
5. Jung SY, Moon KJ. Factors affecting self-care among community-dwelling hypertensive older adults: a cross-sectional study. Nurs Open 2023; 10(6): 3892–905.
6. Villafuerte FU, Cànaves JL, Montalvo PL, Sancho MLM, Oliver B, Flores PB, et al. Effectiveness of a multifactorial intervention, consisting of self-management of antihypertensive medication, self-measurement of blood pressure, hypocaloric and low sodium diet, and physical exercise, in patients with uncontrolled hypertension taking 2 or more antihypertensive drugs: the MEDICHY study. Medicine (Baltimore) 2020; 99(17): e19769.
7. Han HR, Lee H, Commodore-Mensah Y, Kim M. Development and validation of the Hypertension Self-care Profile: a practical tool to measure hypertension self-care. J Cardiovasc Nurs 2014; 29(3): E11–20.
8. Upoyo AS, Taufik A, Anam A, Nuriya N, Saryono S, Setyopranoto I, et al. Translation and validation of the Indonesian version of the Hypertension Self-care Profile. Open Access Maced J Med Sci 2021; 9(E): 980–4.
9. Leonardo F, Custódio CG, Lira DP, Ferreira DO, Pavan MV, Almeida FA. Hypertension from the patient's perspective: contributions to the care offered by health professionals and self-care—a qualitative study. Sao Paulo Med J 2023; 141(5): e2022314.
10. Pahria T, Nugroho C, Yani DI. Factors influencing self-care behaviors in hypertension patients with complications. Vasc Health Risk Manag 2022; 18: 463–71.
11. Widyaningrum K, Zuhriyah L, Wardhani V, Rudijanto A. Continuum of care for diabetes and hypertension patients during the pandemic era: bridging the gap. Malays J Med Sci 2025; 32(4): 212–23.
12. Sadeghi R, Masoudi MR, Patelarou A, Khanjani N. Predictive factors for the care and control of hypertension based on the Health Belief Model among hypertensive patients during the COVID-19 epidemic in Sirjan, Iran. Curr Hypertens Rev 2022; 18(1): 78–84.
13. Han L, Liu Y, Liu X, Xian P. Development and validation of a scale to measure hypertensive Chinese individual's behavior toward salt reduction consumption. BMC Public Health 2024; 24(1): 1459.
14. Sarfika R, Sulistiawati, Afriyanti E, Saifudin IMMY. Self-care behavior among adult patients with hypertension in Padang, West Sumatra, Indonesia: a cross-sectional study. Belitung Nurs J 2023; 9(6): 595–602.
15. Hussen FM, Adem HA, Roba HS, Mengistie B, Assefa N. Self-care practice and associated factors among hypertensive patients in public health facilities in Harar Town, Eastern Ethiopia: a cross-sectional study. SAGE Open Med 2020; 8: 2050312120974145.
16. Gelaw S, Yenit MK, Nigatu SG. Self-care practice and associated factors among hypertensive patients in Debre Tabor Referral Hospital, Northwest Ethiopia, 2020. Int J Hypertens 2021; 2021: 3570050.
17. Upoyo AS, Sari Y, Sutrisna E, Taufik A, Han HR. Motivation and self-efficacy as key factors influencing self-care in hypertensive adults: a cross-sectional study in Indonesia. J Keperawatan Padjadjaran 2025; 13(2): 182–90.
18. Seabrook JA. Powering nutrition research: practical strategies for sample size in multiple regression. Nutrients 2025; 17(16): 2668.
19. Kurnia AD, Hariyati S, Melizza N, Husna CHA, Amatayakul A, Handoko A. Personal factors related to self-care management among people with hypertension at primary health care: a cross-sectional study. J Keperawatan Padjadjaran 2023; 11(3): 203–13.
20. Setiadi AP, Febriandini A, Trinanda E, Aryaguna W, Chusna IM, Nurlaili Y, et al. Knowing the gap: medication use, adherence and blood pressure control among patients with hypertension in Indonesian primary care settings. PeerJ 2022; 10: e13171.
21. Darvishpour A, Mansour-Ghanaei R, Mansouri F. The relationship between health literacy, self-efficacy, and self-care behaviors in older adults with hypertension in the north of Iran. Health Lit Res Pract 2022; 6(4): e262–9.

22. Salmanpour N, Salehi A, Nemati S, Rahmanian M, Zakeri A, Drissi HB, et al. The effect of self-care, self-efficacy, and health literacy on health-related quality of life in patients with hypertension: a cross-sectional study. BMC Public Health 2025; 25(1): 2630.
23. Giang NH, Lan NTP, Anh LTK, Plancikova D, Rusnakova V, Thang NT, et al. Factors influencing adoption of self-monitoring of blood pressure among hypertensive patients in primary healthcare in Vietnam: a cross-sectional facility-based study. BMC Prim Care 2025; 26(1): 180.
24. Pehopu IA, Irwan AM, Sjattar EL, Changmai S, Aziz NAA. Continuous follow-up intervention of a low-salt diet to control blood pressure among older people with hypertension in rural Indonesia. Clin Epidemiol Glob Health 2025; 32: 101943.
25. Liu Y, Jiang F, Zhang M, Niu H, Cao J, Du S, et al. Health literacy and self-management among middle-aged and young hypertensive patients: a parallel mediation effect of illness perception and self-efficacy. Front Psychol 2024; 15: 1349451.
26. Lin C, Zhu X, Wang X, Wang L, Wu Y, Hu X, et al. The impact of perceived social support on chronic disease self-management among older inpatients in China: the chain-mediating roles of psychological resilience and health empowerment. BMC Geriatr 2025; 25(1): 284.
27. Bulto LN, Roseleur J, Noonan S, Pinero de Plaza MA, Champion S, Dafny HA, et al. Effectiveness of nurse-led interventions versus usual care to manage hypertension and lifestyle behaviour: a systematic review and meta-analysis. Eur J Cardiovasc Nurs 2024; 23(1): 21–32.
28. Mehta SJ, Volpp KG, Troxel AB, Teel J, Reitz CR, Purcell A, et al. Remote blood pressure monitoring with social support for patients with hypertension: a randomized clinical trial. JAMA Netw Open 2024; 7(6): e2413515.
29. Ito M, Tajika A, Toyomoto R, Imai H, Sakata M, Honda Y, et al. The short and long-term efficacy of nurse-led interventions for improving blood pressure control in people with hypertension in primary care settings: a systematic review and meta-analysis. BMC Prim Care 2024; 25(1): 143.

SYSTEMATIC / NARRATIVE REVIEW ARTICLE

# The diagnostic and prognostic role of miRNA-21 and miRNA-223 in laryngeal squamous cell carcinoma: A systematic review with exploratory meta-analysis

**Khoirul Anam, MD[1], Afiati, MD[2], Devy Ariany, M.Biomed[2]**

[1]Department of Otorhinolaryngology Head and Neck Surgery, Faculty of Medicine, Syarif Hidayatullah State Islamic University Jakarta, Indonesia, [2]Department of Anatomical Pathology, Faculty of Medicine, Syarif Hidayatullah State Islamic University Jakarta

## ABSTRACT

**Introduction: Laryngeal squamous cell carcinoma (LSCC) is a common head and neck malignancy often diagnosed at advanced stages, resulting in poor prognosis and high recurrence rates. Circulating microRNAs (miRNAs), particularly miR-21 and miR-223, have emerged as promising non-invasive biomarkers because of their stability in body fluids and involvement in tumour biology. This study systematically reviewed the diagnostic and prognostic significance of circulating miR-21 and miR-223 in LSCC and performed an exploratory diagnostic meta-analysis of miR-21 when sufficient quantitative data were available.**

**Materials and Methods: A systematic search was conducted in PubMed, Google Scholar, and SciSpace. Eligible studies evaluated circulating miR-21 and/or miR-223 in serum or plasma samples from LSCC patients and assessed their association with diagnostic or prognostic outcomes. Data regarding expression levels, diagnostic performance, and survival outcomes were synthesized qualitatively. Exploratory diagnostic meta-analysis was performed by pooling Area Under the Curve (AUC) values using the inverse variance method. Heterogeneity was assessed using the $I^2$ statistic, and a random-effects model was applied.**

**Results: Five studies were included in the qualitative synthesis. Elevated miR-21 expression was consistently associated with advanced tumour stage, nodal involvement, recurrence, and poorer survival outcomes. miR-223 demonstrated dynamic changes following treatment and recurrence, suggesting potential utility for disease monitoring. Only two studies were eligible for exploratory diagnostic meta-analysis, yielding an exploratory pooled AUC of 0.77 (95% CI: 0.50–1.04) with substantial heterogeneity ($I^2$ = 83%).**

**Conclusion: Circulating miR-21 and miR-223 show potential clinical utility in LSCC, particularly for prognosis and recurrence monitoring. However, current evidence remains limited and heterogeneous, and the quantitative findings should be interpreted cautiously.**

**KEYWORDS:**
*LSCC; microRNA-21; microRNA-223; prognosis; biomarker*

## INTRODUCTION

Laryngeal squamous cell carcinoma (LSCC) is the most common malignant tumour of the larynx and remains a major global health problem. Despite advances in surgery, radiotherapy, and chemotherapy, the prognosis of LSCC patients remains suboptimal because many cases are diagnosed at advanced stages and are associated with heterogeneous treatment responses and high recurrence rates. These challenges highlight the urgent need for reliable and minimally invasive biomarkers to improve prognostic assessment, disease monitoring, and post-treatment surveillance.[1-2]

MicroRNAs (miRNAs) are small endogenous non-coding RNAs consisting of approximately 22 nucleotides that regulate gene expression at the post-transcriptional level by promoting messenger RNA degradation or inhibiting translation. miRNAs are involved in multiple biological processes, including cell proliferation, apoptosis, differentiation, invasion, and metastasis. Dysregulated miRNA expression has been widely reported in various human malignancies, including head and neck squamous cell carcinoma (HNSCC), and may reflect underlying tumour biology.[3-4]

Circulating miRNAs detected in serum and plasma have attracted considerable interest as minimally invasive cancer biomarkers because of their relative stability in body fluids. These molecules are protected from RNase degradation through encapsulation within exosomes, microvesicles, or protein complexes, allowing reliable detection in peripheral blood samples.[5-6]

Previous studies in HNSCC have demonstrated that circulating miRNAs may correlate with tumour burden, lymph node metastasis, treatment response, and survival outcomes. Among these, miR-21 is one of the most extensively studied oncomiRs and has been associated with tumour progression and poor prognosis across multiple HNSCC subtypes. In contrast, miR-223 has been implicated in inflammatory regulation and recurrence monitoring, suggesting potential utility in longitudinal disease surveillance.[7-8] However, methodological variability across studies, including differences in specimen processing, normalization controls, detection platforms, and cut-off determination, remains a major challenge for clinical translation.

*This article was accepted: 17 May 2026*
*Corresponding Author: Khoirul Anam*
*Email: khoirul.anam@uinjkt.ac.id*

A previous systematic review entitled "*Diagnostic and Prognostic Value of microRNAs in Patients with Laryngeal Cancer*" demonstrated the emerging role of miRNAs as potential biomarkers in laryngeal malignancies. However, the review evaluated heterogeneous miRNAs collectively, included both tissue and circulating specimens, and combined diagnostic and prognostic objectives. Consequently, the specific prognostic and monitoring significance of circulating miR-21 and miR-223 in LSCC remains incompletely characterized.[9-12]

Therefore, this study aimed to systematically review the available evidence regarding circulating miR-21 and miR-223 in LSCC, with emphasis on their prognostic and monitoring significance. In addition, an exploratory diagnostic meta-analysis of miR-21 was performed when sufficient quantitative data were available.

## MATERIALS AND METHODS

### Registration

This study was developed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA) checklist. The study protocol has been registered with PROSPERO (registration number: CRD420251246629). As this study is a systematic review, ethical approval and patient consent are not required.

### Search Strategy

A comprehensive literature search was conducted in PubMed, Google Scholar, and SciSpace to identify relevant studies evaluating miR-21 and miR-223 in LSCC. PubMed was selected as the principal biomedical database because it incorporates MEDLINE-indexed literature and provides broad coverage of biomedical publications.

Although EMBASE was not directly searched because of access limitations, supplementary searches using Google Scholar and SciSpace were conducted to maximize retrieval sensitivity and minimise the likelihood of missing relevant studies, as these platforms provide broad coverage of academic publications. Articles were selected based on relevance, availability of full text, and fulfilment of the inclusion criteria. Eligible studies involved human patients, evaluated miR-21 and/or miR-223 expression in serum, plasma, and/or tumour tissue samples, and examined their association with diagnostic or prognostic outcomes in LSCC (3,7). Through this multi-step search strategy, we aimed to ensure a comprehensive literature search and minimise the risk of overlooking relevant studies.

Inclusion criteria included human studies involving patients with LSCC that evaluated miR-21 and/or miR-223 expression in circulating samples and/or tumour tissue and analysed their association with diagnostic or prognostic outcomes, such as survival, tumour stage, or recurrence. Only studies with full text available in English were considered. Exclusion criteria included reviews, editorials, and case reports; in vitro or animal-only studies; studies without diagnostic or prognostic data; and studies with insufficient methodological details or unavailable full text.

1. Search Strategy (PubMed):
   ((miRNA-21[Title/Abstract] OR microRNA-21[Title/Abstract] OR miR-21[Title/Abstract]) OR (miRNA-223[Title/Abstract] OR microRNA-223[Title/Abstract] OR miR-223[Title/Abstract])) AND (laryngeal[Title/Abstract] OR larynx[Title/Abstract]) AND (squamous cell carcinoma[Title/Abstract] OR LSCC[Title/Abstract] OR cancer[Title/Abstract]) AND (prognosis[Title/Abstract] OR survival[Title/Abstract] OR biomarker[Title/Abstract] OR prognostic[Title/Abstract]).
2. Search Strategy (Google Scholar & SciSpace):
   ((miRNA-21[Title/Abstract] OR microRNA-21[Title/Abstract] OR miR-21[Title/Abstract]) OR (miRNA-223[Title/Abstract] OR microRNA-223[Title/Abstract] OR miR-223[Title/Abstract])) AND (laryngeal[Title/Abstract] OR larynx[Title/Abstract]) AND (squamous cell carcinoma[Title/Abstract] OR LSCC[Title/Abstract] OR cancer[Title/Abstract]) AND (prognosis[Title/Abstract] OR survival[Title/Abstract] OR biomarker[Title/Abstract] OR prognostic[Title/Abstract]).

### Data Extraction

Data extraction was performed independently by two reviewers (KA and DA), with verification by a third reviewer (AH) to ensure accuracy and consistency. Extracted information included key study characteristics (first author, year of publication, country, study design prospective or retrospective, cohort or case-control sample size for cases and controls, patient demographics such as age, gender, and TNM stage, as well as follow-up duration). Biomarker-related data were also collected, including the specific miRNAs analysed (miR-21, miR-223, or both), sample type (tissue, serum, or plasma), detection method (qRT-PCR, microarray, or sequencing), normalization controls (U6, GAPDH, or cel-miR-39), and reported expression levels with their corresponding cut-off values. Outcome data encompassed prognostic indicators such as overall survival (OS), disease-free survival (DFS), progression-free survival (PFS), recurrence rates, hazard ratios (HR) with 95% confidence intervals (CI), diagnostic performance metrics including Area Under the Curve (AUC), sensitivity, and specificity, as well as statistical significance values (p-values). Studies were excluded from the quantitative meta-analysis if they did not report AUC, sensitivity, specificity, or sufficient data to calculate SE such as the studies by Hu et al.[4], Falco et al.[6] and Hou et al.[7], and (which evaluated miR-223 instead of miR-21) to ensure the validity of the diagnostic analysis.

### Statistical Analysis

Statistical analysis focused on a meta-analysis of the diagnostic accuracy of circulating miR-21 in laryngeal squamous cell carcinoma (LSCC). This diagnostic meta-analysis was conducted using Area Under the Curve (AUC) values and Standard Errors (SE) derived from the 95% Confidence Intervals (CI) reported in the primary studies. The Inverse Variance method was applied to pool individual AUC estimates from each study. Prior to pooling, statistical heterogeneity among studies was rigorously assessed using the $I^2$ statistic. Heterogeneity was considered substantial if $I^2$ exceeded 50%, in which case a Random-Effects Model was applied to combine the data. A random-effects model was selected because it is more conservative and appropriate

**Table I: Study Overview**

| Author (Year) | miRNA Studied | Objective | Methods | Key Findings | Strengths | Weaknesses |
|---|---|---|---|---|---|---|
| Gao et al.[3] | miR-21 | To assess prognostic value of serum miR-21 in LSCC | Serum qRT-PCR on 236 LSCC patients in a multicenter study | High miR-21 levels were significantly associated with advanced stage and poor 5-year overall survival. AUC for miR-21/10a ratio was 0.896 | Large cohort; multicenter design; includes survival data | No post-treatment monitoring or validation cohort |
| Hu et al.[4] | miR-21 | To evaluate miR-21 expression in tumour tissue and association with prognosis | Tumour tissue qRT-PCR in 46 LSCC patients | miR-21 was significantly overexpressed in tumour tissues and associated with worse 5-year survival. AUC = 0.886 | Clear comparison with adjacent normal tissue; includes survival correlation | Tissue-only analysis; no circulating marker data |
| Re et al.[5] | miR-21-5p | To determine expression of miR-21-5p and its relation to recurrence | Tumour tissue qRT-PCR on 43 LSCC patients | 83.7% of samples showed miR-21-5p overexpression; significantly associated with nodal involvement and recurrence | Targeted marker study; includes clinical-pathological correlation | No blood data; relatively small sample size |
| Falco et al.[6] | miR-223 | To develop a serum diagnostic miRNA signature including miR-223 | Serum qRT-PCR on 130 LSCC patients and healthy controls | miR-223 was part of a high-performing diagnostic panel. Panel AUC = 0.89, sensitivity 88%, specificity 90% | Well-validated diagnostic panel; good control comparison | No survival or longitudinal data; cross-sectional study |
| Hou et al.[7] | miR-21, miR-223 | To examine circulating miRNAs pre- and post-treatment in LSCC | qRT-PCR in plasma and tumour tissue from 25 LSCC patients | miR-223 levels decreased after surgery and increased again with recurrence. miR-21 remained elevated | Shows dynamic behavior of miRNAs; matched tissue and plasma data | Small sample; short follow-up; limited statistical power |

when inter-study variability is substantial. Finally, the test for overall effect was performed using the Z statistic to evaluate the significance of the pooled diagnostic effect, with $p<0.05$ considered indicative of a statistically significant diagnostic role.

### Quality Assessment and Biomarker Measurement

Methodological quality and risk of bias were independently assessed using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool. Particular attention was given to participant selection, outcome assessment, and biomarker measurement methods, including specimen type, qRT-PCR platform, normalization controls, and cut-off determination. Considerable methodological heterogeneity across studies was identified and taken into account during interpretation of the findings.

## RESULTS

### Study Selection

A total of 566 records were identified through database searching in PubMed, Google Scholar, and SciSpace. After removal of 156 duplicate records, 410 studies underwent title and abstract screening, of which 358 were excluded for irrelevance to the study objective. Subsequently, 52 full-text articles were assessed for eligibility. Of these, 47 studies were excluded because they: (1) evaluated tissue miRNAs without relevant diagnostic or prognostic outcomes related to the objectives of the present review, (2) lacked prognostic or recurrence-related outcomes, (3) did not specifically investigate miR-21 or miR-223, (4) were review or experimental-only studies, or (5) did not provide sufficient quantitative data for meta-analysis. The majority of excluded studies either focused exclusively on tissue-based biomarkers or did not provide sufficient outcome data relevant to the objectives of the present review.

Five studies fulfilled the criteria for qualitative systematic review and were included in the narrative synthesis. However, only two studies (Gao et al.[3] and Re et al.[5]) provided extractable diagnostic parameters, including Area Under the Curve (AUC) values and variance-related measures, suitable for exploratory quantitative pooling. The remaining studies were included only in the qualitative synthesis because they did not provide sufficient statistical parameters required for diagnostic meta-analysis, such as confidence intervals or standard error values for AUC estimates. Therefore, the quantitative synthesis was limited to the two studies with complete diagnostic data and should be interpreted as exploratory rather than confirmatory evidence (Figure 1).

### Study Characteristics

Table I summarizes five studies evaluating the diagnostic and prognostic significance of miR-21 and miR-223 in LSCC using circulating and/or tissue-based specimens. Although the primary focus of this review was circulating biomarkers,

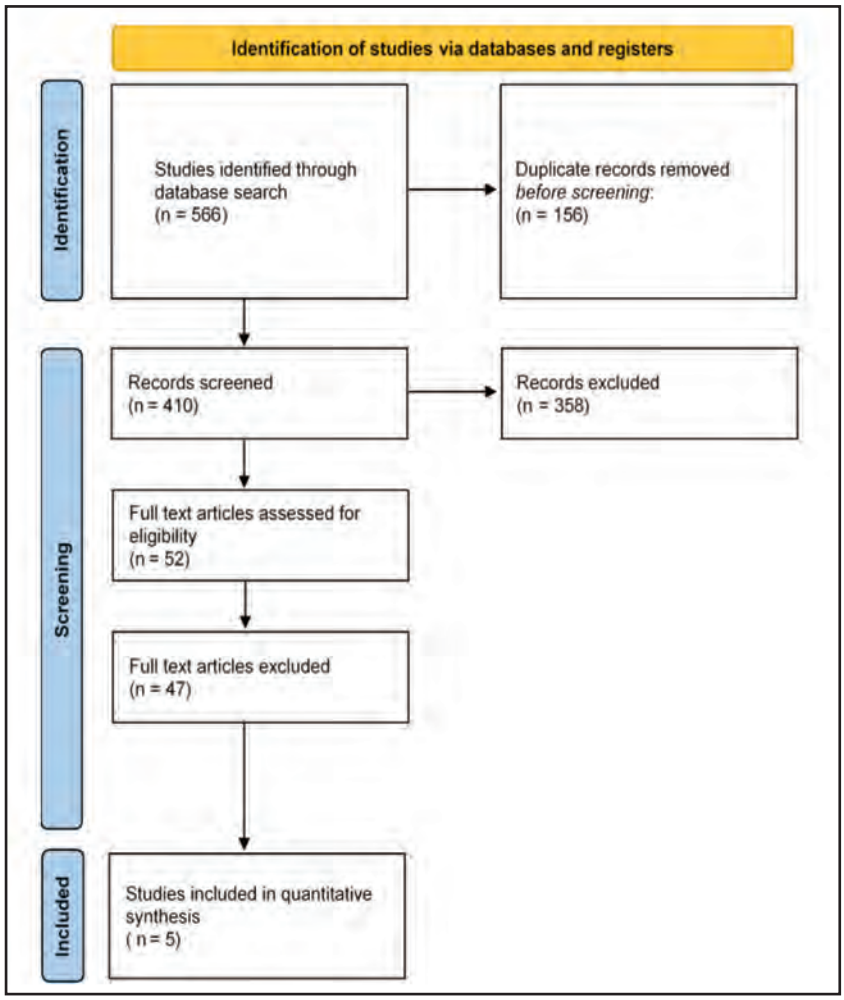



**Fig. 1:** PRISMA flow diagram

**ROBINS-I Risk of Bias Assessment**
**miRNA-21 and miRNA-223 in Laryngeal Squamous Cell Carcinoma Studies**

| Study | Bias due to confounding | Bias in selection of participants | Bias in classification of interventions | Bias due to deviations from intended intervention | Bias due to missing data | Bias in measurement of outcomes | Bias in selection of reported result | Overall risk of bias |
|---|---|---|---|---|---|---|---|---|
| Hu et al. 2014 | Moderate | Moderate | Low | Low | Moderate | Moderate | Moderate | Moderate |
| Re et al. 2017 | Moderate | Moderate | Low | Low | Low | Moderate | Moderate | Moderate |
| Gao et al. 2020 | Moderate | Low | Low | Low | Low | Low | Moderate | Moderate |
| Falco et al. 2024 | Moderate | Low | Low | Low | Low | Low | Moderate | Moderate |
| Hou et al. 2015 | Serious | Moderate | Low | Low | Moderate | Moderate | Moderate | Serious |

**Fig. 2:** Risk of Bias

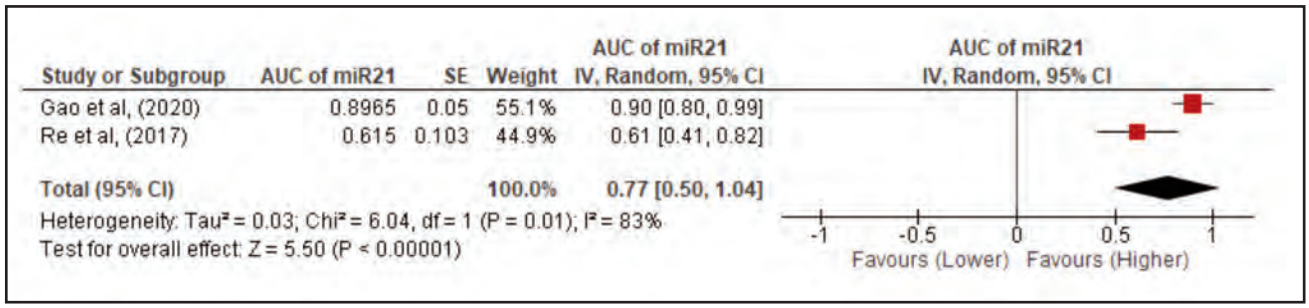



**Fig. 3:** Exploratory diagnostic meta-analysis of miR-21

several eligible studies evaluating tissue-based miRNA expression were also included because they provided clinically relevant prognostic data related to LSCC progression and recurrence.

