Official Journal of the
Malaysian Medical Association

The Medical Journal of Malaysia

Volume: 81

Issue No: 2

March 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 2 March 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

Original Articles

CONTENTS Page

LIVERSTAT for the diagnosis of compensated advanced chronic liver disease in patients with type 2 diabetes

Joshua Shan-Chen Lee, MBBS[1], Nicholas Ming-Zher Chee, MBBS[1], Lee-Lee Lai, PhD[1], Shireene Ratna Vethakkan, MD[2], Wah-Kheong Chan, PhD[1]

[1]Gastroenterology and Hepatology Unit, Department of Medicine, Faculty of Medicine, Universiti Malaya, Kuala Lumpur, Malaysia, [2]Endocrinology Unit, Department of Medicine, Faculty of Medicine, Universiti Malaya, Kuala Lumpur, Malaysia

ABSTRACT

Introduction: LIVERSTAT is a non-invasive artificial intelligence-based test that provides risk stratification for metabolic dysfunction-associated steatotic liver disease. We aimed to study the performance of LIVERSTAT compared with the Fibrosis-4 Index (FIB-4) as a stand-alone test and as a first-line test to identify patients for liver stiffness measurement (LSM) for the diagnosis of compensated advanced chronic liver disease (cACLD) in patients with type 2 diabetes (T2D).

Materials and Methods: This is a cross-sectional study of patients with T2D who underwent transient elastography. cACLD was defined as LSM ≥10 kPa. As a stand-alone test, LIVERSTAT Class D and increased FIB-4 ≥1.3 (≥2.0 if age ≥65 years old) were considered as having cACLD. As a first-line test, LIVERSTAT Class D and increased FIB-4 were considered as requiring LSM.

Results: We analysed data for 221 patients (mean age 61 years, 41% male, cACLD 26%). The area under the receiver operating characteristic curve, sensitivity, specificity, positive predictive value, negative predictive value and misclassification rate for LIVERSTAT were 0.66, 32%, 88%, 47%, 79% and 27%, respectively. The corresponding values for FIB-4 were 0.61, 39%, 81%, 41%, 79%, and 30%, respectively. When using LIVERSTAT as a first-line test, the proportion of patients requiring LSM was 17% (38/221), while the proportion of false negatives was 19% (34/183). The corresponding values for FIB-4 were 24% (54/221) and 19% (31/167), respectively.

Conclusion: LIVERSTAT has similar accuracy as FIB-4 when used as a stand-alone test or as a first-line test to identify patients for LSM for the diagnosis of cACLD in patients with T2D.

KEYWORDS:
Metabolic dysfunction-associated steatotic liver disease, MASLD, cACLD, Fibrosis-4 Index, fibrosis

INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common cause of chronic liver disease, affecting an estimated 38% of the general population.[1] The prevalence of MASLD is even higher among patients with type 2 diabetes (T2D) and was found to be 50-72% in previous studies in our centre.[2-3] Moreover, T2D is an independent factor associated with more severe MASLD, and a substantial proportion of patients with T2D have more severe liver disease.[3-4] Therefore, patients with T2D represent an important target group for identifying patients with more severe MASLD.[5]

The term compensated advanced chronic liver disease (cACLD) was introduced to reflect the continuum of advanced fibrosis and cirrhosis in asymptomatic patients who are at risk of developing clinically significant portal hypertension (CSPH).[6] A pragmatic definition of cACLD based on liver stiffness measurement (LSM) was introduced with the aim to stratify the risk of CSPH and decompensation at the point of care, irrespective of the histological stage or the ability of LSM to identify these stages.[6]

The Fibrosis-4 index (FIB-4) is one of the most widely used biomarkers of liver fibrosis and has been recommended for the evaluation of fibrosis in patients with MASLD.[7–13] LIVERSTAT (Fibronostics, Indian Harbour Beach, FL, United States) is an artificial intelligence-based test incorporating anthropometric measurements and blood biomarkers for screening and risk stratification for MASLD.[14] Similar to FIB-4, LIVERSTAT uses readily available parameters, but it may be better than FIB-4. In a previous study, we found LIVERSTAT to have a higher negative predictive value compared with FIB-4 and a lower misclassification rate compared with FIB-4 when used in a two-step approach in combination with LSM for the diagnosis of advanced liver fibrosis.[14] We hypothesized that LIVERSTAT may be better, or at least as good as FIB-4, when used in patients with T2D. Therefore, we conducted this study with the objectives of assessing LIVERSTAT as a stand-alone diagnostic tool for cACLD and as a first-line test to identify patients for further evaluation using LSM to diagnose cACLD, compared with FIB-4, in patients with T2D.

MATERIALS AND METHODS

This study utilised previously collected, anonymised data from patients with T2D who had undergone transient elastography in a cross-sectional study. The study was conducted to determine the prevalence of non-alcoholic fatty

This article was accepted: 10 January 2026
Corresponding Author: Wah-Kheong Chan
Email: wahkheong2003@hotmail.com

liver disease and its more severe form among patients with T2D and enrolled consecutive adult patients (aged ≥18 years) who were seen by a senior endocrinologist at the Diabetes Clinic, Universiti Malaya Medical Centre, Kuala Lumpur, Malaysia between December 2016 and December 2017.[2] Demographic, anthropometric, clinical, and laboratory data were recorded using a standard protocol. Patients with incomplete data for the calculation of FIB-4 and/or LIVERSTAT were excluded from the study. The study conformed to the ethical guidelines of the 1975 Declaration of Helsinki, and ethical approval was obtained from our institutional review board (MREC ID No.: 20159-1650). All patients who participated in the study provided written informed consent.

Transient elastography

All patients underwent vibration-controlled transient elastography using FibroScan (Echosens, Paris, France). The examination was performed after overnight fasting by an experienced operator (LLL) using either M probe or XL probe based on the device recommendation. The examination was considered reliable if there were 10 valid acquisitions with an inter-quartile range over median of ≤ 30% for LSM.[15] We used LSM ≥10 kPa to define cACLD in accordance with the Baveno VII consensus and local guidelines.[5,6,12,13] Patients with controlled attenuation parameter (CAP) ≥263 dB/m were considered as having significant hepatic steatosis.[2,16]

LIVERSTAT

The LIVERSTAT result for each patient in this study was generated using the online platform by Fibronostics (https://portal.fibronostics.com/) using de-identified anthropometric and laboratory data and blinded to LSM data. LIVERSTAT uses a proprietary algorithm incorporating eleven variables, namely age, weight, height, gender, triglycerides, total cholesterol, fasting glucose, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma glutamyl transferase to categorise patients into four diagnostic categories. The diagnostic categories were based on a quantitative normalised score (0.00-1.00) for fibrosis assessment and a binary assessment for steatosis. The diagnostic categories were Class A (no presumed fibrosis and no presumed steatosis >5%), Class B (no presumed fibrosis but presumed steatosis >5%), Class C (presumed mild or moderate fibrosis without bridging), and Class D (presumed severe fibrosis with bridging). For this study, patients with LIVERSTAT Class D were considered as having cACLD, and patients with LIVERSTAT Class A were considered as not having significant hepatic steatosis, while patients with LIVERSTAT Class B were considered as having significant hepatic steatosis.

FIB-4

FIB-4 was calculated using the formula: age (years) * AST / [platelet ($x10^9$/L) * square root (ALT)]. For this study, patients with a FIB-4 score ≥1.3 (≥2 if age ≥65 years old) were considered as having cACLD.

Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics 27.0 (IBM, Armonk, NY, USA) and R.[17] Data was expressed as absolute values and percentages for categorical variables and analysed using the Chi-square test or Fisher's exact test, where appropriate. Continuous variables were expressed as mean with standard deviation or median with interquartile range and analysed with Student's t-test or the Mann-Whitney U test, where appropriate. The accuracy of LIVERSTAT and FIB-4 for the diagnosis of cACLD was assessed using the area under the receiver operating characteristic curve (AUROC). AUROCs were interpreted as follows: 0.90-1.00 = excellent, 0.80-0.90 = good, 0.70-0.80 = fair, <0.70 = poor. The sensitivity, specificity, positive predictive value, negative predictive value and misclassification rate were determined. The accuracy of LIVERSTAT for the diagnosis of cACLD was compared with that of FIB-4 using DeLong's test. Significance was assumed if p was <0.05. Calibration of predicted probabilities against observed risk was evaluated using bootstrap-corrected calibration curves (500 resamples). We assessed the clinical utility of LIVERSTAT and FIB-4 using decision-curve analysis to compare net benefit across clinically relevant threshold probabilities. In the analysis to compare LIVERSTAT with FIB-4 as a first-line test to identify patients for further evaluation using LSM, patients with LIVERSTAT Class D, and patients with FIB-4 ≥1.3 (≥ 2.0 if age ≥65 years old), were considered as requiring further evaluation using LSM. The proportion of patients requiring further evaluation using LSM (i.e., the referral rate) and the false negative rate when using LIVERSTAT and FIB-4 as a first-line test to identify patients for further evaluation using LSM were determined.

RESULTS

Patient characteristics

The data for 221 patients were included in the final analysis for this study. A total of 336 patients from the original research project were excluded from this study due to missing data to calculate LIVERSTAT and/or FIB-4, mainly AST and platelet count. The patient characteristics are presented in Table I. The mean age of the study population was 60.8 ± 11.3 years, and 41% were male. The majority of patients were obese (75%) and centrally obese (81%). Significant hepatic steatosis was found in 82% of patients, while cACLD was found in 25.8%. Patients with cACLD were more likely to have central obesity and had higher weight, body mass index and waist circumference. They had significantly higher serum triglyceride, alanine aminotransferase, aspartate aminotransferase and gamma glutamyl transferase levels, and lower high-density lipoprotein cholesterol and platelet count.

LIVERSTAT and FIB-4 for the diagnosis of cACLD

The receiver operating characteristic curve of LIVERSTAT and FIB-4 for the diagnosis of cACLD is shown in Figure 1. LIVERSTAT had an AUROC of 0.66 (95% CI, 0.58-0.74), while FIB-4 had an AUROC of 0.61 (95% CI, 0.52-0.70), for the diagnosis of cACLD (p = 0.27). The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of LIVERSTAT for the diagnosis of cACLD were 32% (95% CI, 19% - 45%), 88% (95% CI, 82% - 92%), 47% (95% CI, 34% - 61%), 79% (95% CI, 75% - 82%) and 73% (95% CI, 67% - 79%), respectively. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of FIB-4 for the diagnosis of cACLD were 39% (95% CI, 26% - 52%), 80% (95% CI, 74% - 86%), 41% (95% CI, 30% - 52%), 79% (95% CI, 75% - 82%) and 70% (95% CI, 63% - 76%),

Table I: Patient characteristics of the study (N=221)

Variables	Overall population, N=221	Patients with cACLD, n=57	Patients without cACLD, n=164	p-value
Age, years	60.8±11.3	60.6±10.3	60.9±11.7	0.86
Male, n (%)	91 (41)	27 (47)	64 (39)	0.27
Weight, kg	72.9±15.2	77.2±15.9	71.4±14.7	0.02
Height, m	1.60±0.09	1.60±0.1	1.60±0.09	0.83
BMI, kg/m^2	28.4±5.2	29.9±4.6	27.9±5.3	0.012
Obesity, n (%)	165 (75)	49 (86)	117 (71)	0.054
Waist circumference, cm	95.6±13.1	100.7±13.6	93.8±12.4	0.001
Central obesity, n (%)	180 (81)	52 (91)	128 (80)	0.045
SBP, mmHg	138±19	135±17	139±19	0.15
DBP, mmHg	77±11	76±11	78±11	0.43
FBS, mmol/L	8.6 (6.30-9.7)	9.0 (6.7-10.4)	8.5 (6.2-9.5)	0.205
Triglyceride, mmol/L (IQR)	1.7 (0.6-6.9)	1.9 (0.7-4.6)	1.7 (1-2)	0.016
TC, mmol/L	4.4 (1.5-8.2)	4.3 (2.6-8.2)	4.4 (3.6-5.1)	0.269
HDL cholesterol, mmol/L	1.3±0.4	1.2±0.3	1.3±0.4	0.014
LDL cholesterol, mmol/L	2.3 (1.7-2.8)	2.3 (1.6-2.8)	1.8 (1.8-2.8)	0.21
ALT, U/L	33 (17-39)	42 (23-48)	30 (17-37)	<0.001
AST, U/L	30 (19-32)	37 (21-47)	28 (18-29)	0.001
GGT, U/L	59 (21-55)	104 (29-113)	44 (20-43)	<0.001
Albumin, g/L	41.7±4.6	41.5±3.7	41.8±4.9	0.85
Bilirubin, µmol/L	11 (7-13)	11 (7-13)	11 (8-13)	0.67
Platelet count x10^9/L	282 (227-334)	259 (201-305)	290 (235-344)	0.015

cACLD, compensated advanced chronic liver disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood sugar; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase

Table II: The status of compensated advanced chronic liver disease and significant hepatic steatosis according to LIVERSTAT and Fibrosis-4 index categories

Indexes/Tests	Categories	cACLD*	No cACLD*	Significant hepatic steatosis**	No significant hepatic steatosis**
LIVERSTAT categories	Class A	2	33	23	12
	Class B	12	46	54	4
	Class C	25	65	74	16
	Class D	18	20	31	7
LIVERSTAT***	Positive	18	20	31	7
	Negative	39	144	151	32
FIB-4 categories	<1.3 (age <65) or <2 (age ≥65)	35	132	140	27
	≥1.3 (age <65) or ≥2 (age ≥65)	22	32	42	12
FIB-4****	Positive	22	32	42	12
	Negative	35	132	140	27

*cACLD based on liver stiffness measurement ≥10 kPa
**Significant hepatic steatosis based on controlled attenuation parameter ≥263 dB/m
***LIVERSTAT Class D was considered as positive for cACLD,
****FIB-4 ≥1.3 (age <65) or ≥2 (age ≥65) was considered as positive for cACLD
cACLD, compensated advanced chronic liver disease

respectively. The cACLD status according to LIVERSTAT and FIB-4 categories is shown in Table II.

Calibration plots for LIVERSTAT and FIB-4 for the diagnosis of cACLD is shown in Figure 2. LIVERSTAT demonstrated good agreement between predicted and observed risk for cACLD (mean absolute error 0.03). FIB-4 showed moderate calibration, with slight underestimation of risk at higher predicted probabilities (mean absolute error 0.04). Apparent and bias-corrected curves were closely aligned for both models, indicating minimal overfitting. Decision-curve analysis is shown in Figure 3. Both LIVERSTAT and FIB-4 provided greater net clinical benefit than the "treat-all" and "treat-none" strategies across a range of threshold probabilities. LIVERSTAT achieved a superior net benefit to FIB-4 between approximately 10–25% threshold probability, representing the clinically relevant range for referring patients for LSM.

LIVERSTAT and FIB-4 as a first-line test to identify patients for further evaluation with LSM for the diagnosis of cACLD

The use of LIVERSTAT and FIB-4 as a first-line test to identify patients for further evaluation using LSM for the diagnosis of cACLD is presented in Figure 3. When using LIVERSTAT as a first-line test to identify patients for further evaluation with LSM for the diagnosis of cACLD, the referral rate was 17% and the false negative rate was 19%. When using FIB-4 as a first-line test to identify patients for further evaluation with LSM for the diagnosis of cACLD, the referral rate was 24% and the false negative rate was 19%. The median (IQR) LSM among patients with false negative LIVERSTAT and FIB-4 was

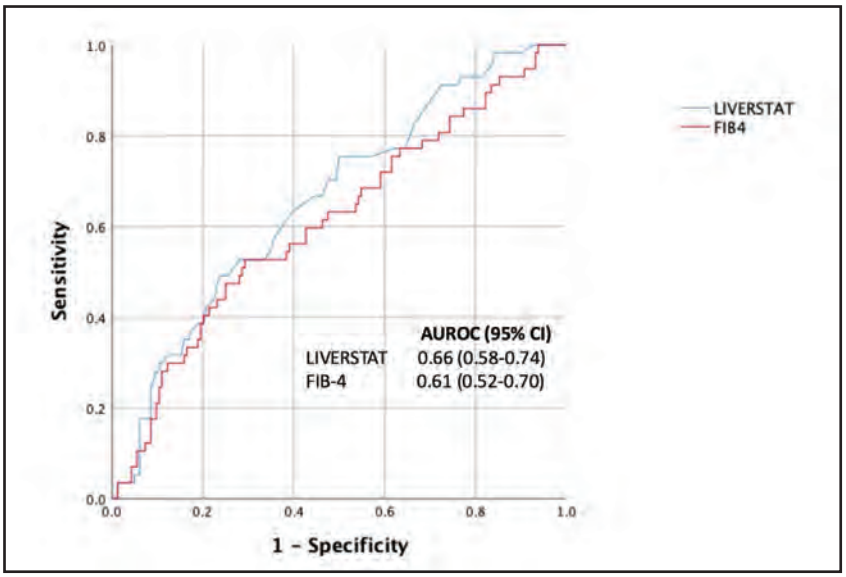


Fig. 1: Area under receiver operating characteristics curve of LIVERSTAT and Fibrosis-4 index for the diagnosis of compensated advanced chronic liver disease

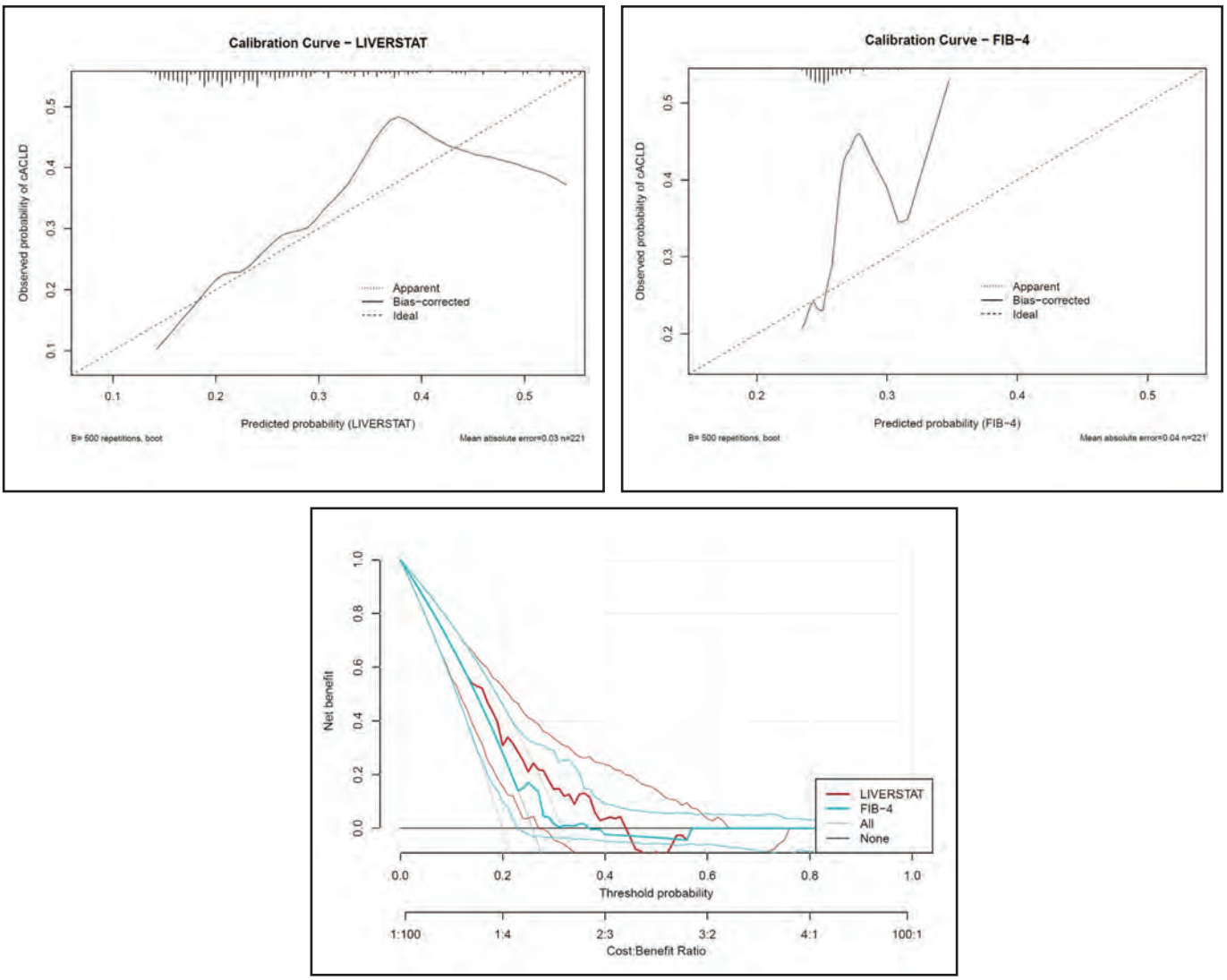


Fig. 2: Calibration plots for (a) LIVERSTAT and (b) FIB-4, and (c) decision-curve analysis for LIVERSTAT and FIB-4, for the diagnosis of cACLD

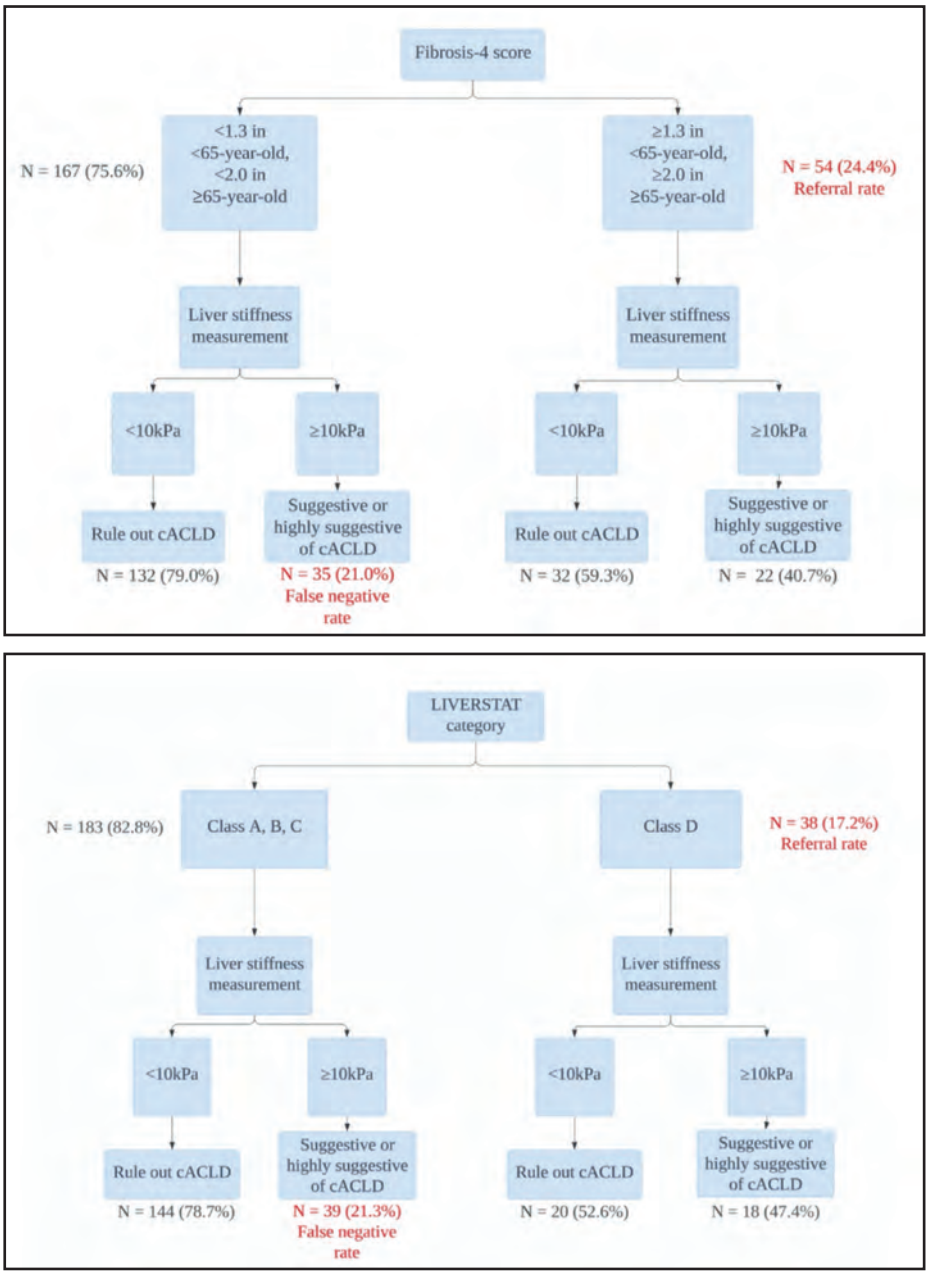


Fig. 3: Distribution of patients according to (a) LIVERSTAT and liver stiffness measurement, and (b) Fibrosis-4 index and liver stiffness measurement. Referral rates and false negative rates highlighted in bold

12.2 (10.9-17.2) kPa and 11.8 (10.8-16.0) kPa, respectively. Among patients with false negative LIVERSTAT, the proportion of patients with LSM 10-15 kPa and ≥15 kPa was 68% and 32%, respectively. Among patients with false negative FIB-4, the proportion of patients with LSM 10-15 kPa and ≥15 kPa was 71% and 29%, respectively.

LIVERSTAT for the diagnosis of significant hepatic steatosis

The sensitivity, specificity, positive predictive value, negative predictive value and misclassification rate of LIVERSTAT for the diagnosis of significant hepatic steatosis were 70%, 75%, 93%, 34% and 29%, respectively. The status of significant hepatic steatosis according to LIVERSTAT categories is shown in Table II.

DISCUSSION

In this study on patients with T2D, we found that LIVERSTAT exhibited a similar performance to FIB-4 as a stand-alone diagnostic test for cACLD and as a first-line test to identify patients for further evaluation with LSM for the diagnosis of cACLD. Although the accuracy of LIVERSTAT and FIB-4 as a stand-alone test for the diagnosis of cACLD was considered poor based on their AUROCs of <0.70, the tests demonstrated fairly high specificity of 81-88%. Both LIVERSTAT and FIB-4 demonstrated acceptable calibration, with minimal divergence between predicted and observed probabilities. This indicates that, despite their modest AUROC values, the predicted risks generated by each test are reasonably aligned with actual cACLD. Decision-curve analysis further supported the potential clinical utility of these tools. Both LIVERSTAT

and FIB-4 provided greater net benefit than 'treat-all' or 'treat-none' strategies across a broad range of threshold probabilities. Notably, LIVERSTAT offered a higher net benefit than FIB-4 between approximately 10–25%, which aligns with the threshold range where clinicians typically consider referral for LSM. This suggests that LIVERSTAT may provide modest but meaningful improvement in triage efficiency in diabetes clinic settings.

The use of non-invasive tests to stratify the severity of chronic liver disease has been incorporated into international guidelines and clinical practice, notably the sequential use of FIB-4 followed by LSM for MASLD.[8-13] The fairly high specificity positions LIVERSTAT and FIB4 as potentially useful first line tests to identify T2D patients who are unlikely to have cACLD, who can then be managed in primary care or non-liver specialist clinics, with only a small proportion of patients requiring referral for further evaluation with LSM. This can help control the burden and cost in the implementation of assessment and referral pathways for MASLD in patients with T2D. Earlier identification of patients with more severe liver disease enables more intensive lifestyle interventions and pharmacological therapy that can alter the natural history of the disease and improve patient outcome. While performing LSM on all patients with T2D is an option, this is associated with access concerns in resource-limited settings and where the test is not reimbursed. In our study, the use of LIVERSTAT or FIB-4 as a first-line test translated to a referral rate for further evaluation with LSM of only 17-19%. On the other hand, the use of LIVERSTAT or FIB-4 as a first-line test was associated with a false negative rate of 19%. However, most of the patients with false negative results had LSM 10-15 kPa and would be considered as only having the possibility of cACLD as opposed to assumed cACLD with LSM ≥15 kPa.[6,18] Furthermore, patients with LSM 10-15 kPa have lower rates of liver-related events compared with patients with LSM ≥15 kPa.[18]

We observed some differences in the results of this study when compared with other recent studies on LIVERSTAT and FIB-4.[14,19] In both studies, LIVERSTAT and FIB-4 were found to have better diagnostic accuracy for the diagnosis of advanced liver fibrosis, with an AUROC of 0.79 for both tests in one study, and an AUROC of 0.76 for both tests in the other study.[14,19] Although LIVERSTAT and FIB-4 were found to have similar diagnostic accuracy, the use of LIVERSTAT was associated with a higher referral rate and a lower false negative rate compared with FIB-4.[14] These observed differences may be due to differences in patient characteristics and the different reference standard that was used. The current study consists of only patients with T2D, whereas previous studies included patients without T2D. The performance of non-invasive tests may be different in patients with and without T2D.[20] Furthermore, the previous studies used histology, i.e. advanced liver fibrosis based on liver biopsy, as the reference standard, whereas the current study used LSM as the reference standard in line with the concept of cACLD. Besides the evaluation of fibrosis, LIVERSTAT was developed for the diagnosis of hepatic steatosis. To the best of our knowledge, this is the first study to report on the performance of LIVERSTAT for the diagnosis of significant hepatic steatosis in patients with T2D. We found LIVERSTAT to have poor negative predictive value for significant hepatic steatosis. This is likely due to the high prevalence of significant hepatic steatosis in patients with T2D and the limitation of anthropometric and laboratory data to distinguish between patients with and without significant hepatic steatosis in this population.

Despite our best efforts, this study had several limitations. Firstly, a relatively large number of patients from the original research project had to be excluded from this study due to missing data to calculate LIVERSTAT and/or FIB-4. Serum AST and platelet count were not yet routinely performed for patients with T2D in the diabetes clinic of our institution at that time. The high number of excluded patients introduces potential selection bias and may limit generalizability to the broader T2D population. Nevertheless, the sample size of 221 patients was considered reasonable as all included patients were well-characterised and the data were obtained prospectively. Secondly, we did not have a liver biopsy for the majority of patients and could not analyse the data using histology as the reference standard. Liver biopsy is an invasive procedure associated with a small risk of serious complications, including mortality.[21] Furthermore, the use of liver biopsy as a reference test is inherently limited by sampling variability and observer variability.[22–24] Therefore, the field of MASLD is moving towards the use of non-invasive tests.

CONCLUSION

In conclusion, LIVERSTAT demonstrated comparable diagnostic performance to FIB-4, both as a stand-alone tool and as a first-line test to select patients with T2D for further evaluation with LSM for the diagnosis of cACLD. Its relatively high specificity can help reduce referral for LSM. Further longitudinal studies are needed to evaluate the role of LIVERSTAT in prognostication and stratification of patients according to long-term liver-related outcomes. In addition, studies comparing LIVERSTAT with other non-invasive tests can help develop a better understanding of its use in different clinical settings. Overall, LIVERSTAT has the potential to be an alternative to FIB-4 in the clinical care pathway for patients with T2D and MASLD. However, due to its proprietary algorithm, the additional cost associated with using LIVERSTAT should be considered, especially with the free availability of alternative tests such as FIB-4.

CONFLICT OF INTEREST

WKC has served as a consultant for Abbott, Abbvie, Boehringer Ingelheim, IPSEN, Kowa, Novo Nordisk, Roche and Zuellig Pharma, a speaker for Abbott, Echosens, Hisky Medical, Novo Nordisk, Roche and Viatris, and received research grant from Abbott and Roche. The other authors have no conflict of interest to declare.

ACKNOWLEDGEMENTS

The authors would like to thank Dr Ng Kar Aik, Madam Wan Noor Hidayu, Madam Talvant Kaur, and Madam Soudamany Nair for their assistance in data collection in the original research project. The authors would like to thank

Fibronostics for providing unrestricted use of their online platform to generate LIVERSTAT results.

FUNDING

This study used data from a research project that was funded by the University of Malaya Special Research Fund (Project No.: BK006-2016 and BKS067-2017).

REFERENCES

1. Younossi ZM, Kalligeros M, Henry L. Epidemiology of metabolic dysfunction-associated steatotic liver disease. Clin Mol Hepatol. 2025; 31(Suppl): S32-50.
2. Lai LL, Wan Yusoff WNI, Vethakkan SR, Nik Mustapha NR, Mahadeva S, Chan WK. Screening for non-alcoholic fatty liver disease in patients with type 2 diabetes mellitus using transient elastography. J Gastroenterol Hepatol 2019; 34(8): 1396-403.
3. Chan WK, Tan AT, Vethakkan SR, Tah PC, Vijayananthan A, Goh KL. Non-alcoholic fatty liver disease in diabetics--prevalence and predictive factors in a multiracial hospital clinic population in Malaysia. J Gastroenterol Hepatol 2013; 28(8): 1375-83.
4. Chan WK, Treeprasertsuk S, Imajo K, Nakajima A, Seki Y, Kasama K, et al. Clinical features and treatment of nonalcoholic fatty liver disease across the Asia Pacific region-the GO ASIA initiative. Aliment Pharmacol Ther 2018; 47(6): 816-25.
5. Malaysia Endocrine & Metabolic Society, Ministry of Health Malaysia, Academy of Medicine Malaysia, Diabetes Malaysia and Family Medicine Specialists Association of Malaysia, Putrajaya. 2020. Clinical Practise Guidelines Management of Type 2 Diabetes Mellitus (6th Edition).
6. de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C, Baveno VIIF. Baveno VII - Renewing consensus in portal hypertension. J Hepatol 2022; 76(4): 959-74.
7. Patel K, Sebastiani G. Limitations of non-invasive tests for assessment of liver fibrosis. JHEP Rep 2020; 2(2): 100067.
8. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, Abdelmalek MF, Caldwell S, Barb D, et al. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology 2023; 77(5): 1797-835.
9. European Association for the Study of the Liver. Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis - 2021 update. J Hepatol 2021; 75(3): 659-89.
10. Eslam M, Sarin SK, Wong VW, Fan JG, Kawaguchi T, Ahn SH, et al. The Asian Pacific Association for the Study of the Liver clinical practice guidelines for the diagnosis and management of metabolic associated fatty liver disease. Hepatol Int 2020; 14(6): 889-919.
11. Chan WK, Wong VW, Adams LA, Nguyen MH. MASLD in adults: non-invasive tests for diagnosis and monitoring of MASLD. Hepatol Int. 2024; 18(Suppl 2): 909-21.
12. Chan WK, Tan SS, Chan SP, Lee YY, Tee HP, Mahadeva S, et al. Malaysian Society of Gastroenterology and Hepatology consensus statement on metabolic dysfunction-associated fatty liver disease. J Gastroenterol Hepatol 2022; 37(5): 795-811.
13. Chan WK, Chuah KH, Rajaram RB, Lim LL, Ratnasingam J, Vethakkan SR. Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD): A State-of-the-Art Review. J Obes Metab Syndr 2023; 32(3): 197-213.
14. Leow YW, Chan WL, Lai LL, Mustapha NRN, Mahadeva S, Quiambao R, et al. LIVERSTAT for risk stratification for patients with metabolic dysfunction-associated fatty liver disease. J Gastroenterol Hepatol 2024; 39(10): 2182-9.
15. Boursier J, Zarski JP, de Ledinghen V, Rousselet MC, Sturm N, Lebail B, et al. Determination of reliability criteria for liver stiffness evaluation by transient elastography. Hepatology 2013; 57(3): 1182-91.
16. Chan WK, Nik Mustapha NR, Mahadeva S. Controlled attenuation parameter for the detection and quantification of hepatic steatosis in nonalcoholic fatty liver disease. J Gastroenterol Hepatol 2014; 29(7): 1470-6.
17. Team RC. R: A Language and Environment for Statistical Computing 2024 [accessed June 2024]. Available from: https://www.R-project.org.
18. Yip TC, Lee HW, Lin H, Tsochatzis E, Petta S, Bugianesi E, et al. Prognostic performance of the two-step clinical care pathway in metabolic dysfunction-associated steatotic liver disease. J Hepatol 2025; 83(2): 304-14.
19. Quiambao R, Hermabessière P, Delamarre A, Alam I, Perez JMM, Lee J, et al. LIVERFASt GP+, first-line screening tool in at-risk MASLD patients outperforms the standard-of-care (SOC) FIB-4. J Hepatol 2023; 78(Suppl 1): S674-5.
20. Chan WK, Petta S, Noureddin M, Goh GBB, Wong VW. Diagnosis and non-invasive assessment of MASLD in type 2 diabetes and obesity. Aliment Pharmacol Ther 2024; 59(Suppl 1): S23-40.
21. Al Knawy B, Shiffman M. Percutaneous liver biopsy in clinical practice. Liver Int 2007; 27(9): 1166-73.
22. Ratziu V, Charlotte F, Heurtier A, Gombert S, Giral P, Bruckert E, et al. Sampling variability of liver biopsy in nonalcoholic fatty liver disease. Gastroenterology 2005; 128(7): 1898-906.
23. Davison BA, Harrison SA, Cotter G, Alkhouri N, Sanyal A, Edwards C, et al. Suboptimal reliability of liver biopsy evaluation has implications for randomized clinical trials. J Hepatol 2020; 73(6): 1322-32.
24. Leung HH, Puspanathan P, Chan AW, Nik Mustapha NR, Wong VW, Chan WK. Reliability of the nonalcoholic steatohepatitis clinical research network and steatosis activity fibrosis histological scoring systems. J Gastroenterol Hepatol 2022; 37(6): 1131-8.

ORIGINAL ARTICLE

Evaluation of analytical performance of blood gases, electrolytes, and metabolites in critical care using the blood gas analyzer cartridge-electrochemical principle

Fashihah Sherina Abdul Hadi Sabri, MBBCh[1,3], Wan Norlina Wan Azman, MPath[1,3], Wan Mohd Saifuhisam Wan Zain, MPath[1,3], Mohd Zulfakar Mazlan, MMed(Anaes)[2,3], Say Koon Tan, MSc[1,3], Muhammad Anshorul Haq Zable, DMA[2,3]

[1]Department of Chemical Pathology, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, 16150, Kubang Kerian, Kelantan, Malaysia, [2]Department of Anaesthesiology and Intensive Care, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, 16150, Kubang Kerian, Kelantan, Malaysia, [3]Hospital Pakar Universiti Sains Malaysia, Universiti Sains Malaysia, 16150, Kubang Kerian, Kelantan, Malaysia

ABSTRACT

Introduction: Rapid assessment of blood gases, electrolytes, and metabolites is crucial in critical care settings. This study evaluates the performance and interchangeability of a portable blood gas analyser that operates on the cartridge-electrochemical principle.

Materials and Methods: This prospective study evaluates the precision of this analyser, which uses an electrochemical sensor within single-use cartridges. We compare its performance to that of a cartridge-based sandwich sensor cassette; the blood gas analyser used in intensive care units (ICU). A total of forty arterial blood samples were collected between July and November 2024. Performance was statistically assessed using Passing-Bablok regression, Bland-Altman plots, and the Intraclass Correlation Coefficient (ICC).

Results: The blood gas analysis using the electrochemical sensor method demonstrated excellent within-run imprecision (CV%<5%) across all evaluated analytes, with total imprecision consistent with the manufacturer's specifications. Method comparison revealed a strong correlation (ICC>0.9) and agreement for most parameters between the two methods, including pH, partial pressure of carbon dioxide (pCO_2), sodium (Na^+), potassium (K^+), chloride (Cl^-), glucose, and lactate. However, Bland Altman showed a systematic bias of 9 mmHg in partial pressure of oxygen (pO_2) and 0.02mmol/L in ionised calcium (iCa^{2+}).

Conclusion: The analyser using the electrochemical sensor provides reliable performance for blood gases and biochemical analytes, with strong agreement with the cartridge-based sandwich sensor cassette principle. Nonetheless, caution is advised for pO_2 and iCa^0 measurements due to observed bias, highlighting the importance of awareness of method-specific differences between analysers in clinical interpretation.

KEYWORDS:
Arterial blood gas, cartridge-electrochemical, point-of-care testing, precision, bias, agreement

INTRODUCTION

Blood gas analysis offers insights into acid-base status and assesses and monitors ventilation across various medical conditions.[1-2] Technological improvements in point-of-care testing (POCT) have revolutionised patient care in recent years. POCT is not only easy to use but also enhances patient satisfaction and reduces comorbidities by improving rapid clinical decision-making and earlier focused management of patients.[3] Integrating sensor cassettes designed for potentiometric, amperometric, or optical sensors, the development of dry cartridge electrochemistry and microfluidic technology significantly transforms blood gas analysis. These advancements facilitate the creation of portable and compact medical devices, enhancing the accessibility and efficiency of diagnostic processes.

The contemporary blood gas analyser is manufactured to quantitatively evaluate various blood gas parameters, including the pH of whole blood, the partial pressure of carbon dioxide (pCO_2), and partial pressure of oxygen (pO_2). Furthermore, it provides measurements for various electrolytes, such as sodium (Na^+), potassium (K^+), chloride (Cl^-), and ionised calcium (iCa^{2+}), in addition to glucose and relevant metabolites, including lactate and total bilirubin.[4] In contrast, the Henderson-Hasselbalch equation estimates the bicarbonate (HCO_3-) level and base excess (BE).[5] POCT blood gas analyses with the availability of rapid results enable earlier diagnosis and management of critically unwell patients, especially when biochemical values surpass the clinical reference range, requiring prompt and efficient therapy. Thus, POCT analysers are appealing therapeutic tools in acute patient care.

In many institutions, different blood gas POCT analysers are employed in multiple locations. The performance of these devices differs due to variations in their foundational technologies, reagents, and quality control materials.[6] Addressing blood gas analysis is often complicated by discrepancies in methodological changes over time, leading to debates that may influence the interpretation of results. It is essential to ascertain whether different analysers can yield clinically significant variation and interchangeability of

This article was accepted: 10 January 2026
Corresponding Author: Wan Norlina Wan Azman
Email: dr_wannorlina@usm.my

results.[7] Besides the pre-analytical steps and established results on accuracy, blood gas analysis is susceptible to inter- and intra-instrumental variation.[8] Given that, the Clinical Laboratory Improvement Amendments (CLIA) require a clinical instrument to undergo strict analytical method verification, including accuracy, precision, reportable range, analytical sensitivity and specificity, limit of detection and reference intervals. Consequently, it must ensure that the analytical performance's representative characteristics fulfil the testing implementation standards.[9]

A notable gap exists in the literature regarding the comparative performance of electrochemical single-use cartridges versus cartridge-based sandwich sensor cassette systems, particularly in blood gas analysers. The conventional blood gas analyser, which employs a cartridge-based sandwich sensor cassette, is recognised for its high accuracy and reliability in clinical settings, demonstrating excellent correlation coefficients across various parameters.[6] Nonetheless, it encounters challenges associated with preanalytical errors, such as the presence of blood clots, which can introduce significant measurement inaccuracies. Emerging sensor technologies, such as electrochemical sensor cartridges, present potential advancements in sensitivity and capabilities for long-term monitoring. A prospective study could evaluate whether the Wondfo BGA-102 offers comparable or superior analytical performance in terms of accuracy and precision relative to established blood gas analysers. Specifically, it remains unclear whether these new cartridges can deliver analytical performance that is non-inferior to existing systems, particularly with respect to parameters such as pH, pO_2, pCO_2, electrolytes, glucose, and lactate levels. Furthermore, the potential advantages of single-use cartridges regarding within-run and between-lot precision, as well as their susceptibility to interfering with substances and environmental factors like temperature and humidity, have yet to be thoroughly investigated. A deeper understanding of these aspects is vital to establish their real-world suitability in point-of-care settings. Yet, to date, there has been a lack of peer-reviewed research that independently assesses the analytical performance of the Wondfo BGA-102, particularly in comparison to gold-standard laboratory or existing blood gas analysers.

The study focused on two platforms based on distinct sensing technologies; the Wondfo BGA-102 employs an electrochemical sensor within single-use cartridges, while the ABL90 FLEX utilises a cartridge-based sandwich sensor cassette[10] in the ICU as a reference standard. This study aims to evaluate whether it may impact measurement reproducibility, analytical bias, and agreement, ultimately assessing the interchangeability of results in clinical practice regarding key blood gas and electrolyte parameters in critical care settings

MATERIALS AND METHODS

Subjects/Materials

The analytical performance study of the electrochemical sensor within single-use cartridges (Wondfo BGA-102) analyser in comparison with the cartridge-based sandwich sensor cassette (Radiometer ABL-90 FLEX) blood gas analyser in the Intensive Care Unit (ICU) Hospital Pakar Universiti Sains Malaysia (HPUSM) was conducted between July 2024 and November 2024.

Residual arterial blood gas samples from the routine ICU of patients 18 years and older admitted to the intensive care unit (ICU) within the study period were utilised for testing. Samples were collected using 1ml heparinised syringes, either through direct arterial puncture or existing arterial lines. Notably, the leftover residual samples from routine analyses are utilised for comparative purposes. Exclusion criteria included patients below 18 years old, individuals with severe coagulation disorders, blood samples containing visible clots or air bubbles, and venous samples. Additionally, samples analysed more than five minutes apart were excluded to minimise the influence of time-dependent changes in blood gas parameters. Quality control measurements were performed on all analysers using standardised control solutions, with three-level QC in accordance with the Malaysian Standards International Organization for Standardization (MS ISO) 15189 standards for accreditation. The study participants' data were acquired from hospital records and the laboratory information system.

Precision study

A precision study was conducted on the electrochemical sensor within a single-use cartridge analyser (Wondfo BGA-102), specifically focusing on its repeatability (within-run imprecision) and reproducibility (total imprecision), in accordance with the CLSI EP15-A2 protocol.[11] The study utilised QC materials at three different concentration levels (Lot No. W84812) to cover the analytical measurement range for multiple parameters. The parameters included were pH, pCO_2, pO_2, iCa^{2+}, Na^+, K^+, Cl^-, glucose, and lactate. The study focused exclusively on just one QC lot. This is to ensure that the analyser measures a stable material consistently under identical conditions, rather than due to differences between QC lots. Utilising multiple lots could confound precision estimates due to inter-lot variability, encompassing discrepancies in matrix consistency and target values throughout the precision study. This QC material is liquified externally to the analytical system and introduced by the operator. For each QC level, triplicate measurements were performed daily over five consecutive days, resulting in 15 replicates per parameter per level. This approach ensured sufficient data to evaluate both within-run (intra-batch) and between-day (inter-batch) variability. The standard deviation (SD) and coefficient of variation (CV) were calculated for each parameter at each QC level to assess the analyser's consistency. Within-run imprecision is the variation observed when the same sample is repeatedly tested in a single analytical run. At the same time, total imprecision captures the combined effects of within-run and between-run variability across multiple days. The calculated data were then compared to the manufacturer's claimed performance specifications to verify whether the analyser met acceptable precision standards. This comprehensive evaluation allowed for a robust assessment of the analyser's reliability under routine laboratory conditions, helping to determine its suitability for clinical use in measuring critical parameters in patient blood samples.

Table I: Characteristics of study participants (N=40)

Variable	n(%)
Gender	
Female	12 (30.0)
Male	28 (70.0)
Ethnic group	
Malay	37 (92.5)
Chinese	3 (7.5)
Ventilation	
Yes	33 (82.5)
No	7 (17.5)
Indication for blood gas analysis	
Respiratory failure	35 (87.5)
Altered mental status	2 (5.0)
Elective intubation	3 (7.5)

Table II: Imprecision study results for the electrochemical sensor within single-use cartridges (Wondfo BGA-102) analyser

Analytes	Level	Control	Mean	SD	Total imprecision, CV (%)	Wondfo CV (%)	Analytical Performance Specification, CV Goals (%)	
							Ricos et al (desirable/minimum)	SFBC/RIliBak
pH	level 1	7.135	7.054	0.010	0.135	-	0.1/-	-/0.4
	level 2	7.414	7.373	0.007	0.098	-	0.1/-	-/0.4
	level 3	7.626	7.608	0.007	0.089	-	0.1/-	-/0.4
pO_2 (mmHg)	level 1	99	93	11.33	12.14	15	-/-	1.5/7
	level 2	125	131	10.38	7.92	15	-/-	1.5/5.5
	level 3	155	165	4.84	2.93	15	-/-	1.5/5.5
pCO_2 (mmHg)	level 1	65	70	2.56	3.66	8	2.4/3	3.8/6.5
	level 2	35.8	40.2	1.47	3.64	8	2.4/3	4.5/6.5
	level 3	19.5	21.8	0.88	4.06	8	2.4/3	4.5/7.5
iCa^{2+} (mmol/L)	level 1	1.38	1.30	0.03	2.22	5	0.9/1.3	1.2/7.5
	level 2	1.18	1.11	0.024	2.16	5	0.9/1.3	1.2/7.5
	level 3	0.58	0.56	0.028	4.81	5	0.9/1.3	1.2/14.5
Na^+ (mmol/L)	level 1	113	109	0.88	0.81	3	0.3/0.5	1/3
	level 2	133	129	1.20	0.93	3	0.3/0.5	1/3
	level 3	157	153	1.68	1.10	3	0.3/0.5	0.7/3
K^+ (mmol/L)	level 1	1.8	1.9	0.05	2.60	3	2.3/3.5	1.5/4.5
	level 2	4.3	4.2	0.06	1.38	3	2.3/3.5	1.2/4.5
	level 3	6.4	5.9	0.08	1.34	3	2.3/3.5	1.2/4.5
Cl^- (mmol/L)	level 1	79	71	0.64	0.91	4	0.6/0.9	1.2/4.5
	level 2	96	89	0.94	1.06	4	0.6/0.9	1.2/4.5
	level 3	119	119	0.91	0.76	4	0.6/0.9	1.2/4.5
Glucose (mmol/L)	level 1	5.1	4.5	0.1	2.23	10	2.3/-	2.4/5
	level 2	10.3	11.8	0.74	6.28	10	2.3/-	1.2/5
	level 3	15.2	17.6	1.17	6.66	10	2.3/-	1.2/5
Lactate (mmol/L)	level 1	0.88	0.83	0.09	11.25	15	13.6/-	-/-
	level 2	2.75	2.29	0.16	7.02	15	13.6/-	-/-
	level 3	6.69	6.32	0.34	5.44	15	13.6/-	-/-

SD= standard deviation, CV= coefficient of variation, SFBC= French Society of Clinical Biology, pO2= partial pressure of oxygen, pCO2= partial pressure of carbon dioxide

Method comparison study

We performed a prospective method-comparison study to evaluate the electrochemical single-use cartridges (Wondfo BGA-102) point-of-care blood gas analyser versus the cartridge-based sandwich sensor cassette (Radiometer ABL-90 FLEX) blood gas analyser in the ICU as a reference analyser. The study includes a total of 40 random arterial whole blood samples from 1ml of heparinised syringe, which were tested for pH, pCO_2, pO_2, iCa^{2+}, Na^+, K^+, Cl^-, glucose, and lactate on both blood gas analysers. The minimum sample size of 40 was required for this study according to Clinical and Laboratory Standards Institute (CLSI) EP9-A2 guidelines.[12] Upon placing the blood sample in the first analyser, any air bubbles that may have formed during the aspiration process were promptly removed from the remaining sample. Subsequently, the sample was sealed with an airtight cap and mixed thoroughly by hand before being analysed in the second analyser. The time interval for measuring samples in both analysers is under five minutes. The interval between the two assays was negligible, as the analysers were initially placed close to one another. The samples were randomly tested across the two blood gas analysers without any predetermined sequence to reduce potential bias.