Gao et al.[3] assessed circulating serum miR-21 and demonstrated strong diagnostic performance (AUC=0.896), along with significant prognostic relevance for five-year survival. Re et al.[5] evaluated miR-21-5p expression in FFPE tissue samples and reported moderate diagnostic accuracy (AUC=0.615), with higher expression significantly associated with advanced tumour stage, nodal involvement, and recurrence. Hu et al.[4] also examined tissue miR-21 expression and reported diagnostic potential (AUC=0.772), although incomplete statistical reporting prevented inclusion in the quantitative meta-analysis.

Falco et al.[6] focused on circulating miR-223 and demonstrated high diagnostic accuracy as part of a serum miRNA panel, while Hou et al.[7] investigated perioperative fluctuations in circulating miR-21 and miR-223 but did not provide AUC values or long-term prognostic metrics. Due to variability in study design and reporting, only two studies (Gao et al.[3]; Re et al.[5]) provided extractable AUC values with variance-related parameters suitable for exploratory quantitative pooling.

**Risk of Bias Assessment**

Based on the ROBINS-I assessment of the five studies evaluating the expression of miR-21 and miR-223 in laryngeal squamous cell carcinoma, the bias due to confounding domain was predominantly rated as *moderate risk*, except for one study (Hou et al.[7]), which showed a *serious risk* due to insufficient control of important confounding factors. In the bias in selection of participants domain, four studies were rated as *moderate risk*, whereas one study (Gao et al.[3]) demonstrated *low risk* because the participant selection process was described more clearly and applied in a more structured manner. For bias in classification of interventions, all studies were assessed as *low risk*, as the classification of miRNA expression was consistently conducted using validated laboratory techniques. The bias due to deviations from intended interventions domain was also rated as *low risk* across all studies, with no indications of deviations that could influence the estimated effect. The bias due to missing data domain showed some variation, with three studies rated as *low risk* and two studies as *moderate risk* due to incomplete reporting of data. In the bias in measurement of outcomes domain, all studies were rated as *moderate risk*, largely because of potential variability in outcome assessment methods and limited information regarding outcome assessor blinding. Meanwhile, in the bias in selection of reported results domain, all studies were judged to have *moderate risk*, as none provided preregistered protocols, and selective reporting could not be ruled out. Overall, four studies were classified as having a *moderate risk* of bias, while one study (Hou et al.[7]) demonstrated a *serious* overall risk. These findings indicate that the overall quality of evidence is moderate and should be interpreted with appropriate caution (Figure 2).

**Exploratory Diagnostic Meta-analysis of miR-21**

The pooled analysis suggested potential clinical discriminatory value of miR-21 in LSCC; however, interpretation remains limited by substantial heterogeneity and the small number of eligible datasets. The pooled AUC was 0.77 (95% CI: 0.50–1.04), suggesting performance above chance level in differentiating LSCC from non-LSCC cases. The overall effect was statistically significant ($Z=5.50$, $p<0.001$). However, several important limitations should be considered. First, the high heterogeneity ($I^2 = 83\%$) indicates substantial variability among studies, justifying the use of a random-effects model and warranting cautious interpretation of the pooled estimate. Second, the wide confidence interval, with the lower bound approaching 0.50, reflects considerable imprecision and uncertainty regarding the true discriminatory performance of miR-21 (Figure 3).

Importantly, although five studies evaluating miR-21 were identified in the systematic review, only two studies provided sufficient extractable quantitative data for meta-analysis. This limitation was primarily due to incomplete reporting of statistical parameters, including missing confidence intervals (Hu et al.[4]), absence of AUC reporting (Hou et al.[7]), or differences in biomarker focus and study endpoints (Falco et al.[6], focusing on miR-223). Furthermore, the included studies varied considerably in terms of clinical objectives, specimen types, laboratory methodologies, normalization controls, and outcome measures. These factors constrained the robustness of the pooled analysis and likely contributed to the substantial heterogeneity observed. Therefore, the findings of this meta-analysis should be interpreted cautiously and considered exploratory and hypothesis-generating rather than definitive evidence of clinical utility.

## DISCUSSION

This systematic review demonstrates the potential clinical value of miR-21 and miR-223 as non-invasive circulating biomarkers in laryngeal squamous cell carcinoma (LSCC). Across all included studies, miR-21 was consistently found to be overregulated in LSCC patients, both in tumour tissue and serum or plasma samples, and strongly correlated with advanced clinical stage, lymph node metastasis, and poor prognosis. In a multicentre study by Gao et al.[3], involving 236 LSCC patients, high serum levels of miR-21 and miR-21/miR-10a ratio were significantly associated with poor survival outcomes, with an AUC of 0.896, supporting its prognostic relevance. Similarly, Hu et al.[4] reported that elevated miR-21 expression in tumour tissues was linked to lower 5-year survival and higher recurrence rates, with an AUC of 0.886 for diagnostic performance. Re et al.[5] further validated the role of miR-21-5p in LSCC, showing that 83.7% of tumour tissue samples expressed high miR-21-5p, which correlated with lymph node involvement and recurrence.[5]

miR-21 functions as an oncomiR that negatively regulates tumour suppressor genes, contributing to cellular proliferation, migration, and invasion in malignancies. Although mechanistic insights were not extensively evaluated in these clinical studies, the observed associations between miR-21 levels and tumour aggressiveness provide strong clinical support for its use as a prognostic tool. Importantly, the fact that miR-21 is measurable in serum or plasma underscores its feasibility for non-invasive clinical applications, such as early diagnosis, risk stratification, and post-treatment surveillance.[3,5]

On the other hand, miR-223 was not studied as widely but showed a distinctly dynamic pattern in relation to treatment response and disease recurrence. Hou et al. found that circulating miR-223 levels declined significantly after surgical resection and increased again in patients who experienced recurrence, suggesting its utility as a real-time biomarker for monitoring LSCC progression or relapse.[7] This behaviour supports its potential role in longitudinal follow-up, particularly in post-operative patients who require sensitive and specific tools for recurrence detection. Furthermore, Falco et al. identified miR-223 as part of a 5-miRNA serum diagnostic signature in 130 LSCC patients. This panel achieved an AUC of 0.89, sensitivity of 88%, and specificity of 90%, indicating strong diagnostic potential, although miR-223 was not analysed independently in that study.[6]

miR-21 is one of the most widely studied oncomiRs across head and neck cancers, including HNSCC broadly and LSCC specifically. Its upregulation has been documented not only in laryngeal carcinoma tissue but also in circulating blood components of HNSCC patients, where miR-21 levels decreased after surgical resection in those with good prognosis but remained high in cases with poor outcome. This supports the relevance of miR-21 as a dynamic circulating biomarker for disease monitoring.[10]

Biologically, miR-21 is known to target tumour suppressor pathways such as PTEN and related downstream signalling, which promotes proliferation and inhibits apoptosis. In LSCC, exosomal miR-21 correlates with reduced PTEN expression, indicating a possible negative regulatory effect on tumour suppressor signalling and contributing to invasive behaviour. This mechanistic insight strengthens its potential utility beyond mere association.[11]

In contrast, miR-223 behaves differently. While many reports of circulating miR-223 in HNSCC suggest that this miRNA can be upregulated in tumour tissues, clinical findings in LSCC serum have shown a decrease in exosomal miR-223 relative to healthy controls.[11] This suggests that miR-223 may play a tumour-suppressive role in the laryngeal carcinoma context, possibly through modulation of the inflammatory tumour microenvironment. Recent data in broader HNSCC research further indicate that dynamic changes in circulating miR-223 post-treatment may correlate with recurrence risk, highlighting its utility in longitudinal surveillance strategies.[10] miR-223 has also shown potential as a non-invasive biomarker in head and neck cancers. In a study by Perdomo et al., low miR-223 expression was associated with an increased risk of metastasis and poor prognosis, although its association was not as strong as that of miR-21. miR-223 is believed to play a role in modulating immune and inflammatory responses through its influence on the NF-κB pathway and the regulation of myeloid cells. The loss of miR-223 regulation may contribute to tumour aggressiveness and resistance to therapy.[2]

Modern research in HNSCC emphasizes the emerging role of circulating miRNAs as part of precision oncology approaches, particularly for real-time monitoring of treatment response and recurrence. A recent *observational prospective study* in HNSCC patients demonstrated that circulating miR-21-5p and other miRNAs strongly associate with tumour burden and stage, supporting their potential as markers for ongoing disease monitoring and tailoring of therapy decisions.[12]

Previous systematic reviews have evaluated the role of multiple microRNAs in laryngeal cancer; however, these studies generally included heterogeneous microRNA targets and broader diagnostic or prognostic objectives. In contrast, the present review specifically focused on circulating miR-21 and miR-223 as prognostic biomarkers in LSCC. Although only a limited number of eligible studies were identified, this reflects the current scarcity of focused evidence on these biomarkers and highlights the need for further standardized large-scale investigations. Despite the limited number of included studies, this focused synthesis remains important to summarize the currently available evidence and identify existing research gaps regarding the prognostic utility of miR-21 and miR-223 in LSCC.

Several limitations of this study should be acknowledged. First, the number of eligible studies was limited, with only five studies included in the systematic review and only two studies providing sufficient diagnostic accuracy data for quantitative synthesis. Second, considerable heterogeneity was observed among the included studies, particularly regarding specimen types, laboratory methodologies, normalization controls, patient populations, and reported clinical outcomes. Third, most included studies were observational in design and had moderate risk of bias, which may affect the robustness and generalizability of the findings. In addition, the small

number of studies precluded subgroup analysis and publication bias assessment. Therefore, the results of this meta-analysis should be interpreted cautiously and considered hypothesis-generating rather than definitive evidence for immediate clinical implementation. Further large-scale, standardized, and prospective studies are needed to validate the prognostic utility of miR-21 and miR-223 in LSCC.

## CONCLUSION

Current evidence suggests that miR-21 is associated with aggressive clinicopathological features and poorer prognosis in LSCC, while miR-223 may have potential utility in recurrence monitoring. Nevertheless, the available evidence remains limited due to the small number of eligible studies, methodological heterogeneity, and incomplete quantitative reporting. Therefore, the findings should be interpreted cautiously, and further large-scale, standardized, and prospective studies are required before these biomarkers can be translated into routine clinical practice.

## ACKNOWLEDGEMENTS

The authors would like to thank the research colleagues and research assistants who supported the literature search and data extraction process. We also acknowledge those whose valuable discussions and insights contributed to the refinement of the research framework. We also acknowledge the institutions that provided access to online databases that enabled this comprehensive and systematic literature review for their significant contributions to the field of laryngeal squamous cell carcinoma research.

## CONFLICT OF INTEREST

None.

## ETHICAL APPROVAL

Not required.

## REFERENCES

1. Juwita J. Microrna-21, Microrna-155 dan Microrna-10B: bagaimana perannya pada kanker payudara? J Kedokt Syiah Kuala 2017; 17(2): 119-25.
2. Sanjaya A. An introduction to microRNA: a primer for clinicians and medical researchers. J Med Health 2023; 5(1).
3. Gao S, Xu Q, Zhou Y, Zhang T, Meng X, Chen Z, et al. Serum levels of microRNA-21 and microRNA-10a can predict long-term prognosis in laryngeal cancer patients: a multicenter study. Transl Cancer Res 2020; 9(5): 3680-90.
4. Hu A, Huang JJ, Xu WH, Jin XJ, Li JP, Tang YJ, et al. miR-21 and miR-375 microRNAs as candidate diagnostic biomarkers in squamous cell carcinoma of the larynx: association with patient survival. Am J Transl Res 2014; 6(5): 604-13.
5. Re M, Magliulo G, Gioacchini FM, Marzetti A, Ferrante L, Anzivino R, et al. Expression and clinical significance of miR-21-5p in LSCC. Biomed Res Int 2017; 2017: 3921258.
6. Falco M, Tammaro C, Cossu AM, Imperatore F, La Mantia I, Galli G, et al. Identification and bioinformatic characterization of a serum miRNA signature for early detection of laryngeal squamous cell carcinoma. J Transl Med 2024; 22: 647.
7. Hou B, Ishinaga H, Midorikawa K, Nakamura S, Hiraku Y, Oikawa S, et al. Circulating microRNAs as novel prognosis biomarkers for head and neck squamous cell carcinoma. Cancer Biol Ther 2015; 16(7): 1042-6.
8. Ayaz L, Görür A, Yaroğlu HY, Özcan C, Tamer L. Differential expression of microRNAs in plasma of patients with laryngeal squamous cell carcinoma: potential early-detection markers for laryngeal squamous cell carcinoma. J Cancer Res Clin Oncol 2013; 139(9): 1499-506.
9. Banta A, Bratosin F, Golu I, Toma AO, Domuta EM. Diagnostic and prognostic value of microRNAs in patients with laryngeal cancer: a systematic review. Diagnostics (Basel) 2025; 15(3): 394.
10. Hsu CM, Lin PM, Wang YM, Chen ZJ, Lin SF, Yang MY. Circulating miRNA is a novel marker for head and neck squamous cell carcinoma. Tumour Biol 2012; 33(6): 1933-42.
11. Genc S, Yagci T, Vageli DP, Dundar R, Doukas PG, Doukas SG, et al. Exosomal microRNA-223, microRNA-146, and microRNA-21 profiles and biochemical changes in laryngeal cancer. ACS Pharmacol Transl Sci 2023; 6(5): 820-8.
12. Galindo Torres BP, Alcaraz Ortega R, Saiz López P, Adiego Leza MI, Moradillo Renuncio MDM, García Girón C, et al. New evidence for miRNA testing in head and neck squamous cell cancer patients. Clin Transl Oncol 2025; 27(8): 3399-409.

# Trends in adipokine-related studies in cardiovascular disease: A bibliometric analysis from 2002 to 2024

**Sunita Sunita, Dr.[1,4,7], Mohammad Rizki Akbar, Dr.[2,4], Mohammad Ghozali, Dr.[3,4], Iis Inayati Rakhmat, Dr.[4,5], Agung Riyadi, MPH[6], Annisa Dewi Nugrahani, MSc.[1], Ratih Rinendyaputri, Dr.[8], Gaga Irawan Nugraha, Dr.[3,4], Mas Rizky A A Syamsunarno, Dr.[3,4]**

[1]Faculty of Medicine Universitas Padjadjaran, Bandung, West Java, Indonesia, [2]Department of Cardiology and Vascular Medicine, Hasan Sadikin General Hospital-Faculty of Medicine Universitas Padjadjaran, Bandung, West Java, Indonesia, [3]Department of Biomedical Sciences, Faculty of Medicine Universitas Padjadjaran, Bandung, West Java, Indonesia, [4]Cardiometabolic Working Group Study, Faculty of Medicine Universitas Padjadjaran, Bandung, West Java, Indonesia, [5]Department of Biochemistry, Faculty of Medicine, Jenderal Achmad Yani University, Kota Cimahi, Jawa Barat, Indonesia, [6]Department of Nursing, Poltekkes Kemenkes Bengkulu, Bengkulu, Indonesia, [7]Department of Medical Laboratory Technology, Poltekkes Kemenkes Bengkulu, Bengkulu, Indonesia, [8]Center for Biomedical Research, National Research and Innovation Agency (BRIN), Cibinong Science Centre, Cibinong, West Java, Indonesia.

## ABSTRACT

**Introduction: Adipokines are bioactive proteins secreted by adipose tissue and are increasingly recognised for their role in obesity, inflammation, metabolic dysfunction, and cardiovascular disease (CVD). As research on adipokines and CVD has expanded over the past two decades, bibliometric analysis provides an important approach for mapping publication trends, research hotspots, citation patterns, and international collaboration. This study aimed to analyse global research trends related to adipokines and cardiovascular disease from 2002 to 2024.**

**Materials and Methods: A bibliometric analysis was conducted using publications retrieved from the Scopus database. Publications were identified using predefined search terms related to adipokines and cardiovascular disease. Bibliometric indicators included publication trends, author keywords, citation patterns, country contributions, and international collaboration. The retrieved data were analysed using Biblioshiny and VOSviewer version 1.6.16 to visualise bibliometric networks and research patterns.**

**Results: A total of 1,283 documents from 602 sources were included in the analysis. Annual publication output increased substantially from 2002 and peaked around 2013–2014. Keyword analysis identified obesity, adiponectin, leptin, inflammation, and metabolic dysfunction as dominant research themes associated with cardiovascular disease. Citation analysis demonstrated several highly influential publications related to adipokines and cardiometabolic disorders. The United States contributed the largest publication output, citation impact, and international collaboration within the field.**

**Conclusion: Research on adipokines and cardiovascular disease has expanded substantially over the past two decades, with major thematic emphasis on obesity, metabolic dysfunction, and inflammatory pathways. This bibliometric analysis provides a comprehensive overview of the intellectual structure and global research landscape in this field. The findings may help identify future research priorities related to adipokines as potential biomarkers, preventive targets, and therapeutic approaches in cardiovascular disease.**

**KEYWORDS:**
*Adipokines; bibliometrics; cardiovascular disease*

## INTRODUCTION

Obesity has become a global pandemic contributing substantially to the increasing prevalence of cardiometabolic diseases worldwide.[1-2] Obesity is strongly associated with cardiovascular disease (CVD) through multiple mechanisms, including haemodynamic alterations, insulin resistance, hypertension, dyslipidaemia, and adipose tissue dysfunction.[3]

Adipose tissue functions as an active endocrine organ that secretes cytokines, hormones, growth factors, and adipokines involved in metabolic and inflammatory regulation.[4] In obesity, adipose tissue dysfunction alters adipokine secretion and promotes chronic low-grade inflammation, oxidative stress, endothelial dysfunction, and vascular homeostasis impairment.[5] Several pro-inflammatory adipokines, including leptin, resistin, visfatin, RBP4, IL-6, and FABP-4, have been associated with cardiovascular pathogenesis.[6-7] In contrast, anti-inflammatory adipokines such as adiponectin, FGF-21, and GDF-15 may exert cardioprotective effects.[8-9] These findings indicate that adipokines play an important role in linking obesity with cardiovascular disease.[10]

Given the complexity and growing body of research on adipokines, obesity, and cardiovascular disease (CVD), bibliometric analysis provides a useful approach for mapping the development of this research field. Unlike systematic reviews, which are primarily intended to synthesise evidence related to specific clinical questions, bibliometric analyses evaluate publication trends, citation patterns, collaboration networks, keyword structures, and the intellectual evolution of a scientific field. This approach is therefore useful for identifying dominant themes, emerging

*This article was accepted: 30 May 2026*
*Corresponding Author: Mohammad Rizki Akbar*
*Email: dr.m.rizki.akbar@gmail.com*

research hotspots, knowledge gaps, and future research directions.

Bibliometric studies are increasingly used to evaluate scientific productivity and research development through quantitative and visual mapping techniques. These analyses help researchers identify influential publications, leading countries, collaborative networks, and thematic structures within a particular field.[11-12] Although bibliometric analysis does not directly assess clinical effectiveness, it provides important insights into the evolution of adipokine-related cardiovascular research and may support future studies on biomarkers, risk stratification, prevention, and therapeutic targets for cardiometabolic disease. To date, however, no comprehensive bibliometric study has systematically mapped the global research landscape linking adipokines and cardiovascular disease over the past two decades. Therefore, this study aimed to analyse global research trends, citation patterns, keyword structures, and country contributions related to adipokines and cardiovascular disease from 2002 to 2024.

## MATERIALS AND METHODS

### Study design

This study employed a bibliometric analysis to evaluate global research trends related to adipokines and cardiovascular disease from 2002 to 2024. Bibliometric analysis is a quantitative approach used to examine publication trends, citation structures, research collaboration, and thematic development within a scientific field. The reporting structure of this study was adapted from published bibliometric methodological recommendations and reporting guidelines.[12]

### Data source and search strategy

Publications were retrieved from the Scopus database (SciVerse Scopus; Elsevier), which is widely used in bibliometric studies because of its extensive journal coverage and citation indexing features.[13] The database search was conducted on August 2nd 2024. The search strategy used keywords related to adipokines and cardiovascular disease within the title, abstract, and keyword fields. (TITLE-ABS-KEY (cardiovascular disease) AND TITLE-ABS-KEY (adipokines)) AND (LIMIT-TO (SUBJAREA, "MEDI")) AND (LIMIT-TO (DOCTYPE, "ar")) AND (LIMIT-TO (LANGUAGE, "English")) AND (LIMIT-TO (EXACTKEYWORD, "Adipokines")) AND PUBYEAR > 2001 AND PUBYEAR < 2025. Only documents indexed in Scopus during the study period were included in the analysis.

### Eligibility Criteria and Document Selection

Documents were included if they met the following criteria: (1) indexed in the Scopus database; (2) published between 2002 and 2024; (3) written in English; (4) classified as journal articles; (5) categorised within the Medicine subject area; and (6) retrieved using the predefined title, abstract, and keyword search strategy related to adipokines and cardiovascular disease. Documents were excluded if they were not indexed in Scopus, were published outside the study period, were not written in English, were not classified as journal articles, were outside the Medicine subject area, or did not match the predefined Scopus search filters.