Table III: Comparative analysis of analyte measurements: electrochemical single-use cartridges (Wondfo BGA-102) vs. Cartridge-Based Sandwich Sensor Cassette Radiometer ABL-90 FLEX)

Analyte	Passing-Bablok regression			Bland-Altman			ICC (95% CI)
	Y Intercept (95% CI)	Slope (95% CI)	R^2	Mean difference (95% CI)	Lower limit of agreement	Upper limit of agreement	
pH	-0.034 (-0.883 to 0.700)	1.004 (0.904 to 1.112)	0.932	-0.006 (-0.042 to 0.030)	-0.226	0.215	0.982 (0.966-0.991)
pCO_2 (mmHg)	-4.526 (-7.517 to -1.695)	1.070 (1.010 to 1.161)	0.973	-1.2 (-4.7 to 2.3)	-22.4	19.9	0.989 (0.966-0.995)
pO_2 (mmHg)	14.745 (10.233 to 18.636)	0.947 (0.901 to 0.996)	0.961	9 (-3 to 21)	-64	83	0.977 (0.605-0.994)
iCa^{2+} (mmol/L)	0.020 (-0.230 to 0.197)	1.000 (0.836 to 1.231)	0.820	0.02 (-0.01 to 0.05)	-0.19	0.23	0.945 (0.889-0.972)
Na^+ (mmol/L)	-2.000 (-25.833 to 5.631)	1.000 (0.947 to 1.167)	0.904	-2 (-4 to 0.04)	-14	11	0.957 (0.777-0.985)
K^+ (mmol/L)	0.000 (0.000 to 0.203)	1.000 (0.947 to 1.000)	0.970	0.03 (-0.14 to 0.20)	-1.0	1.1	0.992 (0.984-0.996)
Cl^- (mmol/L)	0.500 (-6.767 to 15.182)	1.000 (0.864 to 1.067)	0.922	0.4 (-2.13 to 2.93)	-15	16	0.979 (0.961-0.989)
Glucose (mmol/L)	-0.223 (-0.843 to 0.241)	1.050 (0.984 to 1.135)	0.964	0.2 (-0.8 to 1.2)	-5.9	6.3	0.99 (0.981-0.995)
Lactate (mmol/L)	0.440 (0.329 to 0.547)	0.795 (0.716 to 0.886)	0.976	0.12 (-0.59 to 0.83)	-4.25	4.49	0.985 (0.971-0.992)

pCO_2= partial pressure of carbon dioxide, pO_2= partial pressure of oxygen, iCa^{2+} = ionised calcium, Na^+ = sodium, K^+ = potassium, Cl^- = chloride, R^2= coefficient of correlation, ICC= intraclass coefficient

Statistical analyses

The means, SD and CV for each level of control were determined in the imprecision study. Between-day imprecision, bias and total error (TE) were determined for each analyte on each analyser as follows:

CV = (SD/Mean) x 100; CV% is the coefficient of variation for measuring between-day imprecision, SD is the standard deviation.

$$\text{Bias\%} = \frac{\text{Average absolute deviation from the target value}}{\text{Target}} \times 100$$

TE (%) was calculated as 1.65 x CV (%) + Bias (%).

Considering a Gaussian distribution, the factor 1.65 indicates that 95 % of the outcomes will lie within the TE limit.[13]

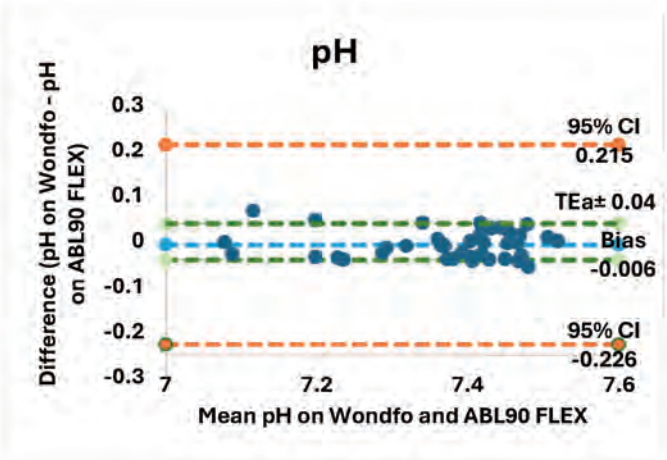
According to the guidelines outlined in EP15-A2, imprecision results should be compared against the manufacturer's claims. When the repeatability and within-laboratory SD are lower than those specified by the manufacturer, the user has successfully demonstrated precision, aligning with these claims and requiring no further calculations. Conversely, if the obtained values exceed those reported by the manufacturer, a statistical test must be conducted to determine whether the observed difference is statistically significant.[14]

Various sources of analytical performance goals were considered for comparison in this study. Preference was given to the database compiled by Ricos et al[15-16], however, certain parameters were either not included (such as pO_2) or were based on outdated evaluations (such as pH) in that database. In such cases, alternative benchmarks were used, including the total allowable error (TEa) criteria from the Royal College of Pathologists of Australasia (RCPA)[17], imprecision goals from the French Society of Clinical Biology (SFBC – Société Française de Biologie Clinique)[18], and the German RiliBÄK guidelines.[19]

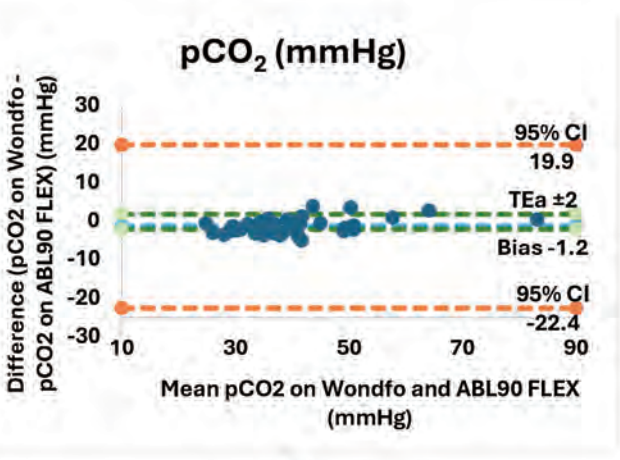
The assumption of normality for the difference data was tested using the Shapiro-Wilk test and visually assessed using a histogram. Data for all the analytes shows sufficient normality for the subsequent application of Bland-Altman analysis. Patient sample-based method comparisons were evaluated by calculating Spearman rank correlation coefficients and the slope and intercept using Passing-Bablok regression analysis with two-sided 95% confidence intervals (CI) calculated for each slope and intercept. An intercept of zero or close to zero indicates no systematic difference between the methods, while a slope close to 1 indicates a strong relationship between them. Intraclass coefficient (ICC) was calculated using a two-way mixed effects model for absolute agreement to assess the correlation between both analysers for different analytes. The relative mean differences, or biases, between the methods were visualised using Bland-Altman difference plots. These plots effectively depict the upper and lower limits of agreement and are derived using the mean difference ± 1.96 multiplied by the standard deviation of the differences. The TEa is used to assess whether the mean difference was clinically relevant. SPSS version 21.0 is utilised in all statistical analyses.

Ethics approval

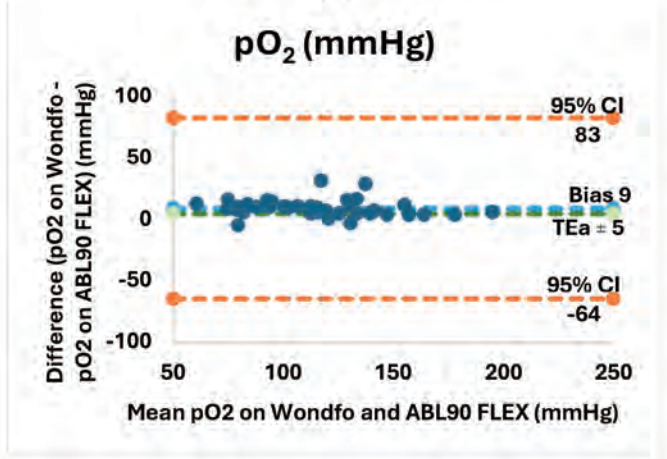
This study was approved by the Human Research Ethics Committee (JEPeM) of Universiti Sains Malaysia, with JEPeM code USM/JEPeM/KK/24040299.


pH
Difference (pH on Wondfo - pH on ABL90 FLEX)
0.3
0.2
0.1
0
-0.1
-0.2
-0.3
95% CI
0.215
TEa± 0.04
Bias
-0.006
95% CI
-0.226
7
7.2
7.4
7.6
Mean pH on Wondfo and ABL90 FLEX

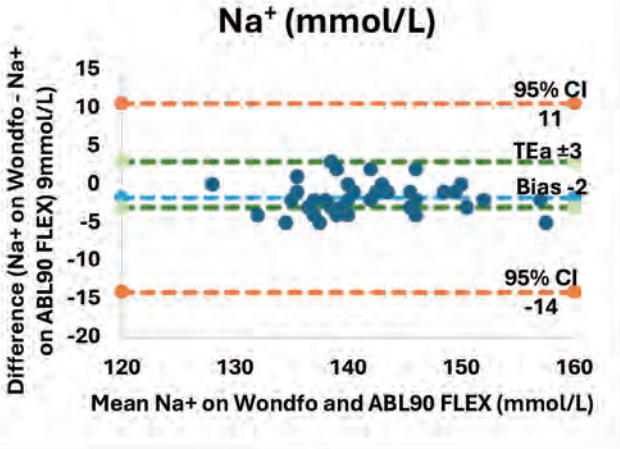
A


pCO2 (mmHg)
Difference (pCO2 on Wondfo - pCO2 on ABL90 FLEX) (mmHg)
30
20
10
0
-10
-20
-30
95% CI
19.9
TEa ±2
Bias -1.2
95% CI
-22.4
10
30
50
70
90
Mean pCO2 on Wondfo and ABL90 FLEX (mmHg)

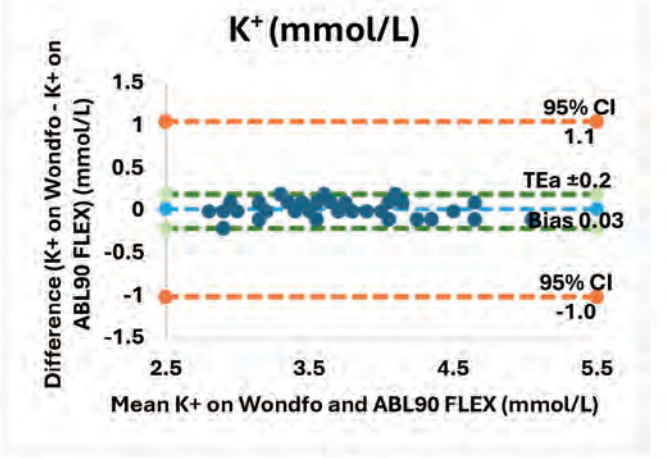
B


pO2 (mmHg)
Difference (pO2 on Wondfo - pO2 on ABL90 FLEX) (mmHg)
100
50
0
-50
-100
95% CI
83
Bias 9
TEa ± 5
95% CI
-64
50
100
150
200
250
Mean pO2 on Wondfo and ABL90 FLEX (mmHg)

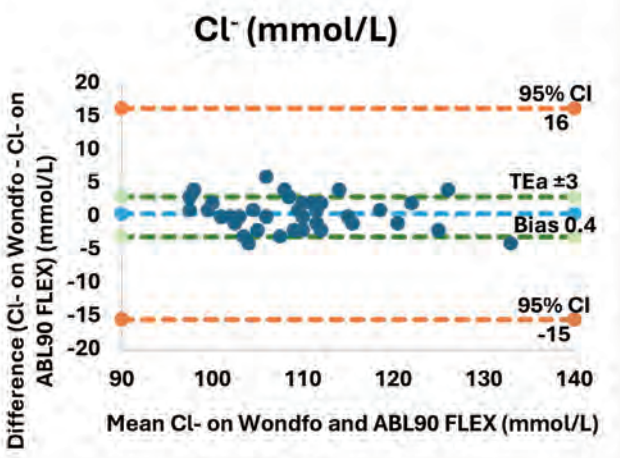
C


Na+ (mmol/L)
Difference (Na+ on Wondfo - Na+ on ABL90 FLEX) 9mmol/L)
15
10
5
0
-5
-10
-15
-20
95% CI
11
TEa ±3
Bias -2
95% CI
-14
120
130
140
150
160
Mean Na+ on Wondfo and ABL90 FLEX (mmol/L)

D


K+ (mmol/L)
Difference (K+ on Wondfo - K+ on ABL90 FLEX) (mmol/L)
1.5
1
0.5
0
-0.5
-1
-1.5
95% CI
1.1
TEa ±0.2
Bias 0.03
95% CI
-1.0
2.5
3.5
4.5
5.5
Mean K+ on Wondfo and ABL90 FLEX (mmol/L)

E


Cl- (mmol/L)
Difference (Cl- on Wondfo - Cl- on ABL90 FLEX) (mmol/L)
20
15
10
5
0
-5
-10
-15
-20
95% CI
16
TEa ±3
Bias 0.4
95% CI
-15
90
100
110
120
130
140
Mean Cl- on Wondfo and ABL90 FLEX (mmol/L)

F

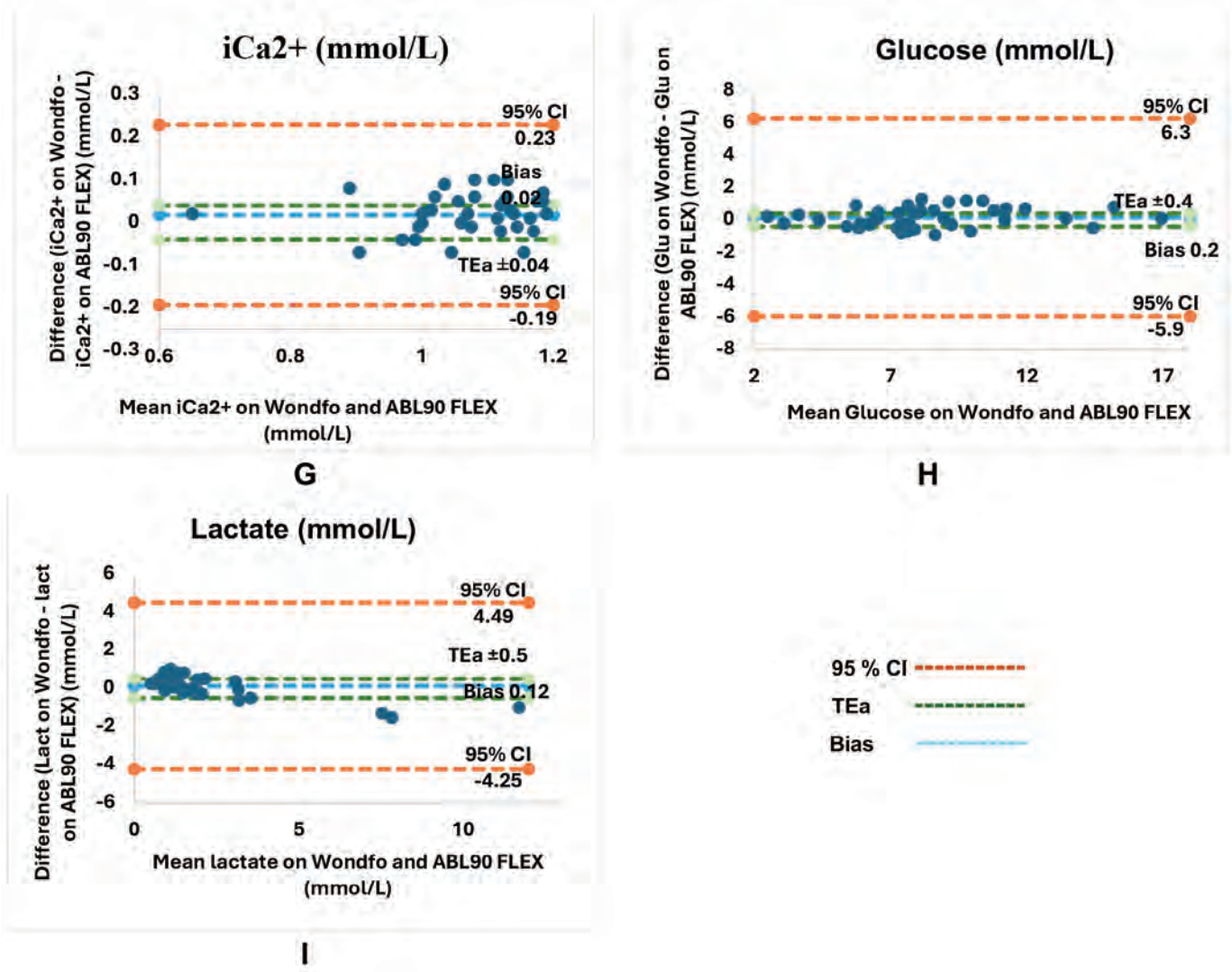


Fig. 1: Bland–Altman plot for agreement between using Wondfo BGA and Radiometer ABL90 FLEX for various parameters: pH (A), pCO2 (B), pO2 (C), sodium (D), potassium (E), chloride (F), ionized calcium (G), glucose (H) and lactate (I)

RESULTS

A total of 40 patients were recruited for the study. The patients' median (25th, 75th percentile) age is 59.0 (43.6-74.4) years. Table I displays the characteristics of the participants involved in the study.

Analysis of precision

Our research showed that the electrochemical sensor within single-use cartridges (Wondfo BGA-102) analyser exhibited a within-run CV of under 5% for all measured analytes, including pH, pCO_2, pO_2, iCa^{2+}, Na^+, K^+, Cl^-, glucose, and lactate. The total imprecision of all the analytes aligns with the manufacturer's claim, indicating that the precision study meets the required standards, as shown in Table II.

Analysis of method comparison study

Forty samples of whole blood in a heparinised syringe were subjected to the method comparison study. The electrochemical sensor within single-use cartridges (Wondfo BGA-102) analyser demonstrates high correlation and agreement with the cartridge-based sandwich sensor cassette (ABL90 FLEX Radiometer) for most analytes. Significant results were observed for pH, K^+, Cl^-, and glucose, showing near-perfect slopes, high coefficient of correlation (R^2) values, narrow Bland–Altman limits, and ICC exceeding 0.98. The analyser showed slightly lower performance for pO_2 and iCa^{2+}, with wider limits of agreement and lower R^2 for iCa^{2+}, though still within acceptable clinical limits. These findings confirm that the analyser provides reliable and accurate measurements for most critical care parameters. Generally, all the parameters measured showed an excellent correlation between both analysers (ICC > 0.9), as shown in Table III and Figure 1.

The mean difference (bias) between both analysers was less than 2, except for the parameter pO_2. The pO_2 showed a bias of 9 mmHg with a limit of agreement between -64 and 83. At the medical decision point (MDP) of different levels, i.e., 99mmHg, 125mmHg and 155mmHg, TE measured exceeded the TEa of 6% based on RCPA. For ionised calcium, at MDP of

1.30mmol/L, 1.05mmol/L and 0.45mmol/L with a bias of 0.02mmol/L, the calculated TE exceeded TEa (± 0.04 if ≤1.00mmol/L, ± 4% if >1.00mmol/L based on RCPA).

DISCUSSION

This study revealed that most patients experiencing respiratory failure and ventilation in the ICU require frequent and particular monitoring of their acid-base status and oxygenation. Accurate blood gas measurements are essential for making immediate clinical decisions and ensuring patient safety.

The precision study conducted according to CLSI EP15-A2 guidelines demonstrated that most parameters for the electrochemical sensor within single-use cartridges (Wondfo BGA-102) analyser met the manufacturer's claim and the desirable CV goals outlined in performance databases such as Ricos et al., RiliBÄK, SFBC, and the RCPA. The results suggest that the analyser delivers consistent performance across a range of critical parameters including pH, pO_2, pCO_2, electrolytes (Na^+, K^+, Cl^-, iCa^{2+}), glucose, and lactate. Nevertheless, in our precision study, the CV for pO_2 at levels 1 and 2 and for glucose at levels 2 and 3 surpassed the permissible limits established by RiliBÄK. This observation is consistent with previously published research, which indicated variability in pO_2 measurements across different POCT platforms.[18] The limitations in precision for pO_2 suggest that this parameter may be more vulnerable to instrument-specific variability or pre-analytical factors. The use of QC materials for precision studies, particularly those prepared externally for the analytical system, poses a risk of introducing temperature fluctuations or air exposure during manual handling. Such variabilities may contribute to the imprecision observed, especially when dealing with highly volatile analytes, such as pO_2.[20-21]

Moreover, the comparative analysis of the electrochemical single-use cartridges (Wondfo BGA-102) versus the cartridge-based sandwich sensor cassette (Radiometer ABL-90 FLEX) blood gas analysers revealed that the results for pH, pCO_2, Na^+, K^+, Cl^-, glucose, and lactate were statistically comparable within a 95% confidence interval, signifying a high degree of analytical agreement. This was supported by strong correlation coefficients and ICC, which support the interchangeability of results for these parameters in clinical settings. These results are comparable to other contemporary POCT validation studies such as those conducted on Abbott i-STAT Alinity[20] and GEM Premier 5000[22], which also demonstrated strong agreement for most core analytes against a core laboratory or established POCT platform. However, the mean difference for pO_2 was 9mmHg suggesting a systematic bias between the two analysers. The pO_2 is widely acknowledged as the most sensitive parameter in blood gas analysis, particularly in relation to pre-analytical factors that can compromise its accuracy and reliability. Various issues can introduce bias into pO_2 measurements. These include the possibility of air bubbles within the syringe barrel or needle hub, air contamination, and insufficient mixing of the sample. Furthermore, delays in analysis, inadequate sample volumes, and calibration discrepancies among different blood gas analysers can negatively affect study outcomes.[23-24]

Another factor that could account for the differences in pO_2 readings is the difference in measurement principles. The Wondfo BGA-102 utilises amperometry for the measurement of 0, whereas the ABL90 FLEX uses an optical system for pO_2. These methodological differences could inherently affect the bias, particularly under varying clinical or environmental conditions. A 9mmHg positive bias in pO_2 is clinically significant. It may lead to a misinterpretation of oxygenation status, especially within the low-to-normal pO_2 range, where even small changes can influence clinical decisions, such as decisions on oxygen therapy or ventilatory adjustments, that are sensitive to relatively small deviations. Therefore, when conducting serial measurements, it is advisable to use the same analyser, as this approach helps minimise analytical variability. Additionally, rigorous adherence to standardised collection protocols, including the immediate expulsion of air bubbles and prompt analysis, is of utmost importance for preserving the integrity of pO_2 measurements.[24-25]

Similar concerns apply to iCa^{2+} measurements, as ABL 90 FLEX uses a potentiometric measuring principle, whereas Wondfo BGA-102 utilises a multi-sensor in one cartridge, which contributes to bias between analysers. Although the mean bias between the two analysers was minimal (0.02 mmol/L) and CV remained within acceptable ranges (2.16%–4.81%), the calculated TE at multiple medical decision points exceeded TEa (± 0.04). This suggests that while the overall performance of iCa^{2+} measurements is deemed satisfactory, the results may not be interchangeable between the two analysers at certain decision thresholds. Clinically, even minor iCa^{2+} biases between blood gas analysers can significantly impact the classification of hypo- or hypercalcemia, which subsequently affects calcium replacement protocols and the care of critically ill and neonatal patients. Supported by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) recommendation in 1991, several pre-analytical variables can influence discrepancies in iCa^{2+} levels. These factors are primarily related to sample handling and processing since iCa^{2+} is highly sensitive to changes in pH. Important considerations include the type and concentration of heparin used, the extent of sample dilution, and any delays in analysis. These variables can lead to altered iCa^{2+} values and create apparent biases between different analysers.[26]

The evaluation of acid-base status is incomplete without considering the estimated HCO_3- and BE, which provide further information on the metabolic component. While these parameters are not directly measured by either the Wondfo BGA-102 or the ABL90 FLEX, they are mathematically derived from measured values (pH and pCO_2) using the Henderson-Hasselbalch equation and standard algorithms5. Since our study found a high correlation and agreement for both pH (ICC = 0.982) and pCO_2 (ICC = 0.989) between the two analysers, it can be inferred that the derived values of HCO_3- and BE would also exhibit a high degree of interchangeability between the two platforms. Nevertheless, it is important to note that any

systematic bias in the measured pH or pCO_2, even if statistically small, could propagate into the calculated values, potentially affecting the precise metabolic interpretation at medical decision points.

Another significant limitation of this study is related to the sample size. Although the CLSI EP9-A2 guidelines recommend a minimum sample size of 40, this may restrict the ability to detect bias across the entire analytical range. As a result, the limited sample size could impact the generalisability of the findings and hinder the identification of subtle biases in measurement accuracy at different concentrations, especially in extreme acidotic and alkalotic conditions. A larger sample size would strengthen the findings and allow for a more comprehensive evaluation of the performance characteristics between the blood gas analysers. Furthermore, the diverse clinical scenarios in the ICU, including conditions like sepsis, trauma, and cardiac arrest represent a spectrum of clinical illnesses. This broad range of patient conditions, particularly those requiring aggressive respiratory or metabolic management can introduce a potential bias of measurement due to extreme physiological values and complex clinical interventions.

CONCLUSION

In conclusion, the Wondfo BGA-102 offers reliable performance for a wide range of blood gas and biochemical analytes, showing strong agreement with the Radiometer ABL90 FLEX for most parameters. Nonetheless, certain biases, especially in pO_2 and iCa^{2+} measurements, highlight the importance of cautious interpretation of the results. The systematic biases observed necessitate the implementation of inter-analyser verification protocols and potentially the need for harmonisation across different POCT platforms within the same clinical setting to ensure patient safety and consistency in care. Clinicians must remain vigilant and well-informed when evaluating patient data from different devices, reinforcing the need to assess the performance of each analyser before its use.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGEMENTS

The authors like to thank the participants of this study.

FUNDING

This study is supported by the External Agency (Industry/Private) Grant code: R504-LR-GAL007-0000000612-M178.

REFERENCES

1. Balzanelli MG, Distratis P, Lazzaro R, Pham VH, Del Prete R, Dipalma G, et al. The importance of arterial blood gas analysis as a systemic diagnosis approach in assessing and preventing chronic diseases, from emergency medicine to the daily practice. Eur Rev Med Pharmacol Sci 2023; 27(23): 11653-63.
2. Chandran J, D'Silva C, Sriram S, Krishna B. Clinical utility of arterial blood gas test in an intensive care unit: an observational study. Indian J Crit Care Med 2021; 25(2): 172.
3. Auvet A, Espitalier F, Grammatico-Guillon L, Nay MA, Elaroussi D, Laffon M, et al. Preanalytical conditions of point-of-care testing in the intensive care unit are decisive for analysis reliability. Ann Intensive Care 2016; 6(1): 57.
4. Wu J, Liu H, Chen W, Ma B, Ju H. Device integration of electrochemical biosensors. Nat Rev Bioeng. 2023; 1(5): 346–60.
5. Todi S. Arterial Blood Gas Analysis: A New Look at the Old Formula. Indian J Crit Care Med 2023; 27(10): 699.
6. Yang L, Chi D, Zhen C, Zhang W, Yang J, Shao J, et al. Clinical performance validation of an integrated cartridge based bedside blood gas analyzer system in the acute care setting. Sci Rep 2025; 15(1): 20620.
7. Korpi-Steiner N, Horowitz G, Tesfazghi M, Suh-Lailam BB. Current issues in blood gas analysis. J Appl Lab Med 2023; 8(2): 372-81.
8. Kapoor D, Srivastava M, Singh P. Point of care blood gases with electrolytes and lactates in adult emergencies. Int J Crit Illn Inj Sci 2014; 4(3): 216-22.
9. Yenice S. Training and competency strategies for point-of-care testing. EJIFCC 2021; 32(2): 167
10. Seeger C, Kawiecki RW, Kristensen HB. Analytical performance of the ABL90 FLEX blood gas analyser. Point Care 2011; 10(3): 108-15.
11. Clinical and Laboratory Standards Institute (CLSI). User verification of performance for precision and trueness; approved guideline—second edition. CLSI document EP15-A2. Wayne (PA): Clinical and Laboratory Standards Institute; 2006.
12. Clinical and Laboratory Standards Institute (CLSI). Method comparison and bias estimation using patient samples; approved guideline—second edition. CLSI document EP09-A2. Wayne (PA): Clinical and Laboratory Standards Institute; 2002
13. Biswas SS, Bindra M, Jain V, Gokhale P. Evaluation of imprecision, bias and total error of clinical chemistry analysers. Indian J Clin Biochem 2015; 30(1): 104-8.
14. Chesher D. Evaluating assay precision. Clin Biochem Rev 2008; 29(Suppl 1): S23.
15. Ricós C, Alvarez V, Cava F, Garcia-Lario JV, Hernandez A, Jimenez CV, et al. Current databases on biological variation: pros, cons and progress. Scand J Clin Lab Invest 1999; 59(7): 491-500.
16. Ricós C, Álvarez V, Perich C, Fernández-Calle P, Minchinela J, Cava F, et al. Rationale for using data on biological variation. Clin Chem Lab Med 2015; 53(6): 863-70.
17. Royal College of Pathologists of Australasia. Allowable limits of performance for biochemistry [cited 2025 Jun 22]. Available from: https://rcpaqap.com.au/resources/chemical-pathology-analytical-performance-specifications/
18. Teksöz D, Işıksaçan N, Koşer M. Blood Gas Measurements Using Point-of-Care Testing Devices in Pediatric Patients. Istanbul Med J 2024; 25(3): 245-9.
19. Ahmad-Nejad P, Bauersfeld W, Baum H, Behre H, Burkhardt R, Cassens U, et al. Revision of the guideline of the German Medical Association on quality assurance in medical laboratory examinations (Rili-BÄK). J Lab Med 2024; 48(6): 263-306.
20. Larcher R, Lottelier M, Badiou S, Dupuy AM, Bargnoux AS, Cristol JP. Analytical performances of the novel i-STAT Alinity point-of-care analyser. Diagnostics (Basel) 2023; 13(2): 297.
21. Tang H, Xiao Y, Luo H, Jiang J, Xu H, Yang J, et al. Analytical performance evaluation of intelligent quality management of blood gas analyser. Pract Lab Med 2025; 1: e00480.
22. Oyaert M, Van Maerken T, Bridts S, Van Loon S, Laverge H, Stove V. Analytical and pre-analytical performance characteristics of a novel cartridge-type blood gas analyzer for point-of-care and laboratory testing. Clin Chim Acta 2018; 478: 116-26.

23. Kristinsdottir EA, Statkevicius S, Sigurdsson MI, Hansson F, Broman ME. Effects of Analysis Delay on pH, pO_2, pCO_2, Bicarbonate, Glucose, Lactate, Electrolytes, and Other Arterial Blood Gas Variables. Acta Anaesthesiol Scand 2025; 69(6): e70049.
24. Pighi L, Salvagno GL, Ferraro R, Celegon G, Henry BM, Lippi G. Impact of an air bubble within the syringe on test results obtained with a modern blood gas analyzer. J. Med. Biochem 2024; 43(5): 690.
25. Çuhadar S, Özkanay-Yörük H, Köseoğlu M, Katırcıoğlu K. Detection of preanalytical errors in arterial blood gas analysis. Biochem Med (Zagreb) 2022; 32(2): 244-52.
26. Boink AB, Buckley BM, Christiansen TF, Covington AK, Maas AH, Müller-Plathe O, et al. IFCC recommendation on sampling, transport and storage for the determination of the concentration of ionized calcium in whole blood, plasma and serum. J Anal Methods Chem 1991;13(5): 235-9.

Implementation and clinical audit of a virtual thoracic oncology MDT in a low-resource setting in Malaysia

Seng Wee Cheo, MRCP[1], Sze Shyang Kho, MRCP[2], Kai Jie Cheng, MD[1], Geok Gee Yeo, FRCR[1], Qin Jian Low, MRCP[1], Chan Sin Chai, MRCP[2], Siew Teck Tie, MRCP[2], Pui Wen Tan, MRad[3], Zuhanis Abdul Hamid, MRad[4], Kiew Siong Lau, MRad[3], Sing Yang Soon, FRCS[5], Teresa Fuh Guang Chua, MPath[6], Adam Malik Ismail, MPath[6], Pei Jye Voon, MRCP[1]

[1]Department of Radiotherapy, Oncology and Palliative Care, Sarawak General Hospital, Sarawak, [2]Respiratory Unit, Department of Medicine, Sarawak General Hospital, Sarawak, [3]Department of Radiology, Sarawak General Hospital, Sarawak, [4]Department of Radiology, Institut Kanser Negara, Putrajaya, Wilayah Persekutuan Putrajaya, [5]Department of Cardiothoracic Surgery, Pusat Jantung Sarawak, Sarawak, [6]Department of Pathology, Sarawak General Hospital, Sarawak

ABSTRACT

Introduction: Cancer care is increasingly complex, and in Sarawak, Malaysia, geographic and resource limitations further complicate management. This clinical audit describes the implementation, structure and workflow of a virtual thoracic oncology multidisciplinary tumor board (MDT) in a resource-limited setting, and describe the cases discussed and key issues raised.

Materials and Methods: A MDT was established in Sarawak, comprising pulmonologists, oncologists, pathologists, thoracic surgeons, and radiologists. Monthly virtual meetings were held to discuss complex cases. This retrospective study analyzed cases from July 2022 to December 2024, focusing on cancer types, challenges, and recommendation. As an audit of clinical practice, no treatment adherence or outcome measures were assessed.

Results: A total of 94 cases were discussed (median age 60 years; 59.6% male). Cases per year: 21 (2022), 24 (2023), and 49 (2024). Common diagnoses included lung cancer (48.9%), lung lesions from other solid cancers (26.6%), suspected lung cancer (12.8%), non-malignant respiratory conditions (9.6%), and thymic cancer (2.1%). Among solid cancers with lung lesions, colorectal cancer (36%) was most frequent, followed by breast (12%), gynaecological (12%), sarcoma (8%), and others (32%). The main reasons for MDT discussions were therapeutic issues (58.5%) and diagnostic challenges (41.5%). Imaging review (83%) and management discussions (80.9%) were the most common points of discussion. Among 46 lung cancer patients, 43.5% had early-stage, 30.4% locally advanced, and 19.6% metastatic disease. Key recommendations included surgery (35.1%), surveillance (16%), systemic therapy (13.8%), biopsy (11.7%), PET/MRI (7.4%), EBUS staging (5.3%), radiotherapy (4.3%), and clinical trials (2.1%).

Conclusion: This audit demonstrates that a virtual thoracic oncology MDT is feasible and can standardize multidisciplinary discussion, and improve access to specialist input in a resource-limited setting. While clinical outcomes were not evaluated, this audit provides insight into operational processes. Future prospective work incorporating structured data collection, MDT adherence and integration of electronic health records will help evaluate the MDT's impact on patient outcomes and guiding service improvement.

KEYWORDS:
Thoracic Oncology, Multidisciplinary Tumor Board, Sarawak, Resource-limited setting

INTRODUCTION

Cancer remains a leading cause of death worldwide, accounting for nearly 10 million deaths in 2020—approximately one in six deaths.[1] In Malaysia, with a population of over 34 million, lung cancer is the third most prevalent cancer and the leading cause of cancer-related mortality, underscoring the need for an integrated approach to treatment.[2] Sarawak, located on the island of Borneo, faces unique challenges in cancer care due to its vast geographical expanse and limited access to specialized healthcare services.[3] These challenges make the need for an integrated and collaborative treatment approach even more critical.

Over the past decades, continuous efforts have been made to enhance cancer care through advancements in diagnostics and therapeutic options. Improved diagnostic methods, more precise staging systems, and the advent of novel treatments have significantly advanced patient management. However, these developments have also introduced new challenges in delivering effective cancer care.[4] The increasing complexity of cancer treatment underscores the necessity of a multidisciplinary approach to optimize patient outcomes. A thoracic oncology Multidisciplinary Tumor Board (MDT) brings together oncologists, pulmonologists, pathologists, thoracic surgeons, and radiologists to provide comprehensive, evidence-based care.[5] This collaborative framework strengthens decision-making, ensuring that each patient receives a personalized and well-informed treatment strategy.

MDT has become an indispensable component of high-quality cancer care and is strongly endorsed by various international guidelines, including the American Society of

This article was accepted: 13 January 2026
Corresponding Author: Seng Wee Cheo
Email: cheosengwee@gmail.com

Clinical Oncology and the European Society for Medical Oncology guidelines.[6-7] Numerous studies have demonstrated the impact of MDT in delivering safe, high-quality care. The benefits of MDT include precise disease staging, improved clinical-radiological-pathological correlation for accurate diagnosis, and the development of appropriate treatment plans, ultimately leading to more efficient care with shorter time to treatment.[8] Additional benefits include the education of junior physicians, the prevention of overtreatment through appropriate diagnostic selection, the identification of patients for clinical trials, and identification of patients who may benefit from early palliative care.[8-9] Most importantly, thoracic oncology MDT, by ensuring the timely delivery of best evidence-based care, have been shown to improve overall survival and quality of life for patients.[9-10]

Despite having its established position internationally since 1995, there remains challenges on how a MDT should be delivered at its best efficiency, the scale of its impact and the ways clinical research be integrated in MDT discussion.[11] In Malaysia, with a population of over 34 million, where only 8,953 specialists serve in the public sector, efficient resource management is crucial to maximizing the effectiveness of MDT meetings.[12] Beyond workforce limitations, geographical barriers further hinder the delivery of high-quality cancer care, as many patients receive treatment in hospitals without in-house subspecialist support.[13] Given these constraints, ensuring the effective and efficient implementation of MDTs is essential to providing the best possible patient care. At present, evidence describing MDT implementation in Malaysia, particularly in resource-limited or geographically challenging settings remains scarce. To address this gap, this clinical audit describes the structure, workflow and implementation of a virtual thoracic oncology MDT in Sarawak, Malaysia. We present an audit of our MDT processes, review the spectrum of cases discussed and summarizes the recommendations arising from these meeting. This work aims to provide insight into how a virtual MDT can be effectively established in resource-limited and geographically challenging environments.

MATERIALS AND METHODS

Audit background and objectives

The thoracic oncology MDT at Sarawak General Hospital (SGH) was established in 2021 as part of a service-improvement initiative to enhance the coordination and quality of care for complex thoracic oncology cases in a resource-limited setting. The MDT comprises pulmonologists, oncologists, pathologists, thoracic surgeons, and radiologists, and meets monthly via the virtual Zoom platform to facilitate participation from health care providers across Sarawak and specialists across Malaysia with real-time sharing of patients' information (Figure 1). The virtual platform was selected to overcome the geographical challenges of serving a large, sparsely populated state with limited specialists' availability.

This clinical audit aims to describe the implementation of a virtual thoracic oncology MDT in Sarawak and evaluate the clinical characteristics and discussion outcomes of cases presented in the MDT. As an audit of practice, the focus is on reviewing existing processes, identifying gaps and informing service improvement rather than demonstrating treatment efficacy or survival outcomes.

The specific objectives of our thoracic oncology MDT include:

a) To provide optimal, personalized, patient-centered management through discussions and recommendations that are based on the best available evidence and consensus, regardless of the patient's geographical location.
b) To create a platform for clinicians to share expertise and knowledge in an open and conducive environment.
c) To foster a cohesive working relationship among different specialties through effective communication.
d) To serve as an educational platform for junior physicians.
e) To facilitate timely referrals between disciplines.
f) To promote research activities and encourage participation in clinical trials.

Audit standard and Pre-MDT Practice

Before the implementation of the thoracic oncology MDT, treatment decisions for thoracic cancer patients were primarily made by individual specialists, with limited input from other disciplines. Typically, the pulmonologist would take the lead in diagnosing the lung cancer and the oncologists would then develop treatment plans based on available imaging, pathology, and clinical assessments. While some cases were discussed informally among specialists, the lack of formalized multidisciplinary collaboration resulted in a less coordinated approach to patient management, particularly for complex or advanced cases. For certain cases, patients may end up seeing many doctors without a unified treatment plan resulting in treatment delay and suboptimal management.

The audit standard used for comparison was the post-implementation of MDT process, characterised by:

- Structured, scheduled monthly meetings
- Mandatory multidisciplinary representation
- Standardized case submission and documentation
- Consensus-based recommendations
- Formal documentation of decisions

As this was a formative audit, no external performance benchmarks were applied.

MDT process and workflow

The MDT meeting is held monthly, typically on the last Friday of the month, and lasts up to two hours via the Zoom platform. Attendees include consultants from each discipline, fellows in training, and medical officers. Given the limited human resources and the commitment required from each specialty, our MDT adopts a targeted approach - only complex cases are discussed, rather than all new lung cancer patients. "Complex" cases were defined as those with diagnostic ambiguity, discordant imaging or pathology findings, or therapeutic dilemmas requiring multidisciplinary input. Eligible cases include thoracic malignancies, non-malignant respiratory conditions and any solid organ cancers with lung lesions. Complex molecular cases requiring MDT input were not covered in this tumor board.

Consultants from various disciplines could submit cases, and the primary team responsible for each patient was required to prepare a concise PowerPoint presentation before the meeting. The presentation had to include the patient's demographic details, diagnosis, molecular profile of lung cancer (if available), relevant imaging, and most importantly, the key discussion points and required specialty input. Cases were submitted at least one week in advance to allow for thorough preparation. During the MDT meeting, the primary team and relevant specialists took turns presenting the patient's clinical information, along with radiology and pathology images, to facilitate discussion. The MDT members then deliberated on each case and reached a consensus on recommendations. Following the meeting, all discussions and recommendations were recorded in an Excel sheet for documentation, audit and future quality-improvement tracking (Figure 2).

Study population and methods

This is a single-center, retrospective clinical audit of all cases discussed in Sarawak Thoracic Oncology MDT between July 2022 to December 2024. Data were obtained through review of MDT records and case database. Variables collected included patient demographics, diagnosis, type of cancer/clinical diagnosis, discussion points, and MDT recommendations. The study was conducted in accordance with the Declaration of Helsinki and was approved by the National Medical Research Register. Given the retrospective nature of the study and anonymized data collection, the requirement for informed consent was waived. Data on survival outcomes, and adherence to MDT were not collected in this audit.

Statistical analysis

The data analysis was performed using the SPSS version 22. Descriptive data will be expressed as mean, frequencies and percentages, unless otherwise stated.

Ethics approval

The study was conducted in accordance with the Declaration of Helsinki, and approved by the National Medical Research Register (NMRR ID-24-01550-GFC).

RESULTS

Patient characteristics (Table I)

From July 2022 to December 2024, the thoracic oncology MDT meeting convened 21 times and a total of 94 patients with complex issues were discussed throughout this period. The average number of patients discussed per MDT meeting was 4.5 (ranging from 2-8). A breakdown of years showed that 21 cases were discussed in year 2022, 24 in year 2023 and 49 in year 2024. The median age of our patients was 60 years (ranging 21 – 78 years), 59.6% were male and 40.4% were female.

The most common diagnosis was lung cancer (n=46, 48.9%), followed by other solid organ cancers with lung lesions (n=25, 26.6%), suspected lung cancer (n=12, 12.8%), non-malignant respiratory conditions (n=9, 9.6%) and thymic cancer (n=2, 2.1%). For patients with lung cancers, the majority were in early stage (n=20, 43.5%), followed by locally advanced disease (n=14, 30.4%) and metastatic disease (n=9, 19.6%). Other solid organ cancers with lung lesions that required thoracic oncology MDT meeting include colorectal cancer (n=9, 36%), breast cancer (n=3, 12%), gynaecological cancer (n=3, 12%), sarcoma (n=2, 8%), and other primary cancers (n=8, 32%).

Main discussion points and outcome of discussion (Table II)

There were various reasons for listing a patient for thoracic oncology MDT discussion. The most common reasons being therapeutic issues (n=55, 58.5%) followed by diagnostic issues (n=39, 41.5%). During the MDT meeting, the main issues that required input were highlighted. Majority of the cases required imaging review by the radiologist (n=78, 83%) and management discussion by the MDT team (n=76, 80.9%). 9 patients (9.6%) required pathology review. In terms of MDT outcomes, the most common recommendations were surgery (n=33, 35.1%), followed by surveillance (n=15, 16%), systemic therapy (n=13, 13.8%), diagnostic biopsy by images-guided/bronchoscopy-guided (n=11, 11.7%), Positron Emission Tomography (PET)/ Magnetic Resonance Imaging (MRI) (n=7, 7.4%), endobronchial ultrasound (EBUS) staging (n=5, 5.3%), radiotherapy (n=4, 4.3%), clinical trial enrolment (n=2, 2.1%), and other recommendations (n=4, 4.3%).

Case illustrations

In this clinical audit, we also illustrate two lung cancer cases in which MDT discussions played a pivotal role in guiding diagnostic evaluation and treatment strategy.

Case 1 (Figure 3)

A 53-year-old never-smoking woman with no comorbidities and ECOG performance status 0 was referred following detection of an abnormal chest radiograph during routine health screening. She was asymptomatic. Computed tomography revealed two right lung nodules (RS1 and RS6, each measuring 1.5cm without mediastinal or hilar lymphadenopathy. FDG PET/CT demonstrated mild uptake in both lung lesions but unexpectedly identified intense uptake in the sigmoid colon, raising concern for a possible primary malignancy.

The case was discussed at our lung MDT, where diagnostic and proposed treatment strategies were discussed. Given the clinical scenario, the possible differential diagnoses include metastatic colon cancer, locally advanced lung cancer or multiple primary lung cancer. During MDT discussion, a stepwise diagnostic approach was recommended, including colonoscopy and endobronchial ultrasound-guided biopsy of both lung nodules, with immunohistochemical testing to exclude a colon primary and molecular testing if lung adenocarcinoma was confirmed.

Colonoscopy revealed a sigmoid polyp, which on histopathological examination showed a tubular adenoma with low-grade dysplasia and no evidence of malignancy. Radial endobronchial ultrasound-guided biopsy and cryobiopsy of both lung lesions confirmed primary lung adenocarcinoma (TTF-1 positive, p40 and CDX-2 negative). Molecular testing demonstrated distinct epidermal growth factor receptor (EGFR) mutations, with L861Q identified in

Table I: Patient characteristics of the study (N=94)

Clinical Characteristics	Numbers (%), [N=94]
Median age (years)	60 (21-78)
Gender	
• Male	56 (59.6%)
• Female	38 (40.4%)
Year of discussion	
• 2022	21 (22.3%)
• 2023	24 (25.5%)
• 2024	49 (52.1%)
Diagnosis	
• Lung cancer	46 (48.9%)
• Other solid organ cancer with lung lesions	25 (26.6%)
• Suspected lung cancer	12 (12.8%)
• Non-malignant respiratory conditions	9 (9.6%)
• thymic cancer	2 (2.1%)
Stages of lung cancers (n=46)	
• Early stage	20 (43.5%)
• Locally advanced	14 (30.4%)
• Metastatic disease	9 (19.6%)
• Missing information	3 (6.5%)
Other solid organ cancers with lung lesions (n=25)	
• Colorectal cancer	9 (36%)
• Breast cancer	3 (12%)
• Gynaecological cancer	3 (12%)
• Sarcoma	2 (8%)
• Others	8 (32%)

Table II: Main discussion points and Outcome of MDT (N=94)

Domains	Numbers (%)
Main reason of listing in MDT	
• Diagnostic issues	39 (41.5%)
• Therapeutic issues	55 (58.5%)
Main point of discussion*	
• Image review	78 (83%)
• Pathology review	9 (9.6%)
• Management discussion	76 (80.9%)
Outcome of MDT	
• Surgery	33 (35.1%)
• Surveillance	15 (16%)
• Systemic therapy	13 (13.8%)
• Diagnostic biopsy	11 (11.7%)
• PET/MRI imaging	7 (7.4%)
• EBUS staging	5 (5.3%)
• Radiotherapy	4 (4.3%)
• Clinical trial enrolment	2 (2.1%)
• Others	4 (4.3%)

*some patients may have more than 1 main point of discussion

the RS1 lesion and L858R in the RS6 lesion, confirming synchronous early-stage primary lung cancers (clinical stage IA2 for both lesions). Following MDT review, the patient was referred for curative-intent surgical management and subsequently placed on surveillance. This case highlights how MDT discussion facilitated accurate staging, avoided misclassification as metastatic disease, and facilitated appropriate curative treatment despite diagnostic complexity.

Case 2 (Figure 4)

A 69-year-old never-smoking man with a background of hypertension, atrial fibrillation, and dyslipidaemia (ECOG performance status 1) was diagnosed with advanced EGFR-mutant non-small cell lung cancer (NSCLC) in January 2022. He was initially treated with first-generation EGFR tyrosine kinase inhibitors (TKIs), receiving gefitinib followed by erlotinib due to treatment-related hepatotoxicity, achieving a partial response. Disease progression subsequently occurred, plasma testing at that time detected an acquired EGFR T790M mutation, and osimertinib was initiated, resulting in a partial response with a progression-free survival of 12 months.

In September 2024, clinical and radiological disease progression was observed while on osimertinib. The case was reviewed at the lung MDT, where key discussion points included mechanisms of resistance to osimertinib, the role of repeat tissue biopsy, and appropriate subsequent systemic therapy in the context of limited targeted treatment options.