The document selection process was conducted using Scopus-based bibliometric filtering rather than manual clinical eligibility screening. After applying the predefined search query and database filters, the final dataset was exported from Scopus and used for bibliometric analysis. Therefore, the screening process was based on database indexing fields, search terms, document type, subject area, language, and publication year, consistent with bibliometric methodology and reporting recommendations.

### Bibliometric indicators and data analysis

The bibliometric indicators analysed in this study included: (1) document type and publication language; (2) annual publication trends; (3) author keyword occurrence and co-occurrence patterns; (4) citation analysis and highly cited documents; (5) the ten most cited countries; and (6) international collaboration patterns. Citation data were obtained directly from the Scopus database, including total citation counts for individual publications. Country-level publication output and citation metrics were also retrieved from Scopus by analysing annual publication and citation distributions across countries. Bibliometric analysis and visualisation were performed using VOSviewer version 1.6.16. and Biblioshiny interface in RStudio.[14-15] These software programs were used to generate and visualise bibliometric networks, including keyword co-occurrence, citation relationships, and collaboration patterns.

## RESULTS

### General bibliometric characteristics

Figure I summarises the general characteristics of the bibliometric dataset related to adipokines and cardiovascular disease. A total of 1,283 documents published between 2002 and 2024 from 602 sources were included in the analysis. The dataset involved 7,121 authors, with an average of 7.06 co-authors per document and an international co-authorship rate of 17.15%. The annual publication growth rate was 3.2%, with an average citation count of 34.78 citations per document. A total of 1,887 author keywords and 55,700 references were identified across the included publications.

### Publication development trend

Figure 2 presents the annual publication trends related to adipokines and cardiovascular disease between 2002 and 2024. Publication output increased substantially from 2005 onward and reached a peak around 2013–2014, with approximately 120 publications per year. After this period, publication activity gradually declined with moderate fluctuations. The lower publication counts observed in recent years may partially reflect incomplete database indexing for 2024.

### Most author keywords

Figure 3 illustrates the keyword co-occurrence network generated using VOSviewer. Five thematic clusters were identified, representing major research areas related to adipokines and cardiovascular disease. The largest clusters were associated with obesity, metabolic disorders, inflammation, disease pathogenesis, biomarkers, and cardiovascular risk factors. These findings demonstrate that adipokine-related cardiovascular research is closely interconnected with obesity-associated metabolic and inflammatory pathways.

**Table I: Top 10 Most Cited Publications Related to Adipokines and Cardiovascular Disease**

| Authors | Years | Journal | PubMed Identifier | Total Citations | Total Citations per Year |
|---|---|---|---|---|---|
| Waschki et al | 2011 | Chest | 21273294 | 746 | 53.29 |
| Adams et al | 2017 | Gut | 28314735 | 740 | 92.50 |
| Goralski et al | 2007 | J Biol Chem | 17635925 | 694 | 38.56 |
| Brien et al | 2011 | Bmj | 21343206 | 576 | 41.14 |
| Neeland et al | 2012 | J Am Med Assoc | 22990274 | 481 | 37.00 |
| Venteclef et al | 2015 | Eur Heart J | 23525094 | 410 | 41.00 |
| Bruun et al | 2006 | Am J Physiol Endocrinol Metab | 16352667 | 352 | 18.53 |
| Trayhurn et al | 2008 | Br J Nutr | 18397542 | 351 | 20.65 |
| Fantuzzi et al | 2008 | J Allergy Clin Immunol | 18061654 | 343 | 20.18 |
| Christiansen et al | 2005 | Int J Obes | 15520826 | 340 | 17.00 |


**Fig. 1:** General bibliometric characteristics of publications related to adipokines and cardiovascular disease from 2002 to 2024. The figure summarises the main dataset indicators, including publication output, sources, authorship, collaboration patterns, references, and citation metrics

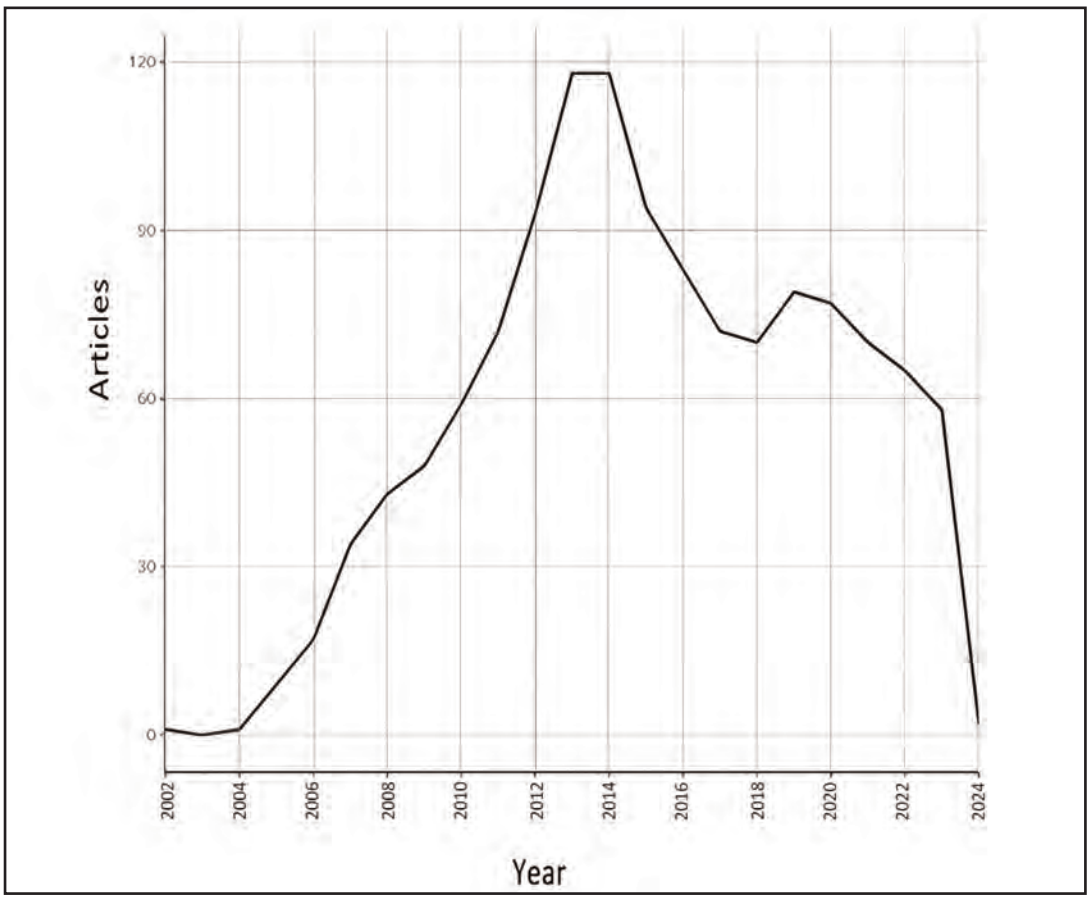



**Fig. 2:** Annual publication trends of studies related to adipokines and cardiovascular disease from 2002 to 2024. Publication output increased markedly after 2005 and reached its peak around 2013–2014

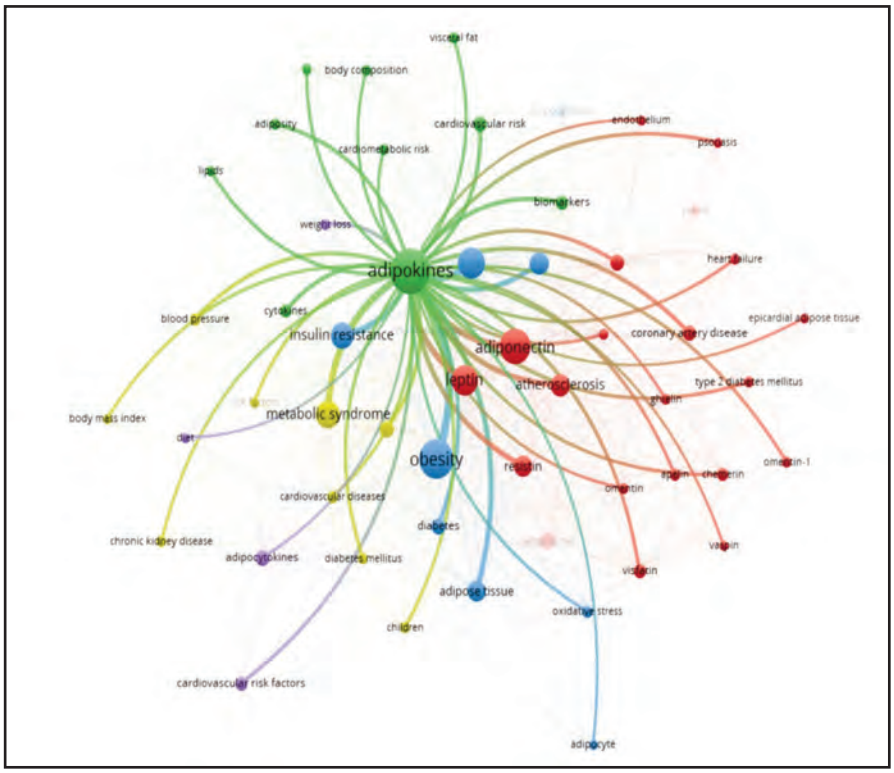



**Fig. 3:** Keyword co-occurrence network related to adipokines and cardiovascular disease generated using VOSviewer version 1.6.16. Node size represents keyword frequency, while line thickness indicates the strength of co-occurrence between keywords. Different colours indicate thematic keyword clusters. Major research themes identified in the network included obesity, metabolic disorders, inflammation, insulin resistance, adiponectin, leptin, atherosclerosis, and cardiovascular risk factors

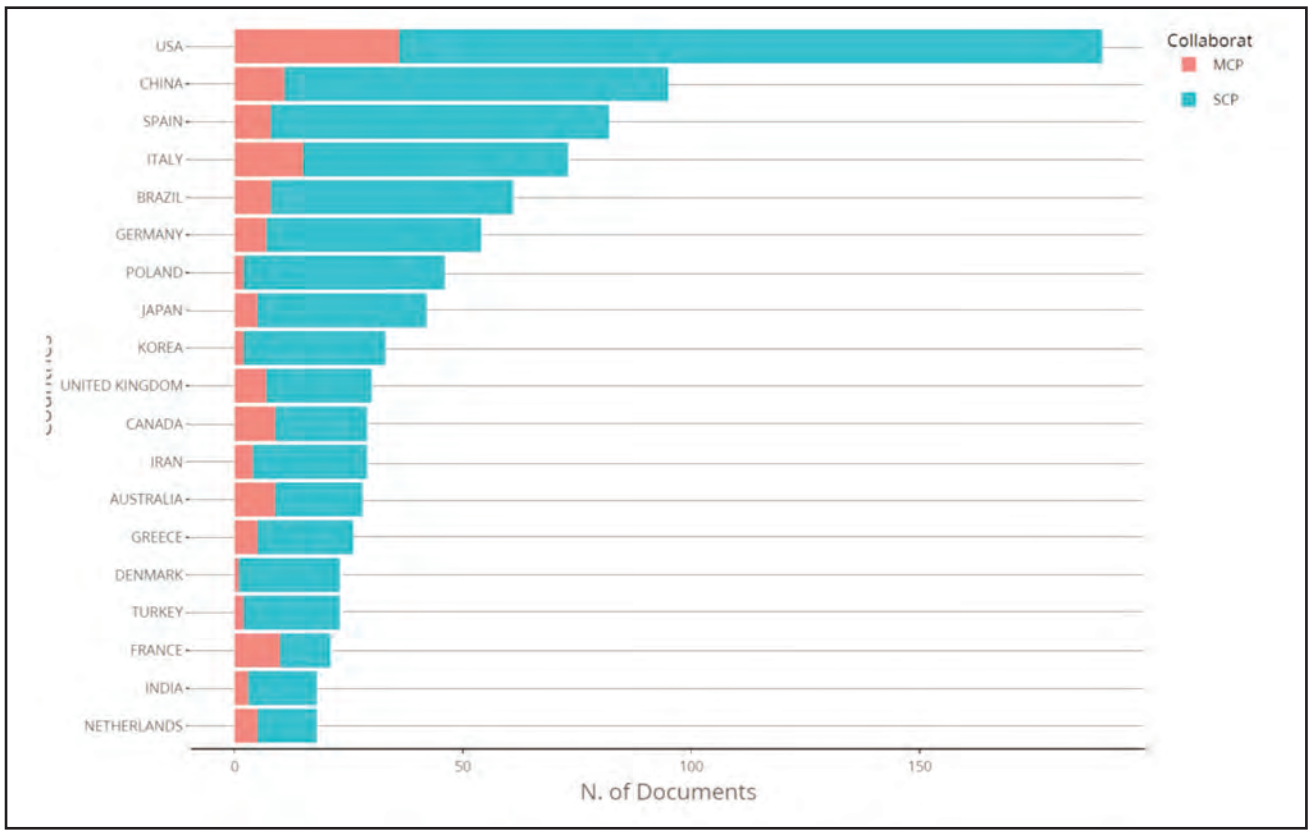



**Fig. 4:** Distribution of single-country publications (SCP) and multiple-country publications (MCP) related to adipokines and cardiovascular disease across contributing countries. SCP represents publications produced within a single country, whereas MCP indicates publications involving international collaboration. The United States demonstrated the highest publication output and international collaborative activity among all countries analysed

**Top 10 most cited documents**

Table I presents the ten most cited publications related to adipokines and disease. Adams et al.[25] published in Gut demonstrated the highest average citations per year (92.50 citations/year), whereas Waschki et al.[24] published in Chest had the highest total citation count (746 citations). Several highly cited publications were related to obesity, metabolic dysfunction, inflammation, and cardiometabolic disorders.

Table I Summarises the ten most cited publications related to adipokines and cardiovascular disease identified from the Scopus database. Total citations represent cumulative citation counts, whereas citations per year indicate annual citation impact.

**Inter-country collaboration regarding the relationship of adipokines to cardiovascular disease**

Figure 4 demonstrates the distribution of single-country publications (SCP) and multiple-country publications (MCP) related to adipokines and cardiovascular disease. The United States showed the highest publication output and international collaboration, followed by China, Spain, and Italy. Most countries demonstrated a predominance of domestic publications, although several countries exhibited notable international collaborative activity. Citation analysis by country indicated that the United States had the highest citation impact, followed by Italy, Germany, Canada, and Spain.

## DISCUSSION

**Search scope and dataset characteristics**

This bibliometric analysis provides an overview of Scopus-indexed publications related to adipokines and cardiovascular disease from 2002 to 2024. The retrieved dataset consisted of 1,283 publications from 602 sources, with an average citation count of 34.78 citations per document. These findings indicate that adipokine-related cardiovascular research has developed into a sizeable and multidisciplinary scientific field over the past two decades.

The bibliometric dataset was analysed using VOSviewer and Biblioshiny to evaluate publication trends, keyword structures, citation patterns, and international collaboration networks. The findings should be interpreted within the methodological scope of Scopus-indexed bibliometric analysis because publications indexed in other databases may not have been captured.[12,16-17]

**Publication development trend**

The annual publication trend indicates a substantial increase in adipokine-related cardiovascular research, with the highest publication output observed around 2013–2014. There was a decline from 2015 to 2018, and there was an increase again in 2019 before there was another decline until 2023. The peak of the increasing publication trend from 2013 to 2014 may reflect growing scientific attention to the role of adipokines in cardiometabolic and cardiovascular research during that period.[18]

However, the decline observed after the peak years should be interpreted cautiously. A lower number of publications does not necessarily indicate a definitive reduction in research interest. It may also reflect changes in terminology, diversification of research topics, database indexing patterns, or incomplete indexing for more recent publication years.[17] Therefore, while the trend suggests a shift in publication output over time, further interpretation should consider methodological and database-related limitations. The observed pattern still indicates that adipokine-related cardiovascular disease research remains relevant, particularly for identifying future directions in biomarker research, risk stratification, and cardiometabolic prevention.[12,16-17]

**Most Author Keywords**

Keyword co-occurrence analysis indicated that adipokine-related cardiovascular research is strongly concentrated around obesity, metabolic dysfunction, inflammation, insulin resistance, adiponectin, leptin, and cardiovascular risk.[12,19] These thematic patterns suggest that adipokines are most frequently studied within the broader context of cardiometabolic dysregulation rather than as isolated biomarkers.

The prominence of obesity, metabolic syndrome, insulin resistance, adiponectin, and leptin indicates that current research has mainly focused on the mechanistic link between adipose tissue dysfunction and cardiovascular disease.[1,16] This finding is biologically plausible because altered adipokine secretion may contribute to endothelial dysfunction, chronic low-grade inflammation, oxidative stress, atherosclerosis, and impaired vascular homeostasis5. Therefore, the keyword structure supports the role of adipokines as important mediators between obesity-related metabolic abnormalities and cardiovascular outcomes.[20-21]

The relatively smaller occurrence of some cardiovascular-specific terms should not be interpreted as indicating low clinical relevance. Rather, it may suggest that the specific cardiovascular implications of adipokines remain an evolving research area.[12,22] Future studies may further investigate adipokines as predictive biomarkers, risk-stratification tools, therapeutic targets, and preventive indicators in cardiovascular disease.[22-23] Less visible nodes, such as adipocytokine and physical activity, should therefore be interpreted as terms with lower frequency within the retrieved dataset rather than terms lacking scientific importance.[12]

**Top 10 Most Cited Documents**

The citation analysis identified influential publications within the retrieved Scopus-indexed dataset. Highly cited documents were mainly related to obesity, metabolic dysfunction, inflammation, fatty liver disease, physical activity, and cardiometabolic outcomes.[24-25] This pattern indicates that adipokine-related cardiovascular research is closely linked to broader cardiometabolic and inflammatory research domains.

However, citation counts should be interpreted cautiously.[12,17] A high citation number does not necessarily indicate direct topic specificity or superior clinical relevance because citation impact may be influenced by publication year, journal

visibility, article type, topic breadth, and citation behaviour within each research field.[12,17] Therefore, highly cited articles in this bibliometric dataset should be interpreted as influential publications within the broader adipokine–cardiometabolic research landscape rather than as direct evidence of clinical effectiveness.

The inclusion of some highly cited articles that are not exclusively focused on adipokines and cardiovascular disease reflects the keyword-based nature of bibliometric retrieval.[12] These articles may have been captured because of their broader relevance to metabolic, inflammatory, or cardiometabolic pathways. This finding highlights the importance of interpreting citation analysis within the methodological scope and limitations of bibliometric mapping.[17]

**Inter-country collaboration regarding the relationship of adipokines to cardiovascular disease**

The country-level analysis demonstrated that adipokine-related cardiovascular research is largely dominated by countries with strong biomedical research infrastructure, particularly the United States, China, Spain, Italy, and Germany.[12,26] This pattern may reflect differences in research funding, institutional capacity, database visibility, international networks, and scientific productivity.[29]

International collaboration, represented by multiple-country publications, may increase research visibility and citation impact by connecting investigators across different scientific environments.[26-27] However, the predominance of single-country publications in several countries suggests that collaboration patterns remain uneven across regions. This finding indicates an opportunity to strengthen cross-national research networks, especially in regions experiencing an increasing burden of obesity and cardiometabolic disease.[28-29]

The absence of Indonesia among the leading contributors should be interpreted cautiously because the analysis was limited to Scopus-indexed publications and was not normalised by population size, number of researchers, national research funding, or institutional publication capacity.[12,30] Nevertheless, this finding may indicate an opportunity for researchers in Southeast Asia, including Indonesia, to contribute more actively to adipokine-related cardiovascular research, particularly because obesity, lifestyle factors, cardiometabolic risk, and cardiovascular disease profiles may vary across populations.[28,29]

## LIMITATIONS

This study has several strengths. First, it provides a broad bibliometric overview of adipokine-related cardiovascular disease research over more than two decades, covering publications from 2002 to 2024. Second, the use of established bibliometric tools, namely VOSviewer and Biblioshiny, allowed the visualisation of publication trends, keyword structures, citation patterns, and international collaboration.[12,19] Third, the analysis included several bibliometric indicators, such as publication output, author keywords, citation counts, country contribution, SCP, and MCP, which provide a comprehensive description of the development of this research field.

However, this study also has several limitations. First, the analysis relied only on the Scopus database; therefore, relevant publications indexed in other databases, such as Web of Science, PubMed, or Google Scholar, may not have been included. Second, the findings depend on the search terms used, meaning that some relevant studies may have been missed if they used different terminology, while some broader articles may have been retrieved if they contained the selected keywords. Third, citation counts are influenced by article age, journal visibility, research field, and publication type; therefore, citation impact should not be interpreted as a direct indicator of study quality or clinical importance. Fourth, bibliometric analysis does not assess methodological quality, risk of bias, or clinical effectiveness of individual studies.[17] Finally, publication trends in recent years should be interpreted cautiously because indexing for the most recent publications may be incomplete. In addition, bibliometric visualisation outputs generated by VOSviewer and Biblioshiny should be interpreted as exploratory mapping tools rather than direct measures of causal or clinical relationships.[12,17]

Despite these limitations, the study provides a useful map of the intellectual development, dominant themes, and global contribution patterns in adipokine-related cardiovascular disease research. The findings may help researchers identify future research priorities, especially in relation to adipokines as potential biomarkers, risk-stratification tools, and therapeutic targets in cardiovascular disease.

## CONCLUSION

This bibliometric study provides an overview of global research trends related to adipokines and cardiovascular disease from 2002 to 2024. The findings indicate that adipokine-related cardiovascular research has expanded substantially over the past two decades, with major themes involving obesity, metabolic dysfunction, inflammation, adiponectin, leptin, and cardiovascular risk. Publication and citation patterns show that developed countries, particularly the United States and China, have contributed substantially to this field of study. However, these findings should be interpreted within the limitations of a Scopus-indexed bibliometric analysis.

In conclusion, this study highlights that the relationship between adipokines and cardiovascular disease remains a relevant area for future scientific investigation. Further studies are needed to strengthen evidence on the role of adipokines as potential biomarkers, risk-stratification tools, and therapeutic targets in cardiovascular disease. Greater international collaboration, including contributions from underrepresented regions such as Southeast Asia and Indonesia, may help broaden scientific understanding of adipokine-related cardiovascular risk across diverse populations.

## ACKNOWLEDGMENTS

We are grateful for the technical assistance provided by Irham L. M. and Sianu R.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## FUNDING

This study was supported by the Ministry of Research, Technology and Higher Education Indonesia Research Grant 2024, Derivative Contract Number: 3938/UN6.3.1/PT.00/2024.

## ETHICAL APPROVAL

Not required for this study type as it is based exclusively on data from published literature.