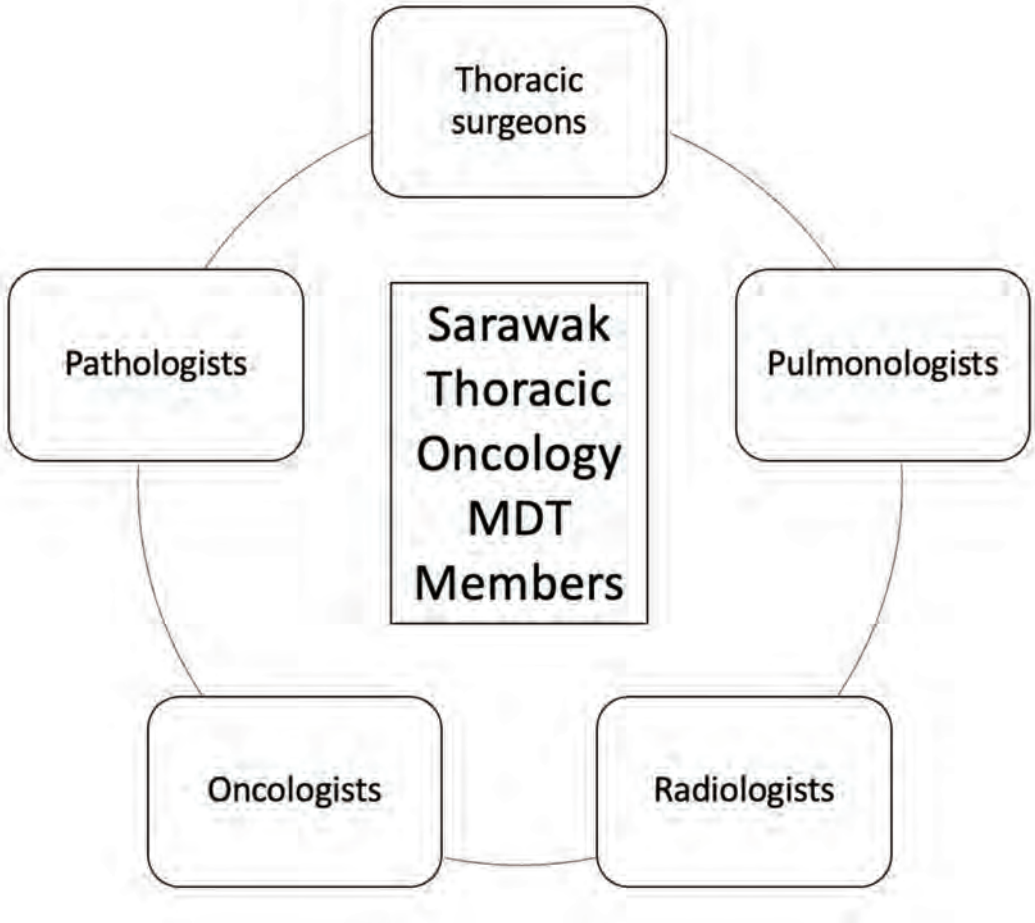


Fig. 1: Team members of our Thoracic Oncology MDT

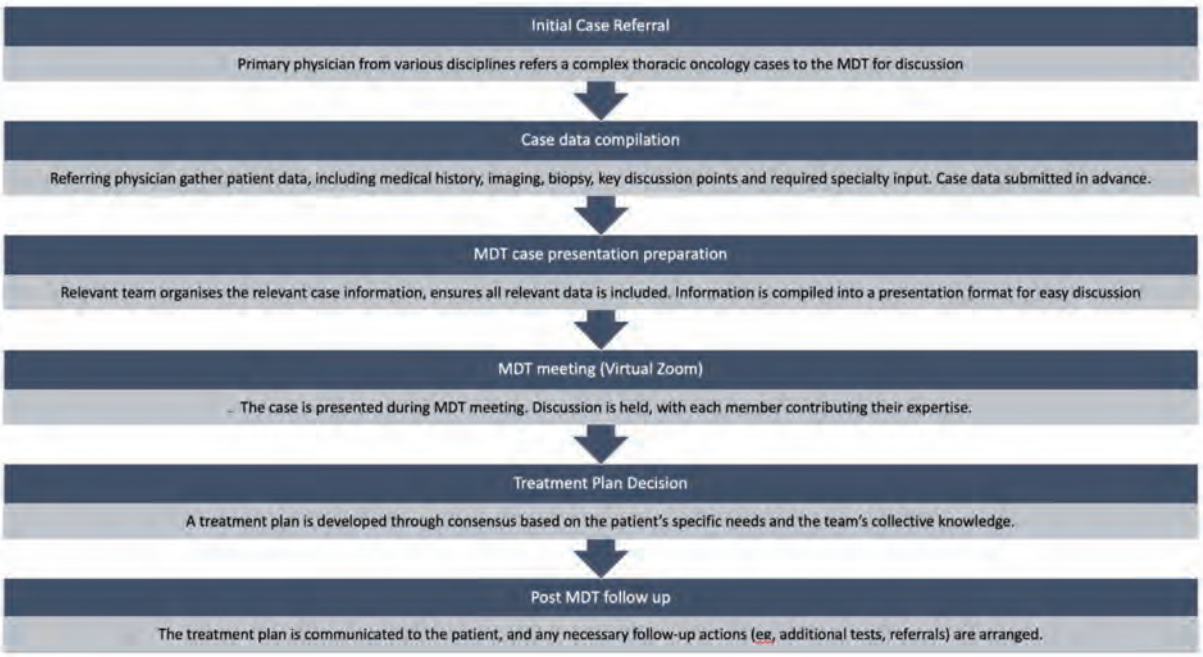


Fig. 2: Workflow of Case Presentations in Thoracic Oncology MDT. This diagram illustrates the process by which complex cases are selected and presented during our MDT meetings. It outlines the steps from initial case referral, the compilation of patient data by the involved team, the preparation for MDT discussion, and the final decision-making process that follows the case review. This workflow ensures that all relevant clinical information is considered and that treatment recommendations are made collaboratively by the multidisciplinary team

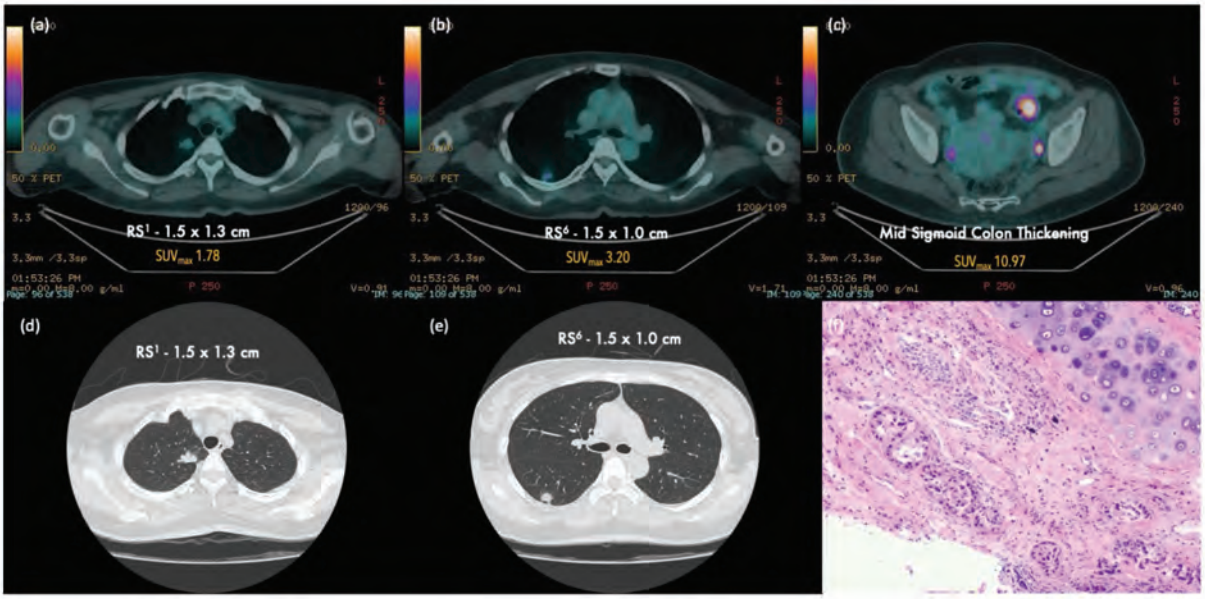


Fig. 3: (a),(b) FDG scan showing FDG-avid lung nodules, (c) FDG-avid sigmoid colon thickening. (d),(e) CT images showing both lung nodules, (f) histopathological examination revealed adenocarcinoma of lung origin

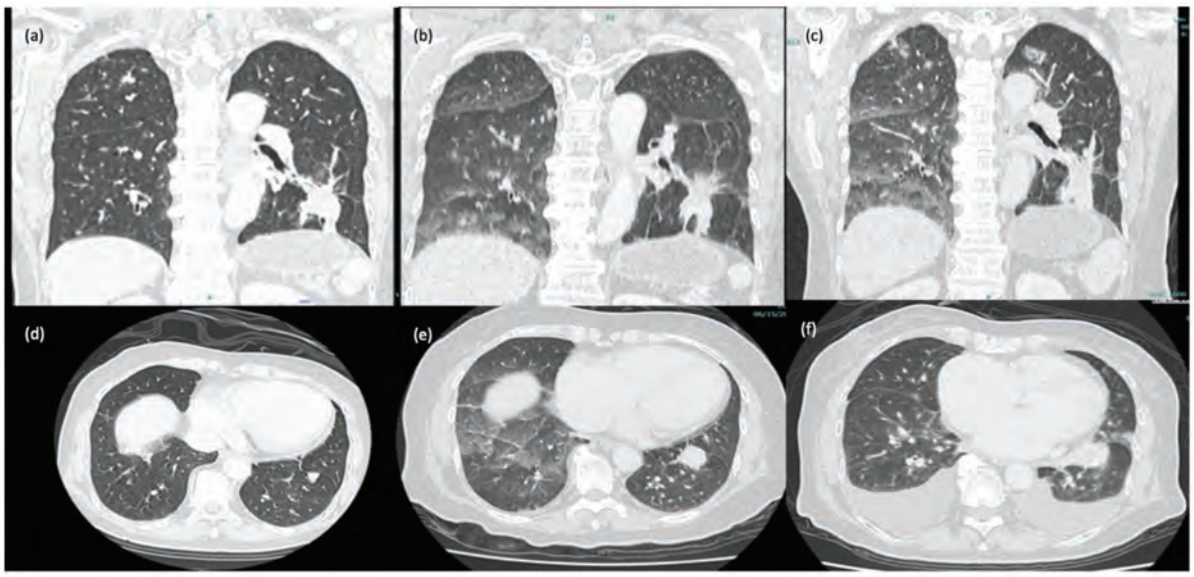


Fig. 4: (a),(d) CT images during first generation TKI treatment. (b),(e) CT images showing disease progression after first generation TKI. (c)(f) CT images showing larger lung nodule with presence of new pleural effusions, confirming disease progression while on osimertinib

Given the clinical scenario and disease progression, the MDT recommended repeat tissue biopsy to evaluate for histologic transformation or alternative resistance mechanisms. The biopsy approach was discussed as well, including lesion to biopsy and approaches.

An endobronchial ultrasound-guided biopsy of a progressing left lower lobe lung lesion revealed small cell carcinoma, consistent with histologic transformation. Due to small cell transformation, the patient was transitioned to platinum-etoposide chemotherapy. Unfortunately, his clinical course was complicated by pneumonia, and he subsequently passed away in December 2024. His overall survival from diagnosis was 47 months. This case illustrates the critical role of MDT discussion at the time of progression on osimertinib, particularly in guiding decisions regarding re-biopsy, identifying histologic transformation, and enabling timely modification of treatment strategy in advanced EGFR-mutant lung cancer.

DISCUSSION

MDT meetings, in which cancer patients are discussed by a group of specialists with the expertise relevant to their clinical management, are an integral part of modern cancer care.[14] It enables coordinated, evidence-based decision-making.[15] In a resource-limited setting, MDT implementation often faces additional logistical, workforce and

infrastructural barriers. In Sarawak, often limited by vast geography, uneven specialist distribution and limited tertiary oncology centers, establishing a functioning thoracic oncology MDT represents an important structural advance in cancer care delivery. This clinical audit describes our institutional experience developing a virtual MDT and highlights operational processes, early observation and lessons learned, rather than presenting outcome-based improvements which we were unable to measure in this retrospective review. Our study also highlights the feasibility and impact of a virtual MDT model in overcoming geographical barriers and optimizing patient outcomes.

Several studies have described how virtual MDTs overcome geographical barriers. In the United Kingdom, a virtual lung cancer MDT linking a district hospital in Southend results in 30% increase in surgical resection, reduced unnecessary investigations, and shortened the time to surgery appointments.[16] In Japan, a virtual lung cancer tumor board connecting eight hospitals reviewed 202 cases over 14 months, with the majority being lung cancer (96%). The primary focus of discussions was treatment strategy (92.6% of cases), while diagnostic strategies were addressed in 7.4% of cases. The virtual MDT meeting led to changes in treatment strategies for 49 out of 202 patients.[17] While international studies demonstrate measurable improvements, our audit focuses on how the MDT operated within local constraints, how case selection was tailored and how multidisciplinary engagement was coordinated across institutions. Our analysis of 94 patients from our MDT revealed that lung cancer constituted nearly half (48.9%) of the cases, followed by other solid organ cancers with lung lesions (26.6%), suspected lung cancer (12.8%), and non-malignant respiratory conditions (9.6%). This difference in distribution is likely due to targeted approach adopted by our team with deliberate focus on complex cases rather than all lung cancers. Similar to the Japanese study, therapeutic issues were more common reasons for MDT listings. In terms of MDT outcomes, 35.1% received surgical recommendation, 16% for surveillance and 13% for systemic therapy.

The main demonstrable benefits of our virtual MDT model is its ability to bridge geographical barriers by connecting clinicians across distant hospitals and compensate for limited local subspecialty availability. The virtual platform has enabled seamless participation from specialists across Malaysia, promoting equitable access to expert opinions regardless of a patient's location. This approach aligns with global efforts to enhance cancer care delivery through telemedicine and virtual MDT in resource limited settings.[18] Besides bridging geographical barriers for patients, virtual MDT has been shown to increase attendance of specialists and reduces the time and burden associated with travel.[8,19] In terms of quality of case discussion, study has found that virtual MDT may have better quality discussion despite comparable ease of reviewing pathology and radiology images, presentation and gathering subspecialty recommendation.[20] This is possibly due to better depth of discussion with personal face-to-face interaction. Other potential significant benefit of virtual MDT including fostering international collaboration to enhance access to expert care and facilitate sharing of expertise.[21] Although we were unable to demonstrate outcome improvement such as faster treatment timeline, enhanced staging accuracy or better survival, our MDT clearly improved coordination of care, reduced reliance on ad hoc consultations and standardized the management of complex thoracic oncology cases.

Our experience establishing a virtual thoracic oncology MDT in a resource-limited setting has also yielded several key lessons. Strong administrative support and structured coordination are essential to sustain regular meetings across institutions. While virtual platforms can effectively bridge geographic and resource gaps, reliable connectivity and standardized documentation remain critical to maintaining meeting quality and continuity. Every meeting should be periodic and fixed at preplanned time and every MDT member should have dedicated time to attend MDT meeting. MDT meeting should be held during core hours and should not clash with any related clinic. Early engagement of stakeholders, including peripheral hospitals, promotes shared ownership and consistent participation. Finally, the development of local data systems and training pathways is vital for ensuring accountability, sustaining multidisciplinary collaboration, and achieving long-term impact.

Despite its benefits, sustaining our virtual MDT presents several challenges. The absence of a uniform electronic medical record system, workforce limitations, the need for streamlined case selection, internet connectivity issues, and logistical constraints in organizing virtual meetings require ongoing optimization. Poor connections can lead to dropped calls, audio clarity issues, and overlapping conversations, all of which can undermine discussion quality and meeting effectiveness.[20,22-23] Additionally, the lack of face-to-face interaction, role uncertainties, and difficulties in engagement may contribute to a less effective virtual MDT.[24] While virtual platforms allow broader participation, maintaining engagement, securing commitment from all disciplines, and ensuring comprehensive case discussions remain key challenges.[19] Implementing well-defined protocols such as structured turn-taking, clear leadership roles, and dedicated MDT coordinators may help mitigate these issues.[23,25] Furthermore, continuous audits of MDT performance, proactive participation, strategic scheduling, and regular team dialogues play a crucial role in sustaining our virtual MDT and overcoming its barriers.[26]

MDT meetings enhance oncology care by reducing reliance on individual decisions and fostering collaborative teams and systems.[8] Effective MDTs have been associated with improved care processes, more accurate treatment recommendations and better survival outcomes.[27–29] Additional benefits include reduced lead times, stronger team dynamics, training opportunities for junior physicians, and better identification of patients for clinical trials.[28] Core features of an effective MDT include effective communication, strong leadership, patient-centered approach, and multidisciplinary collaboration built on mutual respect.[30-31] Regular audits by quality indicators (QI) instruments are essential for maintaining an efficient and high-quality MDT.[32] QIs provide measurable benchmark for

evaluating care quality, and several QIs specific to thoracic oncology MDTs have been developed to assess professional practice, decision-making quality and the patient's perspective.[33-34] Tools like MDT-Metric for the Observation of Decision-making (MDT-MODe) and patient-reported outcome measures can effectively assess the quality of MDT.[35] Although we were unable to apply these QIs due to retrospective data limitations, incorporating them in the future prospective studies will enable more systematic evaluation of MDT performance, adherence to recommendations and impact on patient quality of life.

Our study has several limitations. As a single-center, retrospective analysis, it is subject to selection bias. Only cases deemed complex by the primary team were included for MDT discussion, which may limit the generalizability of our findings to all thoracic oncology cases managed in Sarawak. Additionally, the descriptive nature of our analysis means that we are unable to provide objective evidence of the direct impact of the MDT on key clinical outcomes, such as pre-treatment evaluation, proper staging, adequacy of treatment, time-to-treatment, treatment adherence, or survival. Due to difficulties in systematically collecting outcome data, including long-term follow-up, we were unable to assess the real-world impact of MDT recommendations on these patient outcomes. Moreover, logistical challenges related to data collection, such as the absence of a uniform electronic medical record system and inconsistent follow-up procedures, hindered our ability to track patient outcomes like survival rates and treatment progression. As a result, the evaluation of MDT effectiveness remains limited to descriptive data rather than definitive evidence of improved patient outcomes.

To address current gaps, we plan to prospectively track MDT recommendations and patient outcomes. Each case will be assigned a standardized form capturing recommendation type, implementation date, adherence, and time-to-treatment interval. Survival and progression data will be linked to these records through routine six-monthly follow-up audits. This framework will enable objective assessment of MDT impact on adherence, timeliness, and patient outcomes. Future prospective studies should incorporate systematic tracking tools and robust data collection methods, such as electronic health records, to allow for more thorough evaluations of the MDT's impact on survival, disease progression, treatment adherence, and quality of life. Operational challenges including limited specialist availability and risk of burnout remain significant in Sarawak, highlighting the need for task-sharing, structured scheduling, and collaboration with regional or international experts. We do aim to strengthen MDT composition by integrating palliative care and rehabilitation teams, as early involvement improves quality of life and clinical outcomes.[36-37] Expanding specialist training opportunities will further enhance capacity and support continued advancement of multidisciplinary cancer care.

CONCLUSION

In conclusion, this clinical audit demonstrates the feasibility and process success of establishing a virtual thoracic oncology MDT in Sarawak, which has strengthened multidisciplinary collaboration, improved coordination, and enhanced access to expert opinions in a resource-limited environment. As a descriptive audit, clinical outcomes were not evaluated. Future efforts will focus on developing a prospective framework to monitor MDT adherence, treatment timelines, and survival outcomes, alongside integrating electronic health records to enable more comprehensive data collection. Addressing local barriers such as workforce limitations, infrastructure gaps, and healthcare inequities affecting rural and indigenous populations, will be crucial to realizing the full potential of virtual MDTs in improving cancer care delivery. Ultimately, this work represents an important foundation for sustainable, equitable, and collaborative cancer care in Sarawak and similar resource-limited regions.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

ACKNOWLEDGEMENT

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

FUNDING

This research received no external funding.

REFERENCES

1. Cancer [Internet]. [cited 2025 Oct 11]. Available from: https://www.who.int/news-room/fact-sheets/detail/cancer
2. Rajadurai P, How SH, Liam CK, Sachithanandan A, Soon SY, Tho LM. Lung Cancer in Malaysia. J Thorac Oncol 2020; 15(3): 317-23.
3. Bismelah L, Masron T, Ahmad A, Mohd Ali A, Echoh D. Geospatial assessment of healthcare distribution and population density in Sri Aman, Sarawak, Malaysia. Malaysian Journal of Society and Space 2024; 20: 51-67.
4. Morabito A, Mercadante E, Muto P, Manzo A, Palumbo G, Sforza V, et al. Improving the quality of patient care in lung cancer: key factors for successful multidisciplinary team working. Explor Target Antitumor Ther 2024; 5(2): 260-77.
5. Kreidieh F, Tfayli A. Impact of thoracic multidisciplinary tumor boards on the management of patients with cancer: A retrospective study at the American university of Beirut medical center. Mol Clin Oncol 2022; 18(1): 6.
6. Daly ME, Singh N, Ismaila N, Management of Stage III NSCLC Guideline Expert Panel. Management of Stage III Non-Small Cell Lung Cancer: ASCO Guideline Rapid Recommendation Update. J Clin Oncol 2024; 42(25): 3058–60.
7. Postmus PE, Kerr KM, Oudkerk M, Senan S, Waller DA, Vansteenkiste J, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017; 28(suppl_4): iv1-21.
8. Mano MS, çitaku FT, Barach P. Implementing Multidisciplinary Tumor Boards in Oncology: a Narrative Review. Future Oncology 2022; 18(3): 375–84.
9. Kowalczyk A, Jassem J. Multidisciplinary team care in advanced lung cancer. Transl Lung Cancer Res 2020; 9(4): 1690-8.
10. Heinke MY, Vinod SK. A review on the impact of lung cancer multidisciplinary care on patient outcomes. Transl Lung Cancer Res 2020; 9(4): 1639-53.

11. Selby P, Popescu R, Lawler M, Butcher H, Costa A. The Value and Future Developments of Multidisciplinary Team Cancer Care. Am Soc Clin Oncol Educ Book 2019; 39: 332-40.
12. Ismail H. How Many Doctors Do We Need in the Public Sector?: A Guide to Human Resource Planning and Specialist Training. Malays J Med Sci 2023; 30(2): 1-7.
13. Feliciano EJG, Ho FDV, Yee K, Paguio JA, Eala MAB, Robredo JPG, et al. Cancer disparities in Southeast Asia: intersectionality and a call to action. Lancet Reg Health West Pac 2023; 41: 100971.
14. Munro AJ, Swartzman S. What is a virtual multidisciplinary team (vMDT)? Br J Cancer 2013; 108(12): 2433-41.
15. List H, Kristensen DB, Graumann O. "The highest decision-making level" – Multidisciplinary team meetings as boundary spaces. Social Science & Medicine 2025; 371: 117886.
16. Davison AG, Eraut CD, Haque AS, Doffman S, Tanqueray A, Trask CW, et al. Telemedicine for multidisciplinary lung cancer meetings. J Telemed Telecare 2004; 10(3): 140-3.
17. Takeda T, Takeda S, Uryu K, Ichihashi Y, Harada H, Iwase A, et al. Multidisciplinary Lung Cancer Tumor Board Connecting Eight General Hospitals in Japan via a High-Security Communication Line. JCO Clin Cancer Inform.2019; 3: 1-7.
18. Gottlob A, Schmitt T, Frydensberg MS, Rosińska M, Leclercq V, Habimana K. Telemedicine in cancer care: lessons from COVID-19 and solutions for Europe. Eur J Public Health 2025; 35(1): 35-41.
19. Dharmarajan H, Anderson JL, Kim S, Sridharan S, Duvvuri U, Ferris RL, et al. Transition to a virtual multidisciplinary tumor board during the COVID-19 pandemic: University of Pittsburgh experience. Head Neck 2020; 42(6): 1310-6.
20. Perlmutter B, Said SAD, Hossain MS, Simon R, Joyce D, Walsh RM, et al. Lessons learned and keys to success: Provider experiences during the implementation of virtual oncology tumor boards in the era of COVID-19. J Surg Oncol 2022; 125(4): 570-6.
21. Montgomery ND, Liomba NG, Kampani C, Krysiak R, Stanley CC, Tomoka T, et al. Accurate Real-Time Diagnosis of Lymphoproliferative Disorders in Malawi Through Clinicopathologic Teleconferences: A Model for Pathology Services in Sub-Saharan Africa. Am J Clin Pathol 2016; 146(4): 423–30.
22. Groothuizen JE, Aroyewun E, Zasada M, Harris J, Hewish M, Taylor C. Virtually the same? Examining the impact of the COVID-19 related shift to virtual lung cancer multidisciplinary team meetings in the UK National Health Service: a mixed methods study. BMJ Open 2023; 13(6): e065494.
23. Onifade A, Quaife SL, Holden D, Chung D, Birchall M, Peake MD, et al. Understanding the effectiveness and quality of virtual cancer multidisciplinary team meetings (MDTMs): a systematic scoping review. BMC Health Serv Res 2024; 24(1): 1481.
24. Dharanikota H, Wigmore SJ, Skipworth RJE, Yule S. Are multidisciplinary team meetings remotely efficient? Br J Surg 2024; 111(1): znad429.
25. Caviola G, Daolio J, Pellegri C, Cigarini F, Braglia L, Foracchia M, et al. Learning from Adaptations to the COVID-19 Pandemic: How Teleconsultation Supported Cancer Care Pathways at a Comprehensive Cancer Center in Northern Italy. Cancers (Basel) 2023; 15(9): 2486.
26. Mohamedbhai H, Fernando S, Ubhi H, Chana S, Visavadia B. Advent of the virtual multidisciplinary team meeting: do remote meetings work? Br J Oral Maxillofac Surg 2021; 59(10): 1248-52.
27. Epstein NE. Multidisciplinary in-hospital teams improve patient outcomes: A review. Surg Neurol Int 2014; 5(Suppl 7): S295-303.
28. Rosell L, Alexandersson N, Hagberg O, Nilbert M. Benefits, barriers and opinions on multidisciplinary team meetings: a survey in Swedish cancer care. BMC Health Serv Res 2018; 18(1): 249.
29. Lindblad M, Jestin C, Johansson J, Edholm D, Linder G. Multidisciplinary team meetings improve survival in patients with esophageal cancer. Dis Esophagus 2024; 37(11): doae061.
30. Lawson McLean A, Lawson McLean AC, Hartinger S, Hammersen J, Drescher R, Schuldt S, et al. Tips for Harnessing the Educational Potential of Tumor Boards for Medical Students. Med Sci Educ 2024; 34(6): 1527-32.
31. Soukup T, Lamb BW, Arora S, Darzi A, Sevdalis N, Green JS. Successful strategies in implementing a multidisciplinary team working in the care of patients with cancer: an overview and synthesis of the available literature. J Multidiscip Healthc 2018; 11: 49-61.
32. Evans L, Liu Y, Donovan B, Kwan T, Byth K, Harnett P. Improving Cancer MDT performance in Western Sydney - three years' experience. BMC Health Serv Res 2021; 21(1): 203.
33. Chiew KL, Sundaresan P, Jalaludin B, Chong S, Vinod SK. Quality indicators in lung cancer: a review and analysis. BMJ Open Qual 2021; 10(3): e001268.
34. Guirado M, Sanchez-Hernandez A, Pijuan L, Teixido C, Gómez-Caamaño A, Cilleruelo-Ramos Á. Quality indicators and excellence requirements for a multidisciplinary lung cancer tumor board by the Spanish Lung Cancer Group. Clin Transl Oncol 2022; 24(3): 446–59.
35. Lamb BW, Wong HWL, Vincent C, Green JSA, Sevdalis N. Teamwork and team performance in multidisciplinary cancer teams: development and evaluation of an observational assessment tool. BMJ Qual Saf 2011; 20(10): 849-56.
36. Temel JS, Greer JA, Muzikansky A, Gallagher ER, Admane S, Jackson VA, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 2010; 363(8): 733–42.
37. Cruz Mosquera FE, Murillo SR, Naranjo Rojas A, Perlaza CL, Castro Osorio D, Liscano Y. Effect of Exercise and Pulmonary Rehabilitation in Pre- and Post-Surgical Patients with Lung Cancer: Systematic Review and Meta-Analysis. Medicina (Kaunas) 2024; 60(11): 1725.

ORIGINAL ARTICLE

Cytopeutics umbilical cord-derived mesenchymal stem cells are associated with earlier clinical improvement compared to bone marrow aspirate concentrate with scaffold in knee cartilage injury: A Phase 1 feasibility and Phase 2 randomized controlled trial

Badrul Akmal Hisham Md Yusoff, MD[1], Norlelawati Mohamad, MSports.Med[1], Sze-Piaw Chin, MBBS[2,3], Mohd Nazran Ramlan, MD[4], Mohd Saperi Zool Kipele, MBBS[5], Nik Syazana Izyan Saffery, MMedSci[2], Noor 'Ain Mohd Nasir, MD[6], Ahmad Farihan Mohd Don, MB ChB[1], Shau-Kong Lai, MD[7], Huzlinda Hussin, MD[7], Muhammad Fahmi Yakop, BMedSci[2], S Fadilah Abdul Wahid, PhD[8], Soon-Keng Cheong, MBBS[2,3]

[1]Department of Orthopaedic and Traumatology, Universiti Kebangsaan Malaysia, Kuala Lumpur, [2]Cytopeutics Sdn Bhd, Cyberjaya, Selangor, [3]M. Kandiah Faculty of Medicine and Health Sciences, Universiti Tunku Abdul Rahman-Kampus Sungai Long, Kajang, Selangor, [4]Department of Orthopedics and Traumatology, Hospital Angkatan Tentera Tuanku Mizan, Kuala Lumpur, Wilayah Persekutuan Kuala Lumpur, [5]Department of Orthopedics and Traumatology, Hospital Sultan Idris Shah, Serdang, Selangor, Malaysia, [6]Department of Pathology, Hospital Sultan Abdul Aziz Shah, Universiti Putra Malaysia, Selangor, [7]Department of Pathology, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Selangor, [8]Cell Therapy Centre, Faculty of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Kuala Lumpur, Malaysia

ABSTRACT

Introduction: Despite advances in the development of mesenchymal stem cells (MSCs), the ultimate benefits of MSCs against current cell-based therapies are still limited. This study aimed to assess the safety, feasibility, and efficacy of Cytopeutics® umbilical cord-derived MSCs (Chondrocell-EX) in patients with knee cartilage injury.

Materials and Methods: The study was conducted in two parts: a phase I feasibility study (PI) followed by a phase II randomized controlled trial (PII). Both studies were approved by UKM Research Ethics Committee (PI: UKM PPI/111/8; PII: UKM PPI/111/8/JEP-2019-304). Six patients were involved in the PI study in which all patients received Chondrocell-EX and 28 patients in the following PII study, where 17 patients received Chondrocell-EX with Hyaluronic acid (HA) (Arm A) and 11 patients received commercially available cell-based therapy, which is Bone Marrow Aspirate Concentrate (BMAC) with Hyaluronic acid-based scaffold (HA-S) (Arm B). Safety was assessed based on the occurrence of adverse events, while clinical outcomes were assessed based on the Knee Injury and Osteoarthritis Outcome Score (KOOS) and Pain Visual Analog Scale (VAS). Second-look arthroscopy and histological assessment were performed to assess their structural outcomes at 12 months.

Results: In the PI feasibility study, significant pain reduction began at 3 months, with mean VAS decreasing from 6.83 ± 0.98 at baseline to 4.83 ± 1.17 ($p < 0.01$), 3.00 ± 0.00 at 6 months ($p < 0.01$), and 1.83 ± 0.75 at 12 months ($p < 0.01$). In the PII study, Arm A (Chondrocell-EX + HA) demonstrated significant VAS improvements at all follow-up points compared to baseline ($p < 0.001$), whereas Arm B (BMAC + HA-S) showed significant reductions only from 3 months onward. After adjustment for baseline age and VAS, Arm A achieved significantly lower pain scores than Arm B at 6 months (2.56 ± 1.41 vs 3.09 ± 1.22; $p = 0.015$) and 12 months (2.27 ± 1.49 vs 2.50 ± 1.35; $p = 0.043$), indicating earlier and sustained pain relief with Chondrocell-EX injection. Functional outcomes mirrored pain improvements. In PI, KOOS scores improved significantly from 3 months, reaching 85.83 ± 11.87 at 12 months ($p < 0.01$). In PII, KOOS increased significantly in both arms ($p < 0.001$), but Arm A demonstrated earlier gains at 3 months and significantly higher adjusted KOOS scores than Arm B at 6 ($p = 0.009$) and 12 months ($p = 0.037$). In KOOS subdomains analysis, it showed significantly greater improvements in Arm A, particularly in symptoms and stiffness, activity of daily living (ADL), pain, sport and recreation, and quality of life (QoL) at key time points.

Conclusion: Chondrocell-EX+HA treatment is more convenient, feasible, and minimally invasive with the findings suggesting that it is associated with faster functional improvement and pain relief, along with demonstration of hyaline-like cartilage regeneration, compared to the BMAC+HA-S method.

Trial Registration: NCT05016011; NMRR-19-54-46020.

KEYWORDS:
Cartilage injury, mesenchymal stem cells, BMAC, HA-based scaffold

INTRODUCTION

Knee cartilage injury is a common condition that normally occurs as a result of trauma (e.g., sports injuries), chronic

This article was accepted: 18 January 2026
Corresponding Author: Sze-Piaw Chin
Email: chin.sze.piaw@gmail.com

repetitive use, or progressive degeneration –often known as wear and tear – which frequently progresses to osteoarthritis (OA) due to cartilage's limited capacity for regeneration.[1] Cartilage lesions are present in over 60% of arthroscopic knee procedures, including those in athletes and OA patients.[2] With increasing age and post-injury OA risk, this prevalence is expected to grow, leading to substantial healthcare costs and early workforce exit.[3]

Current treatments focus on symptom relief rather than cartilage recovery, highlighting the need for more effective therapeutic options.[4] Bone marrow aspirate concentrate (BMAC), such as Marrow Cellution, combined with hyaluronic acid-based scaffolds (HA-S) like Hyalofast®, is widely used.[5-6] Mesenchymal stem cell (MSC) therapy is a promising approach for knee cartilage repair due to its immunomodulatory and regenerative effects via paracrine signalling, potentially delaying the need for total knee replacement.[7-8] In particular, umbilical cord-derived MSCs (UC-MSCs) have shown encouraging results in preclinical and clinical settings.[7,9] The approval of umbilical cord blood-derived MSCs (Cartistem®) in Korea for large cartilage defects further supports the clinical potential of MSCs.[10] Our previous studies demonstrated that 60% of patients with moderate to severe osteoarthritis showed improved MRI findings at 12 months post-UC-MSC treatment, including increased cartilage thickness and reduced joint pathology.[11] We also observed full cartilage regeneration in defects >2.5 cm² on arthroscopy, beyond the mainly subjective improvements reported in earlier studies.[12]

Despite progress in MSC-based therapies for knee cartilage repair, direct comparisons with established cell-based treatments remain limited. We conducted a randomized controlled trial to assess the safety and efficacy of Chondrocell-EX with hyaluronic acid (HA) versus BMAC with HA-S. This investigator-led study includes comprehensive clinical and histological evaluations.

MATERIALS AND METHODS

This study is in two phases. The first phase of the study (P1) is a feasibility study which was approved as compassionate use and designed as a single-arm, open-label trial conducted from 2016 to 2018 for patients with International Cartilage Repair Society (ICRS) grade 3 knee articular defects. The primary objective of our PI study was to assess the feasibility and safety of our intra-articular injection of Chondrocell-EX, with a secondary objective to assess the clinical and functional improvement of patients at 1-, 3-, 6-, and 12-month post-infusion.

The second phase of this study (PII) was designed as a prospective, randomized, open-label trial involving patients with ICRS grade 3 or 4 knee cartilage injury due to trauma or osteoarthritis (PII). Both studies were conducted at Hospital Canselor Tuanku Muhriz, Universiti Kebangsaan Malaysia (HCTM-UKM).

Criteria for Eligibility of Patients

In the PI study, patients were included if they had ICRS Grade 3 chondral knee injuries with cartilage defects larger than 2.5 cm² confirmed by arthroscopy, a VAS pain score above 3/10, normal blood parameters, including kidney and liver function, and were able to follow the post-operative rehab program. Exclusion criteria included autoimmune or inflammatory joint diseases, serious comorbidities, immunosuppressive drug use within six weeks, underlying knee ligament instability, significant malalignment, smoking, alcohol abuse, or a history or risk of neoplasia.

In the PII study, eligible patients were aged 18–50, with ICRS Grade 3 or 4 lesions of at least 1.0 cm², and symptoms such as swelling, pain, stiffness, or mechanical dysfunction. Patients were excluded if they had limb deformities over 10° varus or valgus, BMI ≥ 30, recent intra-articular hyaluronic acid (HA) or steroid injections (within three months), or other conditions deemed high-risk by the investigator.

Sample Size Determination

The sample size for the PII study was calculated using a formula from previous literature (Saw et al. 2013). Based on prior data, with a standard deviation (S) of 12.56 and a detectable mean difference (D) of 7.68 and using a significance level of 0.05 with 80% power, the constant (C) was set at 7.85. A minimum of 23 patients per group was required. Accounting for a 10% dropout rate, the target sample size was 25 per group (N = 50). However, due to COVID-19 restrictions, only 28 patients were successfully recruited.

Treatment Groups

In the PI study, all patients received a single intra-articular injection of 25 million cells (25×10^6) one week after undergoing a microfracture procedure. Additionally, patients were administered 2 ml of HA at 2-week intervals over four weeks, including the day of Chondrocell-EX injection.

In the PII study, patients were randomly assigned to two arms: Arm A (Chondrocell-EX+HA) and Arm B (BMAC+HA-S). Permuted block randomisation was generated using Microsoft Excel, and the sequence was concealed in sealed, opaque envelopes prepared by personnel not involved in recruitment. After enrolment, the investigator notified Cytopeutics, who opened the next envelope and assigned the patient to Arm A (Chondrocell-EX + HA) or Arm B (BMAC + HA-S). All patients underwent arthroscopic debridement prior to receiving their assigned treatment. For those patients in Arm B who refused or were unable to undergo BMAC and those patients whose cartilage defects were too large for HA-S treatments, the principal investigator can allow them to Arm A.

Preparation and Administration of Chondrocell-EX+HA (PI & PII: Arm A)

Chondrocell-EX was derived from umbilical cords of full-term, healthy infants with written parental consent. Donors underwent three generational screening for genetic, infectious, and hereditary conditions.[7,13-14] Samples were processed in a GMP-certified laboratory in Cyberjaya, Malaysia, following national stem cell research guidelines. MSCs were isolated through enzymatic digestion and cultured under standard conditions using a proprietary medium. Non-adherent cells were removed after three days,

and adherent MSCs were expanded to the desired quantity. Early-passage cells were cryopreserved for future use, and quality control included immunophenotyping, differentiation assays, and contamination testing. Details of the preparation of the cells were explained in previous literature.[7,13-14]

On the treatment day, the final cell preparation, involving thawing, washing, and suspension of 25-30 x 10^6 viable cells resuspended in 2 mL of saline, was conducted at the treatment center. Under local anesthesia, Chondrocell-EX was injected into the intra-articular route space, followed by 2 mL of HA (Orthovisc, Anika Therapeutics).

Preparation and Administration of BMAC+HA-S (PII: Arm B)

Briefly, under spinal or general anesthesia, a total of 5 mL of BMAC was extracted from the patient's posterior iliac crest using the Marrow Cellution system (Aspire Medical Innovation, Munich, Germany). A HA-S known as Hyalofast® (Fidia Advanced Biopolymers, Abano Terme, Italy) was utilized as a supporting framework for the 5 mL of cells from the Marrow Cellution. Marrow Cellution-filled Hyalofast® was positioned within the knee cartilage defects. The stability of the implanted stamps was assessed from flexion to extension using an arthroscope.

Outcome Measures

Primary Outcomes

The primary endpoints of our PI study, which were the safety assessments, included both local joint evaluation (pain at the site, persistent bleeding, knee swelling, difficulty moving the knee, and signs of infection) and basic systemic monitoring such as temperature and screening for fever, hypersensitivity, or other systemic symptoms. Assessments were performed at baseline, 1, 3, 6, and 12-months. Following that, the PII primary endpoints were based on clinical and functional assessments using the following tools: pain visual analog scale (VAS) and symptoms and functional Knee Injury and Osteoarthritis Outcome Score (KOOS) function score.

Secondary Outcomes

The PI secondary endpoints were VAS and KOOS scores, which assessed treatment efficacy in terms of symptoms and functional outcomes. Additionally, second-look arthroscopy and histological evaluations using Hematoxylin and Eosin (H&E) and Safranin-O staining were performed to assess overall tissue morphology, proteoglycan distribution, and glycosaminoglycan content of the cartilage. The OARSI histopathological grading system was employed for H&E staining assessment, meanwhile immunohistochemical (IHC) staining for collagen type I and collagen type II was evaluated semi-quantitatively using the immunoreactive score (IRS) method, a widely used and established approach for assessing IHC expression.[15-16]

In the PII, secondary endpoints included arthroscopic evaluations, which were conducted at baseline and at 12 months to assess cartilage lesions and regeneration in randomized patients from Arms A and B, whenever feasible. The biopsy samples for histological and immunohistochemical evaluation were obtained only from patients who consented to undergo second-look arthroscopy evaluation at 12 months. No routine biopsies were taken from patients who declined to do the procedure. Additionally, all reported adverse events and serious adverse events were documented and closely monitored throughout the study period.

Statistical Analysis

Descriptive data were presented as the mean (standard deviation [SD]), median (interquartile range [IQR]), and frequency (%). A t-test or Mann-Whitney test was used for between-group comparison, while a repeated measure ANOVA with Bonferroni correction for multiple comparison was used for pre- and post-treatment analysis. To account for significant baseline differences among patients following group reassignment in the PII study, age- and baseline VAS-adjusted analyses were performed using ANCOVA to evaluate outcome measures. All data were analyzed using SPSS ver. 27 (SPSS, Inc., Chicago, IL, USA), and a p-value < 0.05 was considered statistically significant. Outcome assessments were performed by the study investigators independently of sponsor involvement. Statistical analyses were conducted by independent biostatistician.

Ethics approval and consent to participate

This study was approved by UKM Research Ethics Committee (PI: UKM PPI/111/8; PII: UKM PPI/111/8/JEP-2019-304). The PII study was registered in the National Institute of Health registry of Clinical Trials (NCT05016011) and the National Medical Research Register of Malaysia (NMRR-19-54-46020). The study was conducted in accordance with the declaration of Helsinki and the Good Clinical Practice (GCP) Guidelines. Written informed consent was obtained from all participants before they enrolled as per Good Clinical Practice (GCP) Guidelines.

RESULTS

Demographics and Other Baseline Characteristics

Our PI feasibility study involved six women (mean age of 47 ± 6 years). Two patients each were classified as normal weight, overweight, and obese, respectively. The mean duration of knee pain prior to recruitment was 53 weeks (range: 3–96 weeks). All patients had previously undergone at least three months of standard management such as IA HA injections, rest, physiotherapy, and medications for pain relief. All patients completed the full 12-month follow-up period.

In our PII randomized controlled trial, 31 patients with knee cartilage injuries were initially screened for eligibility. Of these, three patients withdrew consent prior to treatment, resulting in a final cohort of 28 participants. Patients were randomized into two groups: Chondrocell-EX+HA (Arm A) and BMAC+HA-S (Arm B). Initially, 13 patients were assigned to Arm B; however, due to the lesion sizes being too large for HA-S treatment, two patients were reallocated to Arm A. As a result, Arm A included 17 patients and Arm B included 11 patients (Figure 1). These patients were analysed in the arm corresponding to the treatment they received as the reassignment happen before they received any treatment.

Table I: Baseline demographics of the study participants (N=34)

Variables	PI	PII		p-value*
	Chondrocell-EX+HA (n=6)	Chondrocell-EX+HA (n = 17)	BMAC+HA-S (n = 11)	
Age, years (mean ± SD)	47 ± 6	46 ± 10	38 ± 9	0.04
Sex				0.41
Male	0 (0.0)	4 (23.5%)	5 (45.5%)	
Female	6 (100.0%)	13 (76.5%)	6 (54.5%)	
BMI, kg/m^2 (mean ± SD)	27.11 ± 4.07	29.33 ± 6.76	28.94 ± 4.20	0.87
KOOS (mean ± SD)	46.49 ± 11.51	37.29 ± 12.28	46.27 ± 12.32	0.07
VAS (mean ± SD)	6.83 ± 0.98	7.29 ± 1.11	6.27 ± 1.35	0.022
Diagnosis				0.26
Chondral injury	-	14 (82.4%)	11 (100%)	
Osteoarthritis	6 (100.0%)	3 (17.6%)	0	

*Comparison between groups in PII (Chondrocell-EX+HA compared with BMAC+HA-S)

This resulted in the patients in Arm A being older and with a higher pain VAS score at baseline compared to Arm B (Table I and Figure 2)

Table I shows baseline demographics and characteristics for the patients. Patients in PII Arm A receiving Chondrocell-EX+HA were much older and, in more pain, based on VAS. The baseline differences observed between groups can be attributed to patient reassignment following randomization due to ineligibility for the HA scaffold procedure based on lesion conditions. No differences were observed in other baseline characteristics of patients between arms.

Safety

A total of 6 injections of Chondrocell-EX+HA. were administered in PI, and 17 injections were given in PII. Additionally, 11 administrations of BMAC+HA-S were performed for patients in Arm B of the PII. In the PI study, three out of six patients showed a minimal degree of knee effusion and swelling up to 1-month post-procedure, but resolved afterwards, and no further side effects were reported from the 3-month mark through the 12-month follow-up (Supplementary Table 1). No side effects were reported following Chondrocell-EX injections in the PII study throughout the entire 12-month follow-up period.

Efficacy

Clinical Outcomes

Visual Analog Scale (VAS) & Knee Injury and Osteoarthritis Outcome Score (KOOS)

Our PI study showed nearly no change in pain scores at 1 month. It demonstrated a significant reduction in pain scores from 3-month post-treatment, with mean VAS scores decreasing from a baseline of 6.83 ± 0.98 to 4.83 ± 1.17 (p<0.01). This reduction persisted at subsequent time points, with scores further declining to 3.00 ± 0.00 at 6 months and 1.83 ± 0.75 at 12 months (both p<0.01). In the PII study, mean VAS score in Arm A (Chondrocell-EX+HA) decreased consistently from baseline (7.21 ± 1.05) to 12-month post treatment (2.00 ± 1.11), with all follow-up time points showing significant reductions compared with baseline (all p < 0.001). In Arm B, VAS scores also declined from baseline (6.30 ± 1.42) to 12-month post treatment (2.50 ± 1.35). However, significant reduction can only be observed from 3-month onwards. Additionally, between-group comparison using age-adjusted analysis showed no significant differences in VAS at 1- and 3-month post treatment with Arm A (Chondrocell-EX+HA) group demonstrated significantly lower VAS scores compared with the Arm B (BMAC+HA-S) at 6-month (2.56 ± 1.41 vs 3.09 ± 1.22; p = 0.015) and 12-month (2.27 ± 1.49 vs 2.50 ± 1.35; p = 0.043).

In term of functional outcomes, KOOS scores in PI study significantly improved from 59.50 ± 3.56 at 3-month to 69.69 ± 6.14 at 6-month, reaching 85.83 ± 11.87 at 12-month (all p<0.01). In the PII study, when comparing with baseline, both groups demonstrated a significant improvement in KOOS scores over time (both p < 0.001). In the Arm A (Chondrocell-EX+HA) group, mean KOOS increased from 38.4 ± 12.7 at baseline to 66.1 ± 14.7 at 3-month, 72.0 ± 13.5 at 6-month, and 73.7 ± 19.2 at 12-month, with all improvements from 3-month onwards being statistically significant (p < 0.001). Similarly, Arm B (BMAC+HA-S) showed a significant change in KOOS over time (p < 0.001), with mean scores increasing from 45.8 ± 12.9 at baseline to 65.4 ± 12.6 at 6-month and 69.4 ± 12.3 at 12-month with the improvements were statistically significant only at 6- and 12-month. After adjustment for age and baseline VAS, there were no significant differences in KOOS scores between both groups at baseline, 1-month, or 3-month. However, Arm A (Condrocell-EX+HA) demonstrated significantly higher adjusted KOOS scores compared with Arm B at 6-month (p = 0.009) and 12-month (p = 0.037).

This mirrors the PII study where a significant improvements can be seen in Arm A KOOS subdomains of symptoms and stiffness (3-month: 80.4 ± 12.4, p=0.005; 6-month: 82.2 ± 16.1, p<0.001; 12-month: 85.5±14.3 p<0.001), ADL (3-month: 77.0±13.3, p=0.008; 6-month: 81.4±12.0 p<0.001; 12-month: 85.4±11.4, p= p<0.001), pain (3-month: 73.1±15.8, p=0.001; 6-month: 78.5±14.2, p<0.001; 12-month: 85.5±12.4, p<0.001) and QoL (3-month: 53.1±18.7, p<0.001; 6-month: 54.5±20.6, p<0.001; 12-month: 56.5±22.3, p<0.001). Meanwhile sports and recreation showed delayed gains, with significant changes only after 6-month (55.0 (32.5,70.0), p=0.003)

In contrast to Arm A, Arm B showed significant improvement only in QoL (3-month: 44.9±19.1, p=0.038; 6-month: 48.9±12.1, p=0.004; 12-month: 50.6±16.0, p=0.001), pain (12-month: 78.9±13.0, p=0.017) and sport and recreation (12-month: 52.5 (38.8,61.3, p=0.047).