## REFERENCES

1. Piche ME, Tchernof A, Després JP. Syndrome, Metabolic Compendium, CVD; Obesity Phenotypes, Diabetes, and Cardiovascular Diseases. Circ Res 2020; 126: 1477-500.
2. Farkhondeh T, Llorens S, Pourbagher-Shahri AM, Ashrafizadeh M, Talebi M, Shakibaei M, et al. An overview of the role of adipokines in cardiometabolic diseases. Molecules 2020; 25(21): 1-16.
3. Lau WB, Ohashi K, Wang Y, Ogawa H, Murohara T, Ma XL, et al. Role of adipokines in cardiovascular disease. Circ J [Internet] 2017; 81(7): 9208.
4. Stanek A, Brożyna-Tkaczyk K, Myśliński W. The role of obesity-induced perivascular adipose tissue (Pvat) dysfunction in vascular homeostasis. Nutrients 2021; 13(11): 1-18.
5. Fasshauer M, Blüher M. Adipokines in health and disease. Trends Pharmacol Sci 2015; 36(7): 461-70.
6. Egbuche O, Biggs ML, Ix JH, Kizer JR, Lyles MF, Siscovick DS, et al. Fatty acid binding protein-4 and risk of cardiovascular disease: the cardiovascular health study. J Am Heart Assoc 2020; 9(7): e014070.
7. van der Ark-Vonk EM, Puijk M V., Pasterkamp G, van der Laan SW. The effects of FABP4 on cardiovascular disease in the aging population. Curr Atheroscler Rep 2024; 26(5): 163-75.
8. Yan Y, Wang L, Zhong N, Wen D. Multifaced roles of adipokines in endothelial cell function. Front Endocrinol (Lausanne) 2024; (November): 1-13.
9. Mcleod K, Datta V, Fuller S. Adipokines as Cardioprotective Factors : BAT Steps Up to the Plate. Biomedicines 2025; 13: 710.
10. Queiroz M, Sena CM. Perivascular adipose tissue: a central player in the triad of diabetes, obesity, and cardiovascular health. Cardiovasc Diabetol 2024; 23(1): 455.
11. Yan L. Mapping the Literature on Academic Publishing : A Bibliometric Analysis on WOS. SAGE Open. 2023; (March): 1-16.
12. Donthu N, Kumar S, Mukherjee D, Pandey N, Lim WM. How to conduct a bibliometric analysis: an overview and guidelines. J Bus Res 2021; 133: 285-96.
13. Falagas ME, Pitsouni EI, Malietzis GA, Pappas G. Comparison of PubMed, Scopus, Web of Science, and Google Scholar: strengths and weaknesses. FASEB J 2008; 22(2): 338-42.
14. Ullah F, Shen L, Shah SHH. Value co-creation in business-to-business context: a bibliometric analysis using histcite and VOS viewer. Front Psychol 2023; 13(January): 1-21.
15. Aria M, Cuccurullo C. Bibliometrix: an r-tool for comprehensive science mapping analysis. J Informetr 2017; 11(4): 959-75.
16. Jouy SH, Mohan S, Scichilone G, Mostafa A, Mahmoud AM. Adipokines in the Crosstalk between Adipose Tissues and Other Organs: Implications in Cardiometabolic Diseases. Biomedicines 2024; 12(2129): 1-55.
17. Montazeri A, Mohammadi S, Hesari PM, Ghaemi M, Riazi H. Preliminary guideline for reporting bibliometric reviews of the biomedical literature (BIBLIO): a minimum requirements. Syst Rev 2023; 1-10.
18. Sierawska O. Interaction between Selected Adipokines and Musculoskeletal and Cardiovascular Systems : A Review of Current Knowledge. Int J Mol Sci 2023; 24: 17287.
19. van Eck N an, Waltman L. Software survey : VOSviewer , a computer program for bibliometric mapping. Scientometrics 2010; 84: 523-38.
20. Dongre UJ. Adipokines in Insulin Resistance: Current Updates. Biosci Biotechnol Res Asia 2021; 18(2): 357-66.
21. Gunturiz Albarracín ML, Forero Torres AY. Adiponectin and Leptin Adipocytokines in Metabolic Syndrome: What Is Its Importance? Dubai Diabetes Endocrinol J 2020; 26(3): 93-102.
22. Würfel M, Blüher M, Stumvoll M, Ebert T, Kovacs P, Tönjes A, et al. Adipokines as Clinically Relevant Therapeutic Targets in Obesity. Biomedicines 2023; 11(1427): 1-26.
23. Gupta L, Thomas J, Ravichandran R, Singh M, Nag A, Binay K. Inflammation in Cardiovascular Disease : A Comprehensive Review of Biomarkers and Therapeutic Targets Methods. Cureus 2023; 15(9): 1-9.
24. Waschki B, Kirsten A, Holz O, Müller KC, Meyer T, Watz H, et al. Physical activity is the strongest predictor of all-cause mortality in patients with COPD: a prospective cohort study. Chest 2011; 140(2): 331-42.
25. Adams LA, Anstee QM, Tilg H, Targher G. Non-alcoholic fatty liver disease and its relationship with cardiovascular disease and other extrahepatic diseases. Gut 2017; 66(6): 1138-53.
26. Prieto-Gutiérrez JJ, Segado-Boj F. Annals of library and information studies: a bibliometric analysis of the journal and a comparison with the top library and information studies journals in Asia and Worldwide (2011–2017). Ser Libr 2019; 77(1-2): 38-48.
27. Xu K, Yu S, Wang Z, Zhang Z, Zhang Z. Bibliometric and visualized analysis of 3D printing bioink in bone tissue engineering. Front Bioeng Biotechnol 2023; 11(July): 1-14.
28. Khetan AK, Palileo-Villanueva LM, Mat-Nasir N, et al. Mortality, Cardiovascular Disease, and Their Associations With Risk Factors in Southeast Asia: A PURE Substudy. JACC Asia 2024; 4(8): 624-633.
29. Biswas T, Townsend N, Gupta D, Ghosh A, Rawal LB, Mørkrid K, et al. Clustering of metabolic and behavioural risk factors for cardiovascular diseases among the adult population in South and Southeast Asia: findings from WHO STEPS data. Lancet Reg Health Southeast Asia 2023; 12: 100164.
30. Szomszor M, Adams J, Fry R, Gebert C, Pendlebury DA, Potter RWK, et al. Interpreting Bibliometric Data 2021; 5(February): 1-20.

# Hospital noise exposure: A systematic review of levels, sources, and effects on patients and staff

**Ailin Razali, PhD[1,2], Nurnajiha Mazeli, BSc[1]**

[1]IIUM Health, Safety, and Environment (IHSEN), Kulliyyah of Medicine, International Islamic University Malaysia, Kuantan, Pahang, Malaysia, [2]Department of ORL-HNS, Kulliyyah of Medicine, International Islamic University Malaysia, Kuantan, Pahang, Malaysia

## ABSTRACT

**Introduction: Noise is often underestimated as a hospital-related hazard. This systematic review aimed to assess noise levels in hospitals, their sources, and the associated physiological and psychological impacts on the hospital community.**

**Materials and Methods: A literature search was conducted through PubMed, ProQuest, Ovid, and Scopus without language or date restrictions. Studies in all languages were considered, non-English articles were assessed using machine translation, although none met the inclusion criteria. This review was registered in PROSPERO under registration number CRD42025112689. Quantitative, qualitative, and mixed-method study designs that assessed hospital noise levels, sources, or effects were included. Risk of bias was appraised using the Joanna Briggs Institute (JBI) critical appraisal tools based on study designs, and the data were synthesised narratively.**

**Results: Eighteen studies were included in the qualitative synthesis, which consisted of cross-sectional (n=10), cohort (n=7), and qualitative (n=1) designs conducted across various countries. Noise levels frequently exceeded World Health Organization (WHO) limits, with mean equivalent levels (LAeq) ranging from 43 to 75.8 dB(A) and peak levels (LAFmax) reaching 100 dB(A). Intensive Care Units (ICUs) and Emergency Departments (EDs) were consistently reported as the noisiest departments. The physiological and psychological impacts experienced by the hospital community included stress, sleep disturbances, annoyance, elevated heart rate, and headaches. In chronic cases, noise-induced hearing loss (NIHL) was diagnosed particularly in hospital staff from the maintenance and service department. The principal noise sources were medical equipment alarms and staff communication.**

**Conclusion: Hospital noise levels consistently exceed recommended limits, posing both clinical and occupational risks. Noise should be considered a health and safety concern requiring institutional management. An integrated approach combining acoustic engineering, administrative policies, staff behavioural training, and continuous monitoring is essential to foster a safer hospital environment.**

**KEYWORDS:**
*Hospital noise, occupational exposure; psychological stress; noise-induced hearing loss; healthcare environment; acoustic management*

## INTRODUCTION

Hospital noise pollution is one of the most ubiquitous and underestimated environmental stressors in healthcare settings, adversely affecting both patient recovery and staff performance.[1] Noise is defined as any undesirable or distressing sound that interferes with human comfort, communication, healing, or occupational function. The World Health Organization's Guidelines for Community Noise recommend that hospital sound levels not exceed 35 dB(A) during the day and 30 dB(A) at night to promote patient relaxation, recovery, and staff concentration.[2]

Yet empirical studies consistently show that actual noise levels far surpass these thresholds across diverse units, including neonatal and adult intensive care units (ICUs), emergency departments (EDs), and general wards.[3-4] Primary contributors include monitoring alarms, ventilators, infusion pumps, mobile equipment, door closures, staff conversations, paging systems, and visitor interactions.[5-6] Together, these sources create a dynamic and persistent acoustic environment. The physiological and psychological effects are substantial, affecting both patients and hospital workers. For patients, particularly vulnerable populations in neonatal and adult ICUs, noise disrupts sleep architecture, elevates heart rate and blood pressure, suppresses melatonin production, precipitates delirium, disturbs circadian rhythms, and impairs neurocognitive function.[7-9]

Hospital staff experience comparable burdens, as chronic noise exposure contributes to fatigue, tension, elevated cortisol levels, reduced concentration, communication errors, and an increased risk of clinical mistakes, including medication dosing errors. The persistent interplay of these sounds undermines overall well-being, safety, and efficiency. Despite the accumulating evidence, the literature remains inconsistent, hampered by methodological variability, heterogeneous settings, and differing outcome measures. This systematic review synthesizes extant research to comprehensively evaluate hospital noise levels, predominant sources, and their physiological, psychological, and

*This article was accepted: 08 June 2026*
*Corresponding Author: Ailin binti Razali*
*Email: ailin@iium.edu.my*

occupational impacts on patients and staff, ultimately informing targeted mitigation strategies.

## MATERIALS AND METHODS

This systematic review was prepared in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) 2020 statement.[10] The review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (ID: CRD42025112689). The review adopted the PEO (Population, Exposure, Outcome) framework defining the population as hospital staff and patients, the exposure as noise in the hospital, and the outcomes as effects of hospital noise on hospital staff and patients. Studies were categorized based on the type of outcomes measured, including noise levels, psychological and physiological effects on hospital staff and patients, and identified noise sources.

### Eligibility Criteria for Studies

#### Type of studies

Eligible study designs included quantitative, qualitative and mixed-methods research such as randomized controlled trials (RCTs), cohort studies, cross-sectional studies, case-control studies, and quasi-experimental designs that reported the noise levels, noise sources, and the effects of noise exposure to patients and hospital staff. Editorials, commentaries, reviews and conference abstracts were excluded. RCTs, case-control studies, and quasi-experimental studies were included in the eligibility criteria, however, none were retrieved through the systematic search.

#### Participants and Study Setting

The population of interest included patients and hospital staff within hospital environments. Hospital workers were defined as all personnel working in hospital settings who may be exposed to occupational noise. This includes both clinical staff, such as physicians, nurses, radiographers, and allied health professionals, as well as non-clinical staff, including administrative personnel, maintenance and engineering staff, and cleaning and support service workers.[11] Studies were included if they assessed noise exposure levels, noise sources, or associated health and occupational outcomes among these groups within hospital settings.

#### Exposure (Validity of Instrument used)

Eligible exposures included noise measurements in decibels collected using calibrated sound level meter (SLM) conforming to IEC61672:2013 or personal noise dosimeters (IEC61252), as well as validated subjective assessments of noise perceptions. Included studies were required to use SLMs compliant with IEC 61672:2013 to ensure a consistent and accurate measurement standard across studies, and traceability to national standards via approved calibration was required.[12]

#### Outcomes measured

The outcomes of interest in patients and hospital staff included physiological outcomes (heart rate and sleep quality), psychological outcomes (stress, fatigue, and burnout), and NIHL. Additionally, outcomes from subjective perceptions of noise such as annoyance and communication quality, were also assessed.

#### Language and publication criteria

Studies published in all languages were considered. Non-English articles were screened and assessed for eligibility using machine translation (Google Translate). Full-text articles were translated where necessary to facilitate evaluation. However, no non-English studies met the inclusion criteria and were not included in the final analysis.

### Search Strategy

The search was conducted through PubMed, ProQuest, Ovid, and Scopus without language or date restriction. The search terminology used and full search strategy are presented in Table I. The final search was conducted on 17 June 2025. Medical Subject Headings (MeSH) terms used for PubMed included tinnitus, hypertension, noise-induced hearing loss, stress, anxiety, and heart rate.

### Data Extraction

Two review authors (AR, NN) independently extracted the data from each selected study. After the extraction, the data were cross-checked by each reviewer. Any discrepancy was resolved through discussion leading to consensus. The characteristics of the data extracted from each study included study details such as authors, year of publication, and country. Information on study design, study setting, and locations of noise level measurements was also collected. In addition, data on the sample population were extracted, including the number of patients, hospital workers, or both, as well as participant characteristics and job designations. Measurement methods, exposure duration, and noise levels were recorded. Outcome measures included identified noise sources and all reported health or occupational outcomes.

### Quality Assessment

Two review authors (AR, NN) independently assessed the quality of the selected studies using the Joanna Briggs Institute (JBI) Critical Appraisal Tools (CATs) for cross-sectional, cohort, and qualitative studies. Any disagreement between reviewers was resolved by discussion. The methodological quality and risk of bias of the included studies were critically appraised to ensure transparency and reliability of the review findings. JBI Critical Appraisal Tools were used, as they are appropriate for a variety of non-intervention and non-randomized research designs.[1] Studies were judged to have a low risk of bias when they reached the minimum score set for each study type, namely at least six "Yes" answers out of eight for cross-sectional studies, seven out of eleven for cohort studies, and six out of ten for qualitative studies.

### Data Synthesis

A meta-analysis was not performed due to substantial heterogeneity among the included studies. The studies varied considerably in terms of design, participant populations, clinical settings, noise measurement methods, and outcome measures, including psychological, physiological, and auditory impacts assessed using different instruments and scales. A narrative synthesis was therefore conducted to summarise the findings across the included studies.

**Table I: Full search strategy**

| Search terminologies | Full search strategy with MeSH terms and filters |
|---|---|
| ("noise pollution" OR "sound pollution" OR "noise exposure" OR "sound monitoring" OR "noise induced hearing loss" OR "noise level") AND ("hospital" OR "ward" OR "medical centre" OR "healthcare facility" OR "clinical setting" OR "medical setting" OR "health institution") AND ("nurse*" OR "doctor*" OR "healthcare staff" OR "hospital workers" OR "clinical staff" OR "medical staff") AND ("exposure" OR "source" OR "effect" OR "impact"). | (("noise pollution" OR "sound pollution" OR "noise exposure" OR "sound monitoring" OR "noise induced hearing loss") AND ("hospital" OR "ward" OR "medical centre" OR "healthcare facility" OR "clinical setting" OR "medical setting" OR "health institution") AND ("nurses" OR "doctors" OR "healthcare workers" OR "hospital staff" OR "clinical staff" OR "medical staff" OR "patient") AND ("exposure" OR "source" OR "effect" OR "impact")) AND (("Article") AND ("English") AND (("hearing loss" OR "hearing protection" OR "tinnitus" OR "patients" OR "ears & hearing" OR "sound" OR "noise levels" OR "humans" OR "acoustics" OR "hospitals" OR "risk factors" OR "age" OR "exposure" OR "intensive care" OR "occupational exposure" OR "otolaryngology" OR "public health" OR "statistical analysis" OR "physiology" OR "quality of life" OR "speech" OR "cognitive ability" OR "nurses" OR "hearing aids" OR "epidemiology" OR "background noise" OR "older people" OR "male" OR "occupational health" OR "hearing" OR "cochlea" OR "anxiety" OR "adult" OR "medical personnel" OR "audiometry" OR "disease" OR "aging" OR "female" OR "heart rate" OR "middle aged" OR "health care" OR "mental depression" OR "noise pollution" OR "patient safety" OR "cohort analysis" OR "nursing" OR "perceptions" OR "audiology" OR "health risks" OR "workers" OR "cross-sectional studies" OR "aged" OR "listening" OR "noise control" OR "population studies" OR "speech perception" OR "stress" OR "auditory system" OR "medical screening" OR "medicine" OR "adults" OR "confidence intervals" OR "data collection" OR "environmental exposure" OR "intensive care units" OR "mental disorders" OR "occupational diseases" OR "otology" OR "pain" OR "paediatrics" OR "cochlear implants" OR "environmental health" OR "hearing loss, noise-induced") AND "noise" NOT ("studies" OR "questionnaires" OR "regression analysis" OR "air pollution" OR "outdoor air quality" OR "mortality" OR "traffic" OR "transportation noise" OR "aircraft" OR "trauma" OR "brain research" OR "dementia" OR "music" OR "roads & highways" OR "body mass index" OR "deafness")) AND ("Scholarly Journals" NOT ("Trade Journals" OR "Reports" OR "Working Papers"))) |

## RESULTS

### Study Selection

Searches of four databases (PubMed, Scopus, Ovid, and ProQuest) yielded 625 records. Two review authors (AR, NN) independently reviewed the results of the search and selected the studies for inclusion using the predefined eligibility criteria. The titles and abstracts were screened, and potentially relevant studies were then retrieved in full-text form and screened for eligibility. Any disagreement between two reviewers was resolved via discussion. Among them, 18 studies met the inclusion criteria and were included in the final review. The study selection process, including the reasons for study exclusion, is presented in the PRISMA flow diagram (Fig. 1).

### Study Quality Assessment

Eighteen studies were assessed using the Joanna Briggs Institute (JBI) critical appraisal tools for cross-sectional, cohort, and qualitative study designs, as presented in Table II. Two reviewers independently evaluated methodological quality and risk of bias, and all included studies were classified as having low to moderate risk of bias. The methodological quality of the included studies was predominantly classified as low risk of bias, with only a small number of studies rated as having moderate risk. Most studies fulfilled key methodological criteria, particularly in clearly defining the study population and employing appropriate and objective measures of noise exposure and outcomes.

The studies classified as having moderate risk of bias were primarily limited by methodological constraints, including inadequate identification and control of confounding factors, insufficient reporting of strategies to address these confounders, lack of baseline outcome assessment, and absence of follow-up, which restricted causal inference.[13-14] Across the included studies, a consistent pattern was the limited control of confounding factors and the predominance of cross-sectional designs, which restricted the ability to establish causal relationships between hospital noise exposure and health outcomes.

The cross-sectional and cohort studies generally demonstrated consistent and reliable measurement of exposure and outcomes, although confounding was not adequately addressed in some cases. The qualitative study met all relevant JBI criteria, indicating minimal risk of bias. No studies were classified as having a high risk of bias. These methodological limitations should be considered when interpreting the findings.

### Characteristics of the Included Studies

Eighteen studies were included in this review, comprising ten cross-sectional, seven cohort, and one qualitative study design. The studies spanned regions including Asia, Europe, the Middle East, Africa, Australia, and North America reflecting global concern regarding hospital noise exposure and its impact on both patients and hospital workers. [4,6-9,18] Across all studies, noise levels consistently exceeded the World Health Organization (WHO) recommended limits indicating non-compliance with recommended hospital noise standards. Most studies measured sound levels in acoustically challenging hospital environments including intensive care units (ICU) (EICU, MICU, SICU, PICU), emergency departments, and cardiac care units (CCU) where continuous background noise was interspersed with intermittent high-level sounds.[13-15,17,20] Healthcare staff, including nurses, doctors, radiographers, and other hospital personnel, were the most frequently studied group. Patients represented the second most commonly studied population, indicating a predominant focus on occupational exposure and psychological strain among hospital workers. Psychological effects such as stress, fatigue, and alarm fatigue were the most frequently reported. Although most studies examined psychological or physiological effects, two studies addressed

**Table II: JBI Appraisal Tool for all studies included**

A) Cross Sectional Studies

| Questions/Studies | Abbasi et al., 2022 [3] | Ali & Alharbi, 2024 [4] | Adams et al., 2024 [7] | Jung et al., 2020 [8] | Amoatey et al., 2022 [5] | Glans et al., 2022 [6] | Daraiseh et al., 2016 [9] | Ryan et al., 2016 [15] | Wongsuwan et al., 2019 [16] | Xie & Kang, 2012 [17] |
|---|---|---|---|---|---|---|---|---|---|---|
| Inclusion criteria | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Study subject and setting | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Validity of exposure measured | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Standard criteria for measurement condition | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Identified confounding factors | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Strategies to deal with confounding factors | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes |
| Validity of measured outcomes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Appropriate statistical analysis | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |

B) Cohort Studies

| Questions/Studies | Yang & Zhou, 2024 [13] | Tang et al., 2024 [14] | Folscher et al., 2015 [18] | Wang et al., 2024 [19] | Tahvili et al., 2025 [20] | Armbruster et al., 2023 [21] | Ituk et al., 2025 [22] |
|---|---|---|---|---|---|---|---|
| Groups recruited within same population | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Exposures measured similarly within groups | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Validity of the exposure measurement | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Identified confounding factors | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Strategies to deal with confounding factors | Yes | Yes | Yes | Yes | No | Yes | Yes |
| Participants free from the outcome at the start of the study | No | Yes | Yes | Yes | Yes | Yes | Yes |
| Validity of the outcome measurement | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Sufficiency of the follow-up time for outcomes to occur | N/A | N/A | Yes | Yes | Yes | Yes | Yes |
| Follow up complete or reason to loss to follow up | N/A | N/A | Yes | Yes | Yes | Yes | Yes |
| Strategies to address incomplete follow up | N/A | N/A | N/A | N/A | Yes | Yes | N/A |
| Appropriate statistical analysis | Yes | Yes | Yes | Yes | Yes | Yes | Yes |

C) Qualitative Study

| Questions/Study | Honan et al., 2015 [23] |
|---|---|
| Congruity between philosophical perspective and research methodology | Yes |
| Congruity between methodology and research question/objectives | Yes |
| Congruity between methodology and data collection methods | Yes |
| Congruity between methodology and representation/analysis of data | Yes |
| Congruity between methodology and interpretation of results | Yes |
| Statement locating the researcher culturally or theoretically | Yes |
| Influence of the researcher on the research and vice-versa | Yes |
| Representation of participants and their voices | Yes |
| Ethical considerations | Yes |
| Relationship between conclusions and data | Yes |

*Note: N/A = Not Applicable

**Table III: Characteristics of the included studies**

| Study | Country | Study Design | Sample Size | Study Setting | Indicator |
|---|---|---|---|---|---|
| Ali & Alharbi., 2024[4] | Saudi Arabia | Cross-sectional | 216 nurses | NICU and PICU | d,e |
| Glans et al., 2022[6] | Sweden | Cross-sectional | 529 MRI and/or | Radiology department | d,e,f |
| Abbasi et al., 2022[3] | Iran | Cross-sectional | CT radiographers 209 nurses | Across all departments | a,d,e |
| Adams et al., 2024[7] | Australia | Cross-sectional | Not applicable (area noise monitoring) | ED | a |
| Jung et al., 2020[8] | South Korea | Cross-sectional | Not applicable (area noise monitoring) | IR, OU, NS, MICU, SICU, and PICU<br>CCU | a<br>a |
| Ryan et al., 2016[15] | USA | Cross-sectional | Not applicable (area noise monitoring) | Gastrointestinal, colorectal surgery, rehabilitation, cardiac step-down, | b,e,f,h |
| Daraiseh et al., 2016[9] | Ohio | Cross-sectional | 65 nurses | medical/surgical, neurology, diabetes/endocrinology, NICU, PICU, complex airway, cardiac intensive care, cystic fibrosis/complex pulmonary, and transitional care units in paediatric inpatient units. | |
| Amoatey et al., 2022[5] | Oman | Cross-sectional | 72 nurses, doctors, and patients | FMW, SLW, EMW, and ICU | a,d,e,h |
| Wongsuwan et al., 2019[16] | Thailand | Cross-sectional | 82 hospital workers (43 males, 39 females) | Physical and Environmental Unit, Maintenance and Repairman Unit, Nutrition and Cooking Unit, Central Service Unit, and the Vehicle and Transportation Unit | c,f,g |
| Xie & Kang., 2012[17] | United Kingdom | Cross-sectional | Not applicable (area noise monitoring) | ICU | a |
| Wang et al., 2024[19] | Taiwan | Cohort study | 21 hospital workers | These included those working in the clinic (n=6), clinical laboratory (n=5), front desk (n=3), central supply centre (n=5), and primarily in janitorial services (n=2) | c,g |
| Tang et al., 2024[14] | China | Retrospective cohort study | 42 hospital workers (group A) in ED and 39 hospital workers (group B) in RD | ED and RD | a,d,e |
| Yang & Zhou, 2024[13] | China | Retrospective cohort study | 200 patients | EICU | a,d,e |
| Folscher et al., 2015[18] | South Africa | Prospective cohort study | 41 doctors | ED | a,d,e |
| Armbruster et al., 2023[21] | Germany | Prospective cohort study | 179 hospital workers | ICUs (anaesthesiologic, neonatological, and neurological) | d,e,h |
| Ituk et al., 2025[22] | USA | Prospective cohort study | 65 women patients undergoing caesarean delivery | OR | a,d,e |
| Honan et al., 2015[23] | USA | Qualitative study | 406 nurses | Based on Health-care Technology Foundation (HTF) survey by using Survey Monkey | d,e |

*Note: a = area noise monitoring, b = personal noise monitoring, c = audiological assessment, d = validated questionnaire, e = psychological outcome, f = physiological outcome, g = noise-induced hearing loss, h = noise source identified, PICU = Paediatric Intensive Care Unit, NICU = Neonatal Intensive Care Unit, CCU = Cardiac Care Unit, MICU = Medical Intensive Care Unit, SICU = Surgical Intensive Care Unit, EICU = Emergency Intensive Care Unit, FMW = Female Medical Ward, EMW = Emergency Ward, SLW = Isolated Ward, OR = Operating Room, IR = Isolation Room, OU = Open Unit, NS = Nursing Station, RD = Rehabilitation Department.

NIHL as primary outcome among hospital workers exposed to hospital noise over the course of their working experience.[16,19] Included studies also identified specific noise sources, with equipment alarms, ventilation systems, and human activity being the most common contributors. Table III presents the detailed characteristics of the included studies.

**Qualitative Synthesis for Outcome Measured**

The included studies were grouped into five outcome categories namely hospital noise levels, psychological and physiological effects on hospital workers and patients, NIHL, and identified noise sources as shown in Table IV. Twelve studies measured noise levels across hospital settings, including general wards, ICUs, EDs, and ORs. Most reported average noise levels above 40 dB(A), often exceeding 60 dB(A) in high-activity areas, far above WHO recommendations as shown in Table IV(A). ICUs and EDs were consistently identified as the noisiest environments, with peaks of 98.8 dB(A) and 99.7 dB(A) respectively.[7,20] In contrast, Folscher et al.[18] reported ED noise levels never exceeded 52 dB(A) indicating that noise sources and clinical activity vary by study location and time of day. Eleven studies

**Table IV: Outcomes measured in the included studies**

A) Noise level reported according to studies — n=11 studies

| Studies | Area measured | Noise Level reported |
|---|---|---|
| Abbasi et al., 2022 [3] | 1510 locations in Iranian hospital | Mean low exposure: 48.8; mean moderate exposure: 54.9; mean high exposure: 61.8 |
| Adams et al., 2024 [7] | 6 locations in ED waiting room and treatment areas | Mean 56.5 dB; ED Wait Room (59.9 ±4.6); Ambulance Bay (56.9 ±5.0); ED Treatment 1 (59.4 ± 3.8); ED Treatment 2 (60.0 ± 3.7); EMU 1 (51.9 ± 3.6); EMU 2 (51.0 ± 3.6) with peaks in Ambulance Bay (102.8 dB) and ED Wait Room (99.7 dB) |
| Jung et al., 2020 [8] | IR, OU, and NS in MICU, SICU, PICU. | IQR 24-hour for all ICUs 54.5 (51.1–57.5) dB(A); MICU (53.8 (50.6-57.0)) dB(A); SICU (55.4 (52.0 – 58.8)) dB(A); PICU (54.1 (50.7 – 56.7)) dB(A). |
| Ryan et al., 2016 [15] | CCU (patient rooms and nurse station) | Nurse station (49.9 - 65.0) dB; Patient Room 1 (43.0 - 54.4) dB; Patient Room 7 (49.7 – 58.9) dB. |
| Amoatey et al., 2022 [5] | FMW, SLW, EMW, ICU wards | Mean FMW: 61.7 dB(A); mean SLW: 58.8 dB(A); mean ICU: 55.2 dB(A). |
| Xie & Kang., 2012 [17] | ICU | Range: 45–70 dB (A) |
| Tang et al., 2024 [14] | ED and RD | ED: (58.7 ± 8.3) dB; RD: (50.5 ± 5.8) dB |
| Yang & Zhou, 2024 [13] | EICU | Ideal sleep group: 52.75 ± 3.21 (peak: 68.44 ± 3.89) dB; non-ideal sleep group: 54.32 ± 4.17 (peak: 69.92 ± 4.76) dB |
| Folscher et al., 2015 [18] | 3 venues in ED | Range: 40–52 dB(A); never > 52 dB(A) |
| Tahvili et al., 2025 [20] | ICU | Mean 68.6 dB; peak 98.8 dB; min 44.2 dB |
| Ituk et al., 2025 [22] | OR | OR1: (53.4 dB); OR2 (58.5 dB); LAeq 60.2–68.4 dB; LCpeak (79.1–122.9 dB (A)) during patient admission |

B) Psychological effects on staff and patients — n=9 studies

| Studies | Subject | Psychological effect |
|---|---|---|
| Abbasi et al., 2022[3] | 209 nurses | Increased annoyance, greater noise sensitivity, and lower perceived quality of care. |
| Glans et al., 2022 [6] | 529 (345 worked with MR, and 392 worked with CT) | Drowsiness, forgetfulness, difficulty concentrating, and sleep problems. |
| Amoatey et al., 2022 [5] | 11 doctors, 29 nurses, 32 patients | Distraction, loss of focus, impaired performance and patient recovery. |
| Tang et al., 2024 [14] | 42 medical staff in emergency department, 39 medical staff in rehabilitation department | Emotional fatigue, work apathy, low achievement, resignation intention. |
| Folscher et al., 2015 [18] | 41 doctors | Lack of concentration, pressure, irritation, and distraction. |
| Armbruster et al., 2023 [21] | 179 hospital workers in ICUs (anaesthesiologic, neonatological, and neurological) | Seek rest after shift, reduced mood, more sensitive to sound. |
| Daraiseh et al., 2016 [9] | 115 nurses in 14 units (gastrointestinal, colorectal surgery, rehabilitation, cardiac step-down, medical/surgical, neurology, diabetes/endocrinology, NICU, PICU, complex airway, CCU, cystic fibrosis/complex pulmonary, and transitional care) | Higher stress level. |

B) Psychological effects on staff and patients (Continued) — n=2 studies

| Studies | Subject | Psychological effect |
|---|---|---|
| Honan et al., 2015 [23] | 410 nurses | Alarm leads to desensitization, affecting patient safety, and fatigue. |
| Ali & Alharbi, 2024 [4] | 216 NICU and PICU nurses | Disrupted patient care, and decrease trust in alarm systems, and experienced alarm fatigue. |
| Yang & Zhou, 2024 [13] | 200 patients (96 ideal sleep group), 104 (non-ideal sleep group) | Sleep disturbance, difficulty falling asleep, nightmares or vivid dreams, and sleepwalking episodes. |
| Ituk et al., 2025 [22] | 65 women undergoing caesarean delivery | Higher noise sensitivity, noise perception and stress. |

C) Physiological effect on staff and patients n=3 studies

| Studies | Subject | Psychological effect |
|---|---|---|
| Glans et al., 2022 [6] | 529 (345 worked with MR, and 392 worked with CT) | Vertigo, nausea, metallic taste, illusion of movement, tinnitus, and headache. |
| Amoatey et al., 2022 [5] | 11 doctors, 29 nurses | Risk of cardiovascular disease, annoyance and sleep disturbances. |
| Folscher et al., 2015 [18] | 41 doctors | Physical distress, headache, and tiredness |

C) Physiological effect on staff and patients (Continued) n=2 studies

| Studies | Subject | Physiological effect |
|---|---|---|
| Daraiseh et al., 2016 [9] | 115 nurses in 14 different units | Nurses with a baseline HR less than 100 bpm, the average HR increased 0.8% when SPLs were greater than 75 dB(A) (2.3% when 90 dB(A)). Time in tachycardia increases as heart rate increases. |
| Wongsuwan et al., 2019 [16] | 82 hospital workers (43 males and 39 females) between June 2018 and July 2018. | 33 had NIHL for workers with more than 18 years working experience. |

D) Noise-induced Hearing Loss n=2 studies

| Studies | Instrument used | Clinical Outcome |
|---|---|---|
| Wongsuwan et al., 2019 [16] | Clinical audiometer, GSI AudioStar ProTM, 2012. | 33 cases of NIHL were identified, with a higher prevalence among smokers (59.3% vs. 25.9%), particularly among workers exposed to noise levels >85 dB in the physical and environmental, maintenance, nutrition, central service, and transportation units. |
| Wang et al., 2024 [19] | Audiometer | Significant hearing threshold shifts in the HNE group after 6 months, particularly at 0.25–0.5 kHz and 0.5–4 kHz frequencies. |

E) Noise sources identified in Hospital n=6 studies

| Studies | Noise sources identified | Noise level (dB (A)) |
|---|---|---|
| Amoatey et al., 2022 [5] | Visitor footsteps, phone ringing, operation of medical equipment, doors, air conditioning, trolley wheels, staff/visitor conversation, alarms. | Range: 55 – 62 dB(A) |
| Yang & Zhou, 2024 [13] | Conversational speech, equipment alarms, ambient hospital background. | Speech: 42–44 dB(A); alarms: 58–60 dB(A); ambient: 49–53 dB(A) |
| Tahvili et al., 2025 [20] | Patient repositioning, medication, suctioning, blood collection, extubating, tracheostomy, drain removal. | Mean 68.6 dB(A); peaks: 98.8 dB(A). |
| Armbruster et al., 2023 [21] | Mechanical ventilator, surveillance monitor alarms, dialysis machine, suction pump, telephones, bed-brakes, door movements, packaging, staff conversations. | Alarm often > 70 dB(A). |
| Daraiseh et al., 2016 [9] | Staff communication, patient/family interaction, equipment uses, door activity, paging systems, procedures, stocking, cleaning, and auxiliary room operations. | Frequent peaks > 75 dB(A); dominant sources: staff conversation 51%. |
| Jung et al., 2020 [8] | Patient monitor alarms, oxygen via facial mask, syringe pump alarms, pneumatic compression, nebulizer, endotracheal suction, wall suction normal, obstruction, warmer, ventilator normal, alarm, physiotherapy, continuous renal replacement alarms. | 43.9 – 91.6 dB(A) overall range across devices. |

*Note: EMU = Emergency Medical Unit, IQR = Interquartile Range, SPL: Sound Pressure Level.

reported the psychological effects of noise, including reduced performance, focus, sleep disturbance and stress as shown in Table IV(B). More than 70% of hospital workers found noise distracting. This is due to increased stress, emotional exhaustion, and sleep disturbances frequently reported.[5] Alarm fatigue was a recurring issue, contributing to reduced alertness and lower confidence in alarm systems.[4,23] Patients also experienced sleep disruption, stress, and impaired recovery.[13] Five studies addressed physiological impacts, reporting headaches, dizziness, and fatigue, particularly among radiology staff as shown in Table IV(C).[7,19] Exposure above 75 dB(A) was associated with elevated heart rates and cardiovascular risks.[9] Two studies investigated NIHL among hospital staff as shown in Table IV(D), identifying permanent hearing damage among long-term staff exposed to sound levels beyond 85 dB(A). Smoking and prolonged exposure were associated with higher prevalence of NIHL in hospital workers. Six studies identified primary noise sources in hospital as shown in Table IV(E). Noise mainly came from alarms, medical devices, and human activities such as conversation, footsteps, and equipment handling.[5,9] Procedures such as suctioning, repositioning, and patient care activities contributed to transient peaks.[20] Overall, hospital environments consistently exceeded safe noise limits, risking the psychological, physiological, and auditory health of the hospital community.

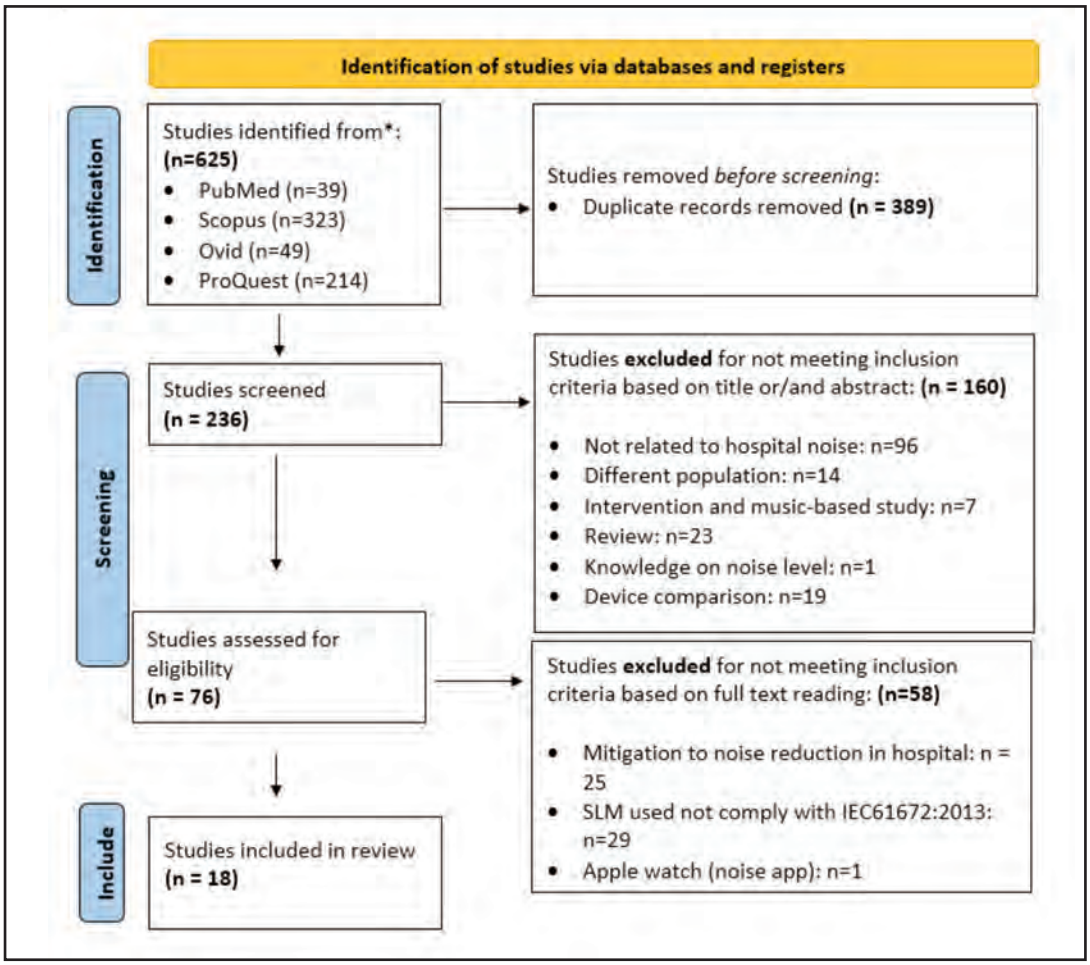



**Fig. 1:** PRISMA 2020 flow diagram showing the identification, screening, eligibility, and inclusion of studies

## DISCUSSION

This systematic review compiled data from eighteen research studies that examined hospital noise exposure, its sources, and the psychological, physiological, and auditory effects including NIHL on hospital staff. According to the WHO, 30 dB(A) is the threshold for sleep disruption, while 45 dB(A) may interfere with learning and create attention problems, especially in sensitive settings like hospitals.[2] Similarly, a variety of non-auditory health effects, such as stress and physiological arousal responses, have been linked to an average of 55 dB(A) for day-night-evening weighted sound pressure level (L_den).[2]

The evidence consistently suggests that hospital noise levels exceeded WHO-recommended limits. Across the studies reviewed for noise levels measurement, equivalent continuous sound levels (LAeq) of intensive care, paediatric, emergency, and surgical units often varied between 51 dB(A) and 75.8 dB(A).[7,9] The majority of the reviewed studies used LAeq as the primary metric of noise exposure, which allowed for cross-study comparison and showed consistency in measuring cumulative sound energy. However, noise levels in hospitals are event-driven, depending on clinical activities, equipment alarms, and human interaction that vary throughout the day. Xie and Kang[17] and Adams et al.[7] documented instantaneous peaks in emergency and multibed ward settings that approached 100 dB(A). Although LAeq reflects the cumulative noise exposure, it is unable to capture the short, high-intensity peaks that occur within less than a second. Several studies combined LAeq with maximum-level metrics such as LAFmax to measure the significant short-term variations. Consistent with that, Daraiseh et al.[9] found a mean LAFmax of 75.8 ± 8.9 dB(A), but Jung et al.[8] reported maximum noise level around 91 dB(A). These findings highlight the need to use numerous acoustic descriptors to describe both continuous exposure and intermittent acoustic stressors in hospital settings. Most studies employed A-weighting, which appropriately reflex human hearing sensitivity, but attenuates low frequency content below 250 Hz. Consequently, it fails to represent mechanical hums from ventilation systems or medical equipment that emit low frequency noise that may lead to negative psychological outcomes. These findings demonstrate that hospital soundscapes are dynamic and acoustically complex. Multiple metrics are therefore required to characterise exposure accurately. LAeq reflects cumulative sound energy, whereas LAFmax and LASmax capture transient peaks and LCpeak identifies impulsive noise events that may be overlooked by A-weighted measurements. The choice of acoustic metric should therefore be guided by the health outcome under investigation, LAeq for long-term exposure evaluation, LAFmax for instantaneous arousal or communication interference, and LCpeak for low-frequency stress potential.

Hospital noise has a significant psychological impact on both hospital workers and patients, acting as a chronic environmental stressor that reduces emotional stability, cognitive efficiency, and well-being. Hospital workers in high-noise departments reported greater emotional exhaustion, indifference, and decreased achievement, with auditory stress reducing desired care performance by 14-23%.[3] Constant alerts in NICU and PICU cause alarm fatigue, with 62.5% of nurses suffering moderate fatigue and 8.3% experiencing severe exhaustion, which is associated with worry and desensitisation.[4] These psychological consequences contribute to poor cognitive function, as exposure to 80-85 dB(A) during clinical activities resulted in 65% distraction and 88% stress in doctors.[18] Noise sensitivity was significantly associated with mental strain and less concentration whereas persistent noise during rest periods was associated with restlessness, anxiety, and dissatisfaction.[15] Intermittent sounds from alarms, especially in high-acuity units, are essential for notifying healthcare staff about the patient's condition, but excessive exposure might affect patient comfort and contribute to alarm desensitization among staff. Over time, constant auditory load reduces the efficiency of patient care and increases the risk of patient safety incidents. Notably, Armbruster et al.[21] found that even moderate 3 dB reductions improved stress and concentration results. Therefore, noise control may represent an effective strategy for reducing occupational risks within the hospital environment. Reducing unnecessary acoustic disturbances can improve emotional resilience, and support clearer communication among healthcare staff. These improvements contribute not only to staff well-being but also to more effective clinical services, smoother workflows, and safer decision-making.

Physiologically, hospital noise may act as a persistent biological stressor, activating the sympathetic nervous system and disrupting homeostatic balance. Prolonged exposure to LAeq levels of 55-62 dB(A) in Omani ICUs was associated with sleep disruption, irritation, and reduced focus, while elevated SPLs of 75.8 ± 8.9 dB(A) in PICU correlated with increased heart rate, indicating acute cardiovascular strain.[9] Amoatey et al.[5] reported that higher noise levels were associated with increased reports of noise sensitivity (56%) and loss of concentration among healthcare staff, alongside notable impacts on work performance (73%) and workplace distraction (70%). These findings suggest that elevated hospital noise may adversely affect cognitive functioning and occupational efficiency.[5] The observed associations were further supported by logistic binary regression analysis, which indicated a positive relationship between noise levels and both noise sensitivity and concentration loss (OR = 1.54–1.61), although the wide confidence intervals suggest variability in the strength of these associations.[5] Beyond acute effects, long-term occupational exposure has been associated with auditory pathology in which 41.5% of Thailand hospital personnel had NIHL, with age over 40 and smoking significantly increasing risk.[16] This finding is consistent with observations in industrial settings, where noise levels above 85 dB(A) in hospitals may present comparable risks to hearing, especially among personnel working in maintenance and service departments. In addition to these physiological responses, prolonged exposure to elevated noise levels may also affect auditory function, particularly among hospital workers working in high-noise environments. The progression from chronic noise exposure to measurable hearing impairment is well established. Wang et al.[19] observed significant changes in hearing thresholds after six months of exposure to noise levels of 70.4 ± 4.5 dB(A). However, the findings by Wang et al.[19] warrant caution. The study's method of determining NIHL used mainly speech-frequency thresholds (0.5, 1, 2 and 4 kHz) instead of the higher frequencies where NIHL typically manifests. The absence of bone conduction testing to confirm the type of hearing loss is also a concern, as NIHL is a sensorineural hearing loss. This could affect the actual incidence which may have been underestimated and the results may reflect pathologies other than noise-induced pathology.