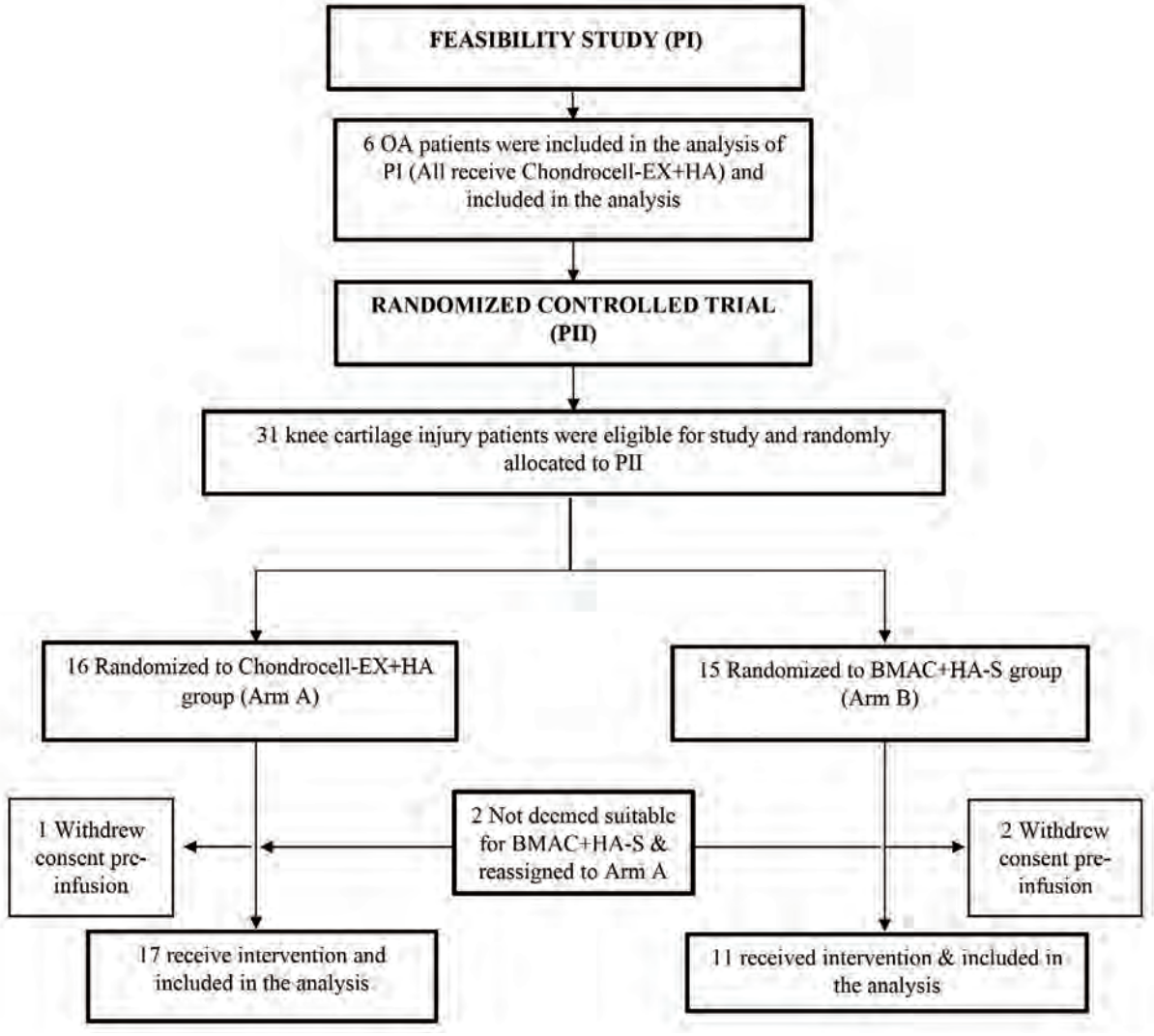


Fig. 1: Patients disposition

Between-group comparisons of KOOS subdomains were assessed using ANCOVA adjusted for age and baseline VAS. Significant difference can be observed in all of subdomains at different time point such as symptoms and stiffness subdomains showed significant differences at 6-month (p=0.037), pain subdomain at 6-month (p=0.002), ADL at 3-month (p=0.001) and 6-month (p=0.018), sport and recreation at 6-month (p=0.030) and 12-month (p=0.024) and QoL at 12-month (p=0.022). The significant differences observed in all of these subdomains were favouring Arm A compared to Arm B as Arm A showed greater improvement compared to Arm B. Details of the scores, 95% CI, effect size (Cohen'f) and p-value were provided in Supplementary Table 2-8.

Structural Outcomes

Second-look arthroscopy was performed on consented patients who had been informed about the purpose of the procedure. In our PI study, all patients showed more than 90% area of coverage with similar integrity to the non-injured cartilage surface area (Figure 3a and b) during second-look arthroscopy.[12] In our PII study, although initial lesions on the counterface area among patients in both arms were healed, patients in Arm A (Figure 3c and d) had larger lesions and exhibited improved healing of articular cartilage lesions without any incorporation of scaffold, compared to those in Arm B (Figure 3e and f). This apparent recovery eliminated the need for further invasive treatment.

Histological (H&E) & Immunohistochemical Staining Evaluation

Representative histological images of the regenerated cartilage sample post-treatment from our PI feasibility study are shown in Figure IV. H&E staining (Figure 4 A & B) of the articular cartilage biopsy specimen showed changes in the contour of the articular surface with notable bone remodelling at the articular surface. Safranin-O staining exhibited hyperchromatic and metachromatic staining, which indicates the presence of matrix proteoglycans.

The regenerated cartilage samples obtained from the five consented patients in the PI study were also stained for type I and type II collagen via immunohistochemical staining (Figure 4 C & D). Results showed that the tissues were

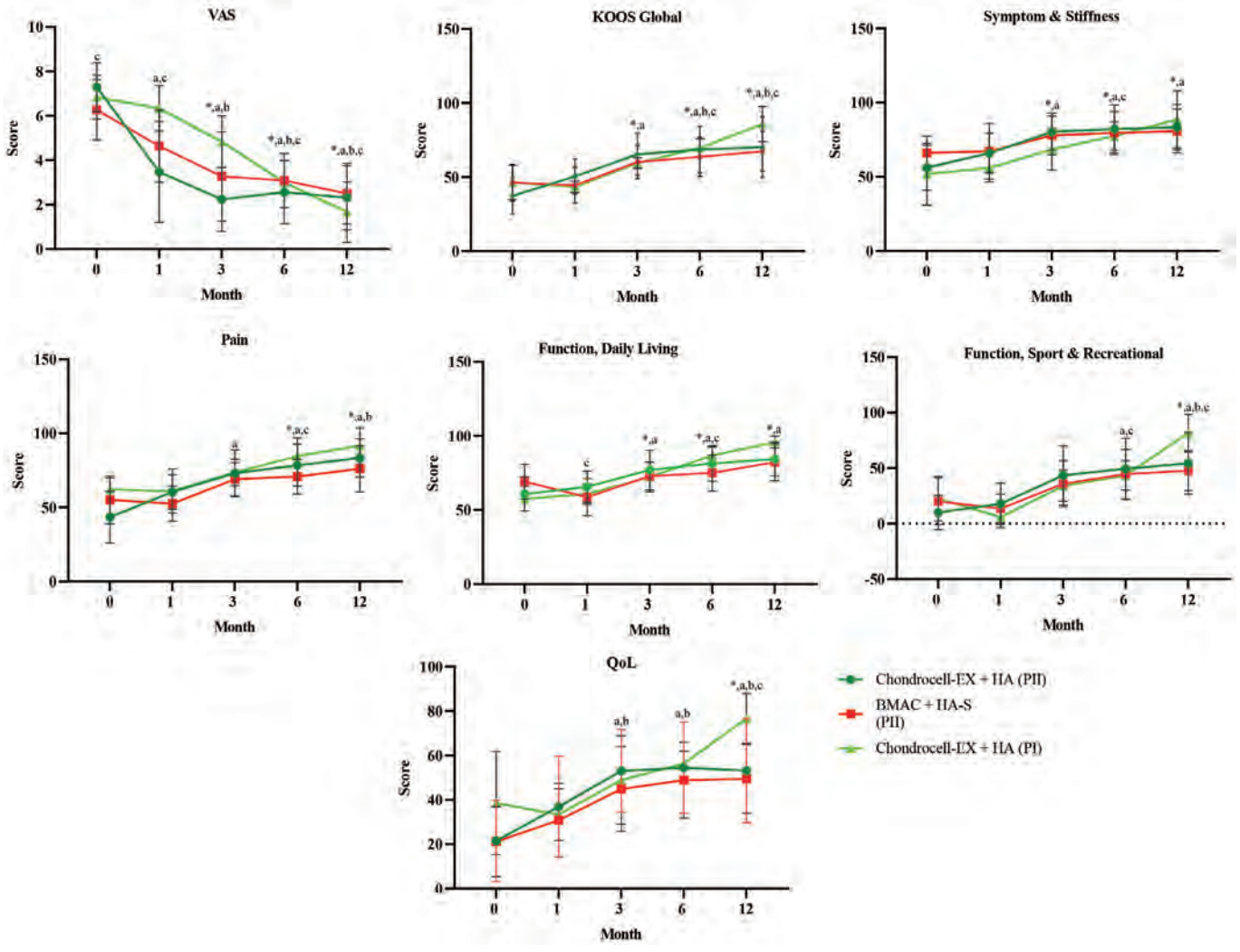


Fig. 2: Comparison of VAS, KOOS and KOOS subdomain of all patients in PI and PII throughout 12-months follow-up. p<0.05 is considered significant [*=from baseline in PI; a= from baseline in Arm A (PII); b= from baseline in Arm B (PII); c=between arms (PII)]

positively stained for type II collagen, with over 75% of the area showing positivity, whereas only foci and weak staining was observed for type I collagen. These results indicated a hyaline cartilage formation rather than fibro-cartilage formation.

DISCUSSION

Current treatments for severe knee cartilage injuries or lesions, including nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and viscosupplements such as HA, are primarily aimed at providing symptomatic relief rather than cartilage repair and regeneration. While autologous chondrocyte implantation (ACI) promotes hyaline-like cartilage regeneration, it has drawbacks such as the need for cell harvesting, reduced efficacy in older patients, and donor site morbidity.[15,17] Consequently, BMAC, especially with HA-based scaffolds like Hyalofast® has become a more accepted cell-based therapy for knee cartilage injuries and osteoarthritis.[18-19] BMAC provides more sustained benefits than HA alone, with clinical improvements becoming more evident beyond 12 months.[19-20] However, as an autologous therapy, it requires bone marrow aspiration, which adds procedural risk and patient discomfort. It's also unsuitable for larger lesions and shows variability in stem cell yield influenced by patient characteristics such as gender, age and health, harvest site, and technique.[21-23] Since the beneficial effects of BMAC is linked to its MSC content, this variability often translates into inconsistent clinical outcomes.[22]

A recent meta-analysis of 15 studies (n = 585) found MSCs significantly improved outcomes; BM-MSCs were superior in pain and ROM, while hUC-MSCs excelled in overall function.[20,24] While these findings highlight the therapeutic potential of hUC-MSCs, to date, no study has directly compared allogeneic hUC-MSCs with established cell-based therapies such as HA, PRP, or BMAC. Our present study addressed this important gap by comparing Chondrocell-EX, an allogeneic hUC-MSC product, to BMAC, a widely used autologous cell-based therapy.

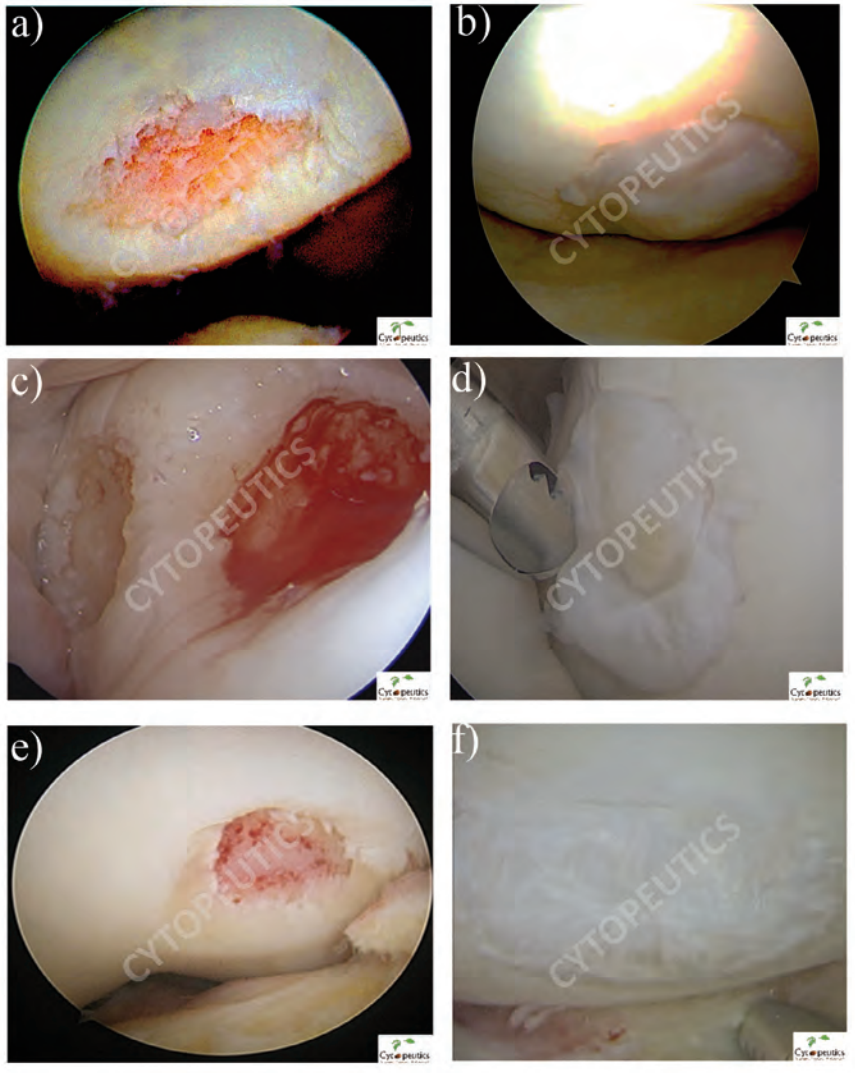


Fig. 3: PI: a) severe cartilage erosion with underlying exposed bone at baseline in PI and b) corresponding cartilage regeneration following treatment with Chondrocell-EX at 12 months follow-up. PII: c) Before Chondrocell-EX: Multiple, large cartilage lesions with complete absence of articular cartilage. d) After Chondrocell-EX: Formation of regenerated cartilage; white smooth surface and firm hyaline-like cartilage which covers the majority of cartilage defects (without HA-S). e) Before BMAC+HA-S: Single, small lesion with nearly complete absence of articular cartilage. f) After BMAC+HA-S: Formation of white regenerated cartilage covering the lesion (HA-S applied). No hypertrophy or abnormal calcification was identified in either of the arms.

Allogeneic hUC-MSCs offer a safe and consistent cell source for cartilage repair, further revolutionizing knee cartilage lesion treatment. Preclinical and clinical studies have demonstrated the safety and efficacy of intra-articular MSC injections, showing benefits such as pain reduction, functional improvement, and cartilage volume gain.[12,25-26] However, most studies have focused on bone marrow-derived MSCs, and clinical evidence specifically for hUC-MSCs in knee cartilage repair remains limited.[27]

The promising results observed in our PI study that showed significant improvements in VAS scores and KOOS functional outcomes, along with evidence of hyaline cartilage regeneration on arthroscopy, histology, and immunohistochemical staining have prompted us to further investigate these findings in our PII study. However, considering the prolonged rehabilitation period required after microfracture that delayed patient recovery, the microfracture procedure was excluded from our PII study protocol. In fact, in the PI study, pain reduction was only significant after 3 months post-Chondrocell-EX administration, likely due to the microfracture procedure performed a week prior. This delayed recovery aligns with previous findings that reported increased immobility, pain, and stiffness when MSCs were injected following microfracture.[28]

The PII study compared Chondrocell-EX+HA with BMAC+HA-S in patients with severe knee cartilage injuries. BMAC was harvested using Marrow Cellution, known for yielding higher-purity bone marrow.[3] Hyalofast®, a biodegradable HYAFF-based scaffold, was used with BMAC to support cell attachment and tissue regeneration and is an established, cost-effective option for cartilage repair.[19,29,30] Meanwhile, UC-

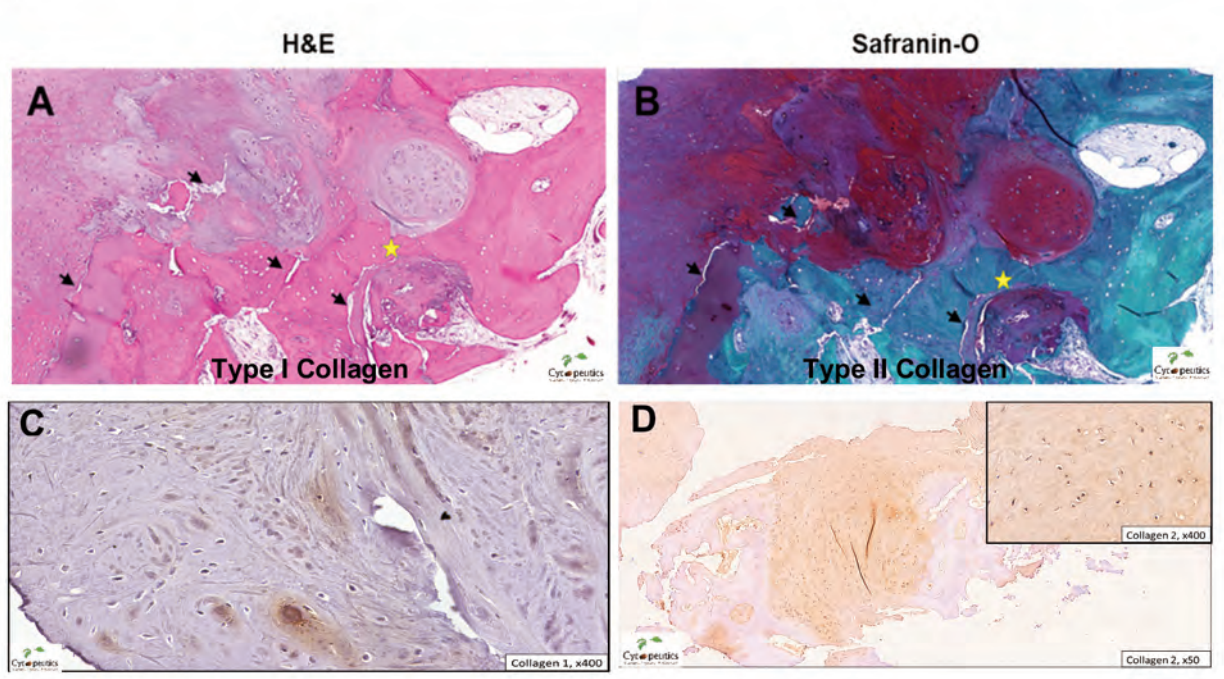


Fig. 4: Microscopic examination of a similar area reveals chondroid-rich cartilage samples post-treatment with Chondrocell-EX in A) H&E (100x), where the cartilage is stained red with Safranin-O (B) (100x). Immunohistochemical studies show that C) only a few foci of the arthroscopic biopsy are stained with type I collagen (400x), compared to D) more areas are stained with type II collagen (50x). These findings correspond to hyaline cartilage formation post-treatment with Chondrocell-EX

MSCs combined with HA have been used clinically – such as in Cartistem®, approved in 2012 with evidence showing that the combination slows cartilage degradation more effectively than HA alone.[31-32] To our knowledge, this is the first study directly comparing UC-MSCs with an active CE-marked comparator therapy widely approved in Europe and Asia.[33] Regarding the safety of Chondrocell-EX, minor side effects were observed in the PI study, that was mainly due to the microfracture, with three out of six patients experiencing mild knee effusion and swelling that resolved within a month. No major adverse events occurred beyond three months. In the PII study, no side effects were reported in either treatment arm throughout the 12-month follow-up. These findings support the safety of intra-articular UC-MSC injections, consistent with previous reviews reporting MSC therapies as generally safe.[27,34] The mild stiffness and swelling observed paralleled previous studies that observed only minor and non-significant side effects.[35] Furthermore, a 7-year follow-up study reported no long-term adverse effects after MSC injection.[31] Collectively, these results reinforce the favourable safety profile of Chondrocell-EX for knee cartilage repair.

Although the study used randomization, there were baseline differences between groups in the PII study, particularly in pain severity, patient age, and lesion size. These differences occurred because some patients were reassigned when their lesion characteristics were unsuitable for the BMAC+HA-S procedure. Despite being older and presenting with more severe pain, patients treated with Chondrocell-EX+HA showed significant pain improvement as early as one month, based on VAS score, compared with patients treated with BMAC+HA-S that only showed significant pain reduction after 3-months. This could be explained by the consistent quality and quantity of allogeneic UC-MSCs, which are derived from younger cells, do not require bone marrow aspiration, and avoid the variability in stem cell yield often observed with autologous BMAC sources.[13,21,23] Similar findings have been reported in several meta-analyses, where MSCs demonstrated pain reduction, although typically observed around six months post-treatment.[36-38] In addition to pain relief, patients treated with Chondrocell-EX with HA also experienced earlier and greater improvement in KOOS and its subdomain such as symptom and stiffness, ADL and QoL, compared to those receiving BMAC+HA-S. Cartilage regeneration was assessed via arthroscopy at baseline and 12 months. In the PI study, all six patients showed over 90% cartilage coverage after treatment with Chondrocell-EX.[12] Similar improvements were seen in both arms of the PII study, with smooth, hyaline-like cartilage covering most defects. Notably, patients in the Chondrocell-EX+HA group were generally older and had larger or multiple lesions in which HA-S use was less practical. Despite this, Chondrocell-EX still resulted in complete cartilage regeneration, as confirmed by arthroscopic evaluation.

Histological analysis confirmed type II collagen expression and increased proteoglycan content, indicating active tissue regeneration. This may be attributed to the production of ECM molecules, as well as the paracrine and anti-inflammatory effects of the treatment.[8] The immunomodulatory properties of Chondrocell-EX have also been reported.[7] The observed improvements in the Chondrocell-EX arm are particularly noteworthy, as they

were achieved through a minimally invasive approach involving a simple intra-articular injection. This contrasts with the more invasive BMAC+HA-S treatment, which requires bone marrow aspiration as well as an arthroscopy procedure that introduces additional complexity, risks, and recovery time. While achieving results equivalent or non-inferior to existing treatments would have been a significant outcome in itself, the better results demonstrated by Chondrocell-EX further emphasize its efficacy and clinical feasibility. Furthermore, Chondrocell-EX applies to patients with larger and more severe lesions, as well as older patients, who often present greater treatment challenges. This makes Chondrocell-EX a promising option, particularly in clinical settings where such patient populations require effective yet less invasive solutions.

Our study has certain limitations. These include the absence of data on important structural factors that may affect cartilage healing and clinical outcomes, such as limb alignment, lesion size or depth, and Kellgren-Lawrence grading for osteoarthritis, which may hinder a full understanding of treatment effectiveness. Secondly, baseline differences in age, VAS, and lesion complexity occur because of patients that were reassigned from the BMAC+HA-S arm to the Chondrocell-EX+HA arm when their lesions were deemed unsuitable for scaffold treatment. Although adjusted analyses were performed to mitigate these imbalances, this reassignment itself represents a limitation. Had those patients remained in Arm B, their unsuitability would have been considered treatment failure and would have lowered the efficacy estimate for BMAC+HA-S. By reassigning them to Arm A, the observed differences between groups were reduced, masking what may have been a larger treatment benefit favouring Chondrocell-EX. In addition, analyses were conducted on a per-protocol basis, which should be considered when interpreting the results. Besides that, the 12-month follow-up restricts the ability to determine the long-term durability of the regenerated cartilage. Nevertheless, previous international MSC studies have reported sustained clinical improvement for up to five years and maintained function with high survival rates up to nine years, suggesting the potential for longer-term benefit.[39-40] Finally, histological evaluation was only performed in patients who consented to second-look arthroscopy, and biopsy samples were limited to accessible, well-healed lesions, which may introduce selection bias. Nevertheless, the consistent clinical and arthroscopic improvement observed across multiple outcome measures supports the strength of our findings.

CONCLUSION

In conclusion, the present study demonstrated the safety, feasibility, and efficacy of Chondrocell-EX, which has potential for earlier pain improvement and functional gains compared to the commercially available cell-based therapy for severe knee cartilage injury. Despite using a minimally invasive intra-articular injection, findings of this study suggested that Chondrocell-EX was associated with earlier pain improvement, faster and sustained functional recovery, and showed evidence of hyaline-like cartilage regeneration, with predominant expression of collagen type II hyaline cartilage, even in older patients with multiple large cartilage injuries.

CONFLICT OF INTEREST

Sze-Piaw Chin advises Cytopeutics Sdn Bhd on regulatory, clinical and research activities. Soon-Keng Cheong sits on the medical advisory board. Nik Syazana Izyan Saffery and Muhammad Fahmi Yakop are the research project coordinators at Cytopeutics Sdn Bhd.

ACKNOWLEDGEMENTS

We would like to express our gratitude to Hospital Canselor Tuanku Muhriz Universiti Kebangsaan Malaysia (HCTM-UKM) for helping us conduct the study.

FUNDING

This study was supported by an unconditional research grant from Cytopeutics Sdn Bhd.

REFERENCES

1. Krych AJ, Saris DB, Stuart MJ, Hacken B. Cartilage injury in the knee: Assessment and treatment options. JAAOS-Journal of the American Academy of Orthopaedic Surgeons. 2020; 28(22): 914-22.
2. Al Maini M, Al Weshahi Y, Foster HE, Chehade MJ, Gabriel SE, Saleh JA, et al. A global perspective on the challenges and opportunities in learning about rheumatic and musculoskeletal diseases in undergraduate medical education: White paper by the world forum on rheumatic and musculoskeletal diseases (wfrmd). Clinical rheumatology. 2020; 39: 627-42.
3. Caradonna E, Mormone E, Centritto EM, Mazzanti A, Papini S, Fanelli M, et al. Different methods of bone marrow harvesting influence cell characteristics and purity, affecting clinical outcomes. JVS-Vascular Science. 2023; 4: 100130.
4. Wiggers TG, Winters M, Van den Boom NA, Haisma HJ, Moen MH. Autologous stem cell therapy in knee osteoarthritis: A systematic review of randomised controlled trials. British Journal of Sports Medicine. 2021; 55(20): 1161-9.
5. Centeno CJ, Busse D, Kisiday J, Keohan C, Freeman M, Karli D. Increased knee cartilage volume in degenerative joint disease using percutaneously implanted, autologous mesenchymal stem cells. Pain physician. 2008; 11(3): 343.
6. Kuebler D, Schnee A, Moore L, Kouri J, McLaughlin A, Hanson R, et al. Short-term efficacy of using a novel low-volume bone marrow aspiration technique to treat knee osteoarthritis: A retrospective cohort study. Stem Cells International. 2022; 2022(1): 5394441.
7. Chin SP, Mohd-Shahrizal MY, Liyana MZ, Then KY, Cheong SK. High dose of intravenous allogeneic umbilical cord-derived mesenchymal stem cells (clv-100) infusion displays better immunomodulatory effect among healthy volunteers: A phase 1 clinical study. Stem Cells Int. 2020; 2020: 8877003.
8. Tai L, Saffery NS, Chin SP, Cheong SK. Secretome profile of tnf-α-induced human umbilical cord mesenchymal stem cells unveils biological processes relevant to skin wound healing. Regenerative Medicine. 2023; 18(11): 839-56.
9. Jeon H-J, Yoon K-A, An ES, Kang T-W, Sim Y-B, Ahn J, et al. Therapeutic effects of human umbilical cord blood-derived mesenchymal stem cells combined with cartilage acellular matrix mediated via bone morphogenic protein 6 in a rabbit model of articular cruciate ligament transection. Stem Cell Reviews and Reports. 2020; 16(3): 596-611.
10. Levy O, Kuai R, Siren EM, Bhere D, Milton Y, Nissar N, et al. Shattering barriers toward clinically meaningful msc therapies. Science advances. 2020; 6(30): eaba6884.
11. Chin SP, Wazir NN, Cheok CY, Wong CY, Then KY, Cheong SK. Intra articular injection of autologous bone marrow-derived mesenchymal stromal cells in patients with moderate to severe osteoarthritis. Cytotherapy. 2013; 15(4): S5.

12. Yusoff BM, Ramlan M, Chin S, Mohamad N, Cheong S, Noor MMA, et al. Arthroscopic evidence of cartilage regeneration in severe knee cartilage defects and osteoarthritis following treatment with allogeneic umbilical cord-derived mesenchymal stromal cells (chondrocell-ex). Cytotherapy. 2019; 21(5): S88-S9.
13. Chin S-P, Poey AC, Wong C-Y, Chang S-K, Teh W, Mohr TJ, et al. Cryopreserved mesenchymal stromal cell treatment is safe and feasible for severe dilated ischemic cardiomyopathy. Cytotherapy. 2010; 12(1): 31-7.
14. Chin S-P, Poey AC, Wong C-Y, Chang S-K, Tan C-S, Ng M-T, et al. Intramyocardial and intracoronary autologous bone marrow-derived mesenchymal stromal cell treatment in chronic severe dilated cardiomyopathy. Cytotherapy. 2011; 13(7): 814-21.
15. Pritzker KP, Gay S, Jimenez S, Ostergaard K, Pelletier J-P, Revell P, et al. Osteoarthritis cartilage histopathology: Grading and staging. Osteoarthritis and cartilage. 2006; 14(1): 13-29.
16. de Gooyer JM, Versleijen-Jonkers YM, Hillebrandt-Roeffen MH, Frielink C, Desar IM, de Wilt JH, et al. Immunohistochemical selection of biomarkers for tumor-targeted image-guided surgery of myxofibrosarcoma. Scientific Reports. 2020; 10(1): 2915.
17. Matricali GA, Dereymaeker G, LUytEn FP. Donor site morbidity after articular cartilage repair procedures: A review. Acta orthopaedica Belgica. 2010; 76(5): 669.
18. Ebert JR, Edwards PK, Fallon M, Ackland TR, Janes GC, Wood DJ. Two-year outcomes of a randomized trial investigating a 6-week return to full weightbearing after matrix-induced autologous chondrocyte implantation. The American journal of sports medicine. 2017; 45(4): 838-48.
19. Gobbi A, Whyte GP. One-stage cartilage repair using a hyaluronic acid–based scaffold with activated bone marrow–derived mesenchymal stem cells compared with microfracture: Five-year follow-up. The American journal of sports medicine. 2016; 44(11): 2846-54.
20. Pabinger C, Lothaller H, Kobinia GS. Intra-articular injection of bone marrow aspirate concentrate (mesenchymal stem cells) in kl grade iii and iv knee osteoarthritis: 4 year results of 37 knees. Scientific Reports. 2024; 14(1): 2665.
21. Jeyaraman M, Bingi SK, Muthu S, Jeyaraman N, Packkyarathinam RP, Ranjan R, et al. Impact of the process variables on the yield of mesenchymal stromal cells from bone marrow aspirate concentrate. Bioengineering. 2022; 9(2): 57.
22. Chahla J, Mannava S, Cinque ME, Geeslin AG, Codina D, LaPrade RF. Bone marrow aspirate concentrate harvesting and processing technique. Arthroscopy Techniques. 2017; 6(2): e441-e5.
23. Allahabadi S, Jawanda H, Khan ZA, Brusalis CM, Chahla J, Cole BJ, et al. Bone marrow aspirate concentrate harvest techniques for the sports medicine surgeon. Arthroscopy Techniques. 2024; 13(2): 102850.
24. Chen X, Zheng J, Yin L, Li Y, Liu H. Transplantation of three mesenchymal stem cells for knee osteoarthritis, which cell and type are more beneficial? A systematic review and network meta-analysis. Journal of orthopaedic surgery and research. 2024; 19(1): 366.
25. Lau S, Chin S, Mansor N, Umran N, Ajat M, Arfuzir NN, et al. Mesenchymal stem/stromal cells: Cytopeutics® human umbilical cord-derived mesenchymal stem cells (chondrocell-ex) prevented cartilage degradation and improved bone microarchitecture in a rat model of osteoarthritis. Cytotherapy. 2023; 25(6): S47-S8.
26. Ishak-Samrin M, Naina-Mohamed I, Zulfarina MS, Abdul Wahid SF, Mohd Don AF, Mohamad N, et al. Treatment of knee osteoarthritis and chondral injury with umbilical cord/wharton's jelly-derived mesenchymal stem cells: A systematic review of safety and efficacy. Journal of Functional Biomaterials. 2025; 16(3): 84.
27. Xiang X-N, Zhu S-Y, He H-C, Yu X, Xu Y, He C-Q. Mesenchymal stromal cell-based therapy for cartilage regeneration in knee osteoarthritis. Stem cell research & therapy. 2022; 13: 1-20.
28. Venosa M, Calafiore F, Mazzoleni M, Romanini E, Cerciello S, Calvisi V. Platelet-rich plasma and adipose-derived mesenchymal stem cells in association with arthroscopic microfracture of knee articular cartilage defects: A pilot randomized controlled trial. Advances in Orthopedics. 2022; 2022(1): 6048477.
29. Gobbi A, Whyte GP. Long-term clinical outcomes of one-stage cartilage repair in the knee with hyaluronic acid–based scaffold embedded with mesenchymal stem cells sourced from bone marrow aspirate concentrate. The American journal of sports medicine. 2019; 47(7): 1621-8.
30. Gobbi A, Scotti C, Karnatzikos G, Mudhigere A, Castro M, Peretti GM. One-step surgery with multipotent stem cells and hyaluronan-based scaffold for the treatment of full-thickness chondral defects of the knee in patients older than 45 years. Knee Surgery, Sports Traumatology, Arthroscopy. 2017; 25: 2494-501.
31. Park Y-B, Ha C-W, Lee C-H, Yoon YC, Park Y-G. Cartilage regeneration in osteoarthritic patients by a composite of allogeneic umbilical cord blood-derived mesenchymal stem cells and hyaluronate hydrogel: Results from a clinical trial for safety and proof-of-concept with 7 years of extended follow-up. Stem cells translational medicine. 2017; 6(2): 613-21.
32. Park Y-B, Lee H-J, Nam H-C, Park J-G. Allogeneic umbilical cord-blood-derived mesenchymal stem cells and hyaluronate composite combined with high tibial osteotomy for medial knee osteoarthritis with full-thickness cartilage defects. Medicina. 2023; 59(1): 148.
33. Riff AJ, Davey A, Cole BJ. Emerging technologies in cartilage restoration. In: Yanke AB, Cole BJ, editor(s). Joint preservation of the knee: A clinical casebook. Cham: Springer International Publishing; 2019. p. 295-319.
34. Zhang P, Dong B, Yuan P, Li X. Human umbilical cord mesenchymal stem cells promoting knee joint chondrogenesis for the treatment of knee osteoarthritis: A systematic review. Journal of Orthopaedic Surgery and Research. 2023; 18(1): 639.
35. Matas J, Orrego M, Amenabar D, Infante C, Tapia-Limonchi R, Cadiz MI, et al. Umbilical cord-derived mesenchymal stromal cells (mscs) for knee osteoarthritis: Repeated msc dosing is superior to a single msc dose and to hyaluronic acid in a controlled randomized phase i/ii trial. Stem cells translational medicine. 2019; 8(3): 215-24.
36. Cui G-H, Wang YY, Li C-J, Shi C-H, Wang W-S. Efficacy of mesenchymal stem cells in treating patients with osteoarthritis of the knee: A meta-analysis. Experimental and therapeutic medicine. 2016; 12(5): 3390-400.
37. Han X, Yang B, Zou F, Sun J. Clinical therapeutic efficacy of mesenchymal stem cells derived from adipose or bone marrow for knee osteoarthritis: A meta-analysis of randomized controlled trials. Journal of Comparative Effectiveness Research. 2020; 9(5): 361-74.
38. Iijima H, Isho T, Kuroki H, Takahashi M, Aoyama T. Effectiveness of mesenchymal stem cells for treating patients with knee osteoarthritis: A meta-analysis toward the establishment of effective regenerative rehabilitation. NPJ Regenerative medicine. 2018; 3(1): 15.
39. Saris TF, de Windt TS, Kester EC, Vonk LA, Custers RJ, Saris DB. Five-year outcome of 1-stage cell-based cartilage repair using recycled autologous chondrons and allogenic mesenchymal stromal cells: A first-in-human clinical trial. The American Journal of Sports Medicine. 2021; 49(4): 941-7.
40. Kim K-I, Lee W-S, Kim J-H, Bae J-K, Jin W. Safety and efficacy of the intra-articular injection of mesenchymal stem cells for the treatment of osteoarthritic knee: A 5-year follow-up study. Stem cells translational medicine. 2022; 11(6): 586-96.

Supplementary File

Table 1: Adverse events (AEs) recorded in the study

Adverse Events	Phase	N (%)	Severity	Remarks
Knee swelling / effusion	Phase I	3 (50%)	Mild	Resolved within 1 month; no recurrence
Injection-site discomfort	Phase II	–	–	–
Stiffness	Phase I	3 (50%)	Mild	Resolved within 1 month; no recurrence
Fever/systemic reaction	Phase I & II	–	–	–
Infection	Phase I & II	–	–	–
Allergic reaction	Phase I & II	–	–	–
Serious adverse events (SAEs)	Phase I & II	–	–	–

Table 2: VAS mean scores for PI and PII throughout 12-months follow-up

VAS	Phase I	Phase II		p-value[a]	95% CI	Cohen'f[b]
		MSC	Control			
Baseline	6.83 ± 0.98	7.29 ± 1.10	6.27 ± 1.35	0.022[c]	(0.20 , 2.28)	0.49
1 Month	6.33 ± 1.03	3.47 ± 2.27*	4.64 ± 1.63	0.134	(-3.36 , 0.48)	0.32
3 Month	4.83 ± 1.17*	2.24 ± 1.44*	3.27 ± 2.00*	0.125	(-2.91 , 0.38)	0.32
6 Month	3.00± 0.00*	2.56 ± 1.41*	3.09 ± 1.22*	0.015	(-2.48 , -0.29)	0.58
12 Month	1.67 ±1.37*	2.27 ± 1.49*	2.50 ± 1.35*	0.043	(-2.34 , -0.04)	0.50

*p<0.05 when compared to baseline (Bonferroni correction for multiple comparisons)
[a]ANCOVA analysis was conducted to compare the outcome measures between the MSC and Control groups while adjusting for age and baseline VAS score.
[b]Cohen's f was calculated to evaluate the effect size, which can be interpreted as small (0.10), medium (0.25) and large (0.40)
[c]Adjusted only for age

Table 3: KOOS Global mean scores for PI and PII throughout 12-months follow-up

KOOS Global Score	Phase I	Phase II		p-value[a]	95% CI	Cohen'f[b]
		MSC	Control			
Baseline	46.49 ± 11.51	37.3± 12.3	46.3 ± 12.3	0.493	(-15.82 , 7.83)	0.14
1 Month	43.40 ± 3.83	50.4 ± 11.8	44.5 ± 12.1	0.132	(-2.86 , 20.58)	0.32
3 Month	59.50 ± 3.56*	65.3 ± 14.0*	60.2 ± 11.3	0.153	(-3.65 , 21.89)	0.30
6 Month	69.69 ± 6.14*	68.7 ± 15.7*	63.7 ± 13.2*	0.009	(4.83 , 29.60)	0.60
12 Month	85.83 ± 11.87*	71.9 ± 19.8*	69.4 ± 12.3*	0.037	(0.73 , 21.01)	0.50

*p<0.05 when compared to baseline (Bonferroni correction for multiple comparisons)
[a]ANCOVA analysis was conducted to compare the outcome measures between the MSC and Control groups while adjusting for age and baseline VAS score.
[b]Cohen's f was calculated to evaluate the effect size, which can be interpreted as small (0.10), medium (0.25) and large (0.40)

Table 4: KOOS Symptom & Stiffness subdomain mean score for PI and PII throughout 12-months follow-up

KOOS Symptom & Stiffness	Phase I	Phase II		p-value[a]	95% CI	Cohen'f[b]
		MSC	Control			
Baseline	51.79 ± 20.79	56.2 ± 15.1	66.0 ± 11.4	0.319	(-20.42 , 6.92)	0.21
1 Month	55.95 ± 9.22	65.9 ± 13.3	67.2 ± 18.9	0.537	(-20.32 , 10.85)	0.13
3 Month	68.45 ± 14.00*	80.4 ± 12.4*	77.9 ± 13.0	0.587	(-9.30 , 16.08)	0.11
6 Month	77.38 ± 9.50*	82.2 ± 16.1*	79.5 ± 14.5	0.037	(0.97 , 28.66)	0.46
12 Month	88.69 ± 19.22*	85.5 ± 14.3*	83.2 ± 13.2	0.159	(-2.92 , 16.62)	0.33

*p<0.05 when compared to baseline (Bonferroni correction for multiple comparisons)
[a]ANCOVA analysis was conducted to compare the outcome measures between the MSC and Control groups while adjusting for age and baseline VAS score.
[b]Cohen's f was calculated to evaluate the effect size, which can be interpreted as small (0.10), medium (0.25) and large (0.40)

Table 5: KOOS Pain subdomain mean score for PI and PII throughout 12-months follow-up

KOOS Pain	Phase I	Phase II		p-value[a]	95% CI	Cohen'f[b]
		MSC	Control			
Baseline	62.04±7.79	43.5 ±17.5	55.1 ± 16.1	0.152	(-21.49 , 3.57)	0.32
1 Month	61.11±14.80	60.5 ± 11.6	52.5 ± 11.7	0.065	(-0.70 , 22.23)	0.40
3 Month	73.61±8.91	73.1 ± 15.8*	69.0 ± 11.3	0.199	(-4.91 , 22.40)	0.27
6 Month	84.72±12.27*	78.5 ± 14.2*	70.8 ± 11.7	0.002	(7.77 , 29.18)	0.74
12 Month	91.67±12.30*	85.5 ± 12.4 *	78.9 ± 13.0*	0.063	(-0.57 , 19.60)	0.44

*p<0.05 when compared to baseline (Bonferroni correction for multiple comparisons)
aANCOVA analysis was conducted to compare the outcome measures between the MSC and Control groups while adjusting for age and baseline VAS score.
bCohen's f was calculated to evaluate the effect size, which can be interpreted as small (0.10), medium (0.25) and large (0.40)

Table 6: KOOS Activity of Daily Living (ADL) subdomain mean scores for PI and PII throughout 12-months follow-up

KOOS Activity of Daily Living (ADL)	Phase I	Phase II		p-value[a]	95% CI	Cohen'f[b]
		MSC	Control			
Baseline	57.60±8.29	60.8 ± 11.5	69.2 ± 11.7	0.085	(-21.28 , 1.47)	0.37
1 Month	60.78±6.75	65.7 ± 10.6	58.7 ± 12.4	0.001	(5.56 , 19.17)	0.80
3 Month	72.30±10.08*	77.0 ± 13.3*	72.9 ± 9.4	0.337	(-6.28 , 17.63)	0.20
6 Month	86.77±5.81*	81.4 ± 12.0*	75.0 ± 12.2	0.018	(2.46 , 23.42)	0.53
12 Month	95.84±3.99*	85.8 ± 11.4*	85.0 ± 9.5	0.266	(-4.35 , 14.93)	0.26

*p<0.05 when compared to baseline (Bonferroni correction for multiple comparisons)
[a]ANCOVA analysis was conducted to compare the outcome measures between the MSC and Control groups while adjusting for age and baseline VAS score.
[b]Cohen's f was calculated to evaluate the effect size, which can be interpreted as small (0.10), medium (0.25) and large (0.40)

Table 7: KOOS Sport & Recreation subdomain mean scores for PI and PII throughout 12-months follow-up

KOOS Sport & Recreation	Phase I	Phase II		p-value[a]	95% CI	Cohen'f[b]
		MSC	Control			
Baseline	22.50 ± 19.94	5.0 (0.0,20.0)	10.0 (5.0,40.0)	0.664	(-12.14 , 18.69)	0.09
1 Month	5.83 ± 9.17	10.0 (5.0,25.0)	10.0 (0.0,25.0)	0.440	(-7.60 , 16.93)	0.16
3 Month	34.17 ± 13.93	50.0 (25.0,70.0)	30.0 (20.0,50.0)	0.392	(-14.16 , 34.89)	0.18
6 Month	43.33 ± 13.29	55.0 (32.5,70.0)*	40.0 (35.0,65.0)	0.030	(2.59 , 46.82)	0.48
12 Month	81.67 ± 16.93*	65.0 (50.0,75.0)*	52.5 (38.8,61.3)*	0.024	(2.80 , 35.75)	0.56

*p<0.05 when compared to baseline (Bonferroni correction for multiple comparisons)
[a]ANCOVA analysis was conducted to compare the outcome measures between the MSC and Control groups while adjusting for age and baseline VAS score.
[b]Cohen's f was calculated to evaluate the effect size, which can be interpreted as small (0.10), medium (0.25) and large (0.40)

Table 8: KOOS QoL subdomain mean scores for PI and PII throughout 12-months follow-up

KOOS QoL	Phase I	Phase II		p-value[a]	95% CI	Cohen'f[b]
		MSC	Control			
Baseline	38.54±23.19	21.5 ± 18.5	21.2 ± 15.8	0.222	(-6.26 , 25.61)	0.25
1 Month	33.33±11.64	36.9 ± 22.7	30.8 ± 16.5	0.105	(-3.42 , 33.92)	0.34
3 Month	48.96±19.93	53.1 ± 18.7*	44.9 ± 19.1*	0.113	(-2.91 , 25.58)	0.35
6 Month	56.25±5.59	54.5 ± 20.6*	48.9 ± 17.1*	0.136	(-4.65 , 32.27)	0.31
12 Month	76.71±11.26*	56.5 ± 22.3*	50.6 ± 16.0*	0.022	(2.34 , 27.35)	0.57

*p<0.05 when compared to baseline (Bonferroni correction for multiple comparisons)
[a]ANCOVA analysis was conducted to compare the outcome measures between the MSC and Control groups while adjusting for age and baseline VAS score.
[b]Cohen's f was calculated to evaluate the effect size, which can be interpreted as small (0.10), medium (0.25) and large (0.40)

ORIGINAL ARTICLE

Quality of life of Hirschsprung disease patients with a stoma

Johana Gracia, MD[1], Shiefa Annisa Qisthi, MD[1], Aulia Ichlasul Rezza, MD[1], Dirgantara Fathurrizki Harfanie, MD[1], Zahra Saliha Izzati, MD[1], Qonita Jayanti, MD[1], Yogi Gradianto Brahmandoko, MD[1], Kristy Iskandar, PhD[2], Eko Purnomo, PhD[3], Gunadi, PhD[1]

[1]Pediatric Surgery Division, Department of Surgery, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada-Dr. Sardjito Hospital, Yogyakarta, Indonesia, [2]Department of Child Health, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada-UGM Academic Hospital, Yogyakarta, Indonesia, 3Pediatric Surgery Division, Department of Surgery, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada-UGM Academic Hospital, Yogyakarta, Indonesia

ABSTRACT

Introduction: Hirschsprung disease (HSCR) is a genetic disorder leading to gastrointestinal obstruction due to the absence of ganglion cells in the submucosal and myenteric plexuses. Treatment typically involves a pull-through surgery, sometimes starting with a colostomy. The COVID-19 pandemic has resulted in restrictions on general patient services, i.e., non-COVID-19 patients, at health facilities, leading to reduced hospital visits, including HSCR patients with stomas. This study aimed to determine whether there were differences in the quality of life (QoL) of HSCR patients with stomas before and after the COVID-19 pandemic.

Materials and Methods: This research was a descriptive study comparing the quality of life (QoL) of HSCR patients with stomas before and after the COVID-19 pandemic. It utilized a cross-sectional study design and assessed QoL using the PedsQL Generic Core Scales 4.0 questionnaire.

Results: There was no significant difference in the QoL of HSCR patients before COVID-19 and after COVID-19, as indicated by parent reports (p=0.88) and child reports (p=0.12). However, there was a statistically significant difference in scores on the social dimension of child reports (p=0.04). Furthermore, there was no statistically significant relationship between parent and child reports (p>0.05).

Conclusion: The QoL of HSCR patients with a stoma before and after the COVID-19 pandemic is similar, except for the social dimension in the child's report. Further studies with more cases are necessary to clarify the findings of this study.

KEYWORDS:
Hirschsprung disease, stoma, quality of life, COVID-19 pandemic; two stages pull-through surgery

INTRODUCTION

Hirschsprung disease (HSCR) is a genetic disorder characterized by a motility issue that causes functional obstruction of the gastrointestinal system.[1] The pathogenesis of HSCR involves the absence of parasympathetic ganglion cells in the submucosal plexus and the myenteric plexus due to disturbances in the migration of neural crest cells to the abdominal wall.[2] The incidence of HSCR in our country is approximately 1 in 3,250 live births.[3] This rate is higher than those of countries in Asia (1 in 3,600), Europe (1 in 6,700), and Africa (1 in 4,800).[4] Treatment for HSCR involves pull-through surgery, which can be performed in one or two stages. In a two-stage pull-through, the procedure starts with creating a stoma through a colostomy.[5] Stoma can enhance the quality of life (QoL) for HSCR patients. However, creating a stoma comes with the risk of potential complications.[6]

Coronavirus disease 2019 (COVID-19) is caused by transmission of the SARS-CoV-2 virus. COVID-19 was declared a pandemic by the World Health Organization (WHO) on March 11, 2020. As a form of control against SARS-CoV-2, the Indonesian government implemented a large-scale social restrictions policy as regulated in Government Regulation Number 21 of 2020 concerning large-scale social restrictions in the context of accelerating the handling of COVID-19.[8] At this time, health service facilities are also affected. Healthcare facilities are reducing services for non-COVID-19 patients and focusing on providing COVID-19 services. This restriction also caused a decrease in patient visits at our institution, including HSCR patients with stomas. Therefore, this research was conducted to determine whether there was a difference in the QoL of HSCR patients with stomas before and after the COVID-19 pandemic.

MATERIALS AND METHODS

Subjects

This research was a cross-sectional study of a population of HSCR patients with a stoma at our hospital in Indonesia. Subjects were taken based on the following criteria: (1) isolated HSCR patients with a stoma at our hospital from January 2018 to May 2022, (2) patients must be at least 2 years old and a maximum of 18 years old, (3) willing to take part in the research and have obtained informed consent from the patient's parents. Subjects with HSCR syndrome, incomplete medical records, and those who could not be contacted/reached were excluded. This study involved 6 HSCR patients with stoma as a group before COVID-19 and 7 HSCR patients with stoma as a group after COVID-19. The ethical research has been agreed upon by our institution's ethical committee.

This article was accepted: 18 January 2026
Corresponding Author: Gunadi
Email: drgunadi@ugm.ac.id

Table I: Characteristics of subjects in the study (N=13)

Characteristics	Before COVID-19 n (%)	After COVID-19 n (%)	p-value
Sex			
▪ Male	4 (66)	4 (57)	0.725
▪ Female	2 (33)	3 (42)	
Age at completing the questionnaire/interview (years old)			
▪ 2-4	1 (16)	4 (57)	0.220
▪ 5-7	4 (66)	1 (14)	
▪ 8-12	1 (16)	1 (14)	
▪ 13-<18	0	1 (14)	
Report type			
▪ Parent reports	6	7	0.797
▪ Child reports	3	3	

Table II: Quality of life scores for patients with HSCR, before and after the COVID-19 pandemic (based on parents' reports)

Variable	Before COVID-19 pandemic		After COVID-19 pandemic		p-value
	N	Score (mean ± SD)	N	Score (mean ± SD)	
PedsQL score	6	88.40 ± 13.48	7	87.57 ± 5.35	0.88

Table III: Quality of life scores for patients with HSCR, before and after the COVID-19 pandemic (based on child's reports)

Variable	Before COVID-19 pandemic		After COVID-19 pandemic		p-value
	N	Score (mean ± SD)	N	Score (mean ± SD)	
PedsQL score	3	77.65 ± 6.8	3	86.95 ± 1.88	0.12

Table IV: Analysis of the differences in PedsQL scores across dimensions based on parents and children's reports

PedsQL scores	Before COVID-19 pandemic (mean ± SD)	After COVID-19 pandemic (mean ± SD)	p-value
Parent reports			
▪ Physical	83.85 ± 22.20	87.49 ± 5.10	0.68
▪ Emotional	81.66 ± 23.38	83.57 ± 12.14	0.85
▪ Social	96.66 ± 4.08	95.00 ± 6.45	0.59
▪ School	94.16 ± 6.64	84.28 ± 15.39	0.17
Child reports			
▪ Physical	85.41 ± 25.20	86.95 ± 1.88	0.50
▪ Emotional	50.00 ± 17.32	81.66 ± 23.62	0.50
▪ Social	83.33 ± 5.77	98.33 ± 2.88	0.04*
▪ School	86.66 ± 15.27	76.66 ± 20.81	0.50

*, p<0.05 is considered significant.

Table V: Correlation of PedsQL scores between parent's and child's reports

PedsQL scores	Before COVID-19				After COVID-19			
	Parent reports Median (IQR) (N=6)	Child reports Median (IQR) (N=3)	p	r	Parent reports Median (IQR) (N=7)	Child reports Median (IQR) (N=3)	p	r
Physical	92.18 (67.18-100)	100(56.2-100)	0.17	0.96	84.37 (84.36-93.75)	93.75 (81.25-93.75)	0.15	0.97
Emotional	92.5 (53.75-100)	40 (40-75)	0.66	0.50	85 (70-90)	90 (55-90)	0.31	0.88
Social	97.5 (93.75-100)	80 (80)	0.67	0.50	100 (90-100)	100 (95-100)	0.66	0.50
School	95 (88.75-100)	90 (70-90)	0.21	0.94	85 (70-100)	70 (60-70)	0.10	0.98

Data collection
Data were obtained from medical records of HSCR patients with stoma at our hospital from January 2018 to March 2020 for the group before the COVID-19 pandemic and April 2020 to May 2022 for the group after the pandemic. The questionnaire was read to the patient and/or the patient's parents after informed consent was obtained from the doctor in charge.

Statistical Analysis
Data are provided in the form of mean, standard deviation, median, and IQR. A higher outcome score indicates a better QoL. The Shapiro-Wilk test was used to perform a normality test. If the data was normally distributed, the independent t-test method was used.

Ethics approval and consent to participate
Our institution's Medical and Health Research Ethics Committee approved this study. The study was conducted in accordance with the Declaration of Helsinki.

RESULTS

Subject Characteristic
In our study, we observed no significant differences in sex, age at the time of completing the questionnaire, or type of report between the groups before and after the COVID-19 pandemic (p>0.05) (Table I).

Quality of life of patients with HSCR before and after the COVID-19 pandemic
According to parents ' and child's reports, the average QoL score for HSCR patients before and after the COVID-19 pandemic was similar. (p=0.88 and 0.12, respectively) (Tables II and III).

Further analysis described how higher physical and emotional scores were obtained in the group after the COVID-19 pandemic, both from parent reports and child report questionnaires. None exhibited significant differences across the dimensions, except for the social dimension in the child reports (p=0.04) (Table IV).

Next, we determined the correlation of PedsQL scores between parent and child reports. None of the dimensions showed any significant differences (p>0.05) (Table V).

DISCUSSION

Our study revealed that there were more male HSCR patients than female patients. This aligns with prior studies, which indicated that the male-to-female ratio among patients was 4:1.[9-11] Concerning the age characteristics of the subjects when completing the questionnaire, the group of HSCR patients aged 5-7 years before the COVID-19 pandemic surpassed those aged 2-4 years and 8-12 years, with a ratio of 4:1:1. Conversely, among the HSCR patients after the COVID-19 pandemic, those aged 2-4 years showed a higher prevalence compared to patients aged 5-7 years, 8-12 years, and 13-<18 years, with a ratio of 4:1:1:1.

The incidence of HSCR in our province is 1 in 3,250 live births. With a population of 4 million and a birth rate of 36,045, or 9 per thousand, it is estimated that 41 babies with HSCR will be born each year in this province.[12-13] The number of HSCR patients at our hospital is higher yearly, as patients come from our province and the southern part of the neighborhood province.

Previously, neonates diagnosed with HSCR had to undergo a colostomy first and wait until they were 6 to 12 months old to have definitive pull-through surgery. However, this approach has become less common over the last three decades, and single-stage pull-through surgery, particularly transanal endorectal pull-through (TEPT), has gained popularity among pediatric surgeons worldwide[14], including in our hospital.[3] In addition, one-stage surgery offers many benefits, including more uncomplicated pre-surgical care, reduced costs, shorter hospital stays, and sparing the patient and their family from the psychological burden of creating a stoma.[15-16] This may explain why fewer HSCR patients with stomas were included in the research sample taken at our hospital.

According to an analysis of the final PedsQL scores reported by parents, the HSCR patient group exhibited a higher mean score following the COVID-19 pandemic. However, the difference between the two groups was not statistically significant. This aligns with a previous study suggesting that children with congenital diseases may already have disorders from the beginning, indicating that the COVID-19 pandemic might not affect children's psychosocial conditions.[17]

In analyzing the physical dimension scores, both groups received moderate classifications. Additionally, the group demonstrated better physical scores in reports from children and parents after the COVID-19 pandemic. However, no significant differences were found. This finding aligns with previous research18, which indicated that there were no significant differences in physical dimension PedsQL scores in children before and after the COVID-19 pandemic.

Next, we examined the emotional and social dimensions. We observed contrasting findings: The social dimension indicated a good QoL with a score > 90, while the emotional dimension showed a poor QoL19, ranking lowest among all PedsQL dimensions. This aligns with a previous study suggesting that children with long-term physical illnesses not involving cerebral function are more vulnerable to emotional disorders than those exhibiting antisocial behavior.[20]

The results regarding the emotional dimension also indicate higher scores in both child and parent reports after the COVID-19 pandemic. However, this difference was not statistically significant. The emotional dimensions are often related to fear and sadness regarding their different conditions compared to normal children. Many patients also experience concerns about stoma leakage during outdoor activities.[21]

In the social dimension, a few problems were identified. The most common complaint was "Unable to do things that his friends can do." Many individuals point out that activities like swimming are not accessible to HSCR patients with a

stoma. Analyzing the difference in scores between the two groups revealed that the score was higher in child reports after the COVID-19 pandemic. The large-scale social restrictions implemented during the pandemic resulted in children being isolated from their friends, leading to a lack of relationships among peers essential for developing children's social skills.[22-23] Other factors impact children's social lives, especially during a pandemic, including parental support and environmental conditions.[24] However, this study did not evaluate other factors that could impact patients' quality of life in the social dimension. One reason the score was higher after the COVID-19 pandemic compared to before may be that no issues were identified in the social dimension post-pandemic, as individuals had fewer opportunities to socialize due to extensive social restrictions.

Two groups showed similar scores on the school dimension. Children struggling with stool control often lack self-confidence and dislike attending school.[25] Interestingly, a change in school regulations was likely underlying the scores that tended to be lower in the group after the COVID-19 pandemic. These changes impact children's mental health.[26-27]

PedsQL scores are categorized as good (>90), moderate (90-75), and poor (<75) [19]. Our study indicated that the QoL for patients with HSCR was categorized as moderate in both the pre and post-pandemic COVID-19 groups. Additionally, the QoL for HSCR patients with stomas is not significantly different from that of normal children.[28-30]

Several factors contribute to a good QoL for HSCR patients with stomas. One of these factors is the parents' knowledge about stoma care. A strong knowledge base also contributes to maintaining a high QoL.[31] This also aligns with a prior study suggesting that education can significantly influence patient quality of life.[32] This education can enhance patient knowledge to prevent future complications.[33-34]

The family's role is also essential in achieving a good QoL for HSCR patients with stomas. These patients require support from family and medical professionals to adjust to social and psychological challenges.[35] Family support can also enhance the patient's self-confidence and psychological well-being.[35-37]

Patients with stomas in our HSCR study reported a good QoL. They were similar to healthy children in terms of QoL, perhaps influenced by several factors, such as the adequate education of the parents, which enabled them to understand how to care for the stoma and achieve good physical function in HSCR patients' stoma. In our study, strong family support for HSCR patients with stomas positively influenced their self-confidence and psychological well-being, ensuring that their social, emotional, and educational functions remained intact. However, our research did not evaluate other factors, such as education and family support, that could affect the quality of life for HSCR patients with a stoma. Every individual's experience is unique. Some children may face more significant challenges, while others may adapt effectively. The small sample size in this study could be seen as a limitation, as it may not adequately represent the broader population.

Our study found no significant correlation between parent and child reports. The consistency between child and parent reports on the PedsQL is low, with intra-class coefficients ranging from 0.02 to 0.23.[38] This occurs because various factors can affect the level of agreement between parent and child reports, including the child's age, the domain being assessed, and the parent's QoL.[39]

CONCLUSION

The QoL for HSCR patients with a stoma before and after the COVID-19 pandemic is similar, except for the social dimension in children's reports. There was no significant correlation between child and parent reports. Further studies with more cases are necessary to clarify our findings.

List of Abbreviations

COVID-19: Coronavirus disease 2019; HSCR: Hirschsprung disease; QoL: quality of life; TEPT: transanal endorectal pull-through; WHO: World Health Organization.

CONFLICT OF INTEREST

The authors declared no potential conflicts of interest regarding this article's research, authorship, and/or publication.

ACKNOWLEDGMENTS

We thank all those who provided excellent technical support and assistance during the study.

FUNDING

This study received no external funding.

REFERENCES

1. Burns AJ, Goldstein AM. Causes and consequences: development and pathophysiology of Hirschsprung disease. World J Pediatr Surg 2024; 7(4): e000903.
2. Montalva L, Cheng LS, Kapur R, Langer JC, Berrebi D, Kyrklund K, Pakarinen M, de Blaauw I, Bonnard A, Gosain A. Hirschsprung disease. Nat Rev Dis Primers 2023; 9(1): 54.
3. Gunadi, Karina SM, Dwihantoro A. Outcomes in patients with Hirschsprung disease following definitive surgery. BMC Res Notes 2018; 11(1): 644.
4. Tang CS, Karim A, Zhong Y, Chung PH, Tam PK. Genetics of Hirschsprung's disease. Pediatr Surg Int 2023; 39(1): 104.
5. Xu TO, Levitt MA, Feng C. Controversies in Hirschsprung surgery. World J Pediatr Surg 2024; 7(3): e000887.
6. Krishnamurty DM, Blatnik J, Mutch M. Stoma Complications. Clin Colon Rectal Surg 2017; 30(3): 193-200.
7. Harris DA, Egbeare D, Jones S, Benjamin H, Woodward A, Foster ME. Complications and mortality following stoma formation. Ann R Coll Surg Engl 2005; 87(6): 427-31.
8. Kementrian Kesehatan Republik Indonesia. Peraturan Menteri Kesehatan Republik Indonesia (Bahasa). Jakarta: Kementrian Kesehatan Republik Indonesia, 2021.
9. Kapoor A, Jiang Q, Chatterjee S, Chakraborty P, Sosa MX, Berrios C, Chakravarti A. Population variation in total genetic risk of Hirschsprung disease from common RET, SEMA3 and NRG1 susceptibility polymorphisms. Hum Mol Genet 2015; 24: 2997-3003.

10. Puri P, Nakamura H. Epidemiology and Clinical Characteristic of Hirschsprung's Disease. In: Hirschsprung's Disease and Allied Disorder. Berlin, Heidelberg: Springer Berlin Heidelberg, 2019.
11. Widyasari A, Pavitasari WA, Dwihantoro A, Gunadi. Functional outcomes in Hirschsprung disease patients after transabdominal Soave and Duhamel procedures. BMC Gastroenterol 2018; 18(1): 56.
12. Badan Pusat Statistik DI Yogyakarta. Proyeksi Jumlah Penduduk menurut Kabupaten/Kota di DIY (Bahasa). 2022 [cited September 2024] Available at: https://yogyakarta.bps.go.id/indicator/12/133/1/jumlah-penduduk-menurut-kabupaten-kota-di-d-i-yogyakarta-.html
13. Badan Perencanaan Pembangunan Daerah. Daerah DIY – Pertumbuhan Penduduk (Bahasa). 2022. [cited September 2024] cited Available at: https://bappeda.jogjaprov.go.id/dataku/data_dasar/cetak/308-pertumbuhan-penduduk?id_skpd=29
14. Elrouby A, Shehata S, Waheeb S, Khairi A, AbdAl-Aziz D, Looka B. One stage transanal versus one stage laparoscopic-assisted transanal endorectal pull-through in managing Hirschsprung's disease in pediatric age group; a retrospective study. BMC Surg 2025; 25(1): 59.
15. Ban HT, Chieu VM, Huynh QTV, Thanh TT, Quang DT, Uy LTN. Long-term outcomes of laparoscopic-assisted versus complete transanal endorectal pull-through technique for classic segment Hirschsprung's disease. Pediatr Surg Int 2024; 41(1): 26.
16. Gołębiewski A, Anzelewicz S, Sosińska D, Osajca-Kanyion M. Transanal Endorectal Pull-Through for Hirschsprung's Disease: Complications and Lessons from Our Practice and the Literature. Children (Basel) 2024; 11(9): 1059.
17. Fuerboeter M, Boettcher J, Barkmann C, Zapf H, Nazarian R, Wiegand-Grefe S, Reinshagen K, Boettcher M. Quality of life and mental health of children with rare congenital surgical diseases and their parents during the COVID-19 pandemic. Orphanet J Rare Dis 2021; 16(1): 498.
18. Ito T, Sugiura H, Ito Y, Narahara S, Noritake K, Takahashi D, Natsume K, Ochi N. Physical Functions among Children before and during the COVID-19 Pandemic: A Prospective Longitudinal Observational Study (Stage 1). Int J Environ Res Public Health 2022; 19(18): 11513.
19. Loganathan AK, Mathew AS, Kurian JJ. Assessment of Quality of Life and Functional Outcomes of Operated Cases of Hirschsprung Disease in a Developing Country. Pediatr Gastroenterol Hepatol Nutr 2021; 24(2): 145-53.
20. Garralda ME. Chronic physical illness and emotional disorder in childhood. Where the brain's not involved, there may still be problems. Br J Psychiatry 1994; 164(1): 8-10.
21. Mitchell KA, Rawl SM, Schmidt CM, Grant M, Ko CY, Baldwin CM, Wendel C, Krouse RS. Demographic, clinical, and quality of life variables related to embarrassment in veterans living with an intestinal stoma. J Wound Ostomy Continence Nurs 2007; 34(5): 524-32.
22. Collaborative for Academic, Social, and Emotional Learning. Effective Social and Emotional Learning Programs. Chicago, 2012 IL: Collaborative for Academic, Social, and Emotional Learning. [cited October 2024] Available at: http://static.squarespace.com/static/513f79f9e4b05ce7b70e9673/t/526a220de4b00a92c90436ba/1382687245993/2013- casel-guide.pdf
23. Pepler D, Bierman K. With a Little Help From My Friends: The Importance of Peer Relationships for Social-Emotional Development. Pennsylvania: Edna Bennett Pierce Prevention Research Center, 2018.
24. Ghosh R, Dubey MJ, Chatterjee S, Dubey S. Impact of COVID -19 on children: special focus on the psychosocial aspect. Minerva Pediatr 2020; 72(3): 226-35.
25. Westfal M, Goldstein A. Diagnosing and managing Hirschsprung disease in the newborn. Neoreviews, 2018; 19(10): 577-88
26. Alves RF, Samorinha C, Precioso J. Knowledge, attitudes and preventive behaviors toward COVID-19: A study among higher education students in Portugal. J Health Res 2021; 35(4): 318-28.
27. Fegert JM, Vitiello B, Plener PL, Clemens V. Challenges and burden of the Coronavirus 2019 (COVID-19) pandemic for child and adolescent mental health: a narrative review to highlight clinical and research needs in the acute phase and the long return to normality. Child Adolesc Psychiatry Ment Health 2020; 14: 20.
28. Buck D. The PedsQL™ as a measure of parent-rated quality of life in healthy UK toddlers: psychometric properties and cross-cultural comparisons. J Child Health Care 2012; 16(4): 331-8.
29. Varni JW, Seid M, Rode CA. The PedsQL: measurement model for the pediatric quality of life inventory. Med Care 1999; 37(2): 126-39.
30. Collins L, Collis B, Trajanovska M, Khanal R, Hutson JM, Teague WJ, King SK. Quality of life outcomes in children with Hirschsprung disease. J Pediatr Surg 2017; 52(12): 2006-10.
31. Romatua S. Relationship of knowledge and attitudes of colostomy patients in stoma care in RSUP H. Adam Malik Medan. Thesis. Universitas Sumatera Utara, 2018.
32. Danielsen AK, Rosenberg J. Health related quality of life may increase when patients with a stoma attend patient education--a case-control study. PLoS One 2014; 9(3): e90354.
33. Mohamed S, Salem G, Mohamed H. Effect of self-care management program on self-efficacy among patients with colostomy. Am J Nurs Res 2017; 5(5): 191-9.
34. Abdullah I, Abdulmutalib M, Abdullah E, Nagshabandi A. Effect of an educational protocol on knowledge and self-care practices among patients with the intestinal ostomy. Am J Nurs Res 2018; 6(6): 553-61.
35. Nam KH, Kim HY, Kim JH, Kang KN, Na SY, Han BH. Effects of social support and self-efficacy on the psychosocial adjustment of Korean ostomy patients. Int Wound J 2019; 16 Suppl 1(Suppl 1): 13-20.
36. Townsend M, Morgan K. Psychiatric Mental Health Nursing: Concepts of Care in Evidence-Based Practice. Philadelphia, PA, USA: FA Davis, 2018.
37. Khalilzadeh Ganjalikhani M, Tirgari B, Roudi Rashtabadi O, Shahesmaeili A. Studying the effect of structured ostomy care training on quality of life and anxiety of patients with permanent ostomy. Int Wound J 2019; 16(6): 1383-90.
38. Cremeens J, Eiser C, Blades M. Factors influencing agreement between child self-report and parent proxy-reports on the Pediatric Quality of Life Inventory 4.0 (PedsQL) generic core scales. Health Qual Life Outcomes 2006; 4: 58.
39. Johnelle Sparks P. 'Mommy knows best': parents' perceptions of their infant's health. J Child Health Care 2009; 13(1): 63-74.

Biologic drug survival in psoriasis: insights from a multi-center retrospective study in West Malaysia

Kam Veng Chan, Adv M Derm[1], Moonyza Akmal Ahmad Kamil, Adv M Derm[1], Azura Mohd Affandi, Adv M Derm[1], Mazliha Mansor, Adv M Derm[1], Jing Wern Kwan, Adv M Derm[2], Latha Selvarajah, Adv M Derm[3], Hock Leng Lee, Adv M Derm[4], Sut Enn Lee, Adv M Derm[5], Evelyn Yap, Adv M Derm[6], Nazatul Shima Abdul Rahim, Adv M Derm[7], Siu Bee Wong, Adv M Derm[8], Choon Sian Lee, Adv M Derm[9], Preamala Gunabalasingam, Adv M Derm[10]

[1]Department of Dermatology, Hospital Kuala Lumpur, Kuala Lumpur, Federal Territory of Kuala Lumpur, Malaysia, [2]Department of Dermatology, Hospital Ampang, Ampang, Selangor, Malaysia, [3]Department of Dermatology, Hospital Sultan Ismail, Johor Bahru, Johor, Malaysia, [4]Dermatology Unit , Hospital Taiping, Taiping, Perak, Malaysia, [5]Dermatology Unit, Hospital Serdang, Serdang, Selangor, Malaysia, [6]Department of Dermatology, Hospital Muar, Muar, Johor, Malaysia, [7]Dermatology Unit, Hospital Putrajaya, Putrajaya, Federal Territory of Putrajaya, Malaysia, [8]Department of Dermatology, Hospital Sultanah Bahiyah, Alor Setar, Kedah, Malaysia, [9]Department of Dermatology, Hospital Melaka, Melaka, Melaka, Malaysia, [10]Department of Dermatology, Hospital Seremban, Seremban, Negeri Sembilan, Malaysia

ABSTRACT

Introduction: Psoriasis is a chronic immune-mediated skin disorder with significant impact on patients' quality of life. Biologic therapies have revolutionized the treatment of moderate-to-severe psoriasis, but data on their long-term effectiveness, measured through drug survival rates, remains limited in Malaysia. This study aimed to analyze the drug survival of biologic therapies and identify factors influencing treatment discontinuation among psoriasis patients in Malaysia.

Materials and Methods: This retrospective cohort study analyzed 285 psoriasis patients receiving 437 biologic treatment courses in 10 tertiary hospitals in West Malaysia. Data on demographic characteristics, clinical profiles, and biologic treatments were collected and analyzed. Drug survival was evaluated using Kaplan-Meier analysis, and predictors of treatment discontinuation were identified using Cox proportional hazards modeling.

Results: The study cohort had a mean psoriasis onset age of 28 (± 13) years, with biologic initiation at 39 (± 16) years. Secukinumab (53.7%) was the most commonly prescribed first-line biologic, followed by Ustekinumab (28.1%). Loss of efficacy was the leading cause of discontinuation, increasing from 49.6% in the first line to 100% by the fifth. Kaplan-Meier analysis showed Secukinumab had the longest mean survival (45.5 months), followed by Ustekinumab (41.4 months) and Rizankizumab (41.3 months). Cox regression revealed prior biologic use significantly increased discontinuation risk (HR = 1.415, p = 0.049), while diabetes mellitus approached significance increase discontinuation risk (HR = 1.575, p = 0.054).

Conclusion: Biologic drug survival in Malaysian psoriasis patients reflects global trends, with Secukinumab demonstrating superior durability. Loss of efficacy and funding issues were key barriers to persistence. The findings emphasize the need for optimized treatment strategies with wider access to biological treatment.

KEYWORDS:
Psoriasis, biologic therapy, drug survival, Malaysia, treatment discontinuation

INTRODUCTION

Psoriasis is a chronic, immune-mediated skin disorder characterized by hyperproliferation of keratinocytes and inflammation, significantly impacting patients' quality of life. Immunopathogenesis of the psoriasis involves the abnormal activation of the immune system, particularly T cells, leading to inflammation and hyperproliferation of keratinocytes. Dendritic cells in the skin act as antigen-presenting cells, activating naive T cells and initiating the production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-17 (IL-17), and interleukin-23 (IL-23). These cytokines play pivotal roles in the pathogenesis of psoriasis, driving inflammation and promoting rapid keratinocyte proliferation. IL-17 induces the release of other pro-inflammatory cytokines that recruit neutrophils to the site of inflammation, further exacerbating the disease. IL-23, on the other hand, is crucial for the differentiation and persistence of Th17 cells, which are central to the inflammatory cascade in psoriasis.[1]

Biologic therapies have been designed to target specific cytokines involved in this immunopathogenesis. TNF-α inhibitors, such as adalimumab, etanercept, and infliximab, block the action of TNF-α, which is a key mediator in the inflammatory process of psoriasis.[2] Similarly, IL-17 inhibitors like secukinumab, ixekizumab, and brodalumab block IL-17A or its receptor, thereby preventing the inflammatory effects triggered by IL-17. By targeting IL-17, these biologics reduce the production of other inflammatory mediators and neutrophil infiltration, leading to symptom improvement.[1] IL-23 inhibitors, such as guselkumab, risankizumab, and tildrakizumab, target the p19 subunit of IL-23, which plays a critical role in activating Th17 cells. By inhibiting IL-23, these biologics help reduce the inflammatory response by lowering IL-17 levels and other inflammatory cytokines.[3] Additionally,

This article was accepted:
Corresponding Author: Kam Veng Chan
Email: ckveng@gmail.com

ustekinumab, which targets both IL-12 and IL-23, further helps control inflammation by interfering with the activation of both Th1 and Th17 cells.[4] These biologics represent a significant advancement in psoriasis treatment, offering more specific, targeted therapeutic options that address the underlying immune dysfunction in psoriasis and have shown substantial efficacy in both clinical trials and real-world settings.[5-7]

When selecting a biologic therapy for psoriasis, patient profiling is a critical step to ensure that treatment is tailored to the unique needs of each individual. Factors such as presence of comorbidities, previous treatment history, and the patient's ability to adhere to dosing schedules all play an important role in the decision-making process. The presence of psoriatic arthritis or axial involvement can significantly influence the choice of biologic. For patients with psoriatic arthritis, especially those with spinal inflammation, biologics which target IL-17, are often preferred due to their ability to address both skin and joint symptoms. Comorbidities, such as inflammatory bowel disease (IBD), may lead to the use of biologic, which targets IL-23, providing dual benefits for psoriasis and IBD. The frequency of dosing is also an important consideration, as some biologics require more frequent injections while others offer longer dosing intervals.[8] Additionally, cost considerations and patient access to biologic treatments play a significant role in therapy selection. Ultimately, the selection of biologic therapy should be personalized based on a comprehensive patient profile, ensuring that each treatment choice is optimal for the patient's specific condition, preferences, and lifestyle.

Drug survival, defined as the duration of time a patient remains on a specific treatment before discontinuation, serves as a vital indicator of treatment success and patient adherence.[6] Factors influencing drug survival include the patient's previous treatment history, comorbidities, adverse events (AEs), and the specific characteristics of the biologic agent.[7] For instance, studies have shown that biologics targeting IL-23, such as guselkumab and risankizumab, exhibit superior drug survival rates compared to traditional TNF-α inhibitors.[9-10] Furthermore, the persistence of treatment is often linked to the initial response to therapy, with patients experiencing significant improvements in their psoriasis symptoms more likely to continue their treatment regimen.[9]

In Malaysia, the landscape of psoriasis treatment is evolving, yet there is limited data on the drug survival of biologics within this population. Recent studies have highlighted the need for comprehensive evaluations of treatment outcomes in Malaysian patients, particularly as access to biologic therapies remains restricted compared to Western countries.[11-12] Understanding the drug survival rates of biologics in this demographic is essential for optimizing treatment strategies and improving patient outcomes. This retrospective study aims to analyse the drug survival of biologic therapies among psoriasis patients in a Malaysian hospital setting, contributing valuable insights to the existing body of literature and informing clinical practice.

MATERIALS AND METHODS

This retrospective cohort study was conducted by reviewing electronic records of psoriasis patients treated with biologic agents at the dermatology clinic of 10 tertiary government hospitals in West Malaysia. The inclusion criteria comprised of all patients diagnosed with psoriasis who received at least one biologic treatment from 1st Jan 2006 to 30th Jun 2024(18.5 years).

Data were extracted from patient records and included demographic information such as age, gender, ethnicity, body weight, and body mass index (BMI). The BMI classification followed the World Health Organization guidelines for the Asian population, where BMI values between 23 and 27.49 were classified as overweight, and values of 27.5 or higher indicated obesity. Clinical data included the age of psoriasis onset, the age at biologic initiation, the type of psoriasis (categorized as chronic plaque, pustular, or erythrodermic), the presence of psoriatic arthritis, and any comorbidities, which included hypertension, diabetes mellitus, and dyslipidaemia. Additionally, details on the concurrent use of methotrexate. Information regarding biologic treatment initiation, including PASI score and reasons for discontinuation, were also noted.

Statistical Analysis

Demographic data were analysed using descriptive statistics, with results expressed as counts (n) and percentages (%) for categorical variables. For continuous variables, the mean and standard deviation (SD) were used to summarize normally distributed data, while the median with interquartile range (IQR) was reported for data that were not normally distributed. Comparisons of categorical variables were conducted using chi-square analysis. All statistical analyses were performed with SPSS software, version 29.0 (IBM Corp, Armonk, NY, USA). Drug survival was evaluated through the Kaplan–Meier method, and a Cox proportional hazards model was used for multivariate analysis to identify predictors of drug survival, including factors such as patient age of onset, gender, prior biologic therapy , comorbidities , and concomitant methotrexate use.

Ethics approval

This study received ethical approval from the Ministry of Health Institutional Review Board and the Medical Research Ethics Committee (NMRR ID-24-01376-RE7).

RESULTS

A total of 285 patients who have received 437 treatment courses were analysed.

Baseline Characteristics

This study analysed the demographic and clinical characteristics of 285 patients initiating their first biologic therapy for psoriasis (Table I). The mean age of psoriasis onset was 28 ±13 years, with patients beginning biologic treatment at an average age of 39 ±16 years. Gender distribution was nearly balanced, with 47.4% female and 52.6% male. Ethnically, the cohort was primarily Malay (64.9%), followed by Chinese (21.1%) and Indian (12.6%)

Table I: Demographic and clinical characteristics of study population with all biologic

Characteristics	N (%)	All biologic (N=285)
Age (years, mean ± SD)	Onset	28 ± 13
	Starting biologic	39 ± 16
Gender n(%)		
	Female	135 (47.4)
	Male	150 (52.6)
Ethnicity n(%)		
	Malay	185 (64.9)
	Chinese	60 (21.1)
	Indian	36 (12.6)
	Others	4 (1.4)
Baseline weight (kg, mean ± SD)		76.6 ± 22.1
BMI (mean ± SD)		28.8 ± 7.5
Baseline BSA (mean ±SD)		48.5 ± 27.6
Baseline PASI (mean ± SD)		24.1 ± 13.2
Comorbidities (n, %)		
	Obesity	97 (34.0)
	DM	72 (25.3)
	HPT	101 (35.4)
	Dyslipidemia	90 (31.6)
Type of psoriasis n(%)		
	Chronic plaque psoriasis	253 (88.8)
	Pustular psoriasis	8 (2.8)
	erythrodermic	19 (6.7)
	others	5 (1.8)
Psoriasis arthritis n(%)		53 (18.6)
Nail Psoriatic n(%)		253 (88.8)
Concomitant use of methotrexate n(%)		8 (2.8)

Table II: Type of biologic in this study

Biologic	1st biologic (n, %)	2nd biologic (n, %)	3rd biologic (n, %)	4th biologic (n, %)	5th biologic (n, %)
Etanercept (ETN)	6 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infliximab (IFX)	1 (0.4)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Adalimumab (ADA)	28 (9.8)	5 (4.8)	1 (2.5)	0 (0.0)	0 (0.0)
Ustekinumab (UST)	80 (28.1)	22 (21.0)	5 (12.5)	3 (30.0)	1 (25.0)
Secukinumab (SEC)	153 (53.7)	40 (38.1)	10 (25.0)	0 (0.0)	1 (25.0)
Ixekizumab (IXE)	4 (1.4)	14 (13.3)	5 (12.5)	0 (0.0)	1 (25.0)
Brodalumab (BRO)	1 (0.4)	0 (0.0)	1 (2.5)	1 (10.0)	0 (0.0)
Guselkumab (GUS)	5 (1.8)	16 (15.2)	9 (22.5)	3 (30.0)	1 (25.0)
Rizankizumab (RIZ)	6 (2.1)	7 (6.7)	9 (22.5)	3 (30.0)	0 (0.0)
Certolizumab (CZP)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	285 (100)	105 (100)	40 (100)	10 (100)	4 (100)

Table III: Reason for discontinuation of existing biologic treatment

Reason for discontinuation	1st biologic (n, %)	2nd biologic (n, %)	3rd biologic (n, %)	4th biologic (n, %)	Category total (n, %)
Treatment failure/loss of efficacy	70 (49.6)	31 (65.0)	9 (69.2)	3 (60.0)	2 (100.0)
Adverse event	4 (2.8)	2 (4.1)	0 (0.0)	0 (0.0)	0 (0.0)
Loss to follow up	9 (6.4)	1 (2.1)	0 (0.0)	1 (20.0)	0 (0.0)
Inadequate funding	36 (25.5)	10 (20.4)	3 (23.1)	1 (20.0)	0 (0.0)
Completion of clinical trial	1 (0.7)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Patient request	0 (0.0)	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)
Achieve remission	7 (5.0)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Pregnancy	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death	5 (3.6)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Undisclosed reason/others	8(5.7)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Total	141 (100)	48 (100)	13 (100)	5 (100)	2 (100)

Table IV: Cox regression analyses: Hazard ratio for risk treatment discontinuation of biologic (n=437)

Variable	Value	Confidence Interval	p-value
Gender(1)	2.123	0.753 - 0.788	0.340
Gender(2)	0.971	-0.030 - 0.221	0.894
Age at Biologic Initiation (years)	0.990	-0.010 - 0.007	0.128
Bodyweight (kg)	1.014	0.014 - 0.013	0.268
BMI	0.981	-0.019 - 0.033	0.572
Obesity	0.833	-0.183 - 0.241	0.449
DM (Diabetes Mellitus)	1.575	0.454 - 0.236	0.054
HPT (Hypertension)	0.934	-0.069 - 0.201	0.732
Dyslipidemia	1.056	0.055 - 0.248	0.825
Psoriatic Arthritis	0.935	-0.067 - 0.175	0.700
Nail Psoriasis	1.099	0.095 - 0.235	0.688
BSA (%)	1.000	0.000 - 0.005	0.968
PASI	1.016	0.016 - 0.009	0.087
Previous Biologic Use	1.415	0.347 - 0.176	0.049
Concomitant Systemic Therapy	1.367	0.312 - 0.206	0.129

Table V: Kaplan Meier drug survival for all the biologic treatment (n=437)

Biologic used	Mean Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
Etanercept	31.556	9.233	13.458	49.653
Infliximab	18.500	14.500	.000	46.920
Adalimumab	17.597	3.261	11.204	23.989
Ustekinumab	41.406	4.499	32.589	50.224
Secukinumab	45.470	4.045	37.543	53.398
Ixekizumab	12.526	1.953	8.699	16.354
Brodalumab	7.667	1.785	4.169	11.165
Guselkumab	33.985	5.609	22.991	44.978
Rizankizumab	41.273	4.899	31.671	50.875
Others	9.200	3.184	2.959	15.441
Overall	40.256	2.867	34.636	45.875

patients. This ethnic breakdown is consistent with the percentage of patients seeking treatment at public dermatology centres in Malaysia.

Baseline characteristics indicated a high prevalence of comorbidities, with obesity present in 34% of patients with mean BMI of 28.8 ± 7.5. This is followed by hypertension (35.4%), dyslipidemia (31.6%), and diabetes mellitus (25.3%). In terms of severity, the mean Body Surface Area (BSA) affected was 48.5% ±27.6 with the baseline Psoriasis Area and Severity Index (PASI) score of 24.1 ±13.2.

Majority (88.8%) were diagnosed with chronic plaque psoriasis, with smaller incidences of pustular (2.8%) and erythrodermic psoriasis (6.7%). Additionally, 18.6% of patients presented with psoriatic arthritis, and 88.8% exhibited nail involvement.

Biologic Usage

Table II shows the distribution of biologics used across multiple lines of therapy. In the first line of biologic therapy (n=285), Secukinumab was the most commonly prescribed biologic (53.7%), followed by Ustekinumab (28.1%) and Adalimumab (9.8%). As patients transitioned to the second line of biologic therapy (n=105), Secukinumab remained widely used (38.1%), while the use of Guselkumab (15.2%) and Ixekizumab (13.3%) increased. In the third line of therapy (n=40), Guselkumab and Rizankizumab each accounted for 22.5% of treatments. In the fourth line of therapy (n=10), Ustekinumab, Guselkumab, and Rizankizumab were each prescribed in 30% of cases. By the fifth line of therapy (n=4), there was an equal distribution of Ustekinumab, Secukinumab, Ixekizumab, and Guselkumab, with each constituting 25% of the treatments.

Reasons for Drug Discontinuation

Table III highlights that treatment failure or loss of efficacy was consistently the leading cause of biologic therapy discontinuation across all therapy lines, increasing from 49.6% in the first line to 100% by the fourth line. Inadequate funding was the second most common reason, contributing 25.5% in the first line, 20.4% in the second line, 23.1% in the third line, and 20.0% in the fourth line treatment. Other less frequent causes included loss to follow-up (6.4% in the first line, 20.0% in the fourth line), adverse events (2.8% in the first line), and achieving remission (4.9% in the first line).

Drug Survival

The Cox regression analysis (Table IV) highlighted that diabetes mellitus (HR=1.575, p=0.054) approached significance, suggesting a potential association with biologic treatment discontinuation. Additionally, prior biologic use

was significantly associated with an increased risk of discontinuation, with a hazard ratio of 1.415 (p=0.049). Other factors, including gender, age at biologic initiation, comorbidities (e.g., obesity, hypertension, dyslipidemia, psoriatic arthritis, nail psoriasis), and disease severity measures (body surface area and PASI score), were not significantly associated with treatment discontinuation.

The Kaplan-Meier drug survival analysis (Table IV) shows that Secukinumab had the longest mean survival time at 45.5 months, followed by Ustekinumab at 41.4 months and Rizankizumab at 41.3 months and. Guselkumab also demonstrated a relatively high mean survival time at 34.0 months, while Etanercept had a mean survival of 31.6 months. Adalimumab and Infliximab had shorter mean survival times of 17.6 and 18.5 months, respectively. Ixekizumab and Brodalumab showed the shortest mean survival times, at 12.5 and 7.7 months, respectively. Across all biologics, the overall mean survival time was 40.3 months

DISCUSSION

Baseline characteristic

The baseline characteristics of our study cohort reveal notable demographic and clinical trends compared to those documented in the local data registry.[13] Our study cohort of 285 patients, who were initiating biologic therapy for psoriasis, had a mean age of psoriasis onset at 28 years and began biologic treatment at an average age of 39 years. This is younger than the age reported in the registry, which documented a mean onset age of 34.1 years among adult patients. This is due to the fact that our study cohort only capture patients who received biologic treatment, where it is noted that early onset of psoriasis is related with more severe psoriasis, hence the requirement of biologic therapy.[14]

The gender distribution was nearly equal. Ethnically, Malay patients predominated, followed by Chinese and Indian patients. This finding indeed similar with our local data registry[13] and corresponded to Malaysian racial distribution. Our cohort exhibits a higher rate of comorbidities compared to the registry data, in all diseases including obesity, hypertension, dyslipidemia, and diabetes mellitus (34% vs 31.4%, 35.4% vs 28.5%, 31.6% vs 22.7%, and 25.3% vs 19.2%, respectively). This is likely because the study cohort exclusively included patients initiating biologic therapy, and the severity of the psoriasis is related with higher metabolic syndrome.[15]

Psoriasis severity in our study cohort was reflected by a higher baseline PASI score of 24.1 and a mean BSA involvement of 48.5%, which is in line with current Malaysian Clinical Practice Guidelines (CPG), biological treatment is reserved for severe psoriasis (PASI >20, DLQI >20 BSA >30%) who have failed, contraindicated, or are intolerant to nonbiological treatment.[16] Interestingly, nail involvement was significantly higher in our cohort at 88.8% compared to the local registry data at 57.7% [13], indicating a potentially more severe presentation of psoriasis in patients with nail involvement.[17] Lastly, psoriatic arthritis is present in 18.6% of patients, consistent with the recognized association between psoriasis and joint involvement and almost similar to local registry at 18.8%.[13]

Biologic usage

Secukinumab was the most commonly prescribed biologic in our cohort study, this is similar with our local registry[13], as well as other country where there is increasing of the usage of Secukinumab as initial biologic.[18] This preference is driven by Secukinumab's robust efficacy and favourable safety profile, which have been demonstrated in clinical trials and real-world settings.[19-20] Additionally, compassionate use programs for Secukinumab have contributed to its accessibility and widespread adoption as a first-line biologic option. Upon selection of 2nd biologic onwards, there is a trend of increase usage of IL23, namely Guselkumab and Rizankuzumab. It is largely based on the favourable safety profile, high efficacy, and superior drug survival associated with IL-23 inhibitors.[10,21]

Reason of discontinuation

Treatment failure or loss of efficacy was identified as the leading cause of discontinuation across all lines of therapy, starting at 49.6% in the first line and increasing trend toward the fourth line. Factors contributing to loss of efficacy include drug-related factors, such as the presence of anti-drug antibodies22; patient-related factors, such as genetic susceptibility23; and treatment-related factors, such as dosage interval, frequency, or duration.[22] However, this study did not examine the specific factors associated with treatment failure or loss of efficacy in detail. The second most common reason for discontinuation was inadequate funding. This is particular similar to previous local studies 24, as well as studies in Korea and Asian pacific where cost is a major factor for noncompliance, especially in settings where the treatment is not reimbursed.[25-26]

Drug Survival

The Cox regression analysis indicates that certain factors may influence the discontinuation of biologic treatments. Notably, prior biologic use was significantly associated with an increased risk of discontinuation (HR = 1.415, p = 0.049). This suggests that patients with a history of biologic therapy use or exposure are more likely to discontinue subsequent treatments. This finding aligns with previous research, which has shown that biologic-experienced patients often have higher discontinuation rates compared to biologic-naïve patients.[27] One possible explanation is that biologic-experienced patients tend to have higher rates of treatment resistance or adverse reactions to subsequent biologics, which may contribute to a higher discontinuation rate. This has been noted in real-world evidence studies across multiple countries, where patients previously exposed to biologics are more likely to experience secondary loss of efficacy due to the development of anti-drug antibodies or tolerance to the medication.[22-28] Studies have shown that patients who have failed prior biologic treatments, particularly due to ineffectiveness, tend to have lower drug survival when switching to subsequent biologic therapies. This is likely because these patients may have more complex forms of psoriasis that do not respond well to treatments targeting different mechanisms. For instance, when patients fail to respond to first-line biologics like ustekinumab, their disease may not be driven by the same immune pathways targeted

by second-line treatments such as secukinumab or ixekizumab, leading to poorer outcomes. Additionally, dosing regimens can play a crucial role in treatment failure. Inadequate dosing, especially with IL-17A inhibitors like secukinumab and ixekizumab, can result in higher attrition rates, particularly for patients on second- or third-line treatments. These medications may fail to maintain an effective response in certain patients, leading to early discontinuation.[10] However, in our study, prior biologic use as an indicator for discontinuation only achieved marginal significance. There remains potential that it might not be a definitive factor, as shown in findings from the Danish region.[29]

Additionally, diabetes mellitus approached statistical significance as a factor associated with treatment discontinuation (HR = 1.575, p = 0.054). This suggests a potential link between diabetes and the likelihood of stopping biologic therapy. While the association was not statistically significant in this analysis, it is consistent with other studies that have identified comorbid conditions, including diabetes, as factors that may influence treatment adherence and persistence.[30] There is no clear study explaining the factors that relate comorbidities to drug survival. A possible explanation could be that patients with diabetes, especially those on subcutaneous(SC) insulin, may experience reduced efficacy of drug delivery. SC insulin can alter the local tissue microenvironment in which biologics are administered. The injection site of insulin can experience localized inflammation, which may influence the absorption of subsequent biologics introduced at the same site. This phenomenon raises concerns that insulin administration might hinder the absorption and efficacy of biologics, potentially leading to suboptimal treatment outcomes for psoriasis. Local cutaneous reactions or modifications to the tissue architecture induced by frequent insulin injections may interfere with the pharmacokinetics of biologics, leading to decreased drug survival and efficacy over time. Additionally, the complexity of the disease, such as the need for multiple medications and more systemic inflammation compared to the general population, may contribute to this relationship.

The Kaplan-Meier analysis shows Secukinumab with the longest mean survival time at 45.5 months. This result can be attributed to several factors specific to its use and real-world treatment dynamics. Secukinumab's earlier market introduction compared to newer biologics, such as guselkumab and other IL-23 inhibitors, likely contributed to its observed longevity in the dataset. Approved in 2016 in Malaysia , Secukinumab had a head start in accumulating real-world evidence and was widely adopted as a standard biologic for treating moderate-to-severe psoriasis. Additionally, previous local data from Malaysia showed that ustekinumab had the longest drug survival among biologics compared to others. This is likely because ustekinumab was introduced earlier than secukinumab.[24] This earlier availability allowed for larger sample sizes, longer follow-up periods, and more comprehensive data in real-world studies compared to newer biologics, providing an advantage in Kaplan-Meier survival analysis.[31]

Besides that, patient characteristics, such as treatment-naïve populations and the sequencing of biologics, may contribute to the findings. Secukinumab, being an earlier option for treatment, was more commonly used as a first-line biologic, which is associated with higher persistence rates in treatment. In contrast, newer biologics such as guselkumab might have been prescribed for patients who had previously failed or discontinued other biologics, potentially reducing their drug survival due to prior treatment resistance or adverse experiences.[10,27] In the recent studies, there is also support that IL-23 is having more longer drug survival.[10] When comparing Ustekinumab with Secukinumab, although Ustekinumab has been approved for a longer time, Secukinumab demonstrates the longest drug survival. This aligns with real-world data, where Secukinumab is superior in both efficacy and drug survival compared to Ustekinumab.[32]

Lastly, Rizankizumab had the 3rd-longest mean drug survival then followed by guselkinumab. Several factors may explain this result. Firstly, the small number of patients treated with Rizankizumab compared to other biologics may have contributed to bias in the mean survival estimate in the Kaplan-Meier survival analysis.[31] Secondly, this could be attributed to improved compliance, as the reduced frequency of hospital visits required for Rizankizumab compared to other biologics may enhance adherence to the medication.[33]

An interesting finding from Taiwan, as observed in a 2022 study, is that ustekinumab has the best drug survival, followed by secukinumab. These results are particularly relevant to Taiwan, where the reimbursement system for biologics and the limited use of secukinumab during the data collection period played a role.[34] This finding is similar to a previous study conducted in Malaysia in 2022.[24] However, there is a limited number of studies from other ASEAN countries. This contrasts with meta-analyses suggesting guselkumab is the superior biologic in terms of drug survival.[10]

LIMITATIONS

Our study has several notable limitations. First, as a retrospective analysis, the study lacked random assignment of participants to treatment groups. Additionally, the data on biologic therapies varied due to differences in their timelines of availability. Additionally, the study did not capture the frequency and duration gaps between subsequent biologic injections.

Second, there is potential for selection bias in prescribing patterns commonly observed in routine clinical settings. For instance, our analysis revealed a significantly higher number of patients receiving Secukinumab. This reflects real-world practices, where treatment decisions are influenced by factors such as cost, clinical efficacy, safety profiles, ease of administration, and the preferences of both healthcare providers and patients.

Third, the study did not account for cases where patients returned to a previously used biologic after trying another (e.g., switching from Drug A to Drug B and then back to Drug

A). These switching patterns could have affected the evaluation of treatment durability and overall effectiveness, introducing potential biases.

Fourth, The Kaplan-Meier analysis assessed overall drug survival without distinguishing between biologic-naïve and biologic-experienced patients, limiting the depth of the analysis.

Finally, the study lacked detailed data on the long-term drug survival of newer biologic therapies. Future research should aim to evaluate the sustained duration and performance of recently introduced treatments to provide a more comprehensive understanding of their long-term clinical outcomes.

CONCLUSION

This study highlights the demographic and clinical factors influencing biologic drug survival among psoriasis patients in Malaysia. Secukinumab was the most commonly prescribed biologic, with the longest survival due to its early market introduction and robust efficacy. Loss of efficacy and inadequate funding were the primary reasons for treatment discontinuation, with prior biologic use and comorbidities like diabetes affecting persistence. While IL-23 inhibitors showed promising survival rates, further research is needed to address the study's limitations, including the long-term outcomes of newer biologics and switching patterns. These findings emphasize the need for tailored treatment strategies to enhance patient outcomes.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest to disclose.

ACKNOWLEDGMENT

We would like to thank the Director General of Health Malaysia for his permission to publish this article. We would like to thank Dr. Kubheran Selva Kumar for his assistance in organizing the data in SPSS.

FUNDING

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

REFERENCES

1. Di Cesare A, Di Meglio P, Nestle FO. The IL-23/Th17 axis in the immunopathogenesis of psoriasis. J Invest Dermatol 2009; 129(6): 1339-50.
2. Zaba LC, Cardinale I, Gilleaudeau P, Sullivan-Whalen M, Suarez-Farinas M, Fuentes-Duculan J, et al. Amelioration of epidermal hyperplasia by TNF inhibition is associated with reduced Th17 responses. J Exp Med 2007; 204(13): 3183-94.
3. Daniele SG, Eldirany SA, Damiani G, Ho M, Bunick CG. Structural basis for p19 targeting by anti-IL-23 biologics: correlations with short- and long-term efficacy in psoriasis. JID Innov 2024; 4(2): 100261.
4. Lebwohl M, Papp K, Han C, Schenkel B, Yeilding N, Wang Y, et al. Ustekinumab improves health-related quality of life in patients with moderate-to-severe psoriasis: results from the PHOENIX 1 trial. Br J Dermatol 2010;162(1): 137-46.
5. Caldarola G, Falco GM, Calabrese L, D'Amore A, Chiricozzi A, Mariani M, et al. Drug survival of biologics and non-biologics in patients affected by palmoplantar psoriasis: a "real-world", mono-center experience. Int J Dermatol 2024; 63(1): 51-8.
6. Costanzo A, Malara G, Pelucchi C, Fatiga F, Barbera G, Franchi A, et al. Effectiveness end points in real-world studies on biological therapies in psoriasis: systematic review with focus on drug survival. Dermatology 2018; 234(1-2): 1-12.
7. Augustin M, Jullien D, Martin A, Peralta C. Real-world evidence of secukinumab in psoriasis treatment - a meta-analysis of 43 studies. J Eur Acad Dermatol Venereol 2020; 34(6): 1174-85.
8. Nast A, Smith C, Spuls PI, Avila Valle G, Bata-Csorgo Z, Boonen H, et al. EuroGuiDerm guideline on the systemic treatment of Psoriasis vulgaris - part 1: treatment and monitoring recommendations. J Eur Acad Dermatol Venereol 2020; 34(11): 2461-98.
9. Ruiz-Villaverde R, Rodriguez-Fernandez-Freire L, Galan-Gutierrez M, Armario HJC, Martinez-Pilar L. Drug survival, discontinuation rates, and safety profile of secukinumab in real-world patients: a 152-week, multicenter, retrospective study. Int J Dermatol 2020; 59(5): 633-9.
10. Yiu ZZN, Becher G, Kirby B, Laws P, Reynolds NJ, Smith CH, et al. Drug survival associated with effectiveness and safety of treatment with guselkumab, ixekizumab, secukinumab, ustekinumab, and adalimumab in patients with psoriasis. JAMA Dermatol 2022; 158(10): 1131-41.
11. Robinson S, Moon TM, Eng TK, Yuen TT, Jong TJ, Selvarajah L, et al. Dermatology Life Quality Index in patients with psoriasis treated with biologic versus non-biologic treatment in Malaysia: A retrospective cross-sectional study. Drugs Real World Outcomes 2023; 10(2): 291-8.
12. Mohd Affandi A, Khan I, Ngah Saaya N. Epidemiology and clinical features of adult patients with psoriasis in Malaysia: 10-year review from the Malaysian Psoriasis Registry (2007-2016). Dermatol Res Pract 2018; 2018: 4371471.
13. Robinson ST, MM; Ramalingam R.; Voo SYM; Selvarajah L.; Jamil A.; Kwan Z.; Loo CH. The Twelfth Report of the Malaysian Psoriasis Registry 2020-2022. Kuala Lumpur, Malaysia; 2024.
14. Henseler T, Christophers E. Psoriasis of early and late onset: characterization of two types of psoriasis vulgaris. J Am Acad Dermatol 1985; 13(3): 450-6.
15. Engin B, Kutlubay Z, Yardimci G, Vehid HE, Ambarcioglu P, Serdaroglu S, et al. Evaluation of body composition parameters in patients with psoriasis. Int J Dermatol. 2014;53(12):1468-73.
16. Ministry of Health Malaysia DSoM. Management of Psoriasis Vulgaris. Putrajaya; 2013.
17. Kaeley GS, Eder L, Aydin SZ, Rich P, Bakewell CJ. Nail psoriasis: Diagnosis, assessment, treatment options, and unmet clinical needs. J Rheumatol 2021; 48(8): 1208-20.
18. Strober B, Patil D, McLean RR, Moore-Clingenpeel M, Guo N, Levi E, et al. Utilization trends and impact of secukinumab treatment on clinical outcomes in biologic-naive patients with psoriasis in a US real-world setting. Dermatol Ther (Heidelb) 2022; 12(6): 1351-65.
19. Cai L, Zhang JZ, Yao X, Gu J, Liu QZ, Zheng M, et al. Secukinumab demonstrates high efficacy and a favorable safety profile over 52 weeks in Chinese patients with moderate to severe plaque psoriasis. Chin Med J (Engl) 2020; 133(22): 2665-73.
20. Russo F, Galluzzo M, Stingeni L, Persechino S, Zichichi L, Conti A, et al. Long-term drug survival and effectiveness of secukinumab in patients with moderate to severe chronic plaque psoriasis: 42-month results from the SUPREME 2.0 study. Clin Cosmet Investig Dermatol 2023; 16: 3561-74.
21. Thomas SE, Barenbrug L, Hannink G, Seyger MMB, de Jong E, van den Reek J. Drug survival of IL-17 and IL-23 inhibitors for psoriasis: A systematic review and meta-analysis. Drugs 2024; 84(5): 565-78.