Hospital noise arises from the complex interaction of human, mechanical, and structural sources. Effective mitigation therefore requires a multidisciplinary approach. Behavioural sources, such as staff communication, visitor activity, footsteps, and cleaning, consistently keep ambient levels above 55 dB(A), whereas equipment-related sounds, such as ventilator alarms, suctioning, and monitors, produce frequent peaks of 85-98 dB(A).[6,9-10,20] According to Armbruster et al.[21], recurrent mechanical events contribute to alarm fatigue and desensitisation. Furthermore, activity-based peaks caused by patient repositioning and medication administration indicate procedural rhythms that increase the acoustic load.[20] Hospital noise should be treated as an institutional issue rather than a technical nuisance, necessitating policies that incorporate acoustic awareness into staff training, prioritise alarm algorithms based on urgency, and incorporate low-noise technologies into procurement standards. Addressing these core issues through architectural acoustics, workflow redesign, and behavioural teaching would improve auditory comfort while maintaining patient safety and staff well-being. Strategies that can be implemented include engineering controls through installing sound-absorbing materials, optimising alarm settings, and isolating high-noise equipment, administrative controls instituting visitor regulations, staff training, and quiet hours, and technological controls using smart alarm systems that prioritise critical alerts.[23] These findings suggest that hospital noise may represent an emerging occupational health concern, although further longitudinal studies are required to confirm long-term effects.

## LIMITATIONS

This review has several limitations. Most included studies were cross-sectional or cohort studies, which limits the ability to determine cause and effect between hospital noise and its impacts. There was considerable variation in study design, measurement methods, and hospital settings, making direct comparison of findings and quantitative meta-analysis difficult. Different instruments and noise metrics were used. Variations in ward type, patient load, and activity levels may also have influenced the results. Many studies relied on self-reported outcomes such as stress and annoyance, which may be affected by recall bias.

## CONCLUSION

Hospital noise levels frequently exceeded the WHO recommended limits and were primarily attributed to medical equipment alarms, staff communication, and routine patient care activities. Such excessive noise exposure was associated not only with psychological effects, including stress, burnout, and communication errors among hospital workers, but also with physiological disturbances in patients, such as sleep disruption and altered cardiovascular responses. In addition, prolonged occupational exposure may increase the risk of NIHL among hospital workers, particularly those working in high-noise environments. These findings underscore that hospital noise should not be regarded merely as an environmental nuisance, but as a significant occupational and clinical hazard. Therefore, noise mitigation strategies should be incorporated into hospital design and management practices from the outset, with emphasis on both environmental engineering controls and behavioural interventions, including adaptive alarm management and staff-focused strategies, to enhance patient recovery and staff well-being.

## CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

## REFERENCES


1. Aromataris E, Lockwood C, Porritt K, Pilla B, Jordan Z, editors. JBI manual for evidence synthesis [Internet]. Adelaide (AU): JBI; 2024 [cited 2025 Jun 22]. Available from: https://hotus.fi/wp-content/uploads/2025/10/jbi-manual-for-evidence-synthesis-nov-2024.pdf
2. Berglund B, Lindvall T, Schwela DH, World Health Organization. Guidelines for Community Noise. Geneva: World Health Organization; 1999.
3. Abbasi M, Yazdanirad S, Zokaei M, Falahati M, Eyvazzadeh N. A Bayesian network model to predict the role of hospital noise, annoyance, and sensitivity in quality of patient care. BMC Nurs 2022; 21: 243.
4. Ali TM, Alharbi MF. AF among nurses working in neonatal and paediatric intensive care units: a cross-sectional study. Healthcare (Basel) 2024; 12(16): 1574.
5. Amoatey P, Al-Harthy I, Al-Mushaifari MA, Al-Jabri K, Al-Mamun A. Effect of ambient noise on indoor environments in a health care facility in Oman. Environ Sci Pollut Res Int 2022; 29(10): 15081-97.
6. Glans A, Wilén J, Lindgren L, Björkman-Burtscher IM, Hansson B. Health effects related to exposure of static magnetic fields and acoustic noise—comparison between MR and CT radiographers. Eur Radiol 2022; 32(11): 7896-909.
7. Adams C, Walsan R, McDonnell R, Schembri A. As loud as a construction site: noise levels in the emergency department. Australas Emerg Care 2024; 27(1): 26-9.
8. Jung S, Kim J, Lee J, Rhee C, Na S, Yoon JH. Assessment of noise exposure and its characteristics in the intensive care unit of a tertiary hospital. Int J Environ Res Public Health 2020; 17(13): 4670.
9. Daraiseh NM, Hoying CL, Vidonish WP, Lin L, Wagner M. Noise exposure on pediatric inpatient units. J Nurs Adm 2016; 46(9): 468-76.
10. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021; 372: n71.
11. Organisation for Economic Co-operation and Development (OECD). Hospital workers. In: Health at a glance 2025 [Internet]. Paris: OECD Publishing; 2025 [cited 2025 Jun 22]. Available from: https://www.oecd.org/en/publications/2025/11/health-at-a-glance-2025_a894f72e/full-report/hospital-workers_b1673dc6.html
12. Institute of Acoustics Measurement and Instrumentation Group. A guide to sound level meters [Internet]. Acoust Bull. 2019 Sep-Oct [cited 2025 Jun 22]; 44(5): 35-45. Available from: https://www.ioa.org.uk/sites/default/files/A%20Guide%20to%20Sound%20Level%20Meters.pdf
13. Yang J, Zhou J. Effect of the levels and sources of noise on the sleep quality of conscious patients in emergency intensive care unit. Noise Health 2024; 26(123): 489-94.
14. Tang M, Liu L, Cai J, Yang Y. Effect of noise in the emergency department on occupational burnout and resignation intention of medical staff. Noise Health 2024; 26(121): 102-6.
15. Ryan KM, Gagnon M, Hanna T, Mello B, Fofana M, Ciottone G, et al. Noise pollution: do we need a solution? An analysis of noise in a cardiac care unit. Prehosp Disaster Med 2016; 31(4): 432-5.
16. Wongsuwan K, Rattanaarun K, Kittiwannawong K. Prevalence of noise-induced hearing loss in workers with noise exposure in Panyananthaphikkhu Chonprathan Medical Center, Srinakharinwirot University. J Health Sci Med Res 2019; 37(2): 81-92.
17. Xie H, Kang J. The acoustic environment of intensive care wards based on long period nocturnal measurements. Noise Health 2012; 14(60): 230-6.
18. Folscher LL, Goldstein LN, Wells M, Rees D. Emergency department noise: Mental activation or mental stress? Emerg Med J 2015; 32(6): 468-73.
19. Wang TC, Yu YC, Hsu A, Lin JY, Tsou YA, Liu CS, et al. Impact of occupational noise exposure on the hearing level in hospital staffs: a longitudinal study. Environ Sci Pollut Res Int 2024; 31: 24129-38.
20. Tahvili A, Waite A, Hampton T, Welters I, Lee PJ. Noise and sound in the intensive care unit: a cohort study. Sci Rep 2025; 15: 10858.
21. Armbruster C, Walzer S, Witek S, Ziegler S, Farin-Glattacker E. Noise exposure among staff in intensive care units and the effects of unit-based noise management: a monocentric prospective longitudinal study. BMC Nurs 2023; 22(1): 460.
22. Ituk U, Anderson E, Bremer-Gama MN, Skoog C. Noise perception, sensitivity, and patient outcomes during cesarean delivery. Anesthesiol Res Pract 2025; 2025: 5707084.
23. Honan L, Funk M, Maynard M, Fahs D, Clark JT, David Y. Nurses' perspectives on clinical alarms. Am J Crit Care 2015; 24(5): 387-95.

SYSTEMATIC / NARRATIVE REVIEW ARTICLE

# Quantifying the risk of tuberculosis recurrence in Asia: A systematic review of hazard estimates

**Mohamad Rodi Isa**

Universiti Teknologi MARA, Public Health Medicine, Faculty of Medicine, Universiti Teknologi MARA, Selangor

**ABSTRACT**

**Introduction: Recurrence of tuberculosis (TB) is a major challenge to its control in Asia, even though there is a high treatment success rate of drug-susceptible diseases. TB recurrence contributes to ongoing disease transmission in the community, increases drug resistance and leads to higher TB mortality rates. The study aimed to examine and synthesise the current evidence on determinants of TB recurrence occurring after completed treatment in the Asian setting.**

**Materials and Methods: The PRISMA 2020 framework is used as a guide for this systematic review. A systematic search in PubMed/MEDLINE, Scopus and Web of Science (WOS) until September 30, 2025 was conducted. The eligible studies were cohort studies implemented in Asian countries and reported post-treatment TB recurrence and adjusted risk estimates. The Newcastle-Ottawa Scale was used to assess the methodological quality of the included studies. Since the methodological heterogeneity is rather significant, a narrative synthesis was conducted.**

**Results: The review included a total of 15 cohort studies with sample sizes ranging from 508 to more than 10 million individuals. TB recurrence was 1.5 to 15.1% or 0.47 to 6.5 per 1,000 person-years, with the highest rates seen within two years of post-treatment. Recurrence risk was higher when there were comorbidities like diabetes, chronic lung or kidney disease, low body mass index and behavioural factors like smoking. Additionally, environmental exposure to fine particulate matter ($PM_{2.5}$) and socioeconomic disadvantage were also significant variables. Protective variables observed were high levels of treatment compliance, extended treatment period, the use of fixed-dose combination (FDC) therapy, treatment during the directly observed therapy (DOT) era, smoking cessation, and residential greenness. The quality of the included study was moderate to high.**

**Conclusion: Multiple determinants drive TB recurrence; thus, improving post-treatment surveillance as well as integrating clinical, behavioural and environmental interventions are important to reduce the incidence and mortality of TB recurrence cases.**

**KEYWORDS:**
*Tuberculosis; Recurrence; Reactivation; Time-to-event analysis; Determinants*

## INTRODUCTION

Tuberculosis (TB) is a significant public health concern in Asia and contributes to more than 55% of the global TB burden. According to the World Health Organization (WHO) Global TB Report 2025, as in 2024, it is estimated that 10.7 million individuals contracted TB and 1.23 million died of the disease, which demonstrates that TB is the leading cause of death from an infectious agent after a few years, being replaced by COVID-19.[1-2] The WHO South-East Asia Region is reported to have the highest TB incidence, which makes up to 34% of global cases, closely followed by the Western Pacific Region with 27% and the African region (25%).[2] The Asian region has a complex epidemiological pattern that is affected by multiple factors, including socio-economic determinants and health system insufficiency, making the region a critical focus for research.[3-4] Despite the success rate of the standard WHO regime for drug-susceptible TB (DS-TB) being more than 85%, TB recurrence, which is defined as a new TB episode after completed TB treatment or cured during the previous episode, may still occur and continues to be a challenge to TB control efforts.[5-6]

TB recurrence may contribute to continuous disease transmission in the community, drug resistance and higher mortality, hindering the TB control efforts, especially in Asian high-burden settings.[7] The local epidemiological data on TB in Malaysia also support that TB recurrence has led to ongoing spread in the population and contributes to poor treatment outcomes.[8-10] There are two mechanisms of TB recurrence: either from the relapse of the original strain of *Mycobacterium tuberculosis* or reinfection with a new strain, especially in high-burden settings where sustained exposure is common.[11-12] In Asia, the risk of TB recurrence is increased with population ageing, high prevalence of diabetes mellitus, persistent tobacco use and socioeconomic inequalities. These factors contribute to negative impacts on immune response as well as on treatment outcomes and may help to explain why TB recurrence is significant in Asian populations.[13-14] The epidemiology of TB in the region is also influenced by rapid urbanisation and environmental exposures like ambient air pollution, which increase susceptibility to infection and the development of respiratory diseases in densely populated urban centres across Asia.[15]

TB recurrence is an insufficiently explored challenge to TB control in Asia. Existing studies have reported widely varying estimates, most probably due to heterogeneity in study design, definitions used for recurrence, different lengths of follow-up and analytical approaches. This inconsistency has

*This article was accepted: 01 July 2026*
*Corresponding Author: Mohamad Rodi Isa*
*Email: rodi@uitm.edu.my*

restricted quantitative synthesis and translations of evidence into action, in turn creating a gap in understanding the true burden, determinants and implications of TB recurrence in the region.[16] As a result, although countries with DS-TB have high rates of treatment success, policy-wide integration of recurrence data has not been comprehensive. A structured synthesis of the available evidence is therefore needed to identify the determinants of TB recurrence within Asian populations.[17] Understanding these context-specific determinants may help inform post-treatment surveillance and risk stratification plans that will support the WHO End TB Strategy. Thus, this review aimed to synthesise the existing evidence on the determinants of TB recurrence in Asia.

## MATERIALS AND METHODS

### Study Design and Reporting Framework

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 checklist.18 The review protocol was developed prior to the literature search and followed established methods for evidence synthesis. This systematic review has been registered at PROSPERO (registration no: CRD42024612771).

### PECOT Framework

The search strategy was developed using the PECOT framework to ensure a structured and comprehensive approach to identifying studies relevant to the research question. P (Population) refers to individuals of any age who have completed treatment for active TB, documented as cured or treatment completed and studies conducted in Asian countries (as defined by WHO regions or United Nations geographic classification). E (Exposure) refers to post-treatment exposure to one or more risk factors for TB recurrence, including but not limited to demographic, clinical, behavioural, socioeconomic and environmental factors. C (Comparison) refers to individuals who have completed TB treatment without exposure to the specified risk factor(s). O (Outcome) refers to TB recurrence, defined as a new episode of active TB occurring after treatment completion or cure, including relapse (same strain) and reinfection (different strain), where molecular typing is available. T (Time) refers to observational studies (e.g. cohort studies, case-control studies, cross-sectional studies) and randomized controlled trials reporting post-treatment TB recurrence.

### Research question

Among individuals who have completed TB treatment (P), does exposure to specific risk factors (E), compared with no exposure (C), increase the risk of TB recurrence (O) based on evidence from observational and experimental studies (S)?

### Information Sources and Search Strategy

A comprehensive literature search was conducted across multiple electronic databases, including PubMed/MEDLINE, Scopus, and Web of Science (WOS), from database inception to the most recent search date. The searches have been conducted using MeSH terms, combined key terms, text words and search strings taken from the review questions. To access the records, the following combination key terms was used: ("Survival Analysis" OR "Time-To-Event Analysis" OR "Cox Proportional Hazard" OR "Kaplan Meier") AND (Tuberculosis) AND ("Recurrent" OR "Relapse" OR "Reinfection" AND "previously treated" OR "Retreatment" OR "Reactivation"). Table I shows the search strategy for PubMed, Scopus and WOS databases.

### Eligibility Criteria

Studies were selected based on the following inclusion criteria: Original observational studies including prospective or retrospective cohort studies; involving TB patients who successfully completed treatment (defined as cured or treatment completed); reporting TB recurrence as an outcome, including relapse, reinfection, or recurrent TB. examining risk factors, determinants, or predictors of TB recurrence; conducted in Asian countries; published in English between 1 January 2000 and 30 September 2025. The exclusion criteria: Case reports, case series, reviews, editorials, commentaries, conference abstracts, and modelling studies without primary data; studies focusing exclusively on treatment failure, loss to follow-up, or mortality without recurrence outcomes; involving exclusively multidrug-resistant TB populations; without clear post-treatment follow-up or recurrence definitions.

### Selection Process

All retrieved articles were imported into EndNote for reference management and duplicate removal. The selection process was conducted in three stages: title and abstract screening; Two independent reviewers screened studies for relevance to TB recurrence; full-text assessment: articles meeting initial criteria were reviewed in full to confirm eligibility, and consensus resolution: disagreements were resolved through discussion with a third reviewer.

### Data Extraction

Data from all included studies were extracted using a standardised extraction form. From the selected studies, important information was extracted, such as study design, study setting, sample size, population characteristics, statistical methods used, definitions and measurements of recurrence, length of follow-up, outcomes of TB recurrence, and reported determinants with their effect estimates and confidence intervals (CI) when available. To minimise the error, two independent reviewers extracted the data, and any discrepancies were resolved by cross-checking and consensus.

### Quality Assessment

The quality and risk of bias of the included studies with a cohort as a study design were assessed by using the Newcastle-Ottawa Scale (NOS).19 The evaluation was done based on three domains: First, selection of study groups, whether they were well-defined, had reliable exposure measurement and were representative, allocated with a maximum of four stars. Second, comparability of cohorts that evaluated whether the confounding variables were examined and had well-adjusted analyses for reducing bias were allocated a maximum of two stars. Third, ascertainment of outcomes evaluated whether the outcome measurement and follow-up were appropriate, valid and reliable were allocated with a maximum of three stars. Overall, the total possible score was nine stars for each study.

**Table I: The search strategy for PubMed, Scopus and Web of Science (WOS) databases**

| Database | Search Strategy |
|---|---|
| PubMed | ("Survival Analysis"[Mesh] OR "Proportional Hazards Models"[Mesh] OR "Time-to-Event" OR "time to event" OR "survival analysis" OR "Cox proportional hazard*" OR "Cox model*" OR "Kaplan Meier" OR "Kaplan–Meier" OR "hazard ratio" OR "incidence rate*" OR "person-year*" OR "competing risk*") AND ("Tuberculosis, Pulmonary"[Mesh] OR "Tuberculosis"[Mesh] OR tuberculosis OR TB) AND (recurrent OR recurrence OR relapse OR reinfection OR "previously treated" OR retreatment OR reactivation) AND (adult*[Title/Abstract] OR "Aged"[Mesh] OR "Young Adult"[Mesh] OR "Middle Aged"[Mesh]) |
| Scopus | (("survival analysis" OR" time to event" OR "time-to-event" OR "Cox proportional hazards" OR "Cox proportional hazard" OR "Cox model" OR "Kaplan Meier" OR "hazard ratio" OR "competing risks" OR "competing risk" ) AND (tuberculosis OR "pulmonary tuberculosis ) AND (recurrent OR recurrence OR relapse OR reinfection OR "previously treated" OR retreatment OR reactivation)) |
| WOS | (("survival analysis" OR "time to event" OR "Cox proportional hazard*" OR "Kaplan Meier" OR "hazard ratio" OR "competing risk*") AND (tuberculosis OR TB) AND (recurrent OR recurrence OR relapse OR reinfection OR "previously treated" OR retreatment OR reactivation)) |

By using standard practice, each NOS item allocated with stars and a total score (0-9) was calculated for each study to facilitate comparison across the studies.[19-20] The total scores were classified as follows: high methodological quality and low risk of bias, seven to nine stars, moderate risk of bias, four to six stars, and high risk of bias, zero to three stars. Any discrepancy in scoring was resolved through discussion.

### Data Synthesis

A narrative synthesis was conducted due to the expected methodological diversity among the included studies, such as differences in study design, populations, measurement approaches, and outcome reporting. Key study characteristics, including sample size, setting, participant demographics, exposure definitions, and outcome measures, were extracted and summarised in tables. Due to significant clinical, methodological and statistical heterogeneity between studies on the definition of recurrence, duration of follow-up, study populations and analysis methodologies, a quantitative meta-analysis was not performed. Instead, a structured narrative synthesis was performed. Findings were synthesised thematically across key domains, including sociodemographic factors, disease severity factors, behavioural factors, comorbidity-related factors, treatment-related factors and environmental factors. Consistency and direction of associations were examined across studies, with emphasis on adjusted estimates derived from multivariable models.

## RESULTS

### Study Selection

A total of 2229 records were identified through database searching, including PubMed (n=218), Scopus (n=1717), and WOS (n=294). Prior to screening, 1032 records were removed, comprising 283 duplicate records, 651 records marked as ineligible by automation tools, and 98 records removed for other reasons. The remaining 1197 records were screened based on titles and abstracts, of which 1108 records were excluded for not meeting the inclusion criteria.

Following the screening stage, 89 reports were sought for full-text retrieval; however, 5 full-text articles were not available and were therefore excluded. Consequently, 84 full-text articles were assessed for eligibility. Of these, 68 articles were excluded for the following reasons: irrelevant exposure or outcome (n=20), failure to report risk factors (n = 30), did not assess after successfully treated TB cases (n = 9), and ineligible study design (n=10).

Ultimately, 15 studies met the eligibility criteria and were included in the systematic review. Figure 1 shows the flowchart of the selection of suitable journals using the PRISMA flowchart.

### Characteristics of Included Studies

Across 15 cohort studies conducted in Asia, TB recurrence after treatment completion ranged from approximately 1.5 to 15.1%, or 0.47 per 100 person-years to 6.62 per 1,000 person-years, with a higher risk observed during the first two years post-treatment. Most studies used retrospective registry-based designs and Cox proportional hazards models. Consistent risk factors for TB recurrence observed were markers of high mycobacterial burden (cavitation, smear or culture positivity, delayed 2-month conversion), prior TB history, older age, male sex, and drug resistance. Comorbidities such as diabetes, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), and low body mass index (BMI) were repeatedly associated with elevated risk. Behavioural and social determinants, including smoking, homelessness, and low socioeconomic status, also contributed. Treatment-related factors such as treatment duration, adherence, and regimen type were protective in several studies. The characteristics of included studies, recurrence definition and frequency, statistical approaches, and adjusted risk factors for recurrent TB in Asia are shown in Table II.

### Countries settings

Variation in TB recurrence was observed across 15 studies conducted in East Asia, Southeast Asia, and the Middle East. Studies from high-income settings such as South Korea, Taiwan, and Hong Kong generally reported lower recurrence proportions from approximately 1.5% to 3.5%. Meanwhile, studies from China, Vietnam and Iran reported wider recurrence estimates ranging from 2.6% to 15.1% across different study populations and follow-up periods.

### Study setting and study design

All studies utilise cohort study designs, with the majority of them being retrospective cohorts (11/15, 73.3%) based on national registries, surveillance systems, or administrative databases, and the remaining ones were prospective cohorts.