22. Jullien D, Prinz JC, Nestle FO. Immunogenicity of biotherapy used in psoriasis: The science behind the scenes. J Invest Dermatol 2015; 135(1): 31-8.
23. Bartelds GM, Krieckaert CL, Nurmohamed MT, van Schouwenburg PA, Lems WF, Twisk JW, et al. Development of antidrug antibodies against adalimumab and association with disease activity and treatment failure during long-term follow-up. JAMA 2011; 305(14): 1460-8.
24. Mashor M, Wong K, Tey K, Choon S. A retrospective study on drug survival of biologic among patients with psoriasis seen in tertiary hospital in Johor Malaysia. Med J Malaysia 2022; 77: 689-95.
25. Choi CW, Yang S, Jo G, Kim BR, Youn SW. Economic factors as major determinants of ustekinumab drug survival of patients with chronic plaque psoriasis in Korea. Ann Dermatol 2018; 30: 668-75.
26. Youn SW, Tsai TF, Theng C, Choon SE, Wiryadi BE, Pires A, et al. The MARCOPOLO study of ustekinumab utilization and efficacy in a real-world setting: Treatment of patients with plaque psoriasis in Asia-Pacific countries. Ann Dermatol 2016; 28(2): 222-31.
27. Harrold LR, Stolshek BS, Rebello S, Collier DH, Mutebi A, Wade SW, et al. Impact of prior biologic use on persistence of treatment in patients with psoriatic arthritis enrolled in the US Corrona registry. Clin Rheumatol 2017; 36(4): 895-901.
28. Hsu L, Snodgrass BT, Armstrong AW. Antidrug antibodies in psoriasis: A systematic review. Br J Dermatol 2014; 170(2): 261-73.
29. Thein D, Nielsen ML, Maul JT, Thomsen SF, Thyssen JP, Egeberg A. Impact of the pre-biologic treatment journey on biologic drug survival in psoriasis: A nationwide cohort study. J Eur Acad Dermatol Venereol. 2024.
30. Jung SW, Lim SH, Jeon JJ, Heo YW, Choi MS, Hong SP. Comparison of the efficacy and safety of biologics (secukinumab, ustekinumab, and guselkumab) for the treatment of moderate-to-severe psoriasis: Real-world data from a single Korean center. Biomedicines 2022; 10(5).
31. Bland JM, Altman DG. Survival probabilities (the Kaplan-Meier method). BMJ 1998; 317(7172): 1572.
32. Yiu ZZN, Mason KJ, Hampton PJ, Reynolds NJ, Smith CH, Lunt M, et al. Randomized trial replication using observational data for comparative effectiveness of secukinumab and ustekinumab in psoriasis: A study from the British Association of Dermatologists Biologics and Immunomodulators Register. JAMA Dermatol 2021; 157(1): 66-73.
33. Mourad AI, Gniadecki R. Biologic drug survival in psoriasis: A systematic review & comparative meta-analysis. Front Med (Lausanne) 2020; 7: 625755.
34. Huang YH, Tang CH, Goh CH, Chang CL, Qiu H, Yang YW, et al. Persistence and adherence to biologics in patients with psoriasis in Taiwan: A new biologics user cohort study. Front Pharmacol 2022; 13: 880985.

Attitudes, beliefs and willingness to prescribe medical cannabis among public medical practitioners in Malaysia

Siti Sabrina Kamarudin, PhD[1,2], Ee Vien Low, PhD[3], Ooi Cheng Lee, MBBS[1], Liyana Ahamad Fouzi, MB BCh BAO[4], Afham Mohd Muharam, MD[5], Hajar Ahmad Rosdi, MD[6], Abdul Hadi Sharifudin, MBBS[7], Kalaiarasu M Peariasamy, MSc[8,9]

[1]Institute for Clinical Research, National Institute for Health, Ministry of Health Malaysia, Setia Alam, Shah Alam, Selangor, Malaysia, [2]Clinical Research Centre, Shah Alam Hospital, Ministry of Health Malaysia, Shah Alam, Selangor, Malaysia, [3]Institute For Health Systems Research, National Institute for Health, Ministry of Health Malaysia, Setia Alam, Shah Alam, Selangor, Malaysia, [4]Clinical Research Centre, Sultanah Nur Zahirah Hospital, Ministry of Health Malaysia, Kuala Terengganu, Terengganu, Malaysia, [5]Clinical Research Centre, Cheras Rehabilitation Hospital, Ministry of Health Malaysia, Cheras, Wilayah Persekutuan Kuala Lumpur, [6]Clinical Research Centre, Selayang Hospital, Ministry of Health Malaysia, Batu Caves, Selangor, Malaysia, [7]Clinical Research Centre, Tuanku Ampuan Najihah Hospital, Ministry of Health Malaysia, Kuala Pilah, Negeri Sembilan, Malaysia, [8]School of Medicine, Taylor's University, Subang Jaya, Selangor, Malaysia, [9]SEGi University, Kota Damansara, Petaling Jaya, Selangor, Malaysia

ABSTRACT

Introduction: Currently, several countries have implemented regulations governing the use of medical cannabis. Recreational use of cannabis is illegal under Malaysian laws and it is unclear what medical practitioners think of cannabis when it is used for medical purposes. We conducted a nationwide survey in Malaysia to study the attitudes, beliefs and willingness of public medical practitioners to prescribe medical cannabis.

Materials & Methods: A 23-item online questionnaire was administered to 420 medical practitioners working in government institutions. Participant demographics, clinical specialities, employment history, exposure to knowledge of medical cannabis and case vignettes related to the use of medical cannabis were collected and analysed.

Results: Sixty-five percent of medical practitioners agreed that medical cannabis should be available for certain conditions, particularly pain (87%). Most medical practitioners in the case vignettes were willing to recommend medical cannabis to treat pain due to cancer (74.3%) and chronic pain (66.9%). Logistic regression indicated that both gender and exposure to information on medical cannabis are significant factors ($p<0.05$) in predicting the willingness of medical practitioners to prescribe medical cannabis.

Conclusion: Medical practitioners in the public institutions showed favourable attitudes towards prescribing medical cannabis for chronic pain and cancer pain. However, further work is required to examine factors that drive these attitudes, and potential prescribing behaviour including those in private and university settings. A thorough evaluation of the scientific evidence and related legislation is essential, especially if a regulated pathway is to be adopted. In this situation, medical practitioners must have a clear understanding of clinical practice guidelines regarding pain indications, dosing and monitoring protocols as well as effective pharmacovigilance. Additionally, this should be combined with targeted evidence-based training on medical cannabis for medical practitioners.

KEYWORDS:
Medical cannabis, marijuana, willingness, perception, attitude, pain management, medical practitioners

INTRODUCTION

Medical cannabis is prescribed or dispensed by healthcare professionals in many countries as an alternative treatment for a variety of conditions such as multiple sclerosis, epilepsy, and for patients with chronic pain.[1-2] Around 30 countries including Canada, Australia, the Netherlands, New Zealand, Uruguay, the United Kingdom and several US states have enacted legislations regulating medical cannabis.[3-4] Most medical practitioners avoid prescribing it, partly due to anti-cannabis laws and a lack of high-quality clinical trial evidence. The use of medical cannabis therefore depends on regulation, medical knowledge, clinical practice guidelines and the individual needs of the patient.[5] However, many medical practitioners have expressed concerns about the safety of medical cannabis, in particular its psychoactive effects and the potential for abuse. Nonetheless, some medical experts support medical cannabis as a safe drug with a lower risk of dependence than benzodiazepines.[6]

In Malaysia, current laws such as the Dangerous Drugs Act, Poisons Act, and the Sale of Drugs Act prohibits the possession, planting, harvesting and processing of cannabis.[7] In special cases the import of cannabis-based medicines is permitted for research or clinical trial purposes, subject to prior approval from the Ministry of Health.[8] Given that many countries have enacted laws permitting medical cannabis, there is on-going public debate and growing policy discussion; however, locally generated evidence regarding the views of Malaysian medical practitioners on medical cannabis, particularly in public institutions, remains limited. This includes concerns over safety, robustness of evidence supporting its use, regulation issues, and the absence of

This article was accepted: 20 November 2025
Corresponding Author: Siti Sabrina Kamarudin
Email: ssabrina@moh.gov.my

clinical practice guidelines. To address this gap, we aimed to study the attitudes, beliefs, and willingness to use medical cannabis among medical practitioners in public health institutions in Malaysia.

MATERIALS AND METHODS

Study population & data collection

We conducted a cross-sectional online survey of public health medical practitioners designated as medical officers, specialists or consultants working in six zones (Northern, Central, Southern, East Coast, Sabah, Sarawak) in the Ministry of Health (MOH) Malaysia. University affiliated and private sector medical practitioners were not included. Eligible respondents represented multiple disciplines, including Family Medicine/Primary Care, Internal Medicine, Emergency Medicine, Anaesthesiology, Obstetrics & Gynaecology, Psychiatry, Neurology, Rehabilitation Medicine, Oncology/Haematology, Palliative Care, Surgery, Orthopaedics, Paediatrics, and Public Health. The minimum sample size of 419 respondents was determined using the Raosoft® formula with a margin of error of 5%, a 95% confidence level, and a dropout rate of 10%, based on a total of 28,459 medical practitioners registered with the Ministry of Health Malaysia.[9] Participants were selected through convenient sampling via dissemination of survey links at each designated MOH hospital/department workgroups. The survey period was from 1 September 2022 to 28 February 2023, using the REDcap web application hosted by the Institute for Clinical Research, National Institutes of Health, Ministry of Health Malaysia. Informed consent was obtained online from all study participants.

Measures

The questionnaire was adapted from existing instruments.[5,10] The section on "Attitudes and Beliefs" was based on a questionnaire developed by Philpot et al. (10) to study healthcare providers' attitudes, beliefs, and knowledge about medical cannabis within the Minnesota healthcare system.[10] The section on case vignettes presented patients who qualify for medical cannabis as described by Zolotov et al. (5). These vignettes were validated through a Delphi study that included ten expert physicians, ensuring their validity and significance.[11]

Due to the lack of established guidelines regarding medical cannabis in Malaysia, our study emphasized the importance of content validation and contextual appropriateness through a process that involved three local experts. This validation process, highlighted by unanimous expert approval for most survey items, was evidenced by a high Content Validity Index (CVI). Items 1 and 4 exhibited a low CVI and were therefore revised. In addition, the questionnaire's relevance to the Malaysian context was affirmed by all experts, as well as through a pretest carried out with five medical practitioners for face validation. The five sections of the questionnaire are as follows:

Section A: Socio-demographic characteristics

Medical practitioners were surveyed regarding their gender, area of medical practice, specialty, professional experience, and exposure to information on medical cannabis.

Section B: Medical Practitioners Attitude on medical cannabis for patient treatment

Medical practitioners' attitudes towards medical cannabis were assessed using a 5-point Likert scale.

Section C: Medical Practitioners Beliefs on medical cannabis for patient treatment

Medical practitioners' beliefs on medical cannabis including perceived benefits, increased risks, and the potential for patient improvement were assessed using a 5-point Likert scale along with a "don't know" option.

Section D: Medical Practitioners Willingness to prescribe medical cannabis

Two clinical vignettes were presented; Case 1 involved a patient suffering from chronic pain while Case 2 concerned a patient diagnosed with cancer. Both patients were verified by a panel of experts as being well representative of patients who qualify for treatment with medical cannabis.[5] Respondents were asked to rate their intention to recommend medical cannabis for each clinical vignette using a 5-point Likert scale. The findings were classified into two categories for analysis: "willing" and "not willing" with "unsure" categorized as "not willing".

Statistical Analysis

Data analysis was performed using R version 4.2.3.[12] Demographics and baseline characteristics of the respondents were summarized using descriptive statistics.

The interaction between the variables and willingness to prescribe medical cannabis for both clinical vignettes was assessed. The results showed that the variance inflation factor for the clinical vignettes (chronic pain and cancer pain) exceeded 2.2, indicating that there was absence of multicollinearity. Next, to assess the association between the independent variables and the willingness to prescribe medical cannabis, univariate and multivariate logistic regression was used. The threshold point of 7 years of professional experience was set for mid-level medical practitioners, with work areas categorised into non-clinical, clinical and support services. A two-tailed p value <0.05 was considered statistically significant. All models were controlled for gender, job title, work area, and exposure to information on medical cannabis.

Ethics approval

The study proposal and consent information sheet has been approved by Malaysian Medical Research and Ethic Committee (MREC) with reference number: (NMRR ID-22-02260-DHZ (IIR). Informed consent was obtained from all patients prior to the conduct of the interviews. To protect privacy and confidentiality of participants, all identifiers were not used.

RESULTS

A total of 472 medical practitioners participated in the online survey, and following a thorough review for completeness, 420 questionnaires were evaluated. Table I reports on the demographic characteristics of the respondents in the 6 zones; Klang Valley (29%), Northern region (21%), Southern

Table I: Demographic characteristics of respondents (N=420)

Variables		Value
Age (years) [a]		37.05 (7.24)
Total Years in Service [a]		11.56 (7.17)
Designation	Consultant	49 (11.7)
	Specialist	105 (25.0)
	Medical Officer	266 (63.3)
Fraternity	Medical	63 (15.0)
	Surgical	35 (8.3)
	Psychiatry	33 (7.9)
	Anaesthesiology	33 (7.9)
	Emergency & Trauma	31 (7.4)
	Administration	28 (6.7)
	Clinical Research	27 (6.4)
	Primary Care	24 (5.7)
	Pathology	20 (4.8)
	O&G	18 (4.3)
	Orthopaedic	18 (4.3)
	Rehabilitative Medicine	17 (4.0)
	Ophthalmology	14 (3.3)
	Paediatric	13 (3.1)
	Radiology	12 (2.9)
	Oncology	7 (1.7)
	Palliative Medicine	6 (1.4)
	ORL	6 (1.4)
	Transfusion Medicine	5 (1.2)
	Maxillofacial	2 (0.5)
	Paediatric Dental	1 (0.2)
	Others+	7 (1.7)
Gender	Male	196 (46.7)
	Female	224 (53.3)
Years in Service	Less than 3 years	36 (8.6)
	3 – 6 years	97 (23.1)
	7 – 10 years	94 (22.4)
	11 – 15 years	104 (24.8)
	16 years and above	89 (21.2)
Zone of working place	Klang Valley	122 (29.0)
	Northern Peninsular	86 (21.0)
	Sarawak	77 (18.0)
	Sabah	60 (14.0)
	Southern Peninsular	42 (10.0)
	East Coast	33 (8.0)
Exposure to information on Medical Cannabis	No	196 (40.7)
	Yes	224 (59.3)
If yes, Platform of information received (n = 285)	I have done my own research	141 (29.3)
	CME/lecture	114 (23.7)
	Course	19 (4.0)
	Grand Rounds	11 (2.3)
Case Vignette		
Chronic Pain Case	Willing to prescribe MC	281 (66.9)
	Not Willing to prescribe MC	139 (33.1)
Cancer Pain Case	Willing to prescribe MC	312 (74.3)
	Not willing to prescribe MC	108 (25.7)

[a] reported in mean (SD). Values are n (%) unless indicated otherwise.
Abbreviations: MC, medical cannabis.

region (10%), East Coast (8%), Sabah (14%) and Sarawak (18%). The majority of respondents consisted of medical officers (63%), with about 15% from medical departments. The ages of the respondents ranged from 26 to 58 years with a mean age of 37.05 years (SD=7.24). There was no statistically significant difference in the mean age between male and female medical practitioners (p=0.99). Based on the clinical vignettes, more than two-thirds of respondents expressed a willingness to prescribe medical cannabis as treatment for chronic pain (66.9%) and cancer pain (74.3%), respectively.

Most respondents had positive attitudes regarding medical cannabis and opinionated that medical cannabis could be made available by prescription for certain medical conditions (Figure 1). Additionally, a significant number of medical practitioners expressed confidence in discussing medical cannabis with their patients, with 41% of them believing that patients could benefit from the treatment. However, approximately one third of respondents (31.4%) would refrain from prescribing medical cannabis due to perceived risks of abuse and dependence.

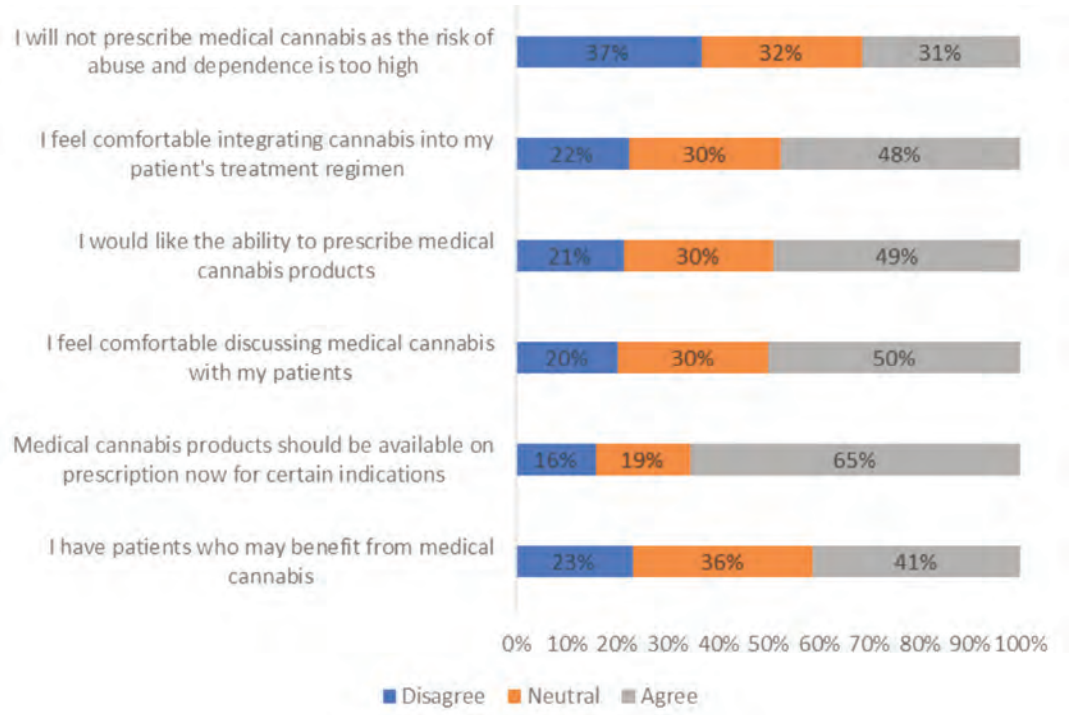


Fig. 1: Attitude on usagae of medical cannabis (N=240)

The most significant scores for medical cannabis treatment were for pain relief (87%), anxiety (65%), and both depression and insomnia (55%). Figure 2A illustrates medical practitioners' opinion on medical cannabis use, based on clinical symptoms. About a third of medical practitioners were unsure about the effectiveness of medical cannabis in treating symptoms such as tics (30%) and seizures (27%). The lowest score was for weight loss (21.4%).

Figure 2B illustrates medical practitioners' perceptions on the usefulness of medical cannabis for specific conditions. The highest scores were attributed to severe/chronic cancer pain, nausea, or severe vomiting, or cachexia or severe wasting (85%), followed by intractable pain (79%), and terminally ill with a life expectancy of less than one year (74%).

On the therapeutic effects of cannabinoids, a significant number of medical practitioners responded as "Don't know" regarding autism (39%), obstructive sleep apnoea (38%), inflammatory bowel disease (42%), amyotrophic lateral sclerosis (42%) and glaucoma (43%) (Figure 3). Approximately one-third of the respondents held the view that medical cannabis may increase the risk of six conditions or symptoms with the highest risk associated with overdose (52%), psychotic symptoms (50%), and accidents (48%).

Multivariate logistic regression indicated that male gender was associated with a lower odd of prescribing medical cannabis for chronic pain (aOR=0.59, 95%CI 0.38, 0.91) and pain due to cancer (aOR=0.58 95% CI 0.36, 0.93) (Table II). Also, exposure to medical cannabis information was associated with lower odds (aOR=0.51 95% CI 0.32, 0.81) of prescribing medical cannabis for pain treatment due to cancer.

DISCUSSION

In this study involving medical practitioners in public institutions, one-third of the practitioners expressed reluctance to prescribe medical cannabis due to concerns about potential abuse or dependency. Most medical practitioners held a positive attitude towards prescribing medical cannabis for specific conditions, such as chronic pain and cancer pain. This finding is consistent with research that shows the benefits of medical cannabis in pain management.[10,13] In Malaysia, there is strong acceptance of traditional and complimentary medicine (TCM) which may explain why medical practitioners have a positive attitude towards medical cannabis. Furthermore, in recent years, there has been an increase in patient demand for complementary and alternative medicines,[14] which is likely to influence medical practitioner's willingness to prescribe medical cannabis. Interestingly, Dapari et al. (15) found that 64.7% of the Malaysian public support the legislation of medical cannabis as implemented in countries like Thailand and Australia, where traditional medicinal products are also well established.[16-17]

Studies show that medical practitioners with a strong understanding of medical cannabis often exercise caution when recommending its use, primarily due to concerns regarding safety and effectiveness.[5] Our findings similarly demonstrated that access to information correlated with a reduced willingness to prescribe. Factors contributing to this may include a lack of high-quality trial evidence for some indications, uncertainty around dosing and product standardisation, drug to drug interaction, variability in formulations, and significant medicolegal risks in settings where routine prescribing is not authorised.[7,19] These findings suggest a need for informed caution rather than simple

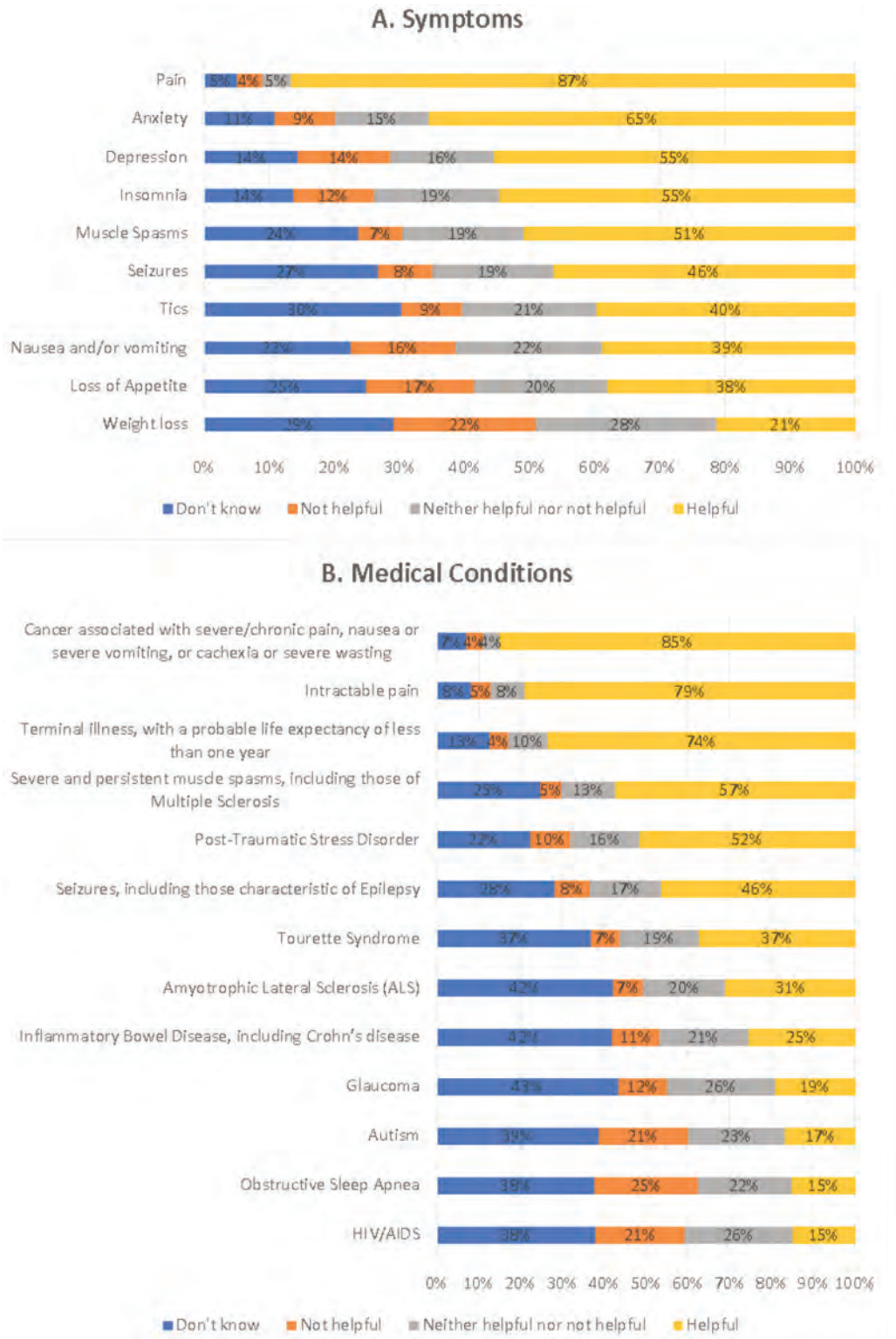


Fig. 2: Belief in helpfulness of medical cannabis

scepticism. The numerous "don't know" responses for various neurological conditions in our findings support this idea and shows an awareness of existing gaps rather than indifference. In adjusted analyses, male medical practitioners were less willing to prescribe medical cannabis for chronic pain and cancer pain. While our cross-sectional data cannot identify the underlying mechanisms, this trend aligns with some surveys reporting female clinicians demonstrate more support for medical cannabis in palliative care settings, suggesting the presence of gender differences in evaluating benefits and risks.[19] Furthermore, existing literature also reveal systematic gender differences in professional styles and perceptions that may influence prescribing intentions, as female physicians too often use more patient centred

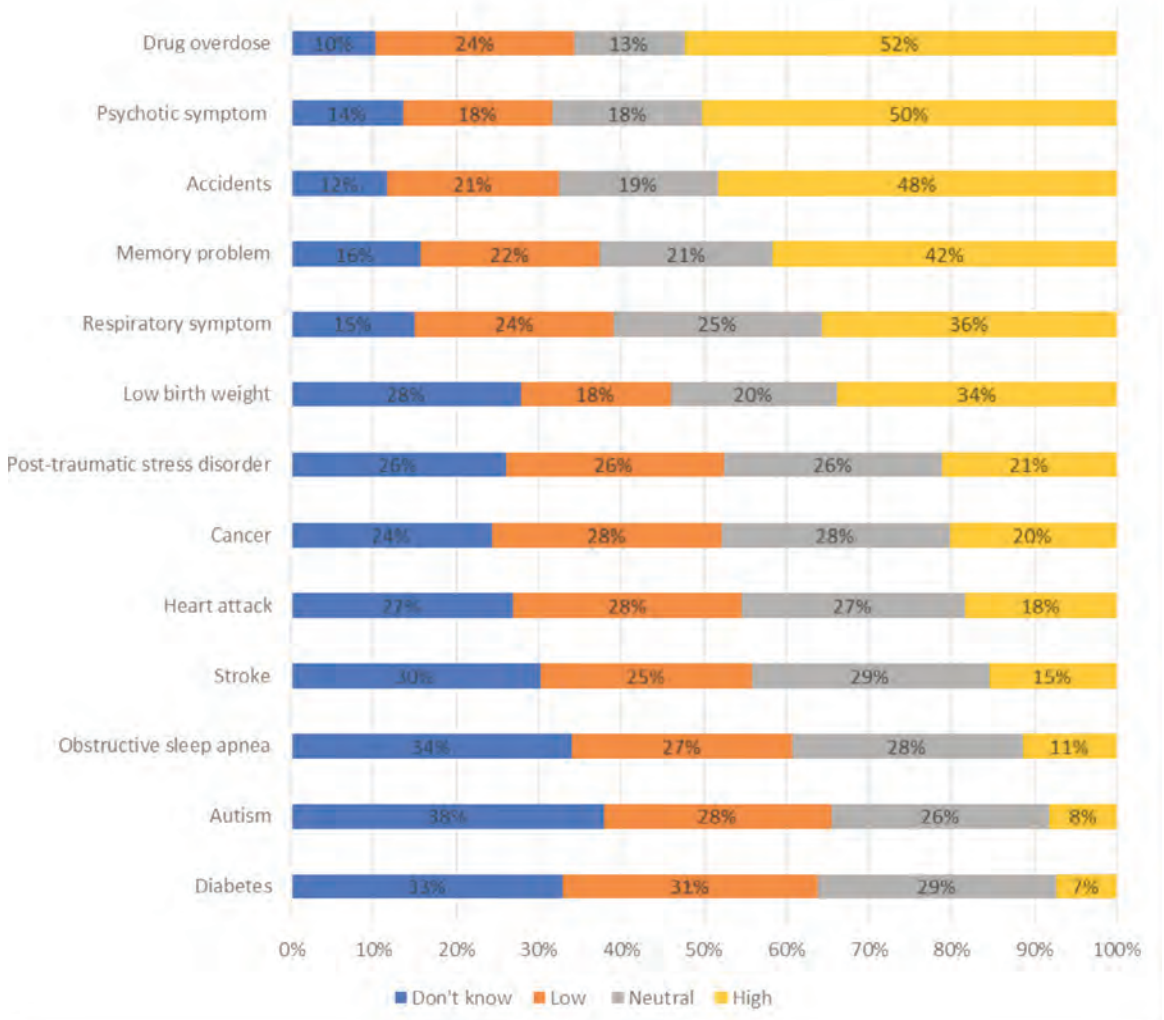


Fig. 3: To what extend the medical cannabis increase the risk for the following conditions

communication, place greater emphasis on prevention, and provide more discussions, counselling, services and concrete recommendations.[23-24] Such approaches may enhance receptivity to adjunctive symptom relief options.[25] Nevertheless, evidence on gender and the adoption of new therapies remains inconsistent and context-dependent, and with factors such as specialty mix or seniority potentially confounding our findings. Future research should stratify by discipline and measure constructs such as medicolegal risk tolerance and communication approach.[26]

Various countries have taken different approaches to medical cannabis use, including broader legalization, decriminalization, and allowing for medical use only. Notably, Canada has established a highly regulated cannabis law system, which has facilitated access for nearly 400,000 patients in Canada's evolving culture of medical cannabis use, especially for chronic pain.[30–32] In the United States, the implementation of medical cannabis laws has not resulted in a significant increase in traffic accidents or cannabis use among adolescents; rather, it has led to a decrease in arrests and an increase in tax revenue.[33-34] Initially, the UK had strict regulations on medical cannabis use, but organizations such as the Medical Cannabis Clinicians Society have developed guidelines beyond the recommendations of the National Institute for Health and Care Excellence (NICE), thereby improving the training of medical practitioners in prescribing medical cannabis.[35] However, patients often resort to the recreational market to avoid the administrative hurdles and costs associated with medical licensing.[37] In some cases, patients have opted to produce their own cannabis products of unknown quality and against medical recommendations.36 To minimize these issues and promote strict regulations, some countries including Thailand, are considering reversing decriminalization in order to focus on medical cannabis.[38]

In Malaysia, there are strict regulations for controlled medicines, for example morphine sulphate, oxycodone and codeine-containing products to prevent misuse and abuse when used to treat patients. It could be argued that similarly stringent regulations could be considered for medical cannabis, based on a prescriber model where controlled law and regulations could be enforced. This will involve placing medical cannabis under the close supervision of prescribing physicians. Additionally, a clinical trial model in which

medical cannabis use is well controlled may be considered. Through clinical research, it is possible to generate new evidence about the effectiveness and safety of medical cannabis. This approach would also allow access to alternative medicine, especially for patients who have not responded to many treatments or have exhausted all other available options.[27] This model of care, implemented in Quebec, Canada highlights the importance of translating evidence-based research into real-world practice.[28]

In summary, global experience advocates for a cautious, pain-focus approach that includes clear prescriber standards, product quality controls and pharmacovigilance. In the context of Malaysia, the key takeaway is to consider the establishment of a well-regulated framework for chronic pain and cancer pain coupled with targeted, evidence-based, medical cannabis case-based training for medical practitioners. Importantly, the overall impact of medical cannabis legalization remains an area that requires on-going analysis and research.

STRENGTHS & LIMITATIONS

Our study has limitations. The study sample only included medical practitioners from public hospitals and may not be representative of physicians working in different settings, such as primary care physicians, university hospitals, and private clinics. Recruitment was via convenience sampling where selection bias may be introduced, as those with stronger views may have been more likely to participate. The instrument used in the study was subjected to an item-by-item analysis and validation was done to affirm its relevance and clarity within the local context. However, a test-retest was not performed due to the homogeneity of the population from the original questionnaire (both survey healthcare practitioners) and the hypothetical nature in a country where medical cannabis is not used as a treatment. Nonetheless, it is recommended for future research endeavours. Finally, limitations in the study design prevented in-depth exploration of other factors that influence the attitudes and beliefs. The strength of our study provides valuable insights on Malaysian medical practitioners' perceived attitudes and their willingness to prescribe medical cannabis for specific disease conditions for which there is good evidence.

CONCLUSION

Medical practitioners in the public institutions showed favourable attitudes towards prescribing medical cannabis for chronic pain and cancer pain. However, further work is required to examine factors that drive these attitudes, and potential prescribing behaviour including those in private and university settings.

CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

ACKNOWLEDGEMENTS

The authors would like to express their sincere appreciation to the Director General of Health, Ministry of Health Malaysia, for granting permission to publish this manuscript. We also wish to thank the members of the cannabis study team for their valuable contribution to data collection and site coordination: Khairul Nisa' Binti Ishak[10], Jacelyn Ong Jia Whey[11], Kishal A/L Ravi[12], Norsarlizna Binti Mat Sari[13], Lim Soo How[14], Siti Nor Afni Binti Baharum[15], Mohamad Asyraf Bin Jamilol Nasir[16], Ang Wei Chern[17], Sivashni Silvanadan[18], Purnima Devi a/p Suppiah[19], Kueh Bing Ling[20], Siti Maisarah binti Md. Ali[21], Hasmein Mohd Razali[22], Devin Kumar A/L Asoka Kumar[23], Juhanah Gimbo[24], Siti Salwa binti Ramly[25], Wong Ka Yan[26], Ooi Xin Yi[27], Chua Aun Aun[28], Shafiq Eiman bin Abdul Razak[29], Jeffrey Lee Soon Yit[30], Tan Shu Zhen[31], Tiong Lee Len[32] and Mohd. Yusran bin Yusoff[33].

[10]Institute for Clinical Research, National Institute for Health.[11] Clinical Research Centre, Hospital Tengku Ampuan Rahimah, Klang.[12] Clinical Research Centre, Hospital Tengku Ampuan Rahimah, Klang.[13] Clinical Research Centre, Hospital Seri Manjung, Perak.[14] Clinical Research Centre, Hospital Miri, Sarawak.[15] Clinical Research Centre, Hospital Tengku Ampuan Afzan, Kuantan.[16] Clinical Research Centre, Hospital Shah Alam.[17] Clinical Research Centre, Hospital Tanko Fauziah, Perlis.[18] Clinical Research Centre, National Cancer Institute, Putrajaya.[19] Clinical Research Centre, Hospital Seberang Jaya, Pulau Pinang.[20] Clinical Research Centre, Hospital Likas, Sabah.[21] Clinical Research Centre, Hospital Sultanah Bahiyah, Kedah.[22] Clinical Research Centre, Hospital Sultanah Aminah.[23] Clinical Research Centre, Hospital Raja Permaisuri Bainun, Perak.[24] Clinical Research Centre, Hospital Queen Elizabeth.[25] Clinical Research Centre, Hospital Sultan Abdul Halim, Kedah.[26] Hospital Likas, Sarawak.[27] Hospital Duchess of Kent, Sarawak.[28] Clinical Research Centre, Hospital Tuanku Ja'afar, Negeri Sembilan.[29] Clinical Research Centre, Hospital Sungai Buloh, Selangor.[30] Clinical Research Centre, Hospital Sibu, Sarawak.[31] Clinical Research Centre, Hospital Bintulu.[32] Clinical Research Centre, Sarawak General Hospital.[33] Clinical Research Centre, Hospital Raja Perempuan Zainab II, Kelantan.

FUNDING

The authors declare no specific grants from any funding agency in any public, commercial or not-for-profit organization.

REFERENCES

1. First L, Douglas W, Habibi B, Singh JR, Sein MT. Cannabis Use and Low-Back Pain: A Systematic Review. Cannabis Cannabinoid Research 2020; 5(4): 283.
2. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division, Washington. 2017. Therapeutic Effects of Cannabis and Cannabinoids - The Health Effects of Cannabis and Cannabinoids. National Academies Press.
3. Aguilar S, Gutiérrez V, Sánchez L, Nougier M. Medicinal cannabis policies and practices around the world 2018 [cited Jan 2022]. Available from: https://idpc.net/publications/2018/04/medicinal-cannabis-policies-and-practices-around-the-world.

4. de Souza MR, Henriques AT, Limberger RP. Medical cannabis regulation: an overview of models around the world with emphasis on the Brazilian scenario. Journal of Cannabis Research 2022; 4(1): 1–-15.
5. Zolotov Y, Vulfsons S, Sznitman S. Predicting Physicians' Intentions to Recommend Medical Cannabis. Journal of pain and symptom management 2019; 58(3): 400-7.
6. Orjuela-Rojas JM, García Orjuela X, Ocampo Serna S. Medicinal cannabis: knowledge, beliefs, and attitudes of Colombian psychiatrists. Journal of Cannabis Research 2021; 3(1): 1-10.
7. Mohamed MHN, Mohamed Nazar NI, Ridzwan IE, Taufek NH, Ab Rahman NS. Preventing Oversight on Medical Cannabis Legislation in Malaysia: Analysis of Risks, Benefits and Regulation Requirements. Journal of the Malaysian Parliament 2022; 2: 248-73.
8. Pharmaceutical Services Division. 2016. Garispanduan Permohonan Ubat KPK. Putrajaya: Ministry of Health.
9. Government of Malaysia, Malaysian Administrative Modernisation and Management Planning Unit (MAMPU). Bilangan Pegawai Perubatan dan Pegawai Perubatan Pakar di KKM mengikut Negeri & Institusi, 2015–2017. [cited Aug 2022]. Available from: https://www.data.gov.my/data/ms_MY/dataset/bil-pegawai-perubatan-dan-pegawai-perubatan-pakar-di-kkm-mengikut-negeri-institusi/resource/7ad93c3c-514f-43a1-9e79-a23c01d9839e.
10. Philpot LM, Ebbert JO, Hurt RT. A survey of the attitudes, beliefs and knowledge about medical cannabis among primary care providers. BMC Family Practice 2019; 20(1): 1-7.
11. Zolotov Y, Sznitman S, Vulfson S. Validation of Clinical Vignettes to Explore Medical Cannabis Practices. The Israel Medical Association Journal 2019; 21(11): 710-5.
12. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing 2023 [cited 2023 Aug 16]. Available from: //www.R-project.org/
13. Sharon H, Goldway N, Goor-Aryeh I, Eisenberg E, Brill S. Personal experience and attitudes of pain medicine specialists in Israel regarding the medical use of cannabis for chronic pain. Journal of Pain Research 2018; 31: 1411-9.
14. Islahudin F, Shahdan IA, Mohamad-Samuri S. Association between belief and attitude toward preference of complementary alternative medicine use. Patient preference and adherence 2017; 10: 913-8.
15. Dapari R, Mahfot MH, Nazan AINM, Hassan MR, Dom NC, Rahim SSSA. Acceptance towards decriminalization of medical marijuana among adults in Selangor, Malaysia. PLoS One 2022; 17(2): e0262819.
16. Aroonsrimorakot S, Laiphrakpam M, Metadilogkul O. Social, religious, recreational and medicinal usage of cannabis in India and Thailand. Interdisciplinary Research Review 2019; 14(4): 43–50.
17. Byard RW, Musgrave I, Maker G, Bunce M. What risks do herbal products pose to the Australian community? Medical Journal of Australia 2017; 206(2): 86–90.
18. Macedo AC, de Faria AOV, Bizzi I, Moreira FA, Colasanti A, Ghezzi P. Online information on medical cannabis may rise unrealistic expectations and downplay potential side effects. arXiv preprint arXiv:2004.02330 2020.
19. Polak K, Wiese A, Crouch TB, Smith W, Svikis DS. Gender Differences in the Support of Medical Marijuana Use Among Primary Care Providers. Women's Health Reports 2024; 1;5(1): 909-15.
20. Ramirez AG, Wildes KA, Napoles-Springer A, Perez-Stable E, Talavera G, Rios E. Physician gender differences in general and cancer-specific prevention attitudes and practices. Journal of Cancer Education 2009; 24(2): 85-93.
21. Diehl K, Gansefort D, Herr RM, Görig T, Bock C, Mayer M, et al. Physician gender and lifestyle counselling to prevent cardiovascular disease: a nationwide representative study. Journal of Public Health Research 2015; 4(2).
22. Roter DL, Hall JA, Aoki Y. Physician gender effects in medical communication: a meta-analytic review. JAMA 2002; 288(6): 756-64.
23. Méndez SJ, Scott A, Zhang Y. Gender differences in physician decisions to adopt new prescription drugs. Social Science & Medicine 2021; 277: 113886.
24. Shim M, Nguyen H, Grootendorst P. Lessons from 20 years of medical cannabis use in Canada. PLoS One 2023; 18(3): e0271079.
25. Arkell TR, Downey LA, Hayley AC, Roth S. Assessment of Medical Cannabis and Health-Related Quality of Life. JAMA Network Open 2023; 6(5): e2312522.
26. Cahill SP, Lunn SE, Diaz P, Page JE. Evaluation of Patient Reported Safety and Efficacy of Cannabis from a Survey of Medical Cannabis Patients in Canada. Frontiers in public health 2021; 9: 626853.
27. Peterson AM, Le C, Dautrich T. Measuring the Change in Health-Related Quality of Life in Patients Using Marijuana for Pain Relief. Medical Cannabis and Cannabinoids 2021; 4(2): 114–20.
28. Dills A, Goffard S, Miron J, Partin E. Policy Analysis The Effect of State Marijuana Legalizations: 2021 Update. Cato Institute, Policy Analysis, no. 908.
29. Leyton M. Cannabis legalization: Did we make a mistake?. Journal of Psychiatry and Neuroscience 2019; 44(5): 291-3.
30. Schlag AK, Baldwin DS, Barnes M, Bazire S, Coathup R, Curran HV, et al. Medical cannabis in the UK: From principle to practice. Journal of Psychopharmacology 2020; 34(9): 931-7.
31. Fitzcharles MA, Rampakakis E, Sampalis J, Shir Y, Cohen M, Starr M, et al. Medical Cannabis Use by Rheumatology Patients Following Recreational Legalization: A Prospective Observational Study of 1000 Patients in Canada. ACR Open Rheumatology 2020; 2(5): 286.
32. Clarke H, Fitzcharles M. The evolving culture of medical cannabis in Canada for the management of chronic pain. Frontiers in Pharmacology 2023; 14: 1153584.
33. Thavisin S. 'New Thai government led by Srettha Thavisin seeks to "rectify" cannabis policy'. The Star. 2023; September 23 [cited Jul 2022]. Available from: https://www.thestar.com.my/aseanplus/aseanplus-news/2023/09/23/new-thai-government-led-by-srettha-thavisin-seeks-to-rectify-cannabis-policy.
34. Van Norman GA. Expanding Patient Access to Investigational Drugs: Single Patient Investigational New Drug and the "Right to Try." JACC: Basic to Translational Science 2018; 3(2): 280.
35. Prosk E, Arboleda MF, Rapin L, Hage C El, Dworkind M. NC-ND license the model of care at a leading medical cannabis clinic in Canada. Complementary therapies in medicine 2021; 60: 102740.

Relationship between post-partum mothers' knowledge and essential newborn care practices in Jambi, Indonesia

Ova Jayanti, M.Keb[1], Ekawaty Lutfia Haksari, PhD[2], Ismarwati, PhD[3], Djauhar Ismail, PhD[2]

[1]Prodi Kebidanan Program Sarjana dan Pendidikan Profesi Bidan, Universitas Baiturrahim, Jambi, Indonesia, [2]Department of Child Health, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia,[3]Magister of Midwifery, Universitas 'Aisyiyah Yogyakarta, Indonesia

ABSTRACT

Introduction: Essential Newborn Care (ENC) is crucial for neonatal survival, which is known to be very significant for the objective of Sustainable Development Goals in 2030 as an attempt to decrease neonatal morbidity and mortality. Mothers play an important role in ENC. This study aimed to delve into the relationship between mothers' knowledge, parity, education level, age, occupation, economic status, and ENC practices in post-partum mothers.

Materials and Methods: A cross-sectional design was conducted in Jambi, Indonesia from June to August 2021. There were 152 post-partum mothers who had neonates aged 0–28 days, consisting of 76 primiparous and 76 multiparous mothers. A questionnaire on ENC knowledge and practice was utilized to collect the data from the instrument of the previous study. The data were examined using univariate, bivariate, and multivariate analyses.

Results: Multivariate analysis on ENC practices revealed that mothers with low knowledge had a higher risk of performing poor ENC practices with OR 10.6 than those with high knowledge, and it was significantly different. Mothers with low educational level had more risks of practicing poor ENC with OR 2.9 than those with high educational level, which was significantly different. Meanwhile, parity, age, occupation, and economic status of post-partum mothers did not present a statistically significant correlation (p>0.05) with ENC practices.

Conclusion: There was a significant difference in ENC practices, with high risk in those who had low knowledge followed by low education. There was no association between ENC practices and parity, age, occupation, and economic status of post-partum mothers. These findings highlight the importance of improving the knowledge of post-partum mothers in supporting ENC practices. The result of the study should nevertheless be interpreted in such a way by considering the limitations of the study design and the instruments used.

KEYWORDS:
Essential newborn care, practices, mothers' knowledge, post-partum mothers

INTRODUCTION

According to World Health Organization (WHO), approximately 66% of infants in the world die in the first 24 hours of life and 34% die after 24 hours of life.[1] Although globally the infant mortality rate decreased from 31 deaths to 18 deaths per 1,000 live births in 2017, the trend of the neonatal mortality rate, however, remains relatively higher than that in other Southeast Asian countries.[2] The risk of death is doubled in babies born to mothers with low economic status and education levels.[3-4] This indicates that neonatal mortality is not only induced by medical causes such as prematurity, pneumonia, and low birth weight, but it can also be fueled by sociodemographic conditions.

Indonesian Demographic and Health Survey (IDHS) reported infant mortality rate in Indonesia decreased significantly from 32 deaths to 24 deaths per 1,000 live births in 2017.[5] Infant mortality is influenced by the quality of newborn care, which is still below the standard.[6] WHO recommends that the standard of essential newborn care (ENC) have to meet three important aspects, namely prevention of heat loss, umbilical cord care and breastfeeding[7-8] Parenting process can describe the mother's knowledge and skills in providing the best care for her baby.[9] Babies born to primiparous mothers are at greater risk of death than those born to multiparous mothers,[10] which suggests parity affects neonatal mortality. Knowledge of newborn care is pivotal for primiparous mothers. Some newborn care practices are known to adopt traditional notions.[11–14] This happens when primiparous mothers have low knowledge.[15]

Neonatal survival is essential to achieve the development goals of the Sustainable Development Goals (SDGs). Health development priorities include family development.[2] As a family component, mothers play an important role in optimizing the growth and development of their children.

MATERIALS AND METHODS

This was a cross-sectional study with an analytical approach, which was conducted in the sub-district of Maro Sebo Ilir, District of Batang Hari, Jambi Province, from June to August 2021. The study population was post-partum primiparous and multiparous mothers who had infants aged 0 - 28 days. Purposive sampling was used to gather the samples. The inclusion criteria were singleton, born vaginally without

This article was accepted: 25 January 2026
Corresponding Author: Ekawaty Lutfia Haksari
Email: ekawatylutfia@ugm.ac.id

equipment assistance with gestational age of 37 - <42 weeks, normal birth weight (2500 - <4000g), and oral feeding. Exclusion criteria, on the other hand, include newborn with congenital anomalies, birth trauma, severely-ill mothers, mothers with post-partum depression, mothers unable to breastfeed their newborns due to their health issues, newborn or mothers remained in the hospital care. The total number of samples in this study was 152, consisting of 76 primiparous mothers and 76 multiparous mothers.

Knowledge of post-partum mothers was the independent variable of this study, whereas the dependent variable was the practice of ENC. Meanwhile, age, education level, economic status, and occupation served as the confounding variables.

We used Google form to collect the data, and were assisted by 1 midwife and 1 research assistant. The data were gathered using a questionnaire of knowledge and ENC practices. The instrument used in the study was adapted from the one that had been employed and validated in the previous research, with Cronbach's alpha 0,76.[16] Validation and reliability tests in this study were not reiterated. This limitation had been regarded in the interpretation of the result of the study and was declared in the Discussion.

The questionnaire was made up of three major domains, namely prevention of heat loss, umbilical cord care, and breastfeeding. The questionnaire evaluated the 3 components as part of newborn care. The scoring of ENC knowledge and practices was based on the percentage of the correct answers from the maximum total score. Knowledge and practice of ENC were considered good if they were ≥75% and were stated insufficient if they were <75%. The cut off 75% to categorize knowledge and practice of ENC was based on Guidelines for Essential Newborn Care, Ministry of Health, Republic of Indonesia)[8] and the previous study,[17] which recommended that adequate knowledge and practice of ENC should reach at least 75% of the evaluated indicator.