**Table II: Characteristics included studies, recurrence definition and frequency, statistical approaches, and adjusted risk factors for TB recurrence in Asia**

| No. | Author (year) | Country / Setting | Study design | Study population & sample size | Key recurrence findings | Main limitations |
|---|---|---|---|---|---|---|
| 1. | Chung et al., 2024.[14] | South Korea (nationwide) | Retrospective national cohort; Cox regression Incidence:982.1 per 100,000 person-years | Drug-susceptible PTB patients from national registry; n=66,690; recurrence ≈3.1% (over 39 months median follow-up), with 50.3% (occurred within 1 year after treatment completion) | Lower household income was associated with recurrence (aHR 1.76, 95% CI 1.49–2.07), with stronger effects observed among males (aHR 2.08, 95% CI 1.71–2.52). | Income used as proxy for socioeconomic status; residual confounding possible. |
| 2. | Golub et al., 2019.[13] | South Korea | Large prospective cohort; time-varying Cox models | Adults with previous TB from national cohort; n= 1,267564; Age standardised recurrence rate≈ 759.4/100000 | Diabetes mellitus significantly increased TB recurrence risk (aHR 1.67, 95% CI 1.12–2.48) and TB-related mortality. | Recurrence identified using administrative data; limited clinical detail. TB recurrence was defined using claim-based in person with prior TB episode, limiting the differentiation between relapse after cure and re-treatment cases. |
| 3. | Hsu et al., 2025.[21] | Taiwan | Retrospective cohort; Cox regression | Successfully treated non-HIV PTB patients; n=1,875; recurrence ≈2.0% (median follow-up: 72 months). The highest rate was seen within 2 years of treatment completion | Low BMI (<20 kg/m²) (aHR 4.38, 95% CI 1.70–11.30), prior history of TB (aHR 4.28, 95% CI 1.77–10.35), and 2-month culture non-conversion (aHR 3.37, 95% CI 1.36–8.38) predicted recurrence. | Single centre; limited generalizability |
| 4. | Shen et al., 2017.[22] | China (Shanghai) | Retrospective cohort with molecular genotyping; Cox regression | Successfully treated bacteriologically confirmed PTB; n=13,417; recurrence≈ 5.3% or 755 cases per 100,000 person-years. Relapse cases occurred earlier, within 3 years after treatment completion while reinfection cases increased as time progressed. | Male sex (aHR 1.40, 95% CI 1.11–1.77), age 30–59 (aHR 1.24, 95% CI 1.03–1.47), cavitation (aHR 1.27, 95% CI 1.06–1.51), diabetes (aHR 1.42, 95% CI 1.13–1.79), smear positive (aHR 2.13, 95% CI 1.19–1.51) and MDR-TB (aHR 2.90, 95% CI 2.20–3.84) increased recurrence; 58.2% due to relapse with similar genotype. | Genotyping was limited (approximately only 27.4% had paired isolates to differentiate the mechanism of recurrence); immigrant populations were excluded. |
| 5. | Ruan et al., 2022.[23] | China (Hangzhou) | Retrospective population cohort; Cox regression | Successfully treated smear-positive non-MDR PTB; n=9,828; recurrence ≈4.9%. More than 50% of recurrences occurred within 1-year post-treatment completion (median follow-up: 51.4 months | Recurrence risk increased with male sex (aHR 1.61, 95% CI 1.30–2.00), age ≥60 (aHR 2.03, 95% CI 1.70–2.44), cavitation (aHR 1.51, 95% CI 1.25–1.82), and 2-month sputum positivity (aHR 1.39, 95% CI 1.12–1.82); prolonged treatment was protective (aHR 0.73, 95% CI 0.61–0.88). | Retrospective design; with potential case underestimation. Lack of socioeconomic (income and employment status) and clinical data (adherence) |
| 6. | Li et al., 2024.[24] | China (national registry) | Retrospective national cohort; Cox regression | Successfully treated PTB cases (2005–2021); n=1,0482271; recurrence≈3.9% or 0.47 per 100 person-years. 48.9% of recurrences occurred within the first 2 years. | Age 65 to 85 years (aHR 2.54, 95% CI 1.65–3.92), minority ethnicity (aHR 1.55, 95% CI 1.25–1.91), treated in general hospital (aHR 2.35, 95% CI 1.26–4.41) increased recurrence, while negative sputum at 2 months (aHR 0.31, 95% CI 0.16–0.58) was a protective factor. | Registry-based data; relapse vs reinfection not distinguished. |
| 7. | Wang et al., 2024.[25] | China (Jiangsu) | Retrospective cohort; Cox regression | Successfully treated PTB patients; n=12,509; recurrence ≈3.5% or 6.62 per 1000 person years (median follow-up: 65.5 months) | Diabetes mellitus (aHR 2.40, 95% CI 1.68–3.45), age ≥60 (aHR 1.39, 95% CI 1.15–1.70), male sex (aHR 1.30, 95% CI 1.03–1.64), and etiologic positivity (aHR 2.42, 95% CI 2.00–2.92) increased recurrence risk, while FDC (aHR 0.77, 95% CI 0.61–0.95) reduced recurrence risk. | No strain typing; reliance on routine surveillance variables. |
| 8. | Yen et al., 2014.[26] | Taiwan | Retrospective cohort; Cox regression | Successfully treated TB patients; n=5,567; recurrence≈1.5% | Heavy smoking (>10 cigarettes/day) doubled recurrence risk (aHR 2.03, 95% CI 1.29–3.18); homelessness (aHR 3.75, 95% CI 1.17–12.07); comorbidities (aHR 2.66, 95% CI 1.22–5.79) and smear positivity (aHR 2.27, 95% CI 1.47–3.49) were additional predictors. | Smoking exposure self-reported; residual socioeconomic confounding. |

**Table II: Characteristics included studies, recurrence definition and frequency, statistical approaches, and adjusted risk factors for TB recurrence in Asia**

| No. | Author (year) | Country / Setting | Study design | Study population & sample size | Key recurrence findings | Main limitations |
|---|---|---|---|---|---|---|
| 9. | Lin et al., 2024.[27] | China | Prospective cohort; Cox regression | TB patients completing treatment; n=634; followed up to 7 years recurrence≈15.1% | Dose–response relationship between smoking intensity and recurrence; smoking cessation during treatment reduced recurrence risk. Heavy smoker who smokes 30+ cigarettes/day (aHR 6.488, 95% CI 2.16–19.46) had the highest recurrence risk compared with non-smokers. | Claim-based smoking status with no biochemical verification; residual confounding such as comorbidities. |
| 10. | Lee et al., 2023.[28] | Taiwan (National Health Insurance Database) | Retrospective database cohort; time-to-event analysis | New TB patients (2008–2017); n=33,298; 2-year recurrence≈ 1.54% | Incomplete adherence (80–89%: aHR 1.57, 95% CI 1.27–1.96; 90–99%: aHR 1.63, 95% CI 1.29–2.07), diabetes (aHR 1.40, 95% CI 1.15–1.70), and COPD (aHR 1.28, 95% CI 1.06–1.55) increased recurrence. | Claims-based adherence and outcome definitions; limited clinical detail. |
| 11. | Di et al., 2025.[15] | China (Quzhou) | Population-based retrospective cohort; Cox regression | PTB registry patients; n=6,732; recurrence≈ 8.2% | High $PM_{2.5}$ exposure markedly increased recurrence risk in a dose-response manner (aHR 15.48, 95% CI 9.28–25.82); residential greenness was protective (aHR 0.86, 95% CI 0.75–0.98 per 0.1 NDVI). | Environmental exposure estimation subject to spatial misclassification. |
| 12. | Leung et al., 2015.[29] | Hong Kong | Prospective cohort; registry linkage; Cox regression | Successfully treated patients; n=13,349; recurrence≈ 3.2% or 396 per 100,000 person-years | Recurrence risk increased from never-smokers to ex-smokers (HR 1.33, 95% CI 1.04–1.71) to current smokers (HR 1.63, 95% CI 1.29–2.06). | Observational design; smoking exposure may be imperfect as it is not quantified. |
| 13. | Huyen et al., 2013.[30] | Vietnam | Prospective cohort with genotyping; Cox regression | Smear-positive PTB patients; n=1,068; recurrence 3.3% (over 18 months follow-up) or 1.39 per 100 person-years. Of recurrent cases, 66% were relapse cases | Beijing genotype infection (aHR 5.48, 95% CI 2.06–14.55) and isoniazid resistance (aHR 5.91, 95% CI 2.16–16.16) strongly predicted relapse. | Limited follow-up time and lack of HIV and radiographic data for confounding adjustment. |
| 14. | Mehrbakhsh et al., 2024.[31] | Iran (Golestan) | Retrospective cohort; penalised Cox models | Smear-positive PTB patients; n=1,548. Recurrence≈ 2.6% (median follow-up time:136.87months) | Relapse associated with age >35 (HR 2.77), CKD (HR 5.36), and married patients (HR 8.49); penalised Cox models improved prediction. | Single centre; covariate availability limited (smoking, alcohol) |
| 15. | Wang et al., 2015.[32] | Taiwan (nationwide) | Retrospective population-based cohort; Cox regression | HIV-infected TB patients who completed anti-TB treatment; n=508; recurrences n=18 (3.5%) | Anti-TB treatment duration 6 to 9 months (>270 days) significantly reduced recurrence risk (aHR 0.24, 95% CI 0.08–0.73); treatment during the DOT era was protective (aHR 0.34, 95% CI 0.12–0.97). | CD4+ and HAART were not included which are common predictors for recurrence in HIV patients. Limited clinical detail (e.g. cavitation, smear conversion). |

Notes:
PTB: Pulmonary tuberculosis; NDVI: Normalised Difference Vegetation Index; COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; DOT: Directly observed therapy; HIV: Human immunodeficiency virus; BMI: Body mass index; FDC: Fixed-dose combination; MDR: Multidrug-resistant; $PM_{2.5}$: Fine particulate matter; HAART: Highly active antiretroviral therapy; aHR: Adjusted hazard ratio; CI: Confidence interval.

**Table III: Stratified Adjusted Hazard Ratios for Determinants of TB Recurrence**

| Domain | Factor | Adjusted Hazard Ratio (Range) | Strength of Association* |
|---|---|---|---|
| Sociodemographic | ▪ Male sex | 1.30 – 1.61 | Mild–Moderate |
| | ▪ Older age (≥60 years) | 1.39 – 2.54 | Mild–Moderate |
| | ▪ Age 30–59 years | 1.24 – 1.50 | Mild–moderate |
| | ▪ Marital status (married) | 8.49 (single study) | Strong (isolated) |
| | ▪ Low household income | 1.76 (1.49–2.07) | Moderate |
| | ▪ Minority ethnicity | 1.55 (1.25-1.91) | Moderate |
| | ▪ Homelessness | 3.75 (1.17–12.07) | Strong |
| Behavioural | ▪ Current smoking | 1.63 (1.29 – 2.06) | Moderate |
| | ▪ Heavy smoking (>30+ cigarettes/day) | 2.03 – 6.49 | Moderate–strong |
| | ▪ Smoking (dose–response) | ↑ HR with intensity | Gradient effect |
| | ▪ Smoking cessation | 0.63 (0.46–0.86) | Protective |
| Comorbidities | ▪ Diabetes mellitus | 1.44 – 2.40 | Moderate |
| | ▪ Low BMI (<18.5- 20 kg/m²) | 1.63 – 4.38 | Moderate–strong |
| | ▪ COPD | 1.28 (1.06–1.55) | Mild |
| | ▪ CKD | 5.36 (single study) | Strong |
| | ▪ HIV infection | Recurrence 3.5% | Elevated risk |
| Disease Severity / Microbiological | ▪ Cavitary disease | 1.27 – 1.51 | Mild–Moderate |
| | ▪ Smear/culture positivity/ | 1.67 – 4.09 | Moderate–strong |
| | ▪ 2-month non-conversion | 1.39 – 3.37 | Moderate–strong |
| | ▪ Prior TB history | 4.28 (1.77–10.35) | Strong |
| | ▪ Any drug resistance | 2.90 – 2.94 | Moderate |
| | ▪ Isoniazid resistance | 5.91 (2.16–16.16) | Strong |
| | ▪ Beijing genotype | 5.48 (2.06–14.55) | Strong |
| Treatment-related | ▪ Incomplete adherence (80–89%) | 1.57 (1.22–1.96) | Moderate |
| | ▪ Incomplete adherence (90–99%) | 1.63 (1.26–2.07) | Moderate |
| | ▪ FDC | 0.77 (0.61–0.95) | Protective |
| | ▪ Treatment >270 days | 0.24 (0.08–0.73) | Protective |
| | ▪ Prolonged regimen | 0.73 (0.61–0.88) | Protective |
| | ▪ DOT era treatment | 0.34 (0.12–0.97) | Protective |
| Environmental | ▪ High $PM_{2.5}$ exposure | 15.48 (9.28–25.82) | Very strong |
| | ▪ Residential greenness (per 0.1 NDVI) | 0.86 (0.75–0.98) | Protective |

Notes:
BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; HIV: Human immunodeficiency virus; FDC: Fixed-dose combination; DOT: Directly observed therapy; $PM_{2.5}$: Fine particulate matter; NDVI: Normalised Difference Vegetation Index.
Strength of association based on adjusted hazard ratio (aHR): Protective: <1.0; Mild: 1.1-1.4; Moderate: 1.5-3.0; Strong: 3.1-10.0; Very strong: >10.[33-34]

**Table IV: Risk of bias assessment of included studies using the Newcastle–Ottawa Scale (NOS)**

| Author (Year) | Selection | | | | Comparability | Outcome | | | Overall Score |
|---|---|---|---|---|---|---|---|---|---|
| | Cohort Representativeness | Non-exposed cohort selection | Exposure ascertainment | Outcome absent at baseline | Cohort comparability | Outcome ascertainment | Sufficient follow-up for outcome | Follow-up adequacy | (0–9) |
| Chung et al. (2024) | * | * | * | * | ** | * | * | * | 9 |
| Golub et al. (2019) | * | * | * | * | ** | * | * | – | 8 |
| Hsu et al. (2025) | * | * | * | – | ** | * | * | – | 7 |
| Shen et al. (2017) | * | * | * | * | ** | * | * | – | 8 |
| Ruan et al. (2022) | * | * | * | * | ** | * | * | – | 8 |
| Li et al. (2024) | * | * | * | * | * | * | * | – | 7 |
| Wang et al. (2024) | * | * | * | * | ** | * | * | – | 8 |
| Wang et al. (2015) | * | * | * | – | * | * | * | – | 6 |
| Yen et al. (2014) | * | * | * | * | * | * | * | – | 7 |
| Lin et al. (2024) | * | * | * | – | ** | * | * | – | 7 |
| Lee et al. (2023) | * | * | * | * | * | * | * | – | 7 |
| Di et al. (2025) | * | * | * | * | * | * | * | – | 7 |
| Leung et al. (2015) | * | * | * | * | ** | * | * | * | 9 |
| Huyen et al. (2013) | * | * | * | – | ** | * | * | – | 7 |
| Mehrbakhsh et al. (2024) | * | * | * | – | ** | * | * | – | 7 |

Time-to-event analysis using Cox proportional hazards models was applied, including penalised and time-varying Cox approaches. However, only two studies distinguished between relapse and reinfection as mechanisms of recurrence using molecular genotyping. Heterogeneity arose from differences in data sources, time window of follow-up, study designs (retrospective or prospective) and modelling strategies.

**Sample size and study population.**
The included studies assessed TB recurrence across diverse post-treatment populations, with sample sizes ranging from 508 to over 1.2 million individuals, including one national registry study exceeding 10 million cases. Most focused on successfully treated pulmonary TB patients, including bacteriologically confirmed, smear-positive, and DS-TB cases; fewer examined new TB patients or human immunodeficiency virus (HIV) infected populations.

**Determinants of TB Recurrence**
The determinants of TB recurrence, as estimated by hazard ratios, are shown in Table III.

Across domains, the strongest associations with TB recurrence were observed for environmental exposures, particularly high fine particulate matter ($PM_{2.5}$) levels (aHR 15.48), drug resistance and bacterial genotype (aHR 5.48–5.91), prior TB history (aHR 4.28). Delayed microbiological response, such as two-month culture non-conversion (aHR 3.37), also showed a strong association. In contrast, modifiable factors were consistently protective, including smoking cessation, which reduced recurrence risk by approximately 35–40% (aHR 0.63), and extended treatment duration (>270 days), which was associated with up to a 76% lower risk of recurrence (aHR 0.24).

**Summary of Study Limitations**
Across the 15 studies, methodological limitations were common. Most studies used retrospective or registry-based designs, limiting causal inference and increasing residual confounding. About one-third relied on single-centre or single-province data, restricting generalisability. Over half (55–60%) used administrative or claims data, often lacked clinical detail and risked misclassification of recurrence. Relapse and reinfection were not differentiated in almost 80% of studies, as molecular genotyping was often available in selected populations or short follow-up. Exposure misclassification was noted, with self-reported behaviours in approximately 25–30% of the studies and spatial misclassification of environmental exposures. Collectively, these issues contributed to heterogeneity, limited synthesis, and reduced programmatic applicability.

**Quality Assessment**
The risk of bias of the included studies was assessed using the Newcastle-Ottawa Scale.[35] There were three domains: selection of study groups, comparability of groups and outcome ascertainment were evaluated. Table IV displays the summary of the risk of bias of the included studies. The included studies generally demonstrated high quality; 14 out of 15 studies (93.3%) had obtained total NOS scores of 7-9, signifying that the studies had a low risk of bias. Only one study scored six, thus it was categorised as having a moderate risk of bias, and no study was noted as having a high risk of bias. The selection domain was good, with all 15 studies rated three or four stars. In contrast, the comparability area had a lower strength, as only 60 per cent (9/15) received up to two stars for full confounder adjustment. All the studies on the outcome domain had at least two out of three stars, but the most overlooked parameter was the adequacy of follow-up. Generally, the results indicate that the findings should be interpreted with caution because residual confounders may potentially serve as a limitation.

## DISCUSSION

The recurrence rates observed in our study range widely from 1.5% to 15% or 0.47 to 6.5 per 1,000 person-years reflecting a diverse epidemiological landscape of TB in Asia. Globally, the upper limit of this range is higher than the reported rate in regions with highly resourced healthcare systems such as the United States and Europe which reported rates between 1.1% and 5.7%.[36-38] Within our study cohort, we observed that high-income Asian countries (South Korea, Taiwan, and Hong Kong) generally reported lower recurrence compared to middle- and lower-income countries (China, Vietnam, and Iran), suggesting a role of economic resources in long-term disease management. In Asian setting, TB recurrence cannot be explained by one single factor, as there is a complex interaction of individual susceptibility and structural determinants of health. Multiple determinants have been found as the key predictors of TB recurrence, which can be divided into several domains: sociodemographic, behavioural, comorbidities, microbiological, treatment-related, and environmental factors.[16] This study demonstrates the importance of sociodemographic and structural determinants that contribute to TB recurrences. Male and older patients are more prone to have recurrence.[14,22-25] The high male incidence could suggest more occupational exposure and lower health-seeking behaviours, while older patients are more likely to have immunological deterioration and more comorbidities (e.g., diabetes, COPD), thereby making adherence and tolerance to treatment difficult and slow bacterial clearance.[39-41]

Socioeconomic disadvantage, such as homelessness, low household income, and being an ethnic minority, also exhibited a quite strong association with TB recurrence. A Korean study found the risk increases as income level decreases, shaped by barriers to high-quality care, increased exposure to transmission environments.[14] These structural determinants influence TB recurrence by impacting treatment adherence and weakened immune response. Homelessness further increases the risks through continuous barriers to healthcare access and suboptimal living conditions.[26,42-43] These factors suggest that TB recurrences are not purely biomedical failures; they represent a complex interaction between biological, social environment and health system. Behavioural factor like smoking is found to be modifiable determinants of long-term TB treatment outcomes, including recurrence.[26-27,29,44] In this analysis, the dose-response relationship in which heavier smoking is associated with higher hazards of TB recurrences is established. This is supported by a recent systematic review

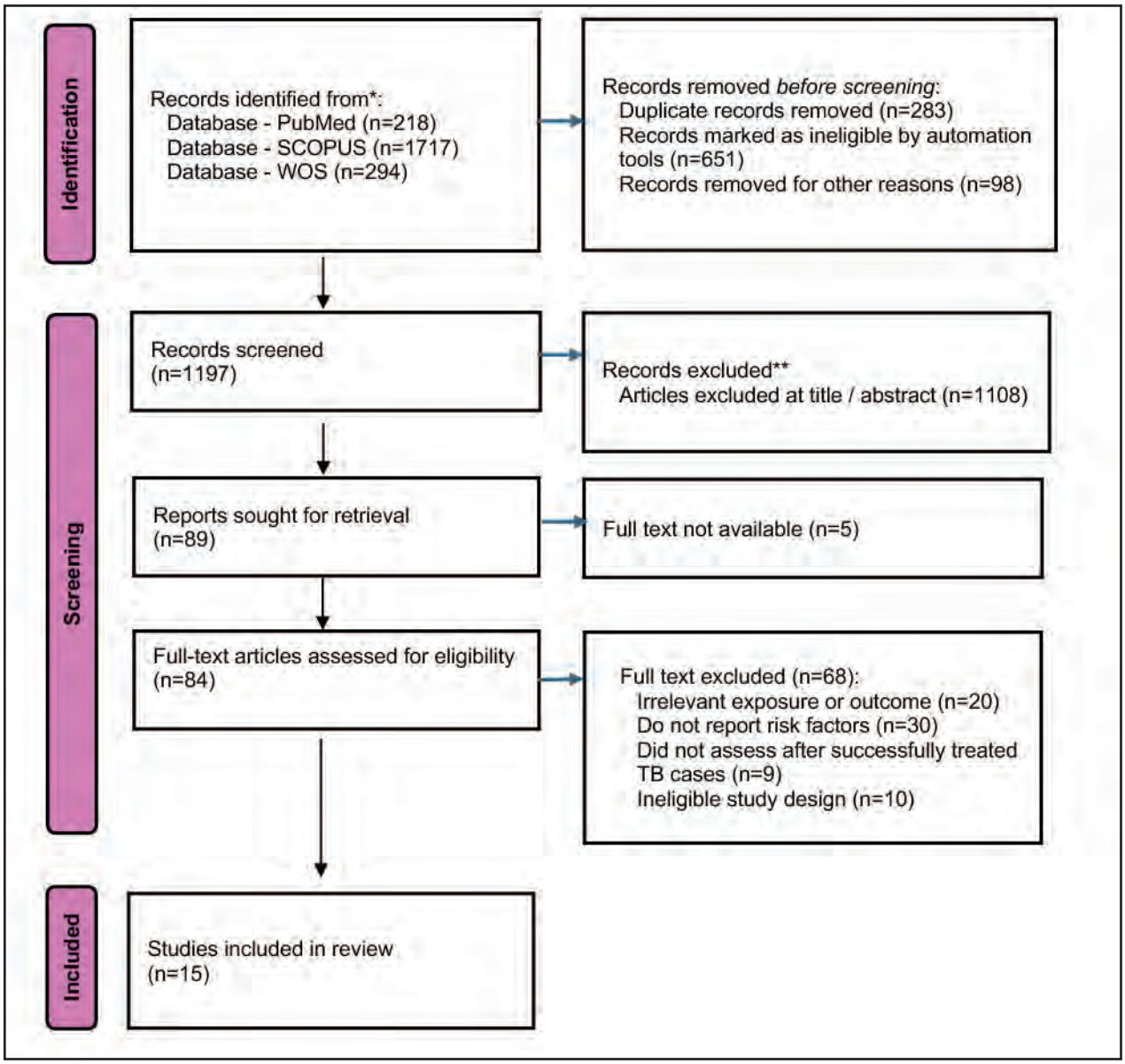



**Fig. 1:** The process of selecting suitable journals using the PRISMA flowchart

and meta-analysis showing that smoking cigarettes is linked to impaired immune defences, reduced macrophage function and delayed clearance of *M. tuberculosis*.[44] The consistencies in dose-responses gradient observed in several studies included in the review and the evidence of smoking cessation reduces the risk of TB recurrence support the biological plausibility, coherence, reversibility and strengthen causal inference under the Bradford Hill framework.[45]

Having comorbidities such as diabetes, COPD, CRF, HIV infection and low BMI tends to increase the risk of developing TB recurrence. From our analysis, those with diabetes have a two times higher risk of developing recurrence, possibly because the condition impairs innate and adaptive immunity and delays sputum conversion.[13,22,25,28] Low BMI and malnutrition are also associated with impaired cell-mediated immunity and reduced CD4 T-cell and interferon-gamma (IFN-γ) responses, thereby increasing the risk of unsuccessful TB outcomes and recurrences.[21,46] Additionally, broader immunosuppressive conditions and therapies, particularly the use of tumour necrosis factor-alpha (TNF-α) inhibitors, are identified as risk factors in other studies.[47-48] As TNF-α is essential for the formation and maintenance of granulomas that contain M. tuberculosis, patient receiving the therapy for inflammatory diseases (eg; rheumatoid arthritis) have compromised immune containment thus increasing their susceptibility to TB reactivation and recurrence.[48]

Furthermore, COPD is also found to have a higher hazard for developing recurrence due to structural lung damage and impaired mucociliary clearance, thus increasing susceptibility to reinfection and reactivation from residual foci, and this finding is supported by recent reviews.[28,49-50] Other than that, CKD also has an increased risk of recurrence, about five times compared to those without it; however, only one study included in our analysis reported

this association. Luczynski et al, through their systematic review, suggest that CKD has immune dysregulation, specifically uraemia-related dysfunction, which alters the pharmacokinetics of TB medication and leads to higher side effects and recurrence.[51] HIV is another common comorbidity associated with an increased risk of recurrence. Evidence from the study conducted on TB-HIV patients suggests that treatment duration and treatment during the DOT era influence the risks; however, this study relied on routine or claim-based data and the independent contribution of clinical aspects, such as CD4+ counts and HAART treatment, could not be fully assessed.[32]

Disease severity and certain microbiological characteristics are also consistently linked with TB recurrence.[16,25-26] Among them are cavitary disease, smear/culture positivity, prior TB and delayed two months smear conversion.[21-23] Pulmonary cavities may result from failure to contain *M. tuberculosis*, producing necrosis that harbours high bacterial loads, delays clearance and elevates the risk for unfavourable treatment outcomes and recurrence.[52] A prior TB episode is another strong risk factor for recurrence, likely reflecting residual cavity or fibrotic lung damage and increased susceptibility to recurrence. Additionally, a high baseline smear grade can act as a marker for high mycobacterial burden and is often associated with delayed conversion and incomplete clearance.[21] Drug resistance has shown strong associations with recurrence, with isoniazid resistance exhibiting the largest hazard ratios.[30] The resistance compromises bactericidal activity and slows its clearance, resulting in higher bacterial loads and an increased risk for recurrence.[53] In addition, Beijing strains were found to be a strong risk factor for recurrence as it frequently associated with higher virulence traits, superior intracellular survival and drug-resistance.[54-55]

The risk of TB recurrence is also contributed by several treatment-related factors. Those with incomplete treatment (80–99%) have a higher risk of recurrence compared to those who fully completed the treatment.[28] An effective cure requires sustained and uninterrupted treatment over a prolonged period. From our analysis, longer treatment which is six to nine months or >270 days, reduces the recurrence risk. To reduce pill burden and maximise adherence, a fixed-dose combination (FDC) was introduced by the WHO, and it is noted to have a protective effect towards disease recurrence compared to loose tablets.[25] Moreover, the directly observed therapy (DOT) strategy that is designed to ensure adherence has also been found to reduce the risk for recurrence.[32,56] Environmental factors, especially exposure to $PM_{2.5}$ are strongly associated with TB recurrence. Our analysis indicates that an individual exposed to high $PM_{2.5}$ has a higher risk, approximately 15 times higher than those in the lower exposure group.[15] $PM_{2.5}$ can penetrate the lungs and weaken the body's natural defence mechanisms, making it easier for TB bacteria to persist and reactivate even after treatment is completed.[57] On the contrary, residential green spaces help to improve air quality and support lung health and possibly reduce risk of respiratory infections and recurrence.[58] These findings suggest that TB recurrence is influenced not only by clinical care but also by the environmental conditions.