Primipara refers to mothers who have given birth to their babies once only, whereas multipara pertains to those who have given birth multiple times or more than once. The age of mothers was divided into 2 groups, namely <20 or >35 years and 20-34 years. Mothers' educational levels were categorized into low if they were <9 years and high if they were 9-12 years. Meanwhile, the economic status of mothers was based on the Regional Minimum Wage (RMG) in Jambi province in 2021, which was Rp 2.630.162, and it was defined as low if the family income was <RMG and high if it was >RMG. Mothers' occupation was described as their daily activities, which belonged to working mothers if they worked outside their homes for salaries and housewives if they worked at home.

Statistical analysis

The data were examined using univariate, bivariate, and multivariate analyses. The correlation between independent and dependent variables was analyzed using a statistical test conforming to $p < 0,05$. The variable with $p<0.25$ based on bivariate analysis will be put into multivariate analysis. The result of multivariate analysis was presented in odds ratio (OR) and confidence interval 95% (IK95%). The data were processed into SPSS 25 (Library of Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada).

Ethics approval

This study was conducted in accordance with relevant guidelines and regulations. Ethical clearance was obtained from the Ethics Commission of Aisyiyah University, Yogyakarta, which was declared ethically appropriate with approval no.1403/KEP-UNISA/V/2021.

RESULTS

The majority of primiparous and multiparous mothers had an age range of 20-35 years, with the level of education ranging from 9 to 12 years. Primiparous mothers had lower economic status than multiparous mothers, with 68.4% and 47.4% respectively. In terms of ENC knowledge, both primiparous and multiparous mothers had the same level of ENC knowledge, with 94.7% having high knowledge. In the practice of ENC, 72.4% primiparous mothers had good ENC practices, and multiparous mothers had 78.9% which was obviously better ENC practice (Table I).

Primiparous mothers with low knowledge were prone to practice poor ENC practices 9 times as much as those who had good knowledge, although it was not statistically significant. Meanwhile, multiparous mothers with low knowledge had the opportunity to have a poor ENC 13 times as much as those with good knowledge, which was statistically significant (Table II). Bivariate analysis on ENC practices showed that mothers whose knowledge was low had the risk of poor ENC practices with OR 10.9 compared with those with high knowledge and it was significantly different. Mothers with low educational level posed the risk of poor ENC practices with OR 3.5, which was significantly different from those with high educational level (Table III).

Multivariate analysis on ENC practices revealed that mothers with poor knowledge had higher risk of performing poor ENC practices with OR 10.6 than those with high knowledge and it was significantly different. Mothers with low educational level had more risks of practicing poor ENC with OR 2.9 than those with high educational level, which was significantly different (Table IV).

DISCUSSION

Correlation between knowledge and essential newborn care (ENC) practices

The result of the study shows a significant relationship between knowledge of post-partum mothers and ENC practices. Mothers with poor knowledge were more likely to perform low quality ENC than those who had better knowledge. This proves that knowledge plays an important role in the care of newborns. Mothers with high-quality knowledge generally have a better understanding of basic intervention in ENC.

The findings of our study was similar to that of a study conducted on 414 post-partum mothers, whereby 55.5% of whom had high knowledge.[18] The same result was obtained

Table I: Characteristics of primiparous and multiparous mothers (N=152)

Characteristic	Primipara (n=76)		Multipara (n=76)		Total (N=152)	
	n	%	n	%	n	%
Age (years)						
<20 and >35	5	6.6%	4	5.3%	9	5.9%
20-35	71	93.4%	72	94.7%	143	94.1%
Education level (years)						
<9 years	17	22.4%	14	18.4%	31	20.4%
9-12 years	59	77.6%	62	81.6%	121	79.6%
Economic status (RMW)						
Low	52	68.4%	36	47.4%	88	57.9%
High	24	31.6%	40	52.6%	64	42.1%
Occupation						
Working mother	20	26.3%	16	21.1%	36	23.7%
Housewive	56	73.7%	60	78.9%	116	76.3%
Knowledge of ENC						
Low	4	5.3%	4	5.3%	8	5.3%
High	72	94.7%	72	94.7%	144	94.7%
ENC Practices						
Poor practices	21	27.6%	16	21.1%	37	24.3%
Good practices	55	72.4%	60	78.9%	115	75.7%

ENC: Essential Newborn Care, RMW: Regional minimum wage

Table II: Relationship between knowledge and essential newborn care practices (N=152)

Group	Knowledge ENC		Practices ENC		X^2	p	OR (95% CI)
			Poor practices	Good practices			
Primipara	Low	n	3	1			
		%	75.0%	25.0%	2.567	0.109	9.00
(n= 76)	High	n	18	54			(0.88-92.06)
		%	25.0%	75.0%			
	Low	n	3	1			
Multipara		%	75.0%	25.0%	4.364	0.037*	13.62
(n=76)	High	n	13	59			(1.31-141.55)
		%	18.1%	81.9%			

* p<0.05= significant difference. CI=confident interval, ENC= Essential newborn care, OR=odds ratio

Table III: Bivariate analysis knowledge and essential newborn care practices (N=152)

Variable	ENC practices				p	OR (95% CI)
	Low		High			
	n	%	n	%		
Knowledge						
Low	6	75.0%z	2	25.0%	0.001*	10.94
High	31	21.5%	113	78.5%		(2.10-56.88)
Parities						
Primipara	21	27.6%	55	72.4%	0.345	1.43
Multipara	16	21.1%	60	78.9%		(0.68-3.02)
Age of mother (years)						
<20 and >35	4	44.4%	5	55.6%	0.147	2.67
20-35	33	23.1%	110	76.9%		(0.68-10.51)
Education						
Low	14	45.2%	17	54.8%	0.002*	3.51
High	23	19.0%	98	81.0%		(1.51-8.13)
Occupation						
Working mother	6	16.7%	30	83.3%	0.219	0.55
Housewife	31	26.7%	85	73.3%		(0.21-1.44)
Economic status						
Low RMW	25	28.4%	63	71.6%	0.239	1.72
High RMW	12	18.8%	52	81.3%		(0.79-3.75)

*p<0.05=significant difference, CI=confident interval, ENC=essential newborn care, OR=Odds Ratio, RMW=Regional minimum wage

Table IV: Multivariate analysis knowledge and essential newborn care practices (N=152)

Variable	p	OR	95% CI
Knowledge	0.007*	10.59	1.92-58.53
Age of mother's	0.412	1.87	0.42-8.29
Education	0.038*	2.90	1.06-7.94
Occupation	0.981	0.99	0.34-2.85
Economic status	0.863	1.08	0.44-2.64

*p<0.05=significant difference, CI=confident interval, ENC=essential newborn care, OR=odds ratio, RMW=Regional minimum wage

from a study in Nepal, where 60% of mothers with good knowledge did not give anything to the umbilical cord,[21] which was consistent with the WHO's recommendation as part of the umbilical cord care - to keep the umbilical cord clean and dry.[7] A study in Ethiopia reported that as many as 80.4% of mothers had good knowledge about ENC.[14]

Optimization of newborn care practices can be influenced by the intervention of knowledge. In line with the results of the research, which stated that there was a relationship between knowledge and practice, mothers with high knowledge were more likely to practice good essential newborn care. This was similar to a study conducted on young mothers in Ethiopia,[14,18] where mothers with good knowledge were more likely to engage in satisfactory practice of ENC.[17,19-21] This is due to the fact that accumulated experience and awareness about safe cord care, thermal care, and breastfeeding would help mothers to put ENC into practice.[17-18]

The findings of Nukpezah's study warrant the need to keep promoting education during the antenatal period to ensure that mothers should initiate breastfeeding right after birth as a critical component of ENC. This can only be achieved when the mothers have the requisite knowledge and understanding of the benefits of early initiations.[20] Efforts to improve knowledge must be in line with the ease, with which mothers access the information. Various programs implemented by the Ministry of Health of the Republic of Indonesia to improve knowledge of pregnant women have been running quite optimally, one of which is through the class for pregnant women.[22]

Correlation between parity and ENC practices

Our study did not find a significant relationship between parity and ENC practices. Nevertheless, multiparous mothers' prior experiences in taking care of their newborns could positively affect their way of applying their knowledge on a daily basis. It shows that parity did not serve as an independent factor in ENC, yet it could be associated with mothers' experiences in taking care of their babies.

Erfina et. al. who studied young mothers during their transition to motherhood found that mothers felt helpless because they were not included in the care of their babies.[15] But, on the other hand, mothers' powerlessness in caring for their babies was also caused by their inability to process emotions and stress to the increasing needs after the birth of the child.[23] Hence, the process of caring for babies is often carried out by parents, grandmothers, or traditional birth attendants based on misunderstandings.[24-25] Multiparous mothers will be more realistic in anticipating their physique and more easily adapt to ENC.[26] Experience provides an opportunity for multiparous mothers not to make the same mistakes. The process of becoming a mother has already been owned.

Meanwhile, Leta et. al. confirmed that parity was significantly associated with ENC practices among post-partum mothers attending post-natal services at the state hospital of Harar town, Eastern Ethiopia.[27]

Correlation between mothers' education and ENC practices

Mothers' education level was significantly associated with ENC practices. The study shows that the majority of mothers had high education (9-12 years). Mothers with higher educational levels presented a significant alliance with knowledge and practice. High education could help mothers prepare for various situations from pregnancy to postpartum period. Education can improve the health and well-being of mothers and babies.[16] Mothers with good education will receive information related to antenatal and post-natal care more easily.[28] The likelihood of adopting the highest level of ENC practices was higher among mothers with relatively higher education.[17,27,29] Nukpezah et. al. explained that education, at least tertiary level, was a significant predictor of good ENC practices.[20] Meanwhile, Abebe's study reported no significant difference between mothers' education and ENC practices. It was a community-based, cross-sectional study that was conducted among mothers who gave birth within the past six months in Gurage Zone, Southwest Ethiopia. For the quantitative part of the mixed study, 624 participants were involved by using a multi-stage sampling method.[30]

Correlation between age, occupation, and economic status of post-partum mothers and ENC practices

Mothers' age did not show a significant difference in ENC practices. Nukpezah et. al. narrated that respondents who were between the ages of 25–29 years (AOR=1.18, 95% CI:0.35–4.01), were more likely to practice good ENC practices than their counterparts.[20]

In our study, working mothers had no significant difference from housewives. A community cross-sectional study in Ethiopia by Abebe reported a similar result - no significant difference between employment and ENC practices.30 Nukpeizah's study identified that self-employed mothers were significant predictors of good ENC practices.[20]

Several studies reported that most of their respondents were housewives who had to take care of their babies by themselves. However, the practice of caring for newborns by primiparous mothers remains unsatisfactory.[31-32] As many as 45% of mothers gave their newborns food other than

breastmilk, and 44.8% of them did not give colostrum.[13] Meanwhile, working mothers complained that they could not spend much time with their babies. Thus, baby care was more often carried out by family members, especially parents.[23] Therefore, the practice of baby care was not only assessed by the intensity or how often the mother spent caring for her baby, but also by the quality of the baby care carried out by the mother.

Our study did not present a significant difference between economic status and ENC practices. A study conducted among postnatal mothers attending post-natal services in the government hospital of Harar town, Eastern Ethiopia, reported average monthly income was significantly associated with ENC practices.[27] A wealth-based equity study in ENC in Ethiopia reported that inequity skin to skin contact and delayed bathing were evident in home delivery.[33] Another study also recounted that neonates born at health facilities had higher, although not optimal, coverage of ENC practices.[34]

LIMITATIONS AND STRENGTHS OF THE STUDY

There were a few limitations of the study. First, cross-sectional design was unlikely to draw a causal conclusion. Second, ENC was measured by the respondents' answers, which potentially resulted in information bias. Third, validation and reliability tests of the instruments in this study were not repeated, although the instruments had been validated and adapted from the previous study. Therefore, the results of this study need to be interpreted by considering the limitations aforementioned. Fourth, the study could not obtain more in-depth knowledge and practice-related information that could support the results of the quantitative research. Fifth, it did not observe directly the ENC practices so that the answers from the respondents tended to be normative. Sixth, despite a significant relationship, there was a very wide range of Confidence Interval in each variable, which shows less precision and needs a higher number of samples. Seventh, single center nature of the study. Future research should be a multi center study in order to obtain a more general result.

The strength of the study is that the manuscript provides a noticeable contribution to the understanding of the factors that affect ENC practices, especially among postpartum mothers in the areas with limited resources such as Jambi.

CONCLUSION

The study reveals a significant correlation between post-partum mothers' knowledge and ENC practices in Jambi, Indonesia. Mothers with high knowledge were likely to practice ENC better. Mothers' education also affected ENC practices, whereas parity, age, occupation, and socio-economic condition did not demonstrate statistically significant correlations.

The study confirms the importance of improving the knowledge of pregnant women in an attempt to support ENC practices. Nevertheless, the results of this study have to be interpreted scrupulously considering that it uses a cross-sectional design and has limitations in instrument measurement. Future research using a mixed-method design must be able to explore deeper behavioral insight and inform community-based interventions.

CONFLICT OF INTEREST

The authors have no relevant financial or non-financial interests to disclose.

ACKNOWLEDGEMENTS

We would like to thank Tony, Agus Herwindo, Ananta, and Khairunnissaa' for their precious assistance to the study.

FUNDING

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

REFERENCES

1. Bhandari SS, Paudyal SS. Knowledge and Practice of Postnatal Mothers on Newborn Care at Hospital Setting. ARC J Nurs Healthc. 2016; 2(1): 25-30.
2. Hug L, Alexander M, You D, Alkema L. National, regional, and global levels and trends in neonatal 9 mortality between 1990 and 2017, with scenario-based projections to 2030: a systematic analysis. Lancet Glob Health. 2019; 7(6): e710-20.
3. Suplee PD, Gardner MR, Borucki LC. Low-Income, Urban Minority Women's Perceptions of Self- and Infant Care during the Postpartum Period. J Obstet Gynecol Neonatal Nurs. 2014; 43(6): 803-12.
4. Lohela TJ, Nesbitt RC, Pekkanen J, Gabrysch S. Comparing socioeconomic inequalities between early neonatal mortality and facility delivery: Cross-sectional data from 72 low- and middle-income countries. Sci Rep. 2019; 9(1): 9786.
5. SDKI. Laporan Pendahuluan Survey Demografi dan Kesehatan Indonesia 2017. In: Survey Demografi Dan Kesehatan Indonesia 2017. 2017.
6. Duysburgh E, Kerstens B, Diaz M, Fardhdiani V, Reyes KA, Phommachanh K, et al. Newborn care in Republic and the Philippines: A comprehensive needs assessment. Indonesia, Lao People's Democratic BMC Pediatr. 2014; 14: 46.
7. World Health Organization (WHO). Recommendations on maternal and newborn care for a positive postnatal experience. Geneva: World Health Organization; 2022.
8. Kementerian Kesehatan RI. Pelayanan Kesehatan Neonatal Esensial. Jakarta: Kemenkes RI; 2018.
9. Hans SL, White BA. Teenage Childbearing, Reproductive Justice, and Infant Mental Health. Infant Ment Health J. 2019; 40(5): 690-709. doi:10.1002/imhj.21803
10. Kementerian Kesehatan Indonesia. Analisis Hubungan Paritas Ibu dengan Kematian Neonatal di Indonesia. Accessed November 8, 2021. http://www.litbang.kemkes.go.id:8080/handle/123456789/20560
11. Zeyneloğlu S, Kısa, S. Traditional practices for maternal and newborn care among Turkish postpartum women. Appl Nurs Res. 2018; 39: 148-53.
12. Buser JM, Moyer CA, Boyd CJ, Zulu D, Ngoma-Hazemba A, Mtenje JT, et al. Cultural beliefs and health-seeking practices: Rural Zambians' views on maternal-newborn care. Midwifery. 2020; 85: 102686.
13. Memon J, Holakouie-Naieni K, Majdzadeh R, Yekaninejad MS, Garmaroudi G, Raza O, et al. Knowledge, attitude, and practice among mothers about newborn care in Sindh, Pakistan. BMC Pregnancy Childbirth. 2019; 19(1): 329.

14. Misgna HG, Gebru HB, Birhanu MM. Knowledge, practice and associated factors of essential newborn care at home among mothers in Gulomekada District, Eastern Tigray, Ethiopia, 2014. BMC Pregnancy Childbirth. 2016; 16(1): 114.
15. Erfina E, Widyawati W, McKenna L, Reisenhofer S, Ismail D. Exploring Indonesian adolescent women's healthcare needs as they transition to motherhood: A qualitative study. Women Birth. 2019; 32(6): e544-51.
16. Shrestha S, Adachi K, Petrini MA, Shuda A, Shrestha S. Nepalese primiparous mothers' knowledge of newborn care. Nurs Health Sci. 2015; 17(3): 347-53.
17. Berhea TA, Belachew AB, Abreha GF. Knowledge and practice of Essential Newborn Care among postnatal mothers in Mekelle City, North Ethiopia: A population-based survey. PLoS One. 2018; 13(8): e0202542.
18. Kebede A. Knowledge, practice and associated factors of newborn care among postnatal mothers at health centers, Bahir Dar City, Northwestern Ethiopia, 2016. BMC Res Notes. 2019; 12(1): 483.
19. Efa BW, Berhanie E, Desta KW, Hinkosa L, Fetensa G, Etafa W, et al. Essential new-born care practices and associated factors among post natal mothers in Nekemte City, Western Ethiopia. PLoS One. 2020; 15(4): e0231354.
20. Nukpezah RN, Konlan KD. Determinants of essential newborn care practices among mothers. A descriptive cross-sectional study in a peri-urban community, Ghana. Reprod Health. 2025; 22(1): 27.
21. Singh DR, Harvey CM, Bohara P, Nath D, Singh S, Szabo S, et al. Factors associated with newborn care knowledge and practices in the upper Himalayas. PLoS One. 2019; 14(9): e0222582.
22. Azhar K, Dharmayanti I, Tjandrarini DH, Hidayangsih PS. The influence of pregnancy classes on the use of maternal health services in Indonesia. BMC Public Health. 2020; 20(1): 372.
23. Deniz C, Ayaz S. Factors causing stress in women with babies 0-3 months old and their coping styles. J Psychiatr Ment Health Nurs. 2014; 21(7): 587-93.
24. Al-Sagarat AY, Al-Kharabsheh A. Traditional practices adopted by jordanian mothers when caring for their infants in rural areas. African J Tradit Complement Altern Med. 2017; 14(1): 1-9.
25. Gbogbo S. Early motherhood: voices from female adolescents in the Hohoe Municipality, Ghana—a qualitative study utilizing Schlossberg's Transition Theory. Int J Qual Stud Health Well-being. 2020; 15(1): 1716620.
26. Kalomiris AE, Kiel EJ. Maternal Anxiety and Physiological Reactivity as Mechanisms to Explain Overprotective Primiparous Parenting Behaviors. J Fam Psychol. 2016; 30(7): 791-801.
27. Leta M. Level of knowledge toward essential newborn care practices among postnatal mothers in governmental hospitals of Harar Town, Eastern Ethiopia. SAGE Open Med. 2022; 10: 20503121221076364.
28. Shahjahan M, Chowdhury HA, Al-Hadhrami AY, Harun GD. Antenatal and postnatal care practices 59 among mothers in rural Bangladesh: A community based cross-sectional study. Midwifery. 2017; 52: 42-8.
29. Khanam SJ, Begum MF, Alam MB, Kabir MA, Khan MN. Factors associated with essential newborn care practices among non-institutional births in urban Bangladesh: evidence from Bangladesh Urban Health Survey 2021. Glob Health Action. 2024; 17(1): 2412152.
30. Abebe H, Adane D, Shitu S. Essential newborn care practice and its associated factors in Southwest Ethiopia. Arch Public Health. 2021; 79(1): 42.
31. Castalino F, Nayak BS, D'Souza A. Knowledge And Practices Of Postnatal Mothers On Newborn Care In Tertiary Care Hospital Of Udupi District. J Health Allied Sci NU. 2014; 04(02): 91-101.
32. Kabwijamu L, Waiswa P, Kawooya V, Nalwadda CK, Okuga M, Nabiwemba EL. Newborn care practices among adolescent mothers in Hoima District, Western Uganda. PLoS One. 2016; 11(11): e0166405.
33. Delele TG, Persson LÅ, Gelaye KA, Schellenberg J, Lemma S, Defar A, et al. Wealth-based equity in essential newborn care practices in Ethiopia: A cross-sectional study. PLoS One. 2025; 20(12): e0338193.
34. Guadu T, Alemu K, Schellenberg J, Berhanu D, Lemma S, Defar A, et al. Essential newborn care practices at health facilities and homes in Ethiopia: a cross-sectional study. BMC Pregnancy Childbirth. 2025; 25(1): 800.

Evaluation of a new quality of life instrument for children with infantile esotropia before and after strabismus surgery

Hussein Waheeda-Azwa, PhD[1,2], Norul Badriah Hassan, PhD[2,3], Sarimah Abdullah, MCommMed[2,4], Jemaima Che Hamzah, PhD[5], Ismail Shatriah, MMed[1,2]

[1]Department of Ophthalmology and Visual Science, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia, [2]Hospital Pakar Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia, [3]Department of Pharmacology, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia, [4]Unit of Biostatistics and Research Methodology, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia, [5]Department of Ophthalmology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia.

ABSTRACT

Introduction: Infantile esotropia impacts the quality of life (QOL) of children and their families. In addition to surgical treatment, QOL assessment is an important tool for evaluating treatment success. Thus, this study aimed to assess QOL before and after strabismus surgery using the newly developed Infantile Esotropia Quality of Life Questionnaire (IEQ).

Materials and Methods: A prospective study was conducted from September 2018 to June 2019 at the Ophthalmology Clinic, Hospital Pakar Universiti Sains Malaysia. Children aged 5-17 years diagnosed with infantile esotropia were recruited. QOL and clinical examinations were measured pre- and post-strabismus surgery. The comparison of QOL scores before and after surgery was analysed using the paired t-test.

Results: A total of 126 children participated in the study: 63 aged 5–8 years and 63 aged 9–17 years. Strabismus surgery significantly improved the QOL scores in both age groups. In the younger group, scores increased from 68.00 preoperatively to 89.36 postoperatively (P < 0.001), while in the older group, scores increased from 78.07 to 90.21 (P < 0.001). No significant association was found between QOL scores and gender, angle of deviation, or stereopsis (P > 0.05).

Conclusion: Strabismus surgery significantly improved the quality of life in children with infantile esotropia in both age groups. The IEQ tool is a useful instrument for assessing functional and psychosocial outcomes in this population. Gender, ocular deviation, and stereopsis did not appear to influence QOL outcomes.

KEYWORDS:
Children, infantile esotropia, quality of life, strabismus surgery

INTRODUCTION

Infantile esotropia affects the functional and psychological quality of life (QOL) of children and their families.[1] It is defined as an early-onset inwards deviation of the eyes that is usually detected within the first six months of life. Studies and populations have different rates of infantile esotropia. One of the most prevalent types of early-onset strabismus is thought to affect approximately 1 in 100 to 500 live infants.[2-3] Certain demographic groups, such as those with a family history of strabismus or related neurodevelopmental disorders, frequently report higher prevalence rates.[2-3] In addition to impairing the development of binocular vision and causing amblyopia, this disease often causes social stigma, low self-esteem, and stressed parent–child relationships because of apparent misalignment and related functional deficiencies.[4-6]

The main treatment for restoring ocular alignment is surgical correction, which often involves bilateral medial rectus recession. The necessity of assessing surgical outcomes not only in terms of alignment success but also with a focus on psychosocial and functional QOL changes.[7] Surgical correction provides major psychosocial advantages. For example, numerous studies have shown that children who have undergone surgery experience less social anxiety, higher self-esteem, and improved social interactions, whereas parents experience less worry and are more satisfied with their child's looks and social skills.[4,7] Additionally, functional results such as stereopsis and binocular visual function increase, especially if surgery is performed early (before 12–24 months of age).[3,8]

Children with strabismus have poorer QOL than visually normal children do, as demonstrated by several studies that used validated questionnaires, including the Hospital Anxiety and Depression Scale (HADS), the 25-item National Eye Institute Visual Functioning Questionnaire (NEI-VFQ-25), the Pediatric Quality of Life Inventory (PedsQL), the Intermittent Exotropia Questionnaire (IXTQ) and, more recently, the Pediatric Eye Questionnaire (PedEyeQ).[8-15] However, these questionnaires were not specifically designed for children with infantile esotropia or for evaluating eye-related QOL (i.e., HADS, PedsQL). Therefore, this study aimed to assess the impact of surgery on QOL among Malaysian children with infantile esotropia by using the newly developed Infantile Esotropia Questionnaire (IEQ).[16] Furthermore, the study also aimed to investigate whether sex, ocular deviation, and stereopsis have any influence on QOL.

This article was accepted: 25 November 2026
Corresponding Author: Waheeda Azwa Hussein
Email: waheedaazwa@usm.my

MATERIALS AND METHODS

This prospective study was conducted at Hospital Pakar Universiti Sains Malaysia (HPUSM) from September 2018 to June 2019. Children with infantile esotropia aged 5–17 years were recruited.

All registered children with infantile esotropia during the study period were screened according to the study criteria. All the children who were screened had been diagnosed with infantile esotropia greater than 40 prism dioptres from 5-17 years of age. The children were excluded from the study if they had other types of strabismus (e.g., Duane syndrome), secondary causes of esotropia (e.g., trauma and sensory), deprivation due to congenital cataracts, corneal opacity, optic atrophy, and macular scars), organic eye diseases, neurological disorders, facial, ocular or cosmetic abnormalities, syndromic or chromosomal anomalies, known intellectual disability, abducens nerve palsy or ocular surgery. Parents with known intellectual disability and psychological illnesses were also excluded. Sixty-three children with infantile esotropia aged 5-8 years and 63 children with infantile esotropia aged 9-17 years were recruited from the Ophthalmology Clinic, HPUSM.

Participants were recruited using a consecutive sampling method, whereby all children with infantile esotropia who attended the Ophthalmology Clinic, Hospital Pakar Universiti Sains Malaysia during the study period and met the inclusion criteria were invited to participate. The sample was subsequently divided into two age groups (5–8 years and 9–17 years) in accordance with the structure of the Infantile Esotropia Quality of Life Questionnaire (IEQ), which comprises age-specific validated child versions. The 5–8-year-old version contains items tailored to early childhood cognitive and emotional development, whereas the 9–17-year-old version includes psychosocial and functional items appropriate for older children and adolescents. This age-based grouping ensured that each participant completed the questionnaire aligned with their developmental stage.

Detailed demographic data, including birth history, onset of esotropia, visual performance, family history of esotropia, and history of prematurity, were obtained. The children underwent a complete clinical assessment, which involved visual acuity tests, assessments for stereopsis using Frisby Stereopsis test, cover tests, tests for extraocular motility, examinations of their pupils, and convergence tests. The children were also examined carefully for signs of anomalies in the anterior and posterior segments. An identified paediatric ophthalmologist examined all the patients who had been recruited, and a trained senior optometrist performed cycloplegic refraction assessments in all patients.

QOL was measured using the newly developed questionnaire, IEQ (Appendix I) (16). The IEQ is a valid and reliable QOL questionnaire for children with infantile esotropia and their proxy/parents. It consists of child (5–8 years old), child (9–17 years old), and proxy/parent questionnaires. The child 5–8 years old version was constructed with two subthemes: social (4 items) and emotional (6 items). The 9–17-year-old version has two subthemes: psychosocial (5 items) and functional (10 items). The proxy/parent version has four subthemes: parents' emotional problems (9 items), children's social problems (4 items), children's emotional problems (6 items) and children's functional problems (6 items).[16]

All the items in the IEQ had satisfactory content evidence (scale level-content validity index, averaging method > 0.8) and good response process evidence (scale-level face validity index, averaging method >0.8). All questionnaires were found to have high internal consistency (Cronbach's alpha: 0.84–0.87 (5–8 years old), 0.83–0.86 (9–17 years old), and 0.85–0.89 (proxy/parent); acceptable intraclass correlation coefficients (r=0.497, p<0.01 (5–8 years old), r=0.728, p<0.01 (9–17 years old) and r=0.746, p<0.01 (proxy/parents); and significant correlations with the Intermittent Exotropia Questionnaire (r=0.780, p<0.01 (5–8 years old), r=0.602, p<0.01 (9–17 years old) and r=0.444, p<0.01 (proxy/parent).[16]

We interviewed children aged 5-8 years to answer the IEQ-5-8-year-old questionnaire on a 3-point scale. Responses for the 3-point scale included "a lot," "sometimes," and "not at all". A higher score indicates a higher QOL. The maximum possible overall score was 100 (best QOL), and the minimum was 0 (QOL). For children aged 5 to 8 years, the questionnaires were administered by reading the instructions and each item to the young child word by word. The interviewer read aloud each question and the response options to the children. The children were requested to circle one response per question. A key card with three faces was used to help the child answer the questions. The intonation was kept neutral during the interview to avoid suggesting an answer to the children when the questions were read aloud.

Older children aged 9-17 years completed the 9-17-year-old child questionnaire with the assistance of a trained interviewer. The responses for the 5-point scale Child 9–17 years old questionnaire and Proxy/parents questionnaire included "Never," "Almost never," "Sometimes," "Often," and "Almost always". The higher the score, the greater the QOL. The maximum possible overall score was 100 (QOL), and the minimum was 0 (worst QOL).

The child should be facing away from the parent when the questionnaire is administered to the child. The question was not interpreted if the child or parent did not understand the meaning of the questions. The question was repeated verbatim. They were asked to answer this question according to their understanding. They were instructed to choose the closest response to how they felt.

To minimise interviewer-related bias, all questionnaire sessions were conducted by the same trained interviewer throughout the entire study. This approach ensured consistency in the delivery of questions, neutrality of tone, and adherence to the standardised IEQ administration protocol, thereby preventing inter-interviewer variability.

All recruited children underwent strabismus surgery at HPUSM during the study period. Three months after surgery, the children were asked to complete the same questionnaires according to their age groups. This evaluation was conducted to determine the effect of strabismus surgery on children's QOL. They were assessed for the same clinical examination as before the strabismus surgery.

Table I: Socio-demographic and clinical characteristics (N=126)

Socio-demographic and clinical data	Infantile esotropia n (%)
Age (years old)	
5 to 8	63 (50.0)
9 to 17	63 (50.0)
Gender	
Female	63 (50.0)
Male	63 (50.0)
Race	
Malay	126 (100.0)
Best corrected visual acuity	
6/6-6/15	97 (77.0)
6/18-6/60	21 (16.7)
Worse than 6/60	8 (6.3)
Stereopsis	
Present	31 (24.6)
Absent	95 (75.4)
Distant angle of deviation (Prism Diopter)	
40-50	76 (60.3)
More than 50	50 (39.7)
Near angle of deviation (Prism Diopter)	
40-50	72 (57.1)
More than 50	54 (42.9)
Refractive error (Spherical equivalent) Diopter	
Low hyperopia (Less than +2.00)	126 (100.0)

Table II: Comparison of quality of life using the Infantile Esotropia Questionnaire in children before and after surgery

Variable	Mean total score (SD)		Mean difference (95 % CI)	t-statistics (df)	p-value*
	Pre	Post			
Children aged 5 to 8 years old Mean total score	68.00 (23.19)	89.36 (11.73)	-21.36 (-28.62, -14.09)	-5.972 (34)	< 0.001
Children aged 9 to 17 years old Mean total score	78.07 (16.82)	90.21 (9.28)	-12.14 (-16.759, -7.527)	-5.346 (34)	< 0.001

**p < 0.05 is considered statistically significant (paired sample t-test)

Table III: Factors associated with quality of life in children in this study

Variables	Simple linear regression		Multiple linear regression		
	Crude ba (95% CI)	p-value	Adj. bb (95% CI)	t-stat	p-value
Child 5-8 years old					
Gender	-4.24 (-16.24, 7.75)	0.482			
Angle of deviation					
Distant	-0.37 (-0.70, 0.04)	0.028	-0.79 (-1.71, 0.13)	-1.73	0.089
Near	-0.31 (-0.66, -0.05)	0.090			
Stereopsis	-4.80 (-0.13, 0.16)	0.480			
Child 9-17 years old					
Gender	4.83 (-3.34, 13.02)	0.243			
Angle of deviation					
Distant	0.22 (-0.01, 0.45)	0.059			
Near	0.21 (-0.04, 0.46)	0.091			
Stereopsis	0.79 (-9.07, 10.64)	0.874			

a Crude regression coefficient
b Adjusted regression coefficient
R^2= 7.7% (Child 5-8 years)
Stepwise, backward and forward multiple linear regression method applied.
Model assumptions are fulfilled.
There were no interactions amongst independent variables. No multicollinearity detected.
Final model equation: Mean total score = 95.46 -0.37*Distant angle of deviation (Child 5-8 years)

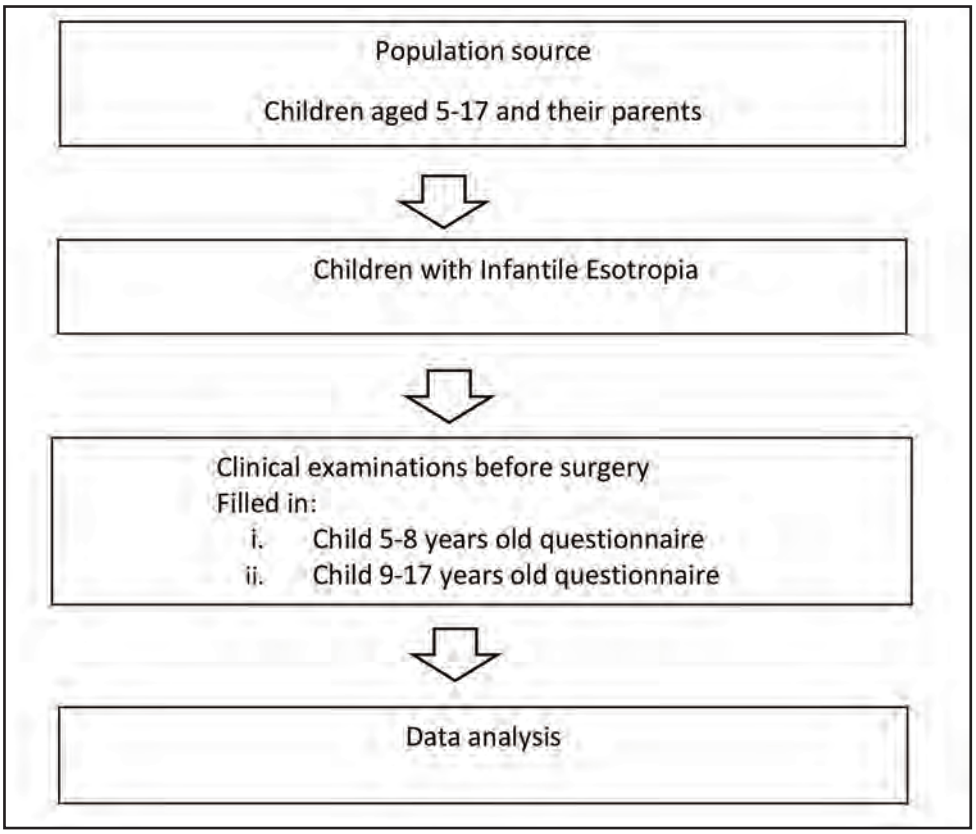


Fig. 1: Flowchart of the study – Evaluation of quality of life for children with infantile esotropia aged 5-17 years old before and after surgery

Statistical analysis and data colleection

Data from case report forms were entered into the Statistical Package for the Social Sciences for Windows version 24.0 (SPSS Inc., Chicago, IL, USA). The normal distributions of the numerical variables were checked via the Kolmogorov–Smirnov test and a histogram. Descriptive statistics were used to summarize the sociodemographic characteristics of the participants. The data are presented as frequencies, means, standard deviations, and percentages. The QOL of the children with infantile esotropia before and after strabismus surgery was compared via paired t tests. The flowchart of the study is summarized in Figure 1.

Ethics approval

The study was conducted following the Declaration of Helsinki. It was approved by the Human Research Ethics Committee of Universiti Sains Malaysia (USM/JEPeM/17010070) and the Medical Research and Ethics Committee of the Ministry of Health, Malaysia (NMRR-16-2555-32051). Written consent was obtained from the parents/guardians, and verbal assent was given by the children.

RESULTS

A total of 126 children with infantile esotropia completed the study. Gender was equally distributed between males (50.0%, 63 children) and females (50.0%, 63 children). All the children were Malay (100.0%, 63 children). The ages were equally distributed between 5 to 7 years (50.0%, 63 children) and 9 to 17 years (50.0%, 63 children). Most children (77.0%, 97 children) had good visual acuity better than 6/18. However, most of the children had an absence of binocular vision (75.4%, 95 children). The majority of them had an angle of deviation between 40 and 50 PD at distant (60.3%, 76 children) and near (57.1%, 72 children) distances. All the children (100%, 126 children) presented with low hyperopia of less than +2.00 diopters (Table I).

The difference between the means (SDs) before and after surgery was statistically significant for children aged 5--8 years [68.00 (23.19) vs. 89.36 (11.73), P<0.001] and children aged 9--17 years [78.07 (16.82) vs. 90.21 (9.28), P<0.001] (Table II).

There was no significant association between the mean total scores of the infantile esotropia questionnaire and any of the factors analysed from the multiple linear regression analysis for the 5–8 year age group. For the 9–17-year-old group, there was no significant association between the mean total score and any of the factors analysed via simple linear regression. Thus, multiple linear regression analysis was not performed (Table III).

DISCUSSION

Numerous studies have consistently demonstrated that strabismus surgery significantly enhances the quality of life (QOL) of affected children and their families. Children with strabismus and their parents report fewer psychological difficulties, reduced anxiety, and improved overall well-being following successful surgical correction.[17] Although children with strabismus generally have lower preoperative QOL scores compared to visually normal person, postoperative assessments reveal significant improvements in psychosocial functioning, reflecting the positive impact of surgical intervention. Patient-reported outcomes among Chinese children with intermittent exotropia further support these findings, showing significant postoperative gains in disease-specific QOL as well as reductions in anxiety and depression symptoms.[18] These results highlight the crucial role of strabismus surgery in restoring not only ocular alignment but also psychological and social well-being for both children and their families.

In the present study, a significant improvement was observed in the mean total QOL scores on both versions of the IEQ following strabismus surgery ($p < 0.001$). Among children aged 5–8 years, the mean total score increased from 68.00 (95% CI: 60.03–75.97) preoperatively to 89.37 (95% CI: 85.33–93.39) postoperatively. Similarly, in children aged 9–17 years, the mean total score improved from 78.07 (95% CI: 72.30–83.85) before surgery to 90.21 (95% CI: 87.03–93.40) after surgery. These results clearly indicate that strabismus surgery led to a significant improvement in the quality of life of children with infantile esotropia across both age groups.

The findings of the present study are consistent with previous research demonstrating that strabismus surgery significantly improves the quality of life (QOL) of children with ocular misalignment. Using the Infantile Esotropia Questionnaire (IEQ), our study showed postoperative improvements across social, emotional, and functional domains, like outcomes reported in studies employing other validated instruments such as the Intermittent Exotropia Questionnaire (IXTQ). These results support the view that QOL enhancement following strabismus correction is not questionnaire-specific but reflects genuine improvements in psychosocial well-being.[4]

Comparable studies have also reported significant postoperative gains in children's QOL. Tan and Shatriah observed increased QOL scores in children aged five to eight years, and similar improvements were found in older children aged nine to seventeen years.[4] Several other studies evaluating the general effects of strabismus surgery have reported consistent results, showing that surgical correction leads to significant improvements in both functional and psychosocial domains.[18-22] Archer et al. also reported significant positive changes in social, emotional, and functional measures of health status following strabismus surgery in children, as assessed by the modified RAND Health Insurance Study QOL questionnaire.[21] These findings are in agreement with our results, further confirming that surgical correction benefits multiple psychosocial dimensions in paediatric strabismus patients.

In addition to visual and functional improvements, several studies have highlighted the psychological benefits of strabismus surgery. Nelson et al. found that surgical correction enhanced patients' self-confidence, self-esteem, and perceived intelligence.[23] Such findings align with our observation that ocular realignment contributes positively to self-image and social interaction among children. A similar conclusion was reported by Wang et al., who found significant increases in Child IXTQ scores following corrective surgery for intermittent exotropia.[24] When compared with adults, as reported by Glasman et al., children in our cohort demonstrated higher preoperative QOL scores.[22] This difference may reflect age-related variations in emotional awareness and perception of social stigma.

Despite the overall improvement in QOL among children following strabismus surgery, our study found no significant association between the mean total IEQ scores and several clinical or demographic factors, namely gender, angle of deviation, and stereopsis, in both child age groups (5–8 years and 9–17 years). These results differ from those of previous studies that identified specific factors influencing postoperative QOL among strabismus patients.

No significant association was found between QOL and gender ($p>0.05$). This finding contrasts with that of Durnian et al., who reported that female strabismic patients had significantly lower QOL scores on the Adult Strabismus Questionnaire (AS-20).2[5] Similarly, Chew-Ean et al. and Nelson et al. observed greater psychosocial improvement among female patients following surgery.[19,26] The lack of gender-related differences in our cohort may be explained by the younger age of our participants, as younger children may be less socially self-conscious and therefore less affected by gender-related differences in appearance or peer perception. At this developmental stage, psychosocial responses may be more influenced by family support and visual function than by gender norms.

We also found no significant relationship between QOL and the angle of deviation ($p>0.05$). This contrasts with findings by Nelson et al., who reported that patients with larger angles of deviation experienced greater negative psychosocial effects due to more noticeable misalignment.[26] In our study, the absence of this relationship could be attributed to children's limited awareness of cosmetic differences compared to adults, as well as the possibility that parents' perceptions and support may lessen the psychosocial effects of larger deviations. Consistent with our findings, Van de Graaf et al. and Ritchie et al. also reported no correlation between angle of deviation and QOL scores, suggesting that psychosocial adaptation may play a greater role than deviation magnitude in determining subjective well-being.[27-28]

Similarly, no significant association was observed between stereopsis and QOL ($p>0.05$). One possible explanation lies in the structure of the IEQ itself. The child 5–8-year-old version does not include items assessing depth or distance perception, as these were excluded during the questionnaire's development phase following factor analysis. For the older group, although one item addressed depth perception, most respondents (65.1%) selected "not at all," suggesting that

stereopsis was not perceived as a major concern affecting daily life. Therefore, while stereopsis is an important clinical measure of binocular function, it may not directly influence perceived QOL in children, who are less aware of subtle depth-related visual limitations. In contrast, Dickmann et al. reported a positive association between improved stereopsis and QOL in adults, possibly reflecting the greater functional and occupational importance of binocular vision in older populations.[29]

Our findings on factors affecting QOL differed from those reported in Western studies.[25-26,29] In our study, gender, angle of deviation, and stereopsis did not influence QOL in children with infantile esotropia. One possible explanation may lie in cultural and perceptual differences between populations. Children in our cohort appeared less concerned about cosmetic appearance or functional limitations such as depth perception. For instance, comments gathered informally during questionnaire administration suggested that some children felt satisfied with their appearance and did not perceive difficulties in everyday tasks such as walking, playing, or pouring water. These informal remarks do not represent structured qualitative data but may reflect a general trend of reduced self-consciousness about appearance among younger Malaysian children.

Although our study did not formally assess cultural attitudes, previous research has shown that sociocultural context can influence perceptions of strabismus. Alzuhairy et al. reported that 70.4% of Arab parents in Saudi Arabia expressed positive attitudes towards strabismus, highlighting how cultural norms and beliefs shape perceptions of the condition.[30] However, this and similar studies primarily focused on parental attitudes rather than children's self-perceived QOL.

Cultural and religious values may also influence perceptions of illness and healthcare-seeking behaviour. Glover et al. suggested that sociocultural background and religious orientation shape individuals' attitudes towards health conditions and their willingness to pursue treatment.[31] In our study, it is possible that similar cultural or religious perspectives influenced how families perceived strabismus and its psychosocial impact. For instance, both Malaysian and Middle Eastern societies share certain values and family-oriented beliefs that may encourage parental acceptance of visible conditions such as strabismus, reducing the stigma experienced by affected children. However, this interpretation remains speculative, as our study did not directly examine religious or cultural determinants of healthcare behaviour. Alzuhairy et al. also reported that cultural norms and traditions may foster understanding and support for children with strabismus.[30] Nonetheless, their study focused on parental attitudes rather than children's self-perceived QOL. Hence, while cultural and religious contexts may help explain variations in psychosocial responses between populations, such conclusions should be drawn cautiously. Future qualitative and cross-cultural studies are recommended to explore in greater depth how beliefs, social norms, and community perceptions influence QOL and healthcare-seeking behaviour in paediatric strabismus.

This study has several limitations that should be considered when interpreting the findings. One major challenge involved the reliability of responses among younger participants, particularly those aged eight years and below. Younger children often required additional explanation, prompting, or parental assistance to understand the questionnaire items. Some were shy, silent, or hesitant to engage with unfamiliar researchers, which may have affected the accuracy of self-reported QOL data. To minimise these challenges, we used age-appropriate IEQ versions; The 5–8-year-old version with simplified language and visual cues, and the 9–17-year-old version with more abstract concepts to improve comprehension and engagement. The research team also used rapport-building strategies and small tokens such as coloured pencils or stickers to enhance cooperation.

Another limitation concerns the single-centre sampling approach. As the study was conducted at a tertiary centre in Kelantan, Malaysia, the majority of participants were of Malay ethnicity. This relatively homogeneous demographic composition limits the generalisability of the results to other ethnic groups and cultural contexts. Cultural norms, parental attitudes, and societal perceptions of strabismus are known to influence QOL outcomes and may differ across populations. Therefore, future multicentre studies involving more diverse and multi-ethnic samples are warranted to enhance external validity and allow for broader comparisons.

Furthermore, the absence of a control group restricts the ability to differentiate between the effects of surgery and other contributing factors, such as natural psychosocial adaptation or parental reassurance over time. Including a non-surgical or observational control group in future research would help strengthen causal inferences regarding the impact of surgery on QOL.

Finally, the relatively short postoperative follow-up period of three months provides only a snapshot of early outcomes. Although significant QOL improvements were observed during this time, these results may not reflect longer-term psychosocial or functional adjustments. As children's adaptation and binocular development continue over time, longitudinal studies with extended follow-up periods (e.g., six to twelve months) are necessary to determine the durability and stability of postoperative QOL gains.

CONCLUSION

In summary, this study demonstrated that strabismus surgery significantly improves the quality of life of children with infantile esotropia across social, emotional, and functional domains. The absence of associations between QOL and factors such as gender, stereopsis, and angle of deviation suggests that postoperative well-being is influenced more by psychosocial adaptation, parental reassurance, and perceived cosmetic improvement than by clinical parameters alone. Cultural and familial contexts may also play a role in shaping children's perceptions and experiences, although further qualitative and multicentre research is needed to confirm these influences.

While the study was limited by challenges in questionnaire reliability among very young participants, single-centre sampling, and a relatively short follow-up duration, the results nonetheless provide valuable insight into the broader psychosocial impact of strabismus correction. Future longitudinal, multicentre studies involving diverse populations and extended follow-up periods are recommended to evaluate the long-term stability of QOL improvements and to better understand the interplay between visual, functional, and cultural factors in paediatric strabismus outcomes.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGEMENTS

We would like to extend our gratitude to the staff of the Ophthalmology Clinics, Hospital Pakar Universiti Sains Malaysia (HPUSM), for their cooperation and support during data collection. Our special thanks to the HPUSM, Kelantan, Malaysia, for permission to conduct this study.

FUNDING

This work was supported by Usains Tech Services Sdn Bhd., Universiti Sains Malaysia (Usains Research Grant 2016/401/PPSP/3410015).