**Clinical and Public Health Implications**

In general, the consistency and strength of associations across multiple domains are suggestive of a multifactorial model of TB recurrence with several modifiable risk factors, which offer opportunities for early prevention. The identification of at-risk patients, including those with drug resistance, late sputum conversion, prior TB or significant environmental exposure, will help in making clinical decisions. This includes risk-stratified surveillance, possible extended and closer post-treatment follow-up to allow early detection of recurrence. These approaches promote more efficient use of health-care resources. Most importantly, an integrated intervention that combines clinical management, behaviour interventions (smoking cessation and adherence support) and environmental as well as living conditions adjustments required to prevent TB recurrences.

**Strengths and Limitations of the Study**

This study offers a comprehensive synthesis of TB recurrence risk determinants by integrating clinical, microbiological, behavioural and environmental factors. The inclusion of emerging environmental data such as $PM_{2.5}$ and residential greenness extends the traditional clinical scope of TB research. By identifying modifiable risk factors, this review provides high translational value for public health programs aiming to reduce TB recurrence. There are a few limitations that should be mentioned. First, the findings rely on observational data, which restricts the causal inference. Second, heterogeneity across studies in the measurement of treatment adherence and environmental exposure is quite high and may result in some misclassification bias.

## CONCLUSION

The review demonstrates that clinical, microbiological, treatment-related, behavioural, and environmental factors interact to cause TB recurrence. The findings support a multifactorial model of recurrence and identify modifiable, prevention-ready targets. Risk-stratified care for high-risk patients, combined with adherence support, behavioural interventions, and environmental improvements, is essential. Integrated, patient-centred, and multisectoral strategies are therefore critical to achieving durable TB cure and reducing recurrent disease burden.

## ACKNOWLEGDEMENTS

The authors thank the Tun Abdul Razak Library (UiTM) for librarian support in assisting comprehensive retrieval of relevant literature. We would also like to acknowledge the Director General of Health, who allowed publication of the article.

## CONFLICT OF INTEREST

None.

## FUNDING

None.

## REFERENCES


1. World Health Organization. South-East Asia leads global TB cases: WHO urges swift action to address gaps and boost progress 2025 [cited Dec 2025]. Available from: https://www.who.int/southeastasia/news/detail/18-11-2025-south-east-asia-leads-global-tb-cases-who-urges-swift-action-to-address-gaps-and-boost-progress.
2. World Health Organization. Tuberculosis 2025 [cited Nov 2025]. Available from: https://www.who.int/news-room/fact-sheets/detail/tuberculosis.
3. Wu J, Dalal K. Tuberculosis in Asia and the Pacific: the role of socioeconomic status and health system development. Int J Prev Med 2012; 3(1): 8-16.
4. Bhatia V, Rijal S, Sharma M, Islam A, Vassall A, Bhargava A, et al. Ending TB in South-East Asia: flagship priority and response transformation. Lancet Reg Health Southeast Asia 2023; 18: 100301.
5. Marx FM, Cohen T, Menzies NA, Salomon JA, Theron G, Yaesoubi R. Cost-effectiveness of post-treatment follow-up examinations and secondary prevention of tuberculosis in a high-incidence setting: a model-based analysis. Lancet Glob Health 2020; 8(9): 1223-33.
6. World Health Organization. Global tuberculosis report 2022. Geneva; 2022.
7. World Health Organization. Global tuberculosis report 2024. Geneva; 2024.
8. Norjeehan J, Raymund D, Ahmad Zamzuri MAI, Osman M. Tuberculosis recurrence and its associated factors among TB referral centre attendees in Negeri Sembilan, Malaysia. Malays J of Public Health Med 2025; 25(2): 127-42.
9. Rameli NAC, Yaacob SS, Ismail N, Azzani M, Harishah T. Determinants of unsuccessful treatment outcomes among relapse tuberculosis patients in Selangor registered in national tuberculosis registry from year 2015-2019. Med J Malaysia 2025; 80(1): 9-16.
10. Tok PSK, Liew SM, Wong LP, Razali A, Loganathan T, Chinna K, et al. Determinants of unsuccessful treatment outcomes and mortality among tuberculosis patients in Malaysia: a registry-based cohort study. PLoS One 2020; 15(4): e0231986.
11. Bryant JM, Harris SR, Parkhill J, Dawson R, Diacon AH, Van Helden PD, et al. Whole-genome sequencing to establish relapse or re-infection with Mycobacterium tuberculosis: a retrospective observational study. Lancet Respir Med 2013; 1(10): 786-92.
12. Guerra-Assunção JA, Houben RM, Crampin AC, Mzembe T, Mallard K, Coll F, et al. Recurrence due to relapse or reinfection with Mycobacterium tuberculosis: a whole-genome sequencing approach in a large, population-based cohort with a high HIV infection prevalence and active follow-up. J Infect Dis 2015; 211(7): 1154-63.
13. Golub JE, Mok Y, Hong S, Jung KJ, Jee SH, Samet JM. Diabetes mellitus and tuberculosis in Korean adults: impact on tuberculosis incidence, recurrence and mortality. Int J Tuberc Lung Dis 2019; 23(4): 507-13.
14. Chung C, Jeong D, Sohn H, Choi H, Kang YA. Low household income increases the risk of tuberculosis recurrence: a retrospective nationwide cohort study in South Korea. Public Health 2024; 226: 228-36.
15. Di Y, Peng Y, Hao X, Xin H, Guo T, Du J, et al. The association between pulmonary tuberculosis recurrence and exposure to fine particulate matter and residential greenness: a population-based retrospective study. One Health 2025; 20: 101035.
16. Victor V, Javier C-S, Sharon R, Kristien V, Carlos S, Larissa O, et al. Risk factors for pulmonary tuberculosis recurrence, relapse and reinfection: a systematic review and meta-analysis. BMJ Open Respir Res 2024; 11(1): e002281.
17. Oh AL, Makmor-Bakry M, Islahudin F, Wong IC. Prevalence and predictive factors of tuberculosis treatment interruption in the Asia region: a systematic review and meta-analysis. BMJ Glob Health 2023; 8: e010592.
18. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021; 372: n71.
19. Wells GAS, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses 2025 [cited Dec 2025]. Available from: https://ohri.ca/en/who-we-are/core-facilities-and-platforms/ottawa-methods-centre/newcastle-ottawa-scale.
20. Li X, Lang X, Peng S, Ding L, Li S, Li Y, et al. Calf circumference and all-cause mortality: a systematic review and meta-analysis based on trend estimation approaches. J Nutr, Health and Aging 2022; 26(9): 826-38.
21. Hsu CM, Wu CJ, Chang CJ, Pan SW, Tseng YH, Huang JR, et al. Recurrence of tuberculosis and associated risk factors among non-HIV patients in Taiwan: a retrospective cohort study. J Infect Public Health 2025; 18(11): 102912.
22. Shen X, Yang C, Wu J, Lin S, Gao X, Wu Z, et al. Recurrent tuberculosis in an urban area in China: relapse or exogenous reinfection? Tuberculosis (Edinb) 2017; 103: 97-104.
23. Ruan QL, Yang QL, Sun F, Liu W, Shen YJ, Wu J, et al. Recurrent pulmonary tuberculosis after treatment success: a population-based retrospective study in China. Clin Microbiol Infect 2022; 28(5): 684-9.
24. Li T, Zhang B, Du X, Pei S, Jia Z, Zhao Y. Recurrent pulmonary tuberculosis in China, 2005 to 2021. JAMA Netw Open 2024; 7(8): e2427266.
25. Wang Y, Shi J, Yin X, Tao B, Shi X, Mao X, et al. The impact of diabetes mellitus on tuberculosis recurrence in Eastern China: a retrospective cohort study. BMC Public Health 2024; 24(1): 2534.
26. Yen YF, Yen MY, Lin YS, Lin YP, Shih HC, Li LH, et al. Smoking increases risk of recurrence after successful anti-tuberculosis treatment: a population-based study. Int J Tuberc Lung Dis 2014; 18(4): 492-8.
27. Lin H, Xiao L, Chen Y, Zeng X, Zhang X, Lin Y. Smoking cessation to prevent death and tuberculosis recurrence after treatment: a prospective cohort study with a seven-year follow-up in China. J Glob Health 2024; 14: 04187.
28. Lee CS, Ho CH, Liao KM, Wu YC, Shu CC. The incidence of tuberculosis recurrence: impacts of treatment duration and adherence to standard anti-tuberculous therapy. J Infect Public Health 2023; 16(11): 1778-83.
29. Leung CC, Yew WW, Chan CK, Chang KC, Law WS, Lee SN, et al. Smoking adversely affects treatment response, outcome and relapse in tuberculosis. Eur Respir J 2015; 45(3): 738-45.
30. Huyen MN, Buu TN, Tiemersma E, Lan NT, Dung NH, Kremer K, et al. Tuberculosis relapse in Vietnam is significantly associated with Mycobacterium tuberculosis Beijing genotype infections. J Infect Dis 2013; 207(10): 1516-24.
31. Mehrbakhsh Z, Roshanaei G, Behnampour N, Tapak L. Factors associated with time to relapse in pulmonary tuberculosis patients using penalized Cox models. BMC Res Notes 2024; 17(1): 333.
32. Wang JY, Sun HY, Wang JT, Hung CC, Yu MC, Lee CH, et al. Nine- to twelve-month anti-tuberculosis treatment is associated with a lower recurrence rate than 6-to 9-month treatment in human immunodeficiency virus-infected patients: a retrospective population-based cohort study in Taiwan. PLoS One 2015; 10(12): e0144136.
33. Chen H, Cohen P, Chen S. How Big is a Big Odds Ratio? Interpreting the magnitudes of odds ratios in epidemiological studies. Commun Stat Simul Comput 2010; 39(4): 860-4.
34. Roberts MR, Ashrafzadeh S, Asgari MM. Research techniques made simple: interpreting measures of association in clinical research. J Invest Dermatol 2019; 139(9): 502-11.
35. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa Hospital Research Institute 2014 [cited 2025 Dec]. Available from: https://ohri.ca/en/who-we-are/core-facilities-and-platforms/ottawa-methods-centre/newcastle-ottawa-scale.

36. Afshar B, Carless J, Roche A, Balasegaram S, Anderson C. Surveillance of tuberculosis (TB) cases attributable to relapse or reinfection in London, 2002-2015. PLoS One 2019; 14(2): e0211972.
37. Erkens C, Tekeli B, van Soolingen D, Schimmel H, Verver S. Recurrent tuberculosis in the Netherlands - a 24-year follow-up study, 1993 to 2016. Euro Surveill 2022; 27(12): 2100183.
38. Kim L, Moonan PK, Heilig CM, Yelk Woodruff RS, Kammerer JS, Haddad MB. Factors associated with recurrent tuberculosis more than 12 months after treatment completion. Int J Tuberc Lung Dis 2016; 20(1): 49-56.
39. Caraux-Paz P, Diamantis S, de Wazières B, Gallien S. Tuberculosis in the elderly. J Clin Med 2021; 10(24): 5889
40. Marçôa R, Ribeiro AI, Zão I, Duarte R. Tuberculosis and gender: factors influencing the risk of tuberculosis among men and women by age group. Pulmonology 2018; 24(3): 199-202.
41. Youn HM, Shin MK, Jeong D, Kim HJ, Choi H, Kang YA. Risk factors associated with tuberculosis recurrence in South Korea determined using a nationwide cohort study. PLoS One 2022; 17(6): e0268290.
42. Abd Rani AY, Ismail N, Zakaria Y, Isa MR. A scoping review on socioeconomic factors affecting tuberculosis loss to follow-up in Southeast Asia. Med J Malaysia 2024; 79(4): 470-6.
43. Gilmour B, Alene KA. Ending tuberculosis: challenges and opportunities. Front Tuberc 2024; 2: 1487518.
44. Vidyasagaran AL, Readshaw A, Boeckmann M, Jarde A, Siddiqui F, Marshall AM, et al. Is tobacco use associated with risk of recurrence and mortality among people with TB?: a systematic review and meta-analysis. Chest 2024; 165(1): 22-47.
45. Fedak KM, Bernal A, Capshaw ZA, Gross S. Applying the Bradford Hill criteria in the 21st century: how data integration has changed causal inference in molecular epidemiology. Emerg Themes Epidemiol 2015; 12: 14.
46. Fâcă AI, Udeanu DI, Arsene AL, Mahler B, Drăgănescu D, Apetroaei MM. Nutritional deficiencies and management in tuberculosis: pharmacotherapeutic and clinical implications. Nutrients 2025; 17(11): 1878.
47. Jahnich N, Arkwright PD. Regional risk of tuberculosis and viral hepatitis with tumor necrosis factor-alpha inhibitor treatment: a systematic review. Front Pharmacol 2023; 14: 1046306.
48. Solovic I, Sester M, Gomez-Reino JJ, Rieder HL, Ehlers S, Milburn HJ, et al. The risk of tuberculosis related to tumour necrosis factor antagonist therapies: a TBNET consensus statement. Eur Respir J 2010; 36(5): 1185-206.
49. Ratnakumar S, Hayward SE, Denneny EK, Goldsmith LP, Evans R, Checkley W, et al. Post-pulmonary tuberculosis lung function: a systematic review and meta-analysis. Lancet Glob Health 2025; 13(6): 1020-9.
50. Yadav S, Rawal G. Understanding the spectrum and management of post-tuberculosis lung disease: a comprehensive review. Cureus 2024; 16(6): 63420.
51. Luczynski P, Holmes T, Romanowski K, Arbiv OA, Cook VJ, Clark EG, et al. Risk of tuberculosis disease in people with chronic kidney disease without kidney failure: a systematic review and meta-analysis. Clin Infect Dis 2023; 77(8): 1194-200.
52. Kim SH, Shin YM, Yoo JY, Cho JY, Kang H, Lee H, et al. Clinical factors associated with cavitary tuberculosis and its treatment outcomes. J Pers Med 2021; 11(11): 1081.
53. Shao Y, Song H, Li G, Li Y, Li Y, Zhu L, et al. Relapse or reinfection: the situation of recurrent tuberculosis in Eastern China. Front Cell Infect Microbiol 2021; 11: 638990.
54. Akhmetova A, Bismilda V, Chingissova L, Filipenko M, Akilzhanova A, Kozhamkulov U. Prevalence of Beijing Central Asian/Russian cluster 94-32 among multidrug-resistant Mycobacterium tuberculosis in Kazakhstan. Antibiotics (Basel) 2023; 13(1): 9.
55. Mourik BC, de Steenwinkel JEM, de Knegt GJ, Huizinga R, Verbon A, Ottenhoff THM, et al. Mycobacterium tuberculosis clinical isolates of the Beijing and East-African Indian lineage induce fundamentally different host responses in mice compared to H37Rv. Sci Rep 2019; 9(1): 19922.
56. Katende-Kyenda LN. Improving tuberculosis medication adherence: a millennial disease in the age of new technologies: application of the World Health Organization-multidimensional adherence model: a review. Appl Sci 2025; 15(24): 12910.
57. Li Z, Wang Z, Lu P, Ning J, Ding H, Zhu L, et al. Association between ambient particulate matter and latent tuberculosis infection among 198 275 students. J Glob Health 2024; 14: 04244.
58. Mueller W, Milner J, Loh M, Vardoulakis S, Wilkinson P. Exposure to urban greenspace and pathways to respiratory health: an exploratory systematic review. Sci Total Environ 2022; 829: 154447.

# Acknowledgement
# July Issue 2026

**The Editorial Board of The Medical Journal of Malaysia gratefully acknowledge the following individuals for publication:**

**Handling Editors:**

1. Prof Dr Chew Keng Sheng
2. Dr Liew Boon Seng

**Reviewers:**

1. Ahmad Hazri Bin Ilyas
2. Aida Maziha Zainudin
3. Anirban Ghosal
4. Azliana Aziz
5. Badrul Hisham Abd Samad
6. Cheng Hoon Chew
7. Choon Seong Ang
8. Chun Wai Chan
9. David Chan Chee Hoong
10. Davinder Singh
11. Ee Vien Low
12. Fahisham bin Taib
13. Faridzal Harrymen Mohd Din
14. Glen Alvin
15. Guillermo Plaza
16. Hairul Hadi Ariff
17. Hamed Adetunji
18. Haris Abdul Rahman
19. Hong Wea Lau
20. Husna Maizura
21. Ikhwan Yuda Kusuma
22. Irfan Mohamad
23. Jasdev Singh Harbhajan Singh
24. Jeyasakthy Saniasiaya
25. Joo Thye Cheng
26. Ju Ying Ang
27. Karuthan Chinna
28. Keyvan Mollarahimi
29. Khairatul Nainey Kamaruddin
30. Khairy Anuar Mohd Khairuddin
31. Liew Boon Seng
32. Lim Yee Chin
33. Mahayuddin Abdul Manap
34. Masnira Jusoh
35. Masnun Mahmood
36. Mohamad Najib Mat Pa
37. Muhammad Harun Achmad
38. Myat Moe Thwe Aung
39. Najwa Aiyob
40. Navin Kumar Devaraj
41. Nik Nairan Abdullah
42. Nktel Faaz Al-saad
43. Noor Azlin Azraini Che Soh
44. Nour El Huda Abd Rahim
45. Nor Iza A.Rahman
46. Norasnieda Md Shukri
47. Norazam Abbas
48. Norsaradatul Akmar Zulkifli
49. Nur Karyatee Kassim
50. Peter Baptista
51. Rafaie Amin

52. Rama Krishna Supramanian
53. Ranjini Ambigapathy
54. Riyadh Shiltagh Alrudaini
55. Rozanah Abd Rahman
56. Saraswathi Bina Rai SK Nagalingam
57. Sasikala Devi Amirthalingam
58. Sharif Ahmad
59. Sheriza Izwa Zainuddin
60. Sholpan Bolatovna Zhangelova
61. Siti Hafsah Abd Halim
62. Siti Nazira Abdullah
63. Sufian Adenan
64. Suresh Kumar Chidambaram
65. Theepa Nesam
66. Verasingam Kumarasamy
67. Victor Hoe Chee Wai
68. Wardatul Jannah
69. Wan Ahmad Hafiz Wan Md Adnan
70. Wai Ping Wong
71. Yilmaz Bulbul
72. Yun Ying Ho
73. Yuni Asri

Singapore General Hospital

SingHealth

WORLD'S BEST HOSPITALS 2019–2026 Newsweek powered by statista

SINGAPORE GENERAL HOSPITAL (SGH)

# Where Care Meets Excellence

Singapore General Hospital, established in 1821, is the largest acute tertiary hospital in Singapore and is ranked among the world's best. It provides the most comprehensive patient-centred care with over 50 clinical specialities on its campus.

As an Academic Medical Centre, it takes pride in training healthcare professionals and conducting cutting-edge research to meet the evolving needs of the nation as well as the region. A not-for-profit institution, SGH is wholly owned by the government of Singapore and is the flagship hospital of the public healthcare system. SGH is part of the SingHealth cluster of healthcare institutions.

We seek suitably qualified candidates to join us as:

## Clinical Associate / Resident Physician / Staff Registrar

### Requirements

- Be in active clinical practice
- Have a basic medical degree from an accredited medical university or medical school
- Passed the relevant national licensing examination in the country of conferment of the basic degree, where applicable
- Have evidence of at least 12 months housemanship / internship with a certificate of satisfactory completion of housemanship or equivalent
- Have more than 3 years of post-housemanship working experience as a MO or equivalent, with relevant experience in the specialty department applied
- Those who have completed residency training and possessed relevant postgraduate qualifications/specialty board registration will have an added advantage
- Provide recent English Language proficiency tests results from IELTS, TOEFL or OET, obtained in a single sitting
- Have been certified to be of good standing by the Medical Council or the relevant national authority

### Application

Please email your application with a detailed curriculum vitae stating full personal and contact particulars, educational and professional qualifications/registrations, current employment details, housemanship/internship postings, training and full career history from the time of completion of internship, periods (including periods of employment gaps), present and expected salary, and the names and contacts of at least two professional referees to **careers.medical@sgh.com.sg**

We regret that only shortlisted applicants will be contacted.