REFERENCES

1. Liebermann L, Leske DA, Castañeda YS, Hatt SR, Wernimont SM, Cheng CS, et al. Childhood esotropia: child and parent concerns. J AAPOS 2016; 20(4): 295-300.e1
2. Birch EE, Stager DR Sr. Long-term motor and sensory outcomes after early surgery for infantile esotropia. J AAPOS 2006; 10(5): 409-13.
3. Shirabe H, Mori Y, Dogru M, Yamamoto M. Early surgery for infantile esotropia. Br J Ophthalmol. 2000; 84(5):536-8.
4. Chew-Ean T, Ghani SA, Shatriah I. Infantile esotropia in Malaysian children: The impact of surgery on health-related quality of life assessment in patients and their parents. Med J Malaysia 2020; 75(5):531-7.
5. Ghiasi GS, Shojaei A, Sanjari M, Kosari M, Aslani M. The psychosocial improvement after strabismus surgery in Iranian patients. Iran J Ophthalmol 2013; 25(3): 211-5.
6. Silva N, Castro C, Caiado F, Maia S, Miranda V, Parreira R, et al. Evaluation of functional vision and eye-related quality of life in children with strabismus. Clin Ophthalmol 2022; 16: 803-13.
7. Mruthyunjaya P, Simon JW, Pickering JD, Lininger LL. Subjective and objective outcomes of strabismus surgery in children. J Pediatr Ophthalmol Strabismus 1996; 33(3): 167-70.
8. Muz OE, Sanac AS. Effects of surgical timing on surgical success and long-term motor and sensory outcomes of infantile esotropia. J Pediatr Ophthalmol Strabismus 2020; 57(5): 319-25.
9. Chai Y, Shao Y, Lin S, Xiong KY, Chen WS, Li YY, et al. Vision-related quality of life and emotional impact in children with strabismus: a prospective study. J Int Med Res 2009; 37(4):1108-14
10. Tu C, Ye L, Jiang L, Wang Y, Li Y. Impact of strabismus on the quality of life of Chinese Han teenagers. Patient Prefer Adherence 2016; 10: 1021-4.
11. Wen G, McKean-Cowdin R, Varma R, Tarczy-Hornoch K, Cotter SA, Borchert M. Multi-ethnic Pediatric Eye Disease Study Group. General health-related quality of life in preschool children with strabismus or amblyopia. Ophthalmology 2011; 118(3): 574-80.
12. Hatt SR, Leske DA, Yamada T, Bradley EA, Cole SR, Holmes JM. Development and initial validation of quality-of-life questionnaires for intermittent exotropia. Ophthalmology. 2010; 117(1): 163-168.e1.
13. Sim B, Yap GH, Chia A. Functional and psychosocial impact of strabismus on Singaporean children. J AAPOS 2014; 18(2):178-82.
14. Hatt SR, Leske DA, Castañeda YS, Wernimont SM, Liebermann L, Cheng-Patel CS, Birch EE, Holmes JM. Association of strabismus with functional vision and eye-related quality of life in children. JAMA Ophthalmol 2020; 138(5):528-535.
15. Leske DA, Hatt SR, Wernimont SM, Castañeda YS, Cheng-Patel CS, Liebermann L, et al. Quality of life and functional vision across pediatric eye conditions assessed using the PedEyeQ. J AAPOS 2021; 25(1): 23.e1-23.e5.
16. Hussein Waheeda-Azwa, Norul Badriah Hassan, Sarimah Abdullah, Jemaima Che Hamzah, Ismail Shatriah. Development and validation of Infantile Esotropia Quality of Life Questionnaire (IEQ): A Malay Version. Mal J Med Health Sci 2024; 20: 210-6.
17. Temeltürk RD, Koçer AM, Yaşar HH. Psychosocial improvements in children and their parents following strabismus surgery. J Pediatr Ophthalmol Strabismus 2022; 59: 261-8.
18. Mao D, Lin J, Chen L, Luo J, Yan J. Health-related quality of life and anxiety associated with childhood intermittent exotropia before and after surgical correction. BMC Ophthalmol 2021; 21(1): 270.
19. Chew-Ean T, Ghani SA, Shatriah I. Infantile esotropia in Malaysian children: The impact of surgery on health-related quality of life assessment in patients and their parents. Med J Malaysia 2020; 75:531-7.
20. Tan JP, Shatriah I (2015). Comparison of two health related quality of life questionnaires in malay children with strabismus and their parent proxy. Dissertation, Universiti Sains Malaysia
21. Archer SM, Musch DC, Wren PA, Guire KE, Del Monte MA. Social and emotional impact of strabismus surgery on quality of life in children. J AAPOS 2005; 9:148-51.
22. Glasman P, Cheeseman R, Wong V, Young J, Durnian JM. Improvement in patients' quality-of-life following strabismus surgery: evaluation of postoperative outcomes using the Adult Strabismus 20 (AS-20) score. Eye 2013; 27: 1249-53.
23. Nelson BA, Gunton KB, Lasker JN, Nelson LB, Drohan LA. The psychosocial aspects of strabismus in teenagers and adults and the impact of surgical correction. J AAPOS 2008; 12:72-76.e1.
24. Wang X, Gao X, Xiao M, Tang L, Wei X, Zeng J, Li Y. Effectiveness of strabismus surgery on the health-related quality of life assessment of children with intermittent exotropia and their parents: a randomized clinical trial. J AAPOS. 2015; 19:298-303.
25. Durnian JM, Owen ME, Baddon AC, Noonan CP, Marsh IB. The psychosocial effects of strabismus: effect of patient demographics on the AS-20 score. J AAPOS 2010; 14:469-71.
26. Nelson BA, Gunton KB, Lasker JN, Nelson LB, Drohan LA. The psychosocial aspects of strabismus in teenagers and adults and the impact of surgical correction. J AAPOS 2008; 12: 72-76.e1.
27. Van de Graaf ES, Van der Sterre, GW, Kempen-du Saar H, Simonsz B, Looman CW, Simonsz HJ. Amblyopia and Strabismus Questionnaire (A&SQ): Clinical validation in a historic cohort. Graefes Arch. Clin. Exp. Ophthalmol 2007; 245: 1589-95.
28. Ritchie A, Colapinto P, Jain S. The psychological impact of strabismus: does the angle truly matter? Strabismus 2013; 21: 203-8.
29. Dickmann A, Aliberti S, Rebecchi MT, Aprile I, Salerni A, Petroni S, et al. Improved sensory status and quality-of-life measures in adult patients after strabismus surgery. J AAPOS 2013; 17: 25-8.
30. Alzuhairy S, Alabdulrazaq ES, Alharbi IM, Alharkan DH. Knowledge and attitude towards strabismus among parents of Saudi children with strabismus. Int Surg J 2019; 6: 438-42.
31. Glover, SM, Mark N. Global health: Why cultural perceptions, social representations, and biopolitics matter. Hum Ecol 2009; 37: 669-70.

ORIGINAL ARTICLE

Comparison between Single Incision Laparoscopic Appendectomy (SILA) and Multi Port Laparoscopic Surgery (MPLA) in paediatric appendectomy patients

Yudi Pratama, MD[1], Andi Dwihantoro, MD[1], Gunadi, PhD[1], Yofizal Idham Ahmad, MD[1], Eko Purnomo, PhD[2]

[1]Pediatric Surgery Division, Department of Surgery, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/ Dr. Sardjito Hospital, Yogyakarta, Indonesia, [2]Pediatric Surgery Division, Department of Surgery, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Academic Hospital, Yogyakarta, Indonesia

ABSTRACT

Introduction: Single Incision Laparoscopic Appendectomy (SILA) and Multiport Laparoscopic Appendectomy (MPLA) are both established techniques for appendectomy, yet their differences in terms of aesthetics, operative wounds, and complications like wound dehiscence remain under study. This research compares the two approaches with a focus on minimizing surgical trauma and reducing infection risks.

Materials and Methods: A retrospective study was conducted involving 49 patients, with 26 undergoing SILA and 23 undergoing MPLA across two hospitals in Yogyakarta. Patient demographics, appendicitis grade, length of stay (LOS), operative time, and postoperative complications, including dehiscence, were analyzed using SPSS.

Results: Dehiscence was evaluated through outpatient follow-up based on wound leakage, while other complications were documented accordingly. The cohort comprised 17 female and 32 male patients (1:2 ratio), with no significant association between gender and appendicitis type (p=0.16). The most common appendicitis grade was grade 1 (36%), followed by grade 2 (34.7%), with chronic appendicitis being the least common (8.2%). was observed in 12.2% of cases, with 87.8% of wounds healing without issue. No significant difference in complication rates was found between SILA and MPLA techniques (p=0.876). LOS (p=0.523) and operative time (p=0.185) also showed no statistically significant differences.

Conclusion: Both SILA and MPLA techniques for appendectomy offer comparable safety profiles, with no significant differences in complications, LOS, or operative time. SILA, however, may offer superior cosmetic outcomes due to fewer incisions.

KEYWORDS:
Laparoscopy, Single Incision Laparoscopic Appendectomy (SILA), Multiport Laparoscopic Appendectomy (MPLA), appendectomy, dehiscence, surgical Outcomes

INTRODUCTION

Appendicitis is one of the most frequent causes of surgical emergencies, and is one of the most frequent causes of abdominal pain in the pediatric population (Gadiparthi and Waseem, 2023). Inflammation of the appendix can be caused by various etiologies, such as fecalith, appendicolith, and lymphoid hyperplasia. In the pediatric population, the most common etiology of appendicitis is lymphoid hyperplasia.[1]

Obstruction of the appendix lumen by any mechanism/etiology can cause bacterial overgrowth which causes acute inflammation and abscess formation. A previous study found that patients with perforated appendicitis had a much higher number of bacterial phyla compared with patients with uncomplicated appendicitis. These findings suggest that the severity and progression of appendicitis may be associated with an increase in the number of bacterial species.[2]

Obstruction of the appendix lumen will also cause an increase in intra-lumen pressure, which will cause distension of the appendix and disrupt blood perfusion to the appendix wall. As a result, ischemia of the appendix wall will occur. If this condition is left untreated, perforation can occur in the appendix wall.[3]

Antibiotics is still the preferred initial treatment to treat cases of appendicitis that have not yet perforated. For perforated appendicitis, antibiotics plus appendectomy surgery is the treatment of choice. Currently, most appendectomy operations are performed laparoscopically. The main factor that determines whether an appendectomy surgery will be performed by open surgery or laparoscopic is the preference or expertise of the surgeon. Generally, a laparoscopic approach is preferred if surgical expertise and equipment are available.[3]

Single Incision Laparoscopic Appendectomy (SILA) and Multiport Laparoscopic Appendectomy (MPLA) are both established techniques for appendectomy, yet their differences in terms of aesthetics, operative wounds, and complications like wound dehiscence remain under study. This research compares the two approaches with a focus on minimizing surgical trauma and reducing infection risks.

This article was accepted: 20 February 2026
Corresponding Author: Eko Purnomo
Email: eko.p@ugm.ac.id

Table I: Baseline Characteristics of the Patients (N=49)

Characteristic	Procedure Group		N (%)
	SILA	MPLA	
Gender			
• Male	13 patients	4 patients	34.69%
• Female	13 patients	19 patients	65.30%
Mean age	10.73 y.o.	11.43 y.o.	
Mean body weight	39.63 kg	38.54 kg	
Post-op diagnosis			
• Grade 1 appendicitis	9 cases	9 cases	36.73%
• Grade 2 appendicitis	11 cases	6 cases	34.69%
• Grade 3 appendicitis	1 case	0 case	2.04%
• Perforated appendicitis	2 cases	3 cases	10.20%
• Acute exacerbation on chronic appendicitis	3 cases	1 case	8.16%
• Chronic appendicitis	0 case	4 cases	8.16%

Table II: Comparison of Outcome between SILA and MPLA

Outcomes	SILA	MPLA	P value
Mean operation duration	96.92 min	85.43 min	0.185
Length of stay post-operation	3.13 days	2.78 days	0.523
Dehiscence complication	3 cases	3 cases	0.876

Figures 1–4 illustrate the comparisons in age, body weight, operative duration, and length of stay between the two groups.

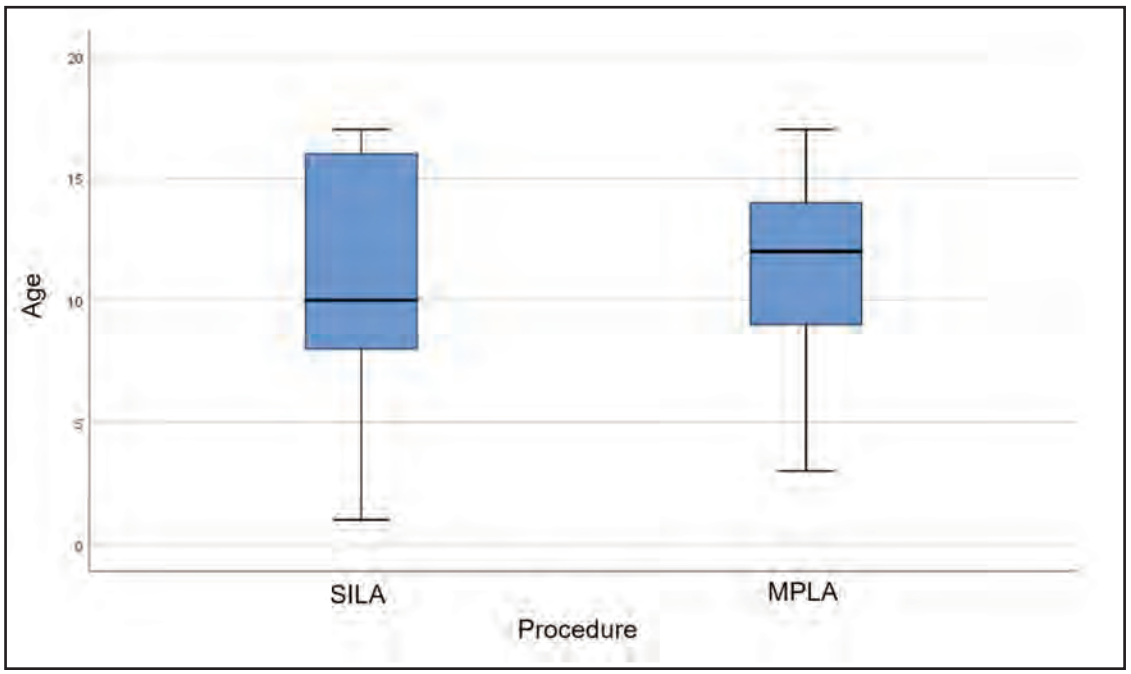


Fig. 1: Plot graphic for patients' age between SILA vs MPLA procedure

MATERIALS AND METHODS

Study Design and Patients

This study is a retrospective cohort study was conducted involving pediatric patients with appendicitis that undergone SILA or MPLA procedure across two hospitals in Yogyakarta from 2023 to 2024. This study aimed to evaluating and comparing the outcomes of SILA and MPLA procedures in those pediatric appendicitis cases.

Data Collection

We evaluate patient demographics, appendicitis grade, length of stay (LOS), operative time, and postoperative complications, including dehiscence. Dehiscence was evaluated through outpatient follow-up based on wound leakage, while other complications were documented accordingly.

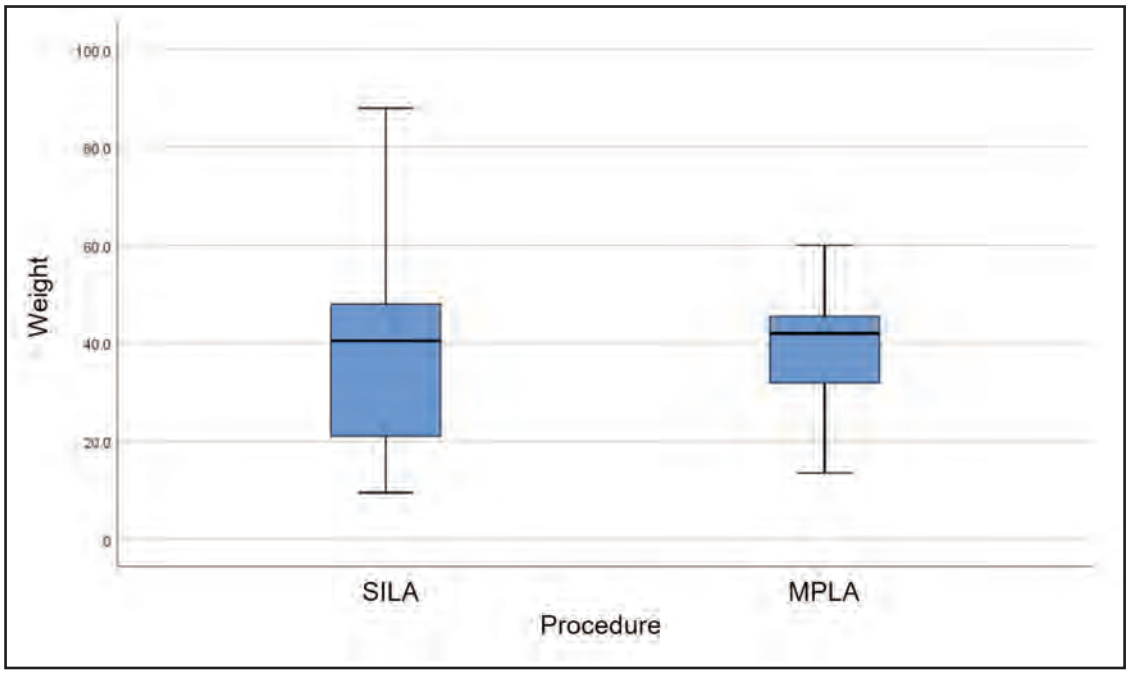


Fig. 2: Plot graphic for patients' body weight between SILA vs MPLA procedure

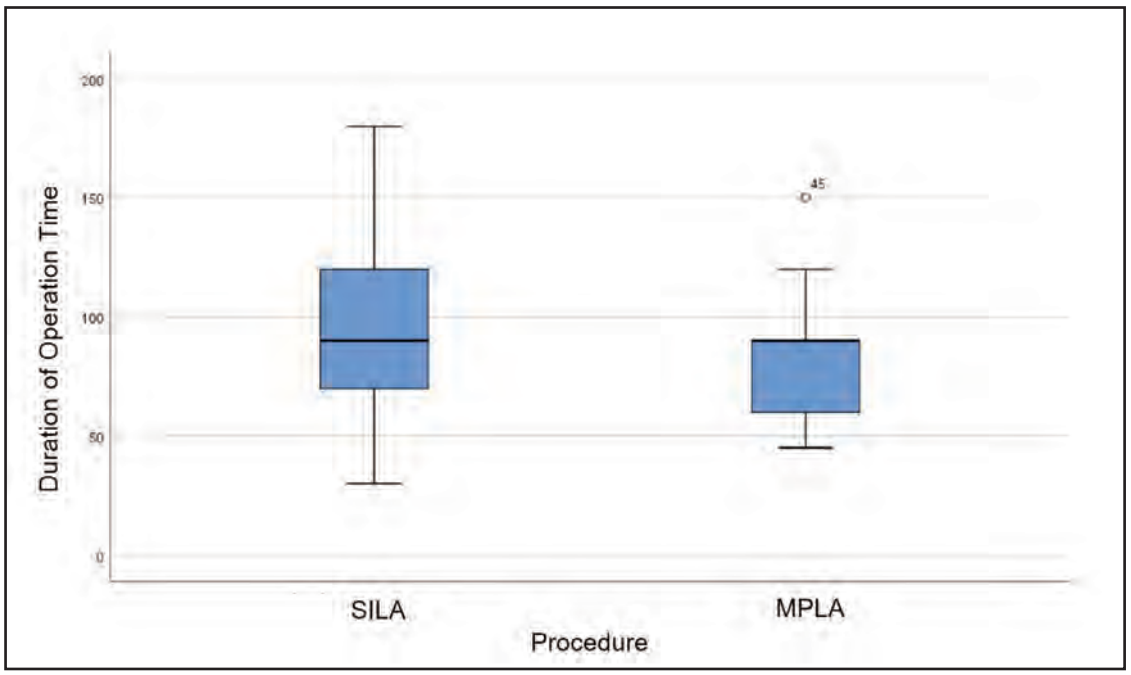


Fig. 3: Plot graphic for operation duration between SILS vs MPLA procedure

Statistical Analysis

The data collected was analyzed using SPSS. We did independent T test to see is there any significant differences of the data between SILA and MPLA procedures. p-value of <0.05 was considered as significant.

RESULTS

There are 49 patients involved in this study, with 26 undergoing SILA and 23 undergoing MPLA across two hospitals in Yogyakarta (Table I). The cohort comprised 17 female and 32 male patients (1:2 ratio), with no significant association between gender and appendicitis type (p=0.16). The most common appendicitis grade was grade 1 (36%), followed by grade 2 (34.7%), with chronic appendicitis being

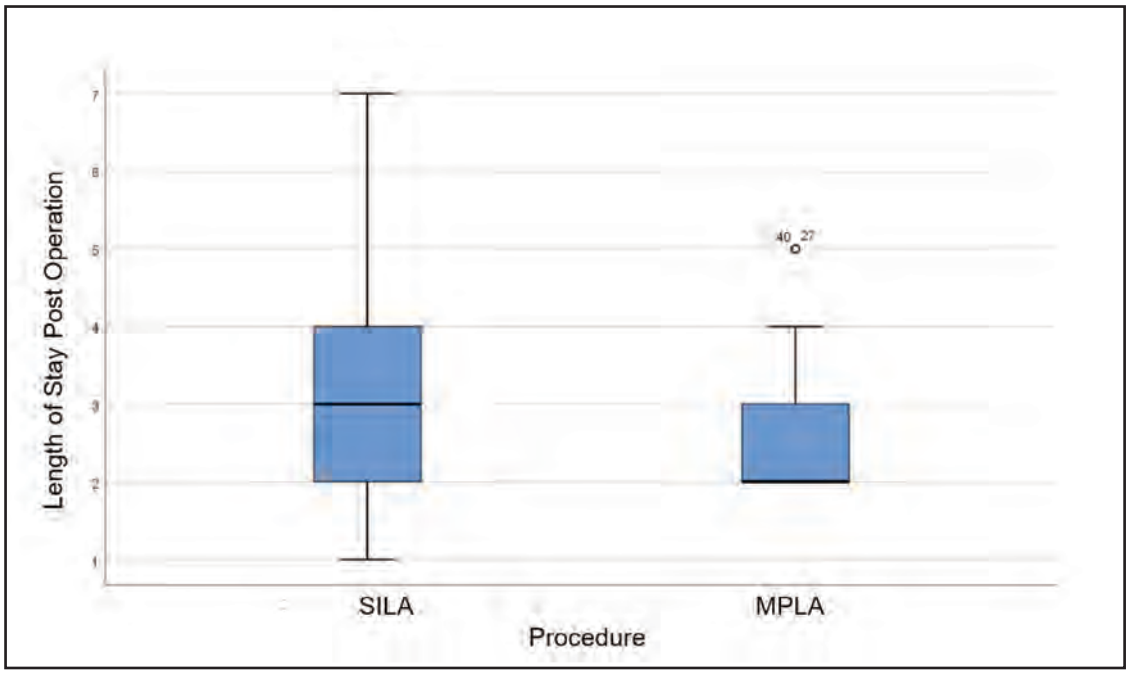


Fig. 4: Plot graphic for patients' length of stay between SILS vs MPLA procedure

the least common (8.2%). Dehiscence was observed in 12.2% of cases, with 87.8% of wounds healing without issue. No significant difference in complication rates was found between SILA and MPLA techniques (p=0.876). LOS (p=0.523) and operative time (p=0.185) also showed no statistically significant differences (Table II).

DISCUSSION

From these data, we can see that there's no significant differences in complications, length of stay, or operative time between SILA and MPLA. These findings are similar with previous studies, stating that both of SILA and MPLA can offer comparable safety profiles in management of appendicitis.[4] However, SILA procedure offer better cosmetic outcomes than MPLA because of fewer incisions.[5]

Another study conducted by Liao, 20206 found that the SILA procedure had a shorter average surgical duration of 8 minutes compared to MPLA, but this time difference was not statistically significant (p = 0.222). However, this study found that the SILA procedure had better recovery parameters, especially in terms of soft diet intake and post-operative hospitalization (p < 0.001).

Research conducted by Chandler and Danielson[7] found that the SILA procedure was better than MPLA in terms of the need for narcotics use (0.9 doses in SILA vs 1.4 doses in MPLA, p = 0.01). However, there were no significant differences regarding complication rates and length of stay.

Another study conducted by Buckley et al8 found that there was no significant difference between SILA and MPLA in terms of duration of operation, length of stay, and level of risk of needing to convert to open appendectomy. Apart from that, there was no significant difference regarding the incidence of complications from SILA and MPLA. These findings are similar to our findings in this study.

Considering that both procedures have equally good safety profiles, without any significant differences between the two, SILA could be a more favorable procedure choice than MPLA, because SILA has better cosmetic outcomes than MPLA.

CONCLUSION

Both SILA and MPLA techniques for appendectomy offer comparable safety profiles, with no significant differences in complications, length of stay, or operative time. SILA, however, may offer superior cosmetic outcomes due to fewer incisions.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGEMENTS

The authors would like to thank the participants of the study.

FUNDING

The authors received no external funding.

REFERENCES

1. Lotfollahzadeh S, Lopez RA, Deppen JG. Appendicitis. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2025, StatPearls Publishing LLC.; 2025.

2. Bhangu A, Søreide K, Di Saverio S, Assarsson JH, Drake FT. Acute appendicitis: modern understanding of pathogenesis, diagnosis, and management. Lancet 2015; 386(10000): 1278-87.
3. Gadiparthi R, Waseem M. Pediatric Appendicitis. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2025, StatPearls Publishing LLC.; 2025.
4. Zaman S, Mohamedahmed AYY, Stonelake S, Srinivasan A, Sillah AK, Hajibandeh S, et al. Single-port laparoscopic appendicectomy versus conventional three-port approach for acute appendicitis in children: a systematic review and meta-analysis. Pediatr Surg Int 2021; 37(1): 119-27.
5. Han Y, Yuan H, Li S, Wang WF. Single-incision versus conventional three-port laparoscopic appendectomy for acute appendicitis: A meta-analysis of randomized controlled trials. Asian J Surg 2024; 47(2): 864-73.
6. Liao YT, Lai PS, Hou YZ, Wu CY, Chou TH, Liang JT. Is single-incision laparoscopic appendectomy suitable for complicated appendicitis? A comparative analysis with standard multiport laparoscopic appendectomy. Asian J Surg 2020; 43(1): 282-9.
7. Chandler NM, Danielson PD. Single-incision laparoscopic appendectomy vs multiport laparoscopic appendectomy in children: a retrospective comparison. Journal of Pediatric Surgery 2010; 45(11): 2186-90.
8. Buckley FP, 3rd, Vassaur H, Monsivais S, Jupiter D, Watson R, Eckford J. Single-incision laparoscopic appendectomy versus traditional three-port laparoscopic appendectomy: an analysis of outcomes at a single institution. Surg Endosc 2014; 28(2): 626-30.

A national survey on the implementation of Kangaroo Mother Care for premature infants in hospitals across Malaysia

Foong Siew Cheng, MRCP(UK)[1], Foong Wai Cheng, MRCPCH[1], Shareena Ishak, MMED(Paeds)[2], Noraihan Ibrahim, MMED(Paeds)[3], Jacqueline J Ho, FRCPCH[1]

[1]Department of Paediatrics, RCSI & UCD Malaysia Campus, George Town, Penang, Malaysia, [2]Faculty of Medicine, Universiti Kebangsaan Malaysia, Cheras, Wilayah Persekutuan Kuala Lumpur, Malaysia, [3]Hospital Raja Perempuan Zainab II, Kota Bharu, Kelantan, Malaysia

ABSTRACT

Introduction: Kangaroo Mother Care(KMC) is essential for preterm infants and strongly recommended by the World Health Organization. However, national data on KMC implementation in Malaysia are lacking. We aimed to describe current KMC practices in Malaysian hospitals and identify factors influencing its adoption.

Materials and methods: We conducted a cross-sectional survey using a self-administered online questionnaire. Ninety-three public and private hospitals providing Level II and/or III neonatal care were identified and invited to participate. The questionnaire covered KMC practices, facility availability, eligibility criteria, and documentation.

Results: Sixty-nine hospitals(74%) responded, including 48 public and 21 private facilities. Of these, 60(87%) hospitals self-reported implementing KMC (33 regularly, 27 occasionally), most commonly in NICUs and SCNs. Among hospitals implementing KMC, 73% allowed KMC for infants on tube feeds, 71% for those on nasal oxygen, 53% for those on intensive respiratory support, and 68% for infants born <32 weeks gestation. Only 55% documented KMC consistently, 37% had protocols, and 25% reported most staff were trained. Key barriers included limited administrative support, training, infrastructure, and comfort amenities. Logistic regression showed that availability of KMC protocols, front-button blouses, training, and documentation showed a borderline association with regular KMC practice. Among non-implementing hospitals, most cited overcrowding and lack of resources; nearly all expressed a need for training.

Conclusion: KMC is practiced in most public and some private Malaysian hospitals, but key gaps remain. Simple measures such as providing front-button blouses, enhancing staff training, and introducing formal protocols can strengthen KMC as routine neonatal care.

KEYWORDS:
Kangaroo Mother Care, healthcare workers, hospital, preterm, barrier, training

INTRODUCTION

Prematurity is a major public health concern globally, contributing significantly to neonatal morbidity and mortality. In 2015, the prevalence of preterm birth in Malaysia was 12.4%, exceeding the global prevalence of 10.6% estimated in 2014.[1] Despite technological advancements in neonatal care, the preterm infants' death related to complications contribute to the second leading cause of death among infants after pneumonia. KMC, defined as prolonged skin-to-skin contact between the newborn and the caregiver, has been shown to promote early and sustained breastfeeding, reduce hospital-acquired infections and enhance overall neonatal survival. It also facilitates earlier discharge for stable premature infants. Recognising these benefits, the World Health Organization (WHO) first recommended KMC in 2003 and in its 2022 update, strongly reaffirmed KMC as essential care for preterm and low birth weight infants.[2-5]

In Malaysia, KMC was formally introduced in 2013 to four hospitals as part of the South East Asia - Using Research for Change in Hospital-acquired Infection in Neonates (SEA URCHIN) project, an evidence-based educational initiative focused on reducing neonatal infections through both provider and trainer capacity building.[6] Subsequently, various national-level efforts have aimed to promote KMC, including widespread training workshops and advocacy initiatives, details of which will be published in a separate paper. In brief, this included the establishment of the Kangaroo Mother Care Advocates Malaysia (KAMY), a dedicated national level non-governmental organisation and the development of a KMC website (www.kangaroomothercaremalaysia.net) to support provider engagement and parental advocacy.

However, the absence of national data on KMC implementation poses a challenge. Without a clear understanding of current practices, it is difficult to assess the impact of these initiatives or identify gaps and opportunities for improvement. This study sought to quantify the extent of KMC implementation nationwide and to identify modifiable institutional factors associated with routine practice.

This article was accepted: 20 February 2026
Corresponding Author: Foong Siew Cheng
Email: scfoong@rumc.edu.my

MATERIALS AND METHODS

Study design

This was a structured, cross-sectional survey conducted in Malaysia between April and August 2024 using a self-administered online questionnaire. All public hospitals (GH) and private hospitals (PH) providing Level II to III neonatal care were invited to participate. Each participating hospital designated a representative knowledgeable about their institution's KMC practice to complete the survey and provide hospital-level insights on KMC implementation. The study exclusively collected aggregate data at the hospital level and did not involve individual staff, patients or their families at any stage.

Inclusion criteria

Only hospitals providing level II or level III neonatal care were invited to participate as these facilities are typically responsible for the management of preterm and low birth weight infants.

Level II neonatal care involves specialised support for newborns who require more than routine care, including care for those transitioning to or from intensive care. Level III neonatal care refers to the management of newborns who are critically ill or at high-risk and require comprehensive intensive care services.[3-5,7]

Recruitment

Eligible public and private hospitals were identified using data from the 2020 Malaysian National Neonatal Registry (MNNR) report and the Malaysian Society for Quality in Health (MSQH) registry.[8-9] Formal approval was first obtained from the hospital directors of all identified facilities. Following approval, an invitation email containing study information and a link to the online Google Form survey was sent to the head of each hospital's neonatal unit. Heads of neonatal units who consented to participate either completed the survey themselves, or nominated a suitably qualified representative.

Study Instrument

Data were collected using a structured, self-administered online questionnaire hosted on Google Forms. The survey comprised 17 items organised into four sections: Section A – informed consent, Section B – hospital demographics, Section C - current KMC implementation practices; and Section D - availability of KMC-related facilities. The questionnaire captured information on hospital location, total and premature deliveries in 2023, KMC implementation practices, infant eligibility criteria, availability of supporting infrastructure and documentation practices. (See Appendix 1: Questionnaire)

The questionnaire was developed specifically for this study by the research team. Content validity was enhanced through pilot testing among healthcare staff in neonatal wards at four hospitals representing different facility types and levels of KMC implementation: one public and one private hospital practising KMC, and one public and one private hospital without KMC. Formal psychometric validation was not undertaken as the survey was descriptive and practice-oriented. Completion of the survey required approximately 15 to 20 minutes.

Data Analysis

Data were analysed using Stata version 13.[10] Categorical variables were summarised as frequencies and percentages. Open-ended responses were reviewed and thematically categorised. Logistic regression analysis was performed to identify factors associated with self-reported regular KMC implementation. Regular KMC was defined as routine provision of KMC to eligible infants, whereas occasional KMC referred to ad-hoc or selective practice without systematic integration. A p-value of < 0.05 was considered statistically significant.

Ethics approval

This study was registered with the National Medical Research Register (NMRR ID-24-00330-TDK) and ethical approval was obtained from the Medical Research & Ethics Committee, Ministry of Health Malaysia (KKM/NIHSEC/P15-583) 24-24-00330-TDK (1). Written informed consent was obtained from the participants prior to the commencement of study.

RESULTS

A total of 93 hospitals in Malaysia were identified as providers of Level II–III neonatal care, of which 69 responded to the survey, yielding an overall response rate of 74%. Responses were received from all 13 states and both Federal Territories in Peninsular Malaysia. Public hospitals demonstrated a higher response rate than private hospitals (89% vs. 55%) (Figure 1).

Reported numbers of preterm birth in 2023 varied widely among participating hospitals. Among public hospitals, 29 reported between 70 and 499 preterm births, 10 reported 500 to 944, and six reported between 1,015 and 3,096; three did not provide data. The median number of preterm births among public hospitals was 380 (IQR 206–889; range 70 – 3,096). Among private hospitals, 17 reported 5 to 80 preterm births, while four did not disclose figures. The median number was 25 (IQR 11–41; range 5 – 80).

KMC Implementation and Practices

Of the 69 participating hospitals, 60 (87%) reported implementing KMC with 33 (48%) practising it regularly and 27 (39%) occasionally; nine hospitals were not practicing KMC at the time of the survey.

Among the 60 hospitals implementing KMC, the practice was most commonly undertaken in neonatal intensive care units (NICUs) and special care nurseries (SCNs), with fewer hospitals supporting KMC in postnatal wards or rooming-in areas. Regarding eligibility, 44 hospitals (73%) permitted KMC for infants receiving tube feeding, 43 (72%) for those on nasal oxygen, and 32 (53%) for those requiring intensive respiratory support (e.g. CPAP, HFNC, or mechanical ventilation). KMC was permitted for infants born before 32 weeks' gestation in 41 hospitals (68%), whereas only one hospital allowed KMC for infants with central lines. (Table I)

Facilities and Support Infrastructure

Regarding maternal comfort and support, 42 hospitals (70%) provided front-button blouses, 41 (68%) had reclining chairs or sofas, and 17 (28%) offered KMC binders.

Table I: Response to questions regarding KMC Implementation, Eligibility Criteria, and Support Among Hospitals Implementing KMC practices (N = 60)

	Total KMC implementation (N = 60)	GH with KMC implementation (n = 42)		PH with KMC implementation (n = 18)
Administrative KMC support	20 (33%)	14 (33%)		6 (33%)
Incentives provided for KMC Implementation	6 (10%)	5 (12%)		1(6%)
Structured training sessions provided for staff	20 (33%)	16 (38%)		4 (22%)
Availability of trained staff		GH with >1000 preterm births (n = 9)	GH with <1000 preterm births (n = 33)	PH (all had fewer than 300 preterm births) (n = 18)
Only a few trained	26 (43%)	3	12	11
Some staff trained	19 (32%)	4	13	2
Most staff trained	15 (25%)	2	8	5
KMC Documentation & Policy				
Documentation of KMC Activities	57 (95%)	41 (98%)		16 (89%)
Availability of Institutional Policy/Protocol	21 (35%)	17 (40%)		4 (22%)
Parent-Focused Support				
KMC binders	17 (28%)	14 (33%)		3 (17%)
Front-button blouses	42 (70%)	35 (83%)		7 (39%)
Privacy screens	42 (70%)	28 (67%)		14 (78%)
Reclining chair/bed, lazy chair, etc	41 (68%)	25 (60%)		16 (89%)

GH: Public Hospital; PH: Private Hospital; KMC: Kangaroo Mother Care; GA: Gestational Age: CPAP: Continuous Positive Airway Pressure; HFNC: High-Flow Nasal Cannula; NICU: Neonatal Intensive Care Unit; SCN: Special Care Nursery, ICU: Intensive Care Unit; HDU: High Dependency Unit

Documentation and Protocols

Nearly all hospitals practising KMC (n=57, 95%) reported some form of documentation, but only 33 (55%) did so consistently. Documentation was mostly recorded in nursing handover notes or infant medical records, with physician notes rarely used (n = 3; 5%). Among hospitals with inconsistent or absent documentation, the main reason cited was the lack of integration into institutional workflow or policy. Only 22 hospitals (37%) had formal KMC protocols or guidelines, and just five (8%) maintained a dedicated KMC census or registry.

Staff Training and Capacity

Seventy-five percent of hospitals reported a need for more structured and routine KMC training. Only 15 hospitals (25%) indicated that most staff caring for newborns had received KMC training, while 11 (18%) reported no trained staff. The remaining hospitals reported that only some staff had received training. (Table I)

Barriers to Implementation

Key challenges reported by hospitals included limited administrative support, insufficient training, overcrowding, lack of privacy and space, inadequate amenities, staff shortages and low public awareness. (Figure 2)

Factors Associated with Regular KMC Implementation

Simple logistic regression identified several factors significantly associated with regular KMC implementation: availability of KMC protocols or guidelines (OR 4.68, 95% CI: 1.43-15.32, p = 0.01), presence of training or CME sessions with trained staff (OR 4.98, 95% CI: 1.36 - 18.23, p = 0.02), regular documentation (OR 2.91, 95% CI: 1.01 - 8.36, p = 0.04), and provision of front-button blouses for mothers (OR 5.29, 95% CI: 1.54 - 17.52, p = 0.01). In the multivariable model, regular KMC remained significantly associated with availability of protocols or guidelines (aOR 3.63, 95% CI: 0.97 – 13.59, p = 0.05), and provision of front-button blouses (aOR 4.25, 95% CI: 1.02 – 17.65, p = 0.04). No significant associations were observed with other maternal comfort amenities (e.g., KMC binders, privacy screens, reclining chairs), institutional incentives, preterm birth burden, or availability of dedicated space. Variables significant in univariable analysis ($p < 0.05$) were included in the multivariable model.

Non-Implementing Hospitals

Among the nine hospitals not implementing KMC, seven (78%) reported space constraints, overcrowded wards and limited resources as key barriers. Eight of nine hospitals (89%) expressed a need for KMC training for their staff.

DISCUSSION

This study represents the first national-level assessment of KMC implementation across Malaysian hospitals providing Level II and III neonatal care. The findings demonstrate encouraging uptake, particularly in the public sector, where the majority of hospitals reported offering at least some form of KMC. This reflects Malaysia's commitment to evidence-based neonatal care, given the substantial burden of prematurity on under-five mortality.[9] The high number of preterm births reported by participating hospitals highlights the ongoing need for effective, low-cost interventions such as KMC, which consistently improves survival and reduces morbidity among preterm and low birth weight infants.[3,11-13] The widespread adoption of KMC in public hospitals suggests that national training and advocacy initiatives, such as those

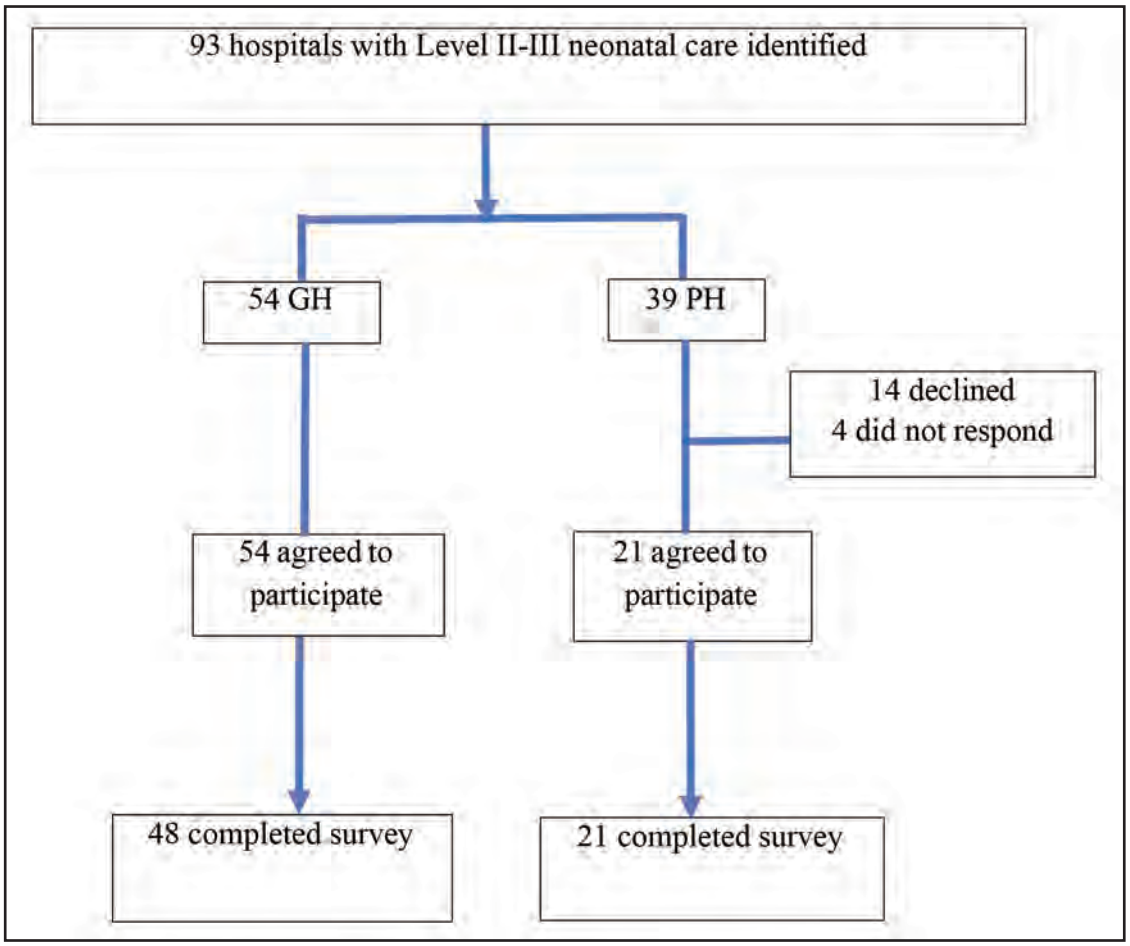


Fig. 1: Study flow chart
(Flow diagram of public hospitals (GH) and private hospitals (PH): approached, responded and included in the final analysis.)

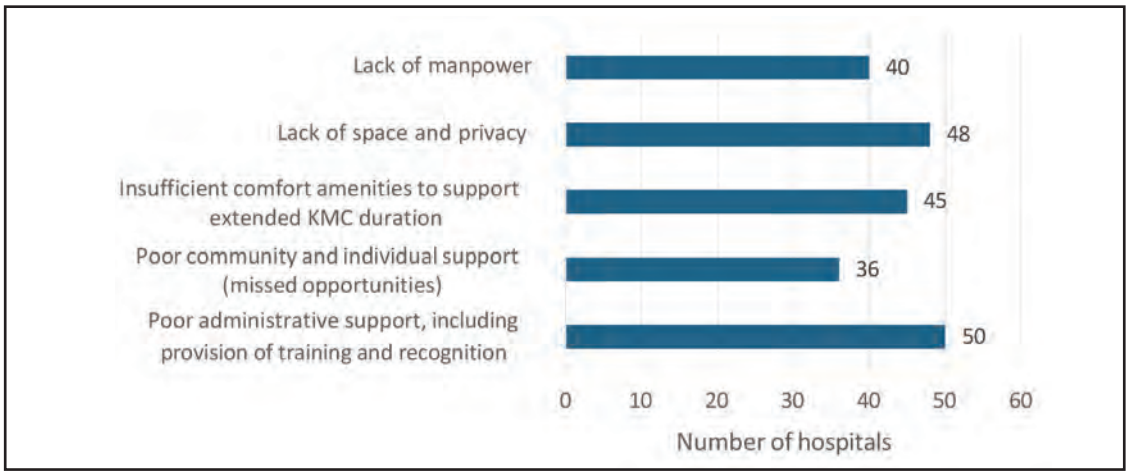


Fig. 2: Barriers to KMC Implementation
(Number of hospitals reporting each barrier to Kangaroo Mother Care (KMC) implementation. Respondents could select more than one barrier).

through the SEA-URCHIN project and supported by KAMY may have had a meaningful impact.

In contrast, the lower response rate among private hospitals may reflect differences in service models and priorities. Anecdotal feedback indicated that some private facilities considered KMC irrelevant to their practice and therefore chose not to participate. This highlights the need for targeted advocacy and training to support routine KMC adoption in the private sector. Consistent with this, our multivariable analysis identified staff training as a key factor associated with regular KMC implementation. Although KMC workshops have been conducted nationwide, their impact appears not to have been sustained, and some hospitals managing large numbers of premature infants reported few or no formally trained staff – a situation likely linked to the non-mandatory nature of KMC training.

Gaps in training may help explain why some hospitals did not permit KMC for very preterm infants requiring more intensive support, such as those on CPAP or receiving enteral feeding, despite strong evidence of benefit.[7,14-16] Similarly, several hospitals restricted KMC for infants receiving tube feeding or oxygen supplementation, even when these infants were clinically stable. Although this study did not explore the specific reasons for these exclusions, findings from our 2018 interviews suggest that KMC was often not considered part of immediate or acute care for smaller or more critically ill infants.[17-18] This perspective contrasts with current evidence and the updated WHO guidance which support KMC in such cases. Targeted training may therefore be critical for shifting these perceptions and enabling more consistent and effective KMC implementation.[13,19-22]

Encouragingly, all hospitals, regardless of their current level of KMC implementation, expressed a clear need for more structured and formalised KMC training. This reflects both recognition of existing gaps and institutional readiness to strengthen or initiate KMC practices. Importantly, unlike infrastructure constraints that require longer-term investment to address, training gaps are more readily addressable and should be prioritised.[4,23-24]

Overcrowded wards and limited physical space were frequently reported as barriers to KMC. One potential solution is to redesign neonatal wards into integrated mother–neonatal units, including mother–neonatal intensive care units (M-NICUs). These models, which prioritise zero separation between mother and infant, are increasingly recognised as critical for facilitating both conventional and immediate KMC as well as for advancing family-centred neonatal care. While such designs require long term planning and investment, they should be considered in national neonatal care strategies.[5,25-26]

We also identified a lack of comfort-related amenities necessary to sustain prolonged KMC sessions including KMC binders, front-button blouses, reclining chairs or sofas, and privacy screens. Few hospitals provided KMC binders, which may contribute to maternal fatigue during prolonged sessions. These findings are consistent with our 2018 key informant interviews, indicating that improvements in KMC infrastructure have yet to be widely implemented.[17-18] In addition, the availability of front-button blouses was independently associated with regular KMC practice. These blouses provide both comfort and modesty, helping mothers overcome discomfort in crowded wards where privacy is limited. At present, such blouses are generally reserved for in-patients and are not available to mothers who are rooming-in or visiting. Unlike large-scale ward restructuring, expanding access to front-button blouses and KMC binders is a low-cost, easily implementable intervention with the potential to improve KMC uptake and consistency.

Limited administrative support emerged as a key barrier to consistent KMC practice. The absence of KMC as a recognised key performance indicator, together with the lack of formalised protocols, may partly explain observed gaps in documentation and variability in practice across hospitals. Without integration into standard ward policies and routine staff training, KMC risks being perceived as a supplementary activity rather than a core component of neonatal care. Strengthened administrative support and commitment from hospital leadership and policymakers has been shown to be essential for successful KMC integration.[5,11, 26-30]

Consistent with previous studies, hospitals with regular and formalised KMC documentation were more likely to report consistent implementation.[26,28,29] Strengthening documentation practices, particularly among doctors may therefore be critical for elevating the clinical importance of KMC and promoting routine practice because our 2018 findings showed that doctors do not routinely document KMC activities.[18]

The absence of a hospital-level KMC census and a national KMC registry further limits the visibility of ongoing activities. Without systematic data collection, it remains challenging to monitor progress, identify implementation gaps, or scale up effective practices. Establishing a centralised national KMC registry could standardise documentation, support monitoring, and inform policy and quality improvement efforts.[21, 24, 31-32]

Our study also found that community awareness of KMC remains limited, which may contribute to suboptimal uptake.[17-18] Integrating KMC education into antenatal care visits is therefore an important strategy, preparing families to participate actively in KMC during the postnatal period.[29]

Interestingly, no clear association was observed between formal incentives and regular KMC practice, suggesting that intrinsic motivation, driven by professional responsibility, belief in KMC benefits, and a culture of compassionate care, may be more influential than formal rewards. This resonates with our 2018 interviews, in which consistent KMC practice was often attributed to staff motivation and supportive team dynamics, highlighting the importance of continuous education, visible leadership endorsement, and an enabling environment where staff feel empowered to provide KMC.[18]

Implications for Policy and Practice

1. **Strengthen administrative support through policy alignment.**
   Greater administrative commitment is needed to integrate KMC into routine neonatal care, including recognising KMC as a key performance indicator, developing formal protocols, and standardising documentation across neonatal wards.
2. **Establish routine KMC monitoring through a census or registry.**
   Implementing a hospital-level KMC census and, ultimately, a national registry, would improve the visibility of KMC activities, enable identification of implementation gaps, and support quality improvement and policy planning.
3. **Prioritise KMC training for all neonatal ward staff.**
   Routine training for doctors and nurses should be prioritised, as it represents an immediately actionable strategy to address knowledge gaps, correct misconceptions and improve consistent KMC practice.
4. **Address practical barriers with basic comfort-related amenities.**
   Ensuring access to front-button blouses, KMC binders, and privacy screens offers low-cost, easily implementable support to sustain KMC within existing infrastructure constraints.
5. **Improve community awareness and antenatal preparation for KMC.** Integrating KMC education into antenatal care services can enhance family awareness and readiness to participate in KMC during the postnatal period.
6. **Plan for long-term redesign of neonatal care environments.**
   Redesigning neonatal wards into integrated mother–neonatal units, including mother–neonatal intensive care units (M-NICUs), should be considered as a longer-term strategy to advance family-centred care and facilitate both conventional and immediate KMC.

Strengths

This study represents the first comprehensive national assessment of KMC implementation in Malaysia. It offers valuable insights into existing practices, common challenges, and critical gaps, offering an evidence-based foundation to inform national strategies for more effective integration of KMC into routine neonatal care.

LIMITATIONS

Data were self-reported by a single representative at each participating hospital, and were not independently verified through clinical observations. As such, the findings reflect individual perspectives that may not fully represent hospital-wide practices, introducing potential reporting bias and variation in interpretation. For instance, some respondents did not select "administrative support" in structured response options but described it in open-text comments, or reported ongoing KMC-related CME despite not selecting training in structured options. These inconsistencies indicate possible differences in interpretation. Furthermore, while the overall response rate was acceptable, the non-participation of some hospitals, particularly from the private sector, may limit the generalisability of the findings to all Level II–III neonatal care facilities in Malaysia. Follow-up qualitative research is needed to explore these themes in greater depth.

CONCLUSION

This national survey provides the first comprehensive overview of KMC implementation in Malaysia, revealing that KMC is practiced in most public hospitals and in some private facilities. Significant gaps remain in administrative support, staff training, documentation practices, and infrastructure. Addressing these gaps is essential to optimise the impact of KMC and improve neonatal outcomes nationwide. Feasible, low cost interventions such as providing front-button blouses, enhancing staff training, and implementing formal KMC protocols, can support more consistent and sustainable integration of KMC into routine neonatal care. These findings provide a pragmatic roadmap for national scale-up of KMC aligned with Malaysia's neonatal care priorities.

CONFLICT OF INTEREST

All authors declare no conflict of interest except that SI and NI work in two of the participating hospitals.

ACKNOWLEDGEMENTS

The authors would like to thank the Director General of Health Malaysia for his permission to publish this article. Special thanks to Dr Shyahlini Devi a/p Rajendran, Ms Helennie binti Jun, Dr Lim Hao Yik and Dr Tan Beng Geok for liaison with the hospitals and to Ms Fairuz Fadzilah binti Rahim for assistance with data analysis. We also acknowledge the approval of all Level II-III Hospital Directors and staff who took filled up the survey form including but not limited to Dr Muhammad Afiq Bin Johari, Dr Fazila Mohamed Kutty, Dr Victor Gong Hee Hung, Dr Nordin Zakaria, Dr Wong Yoke Peng, Dr Rosni Jamalludin, Dr Ismail Haron, Dr Rahimah Ismail, Dr Elaine Wong, Dr Rohaizah Binti Borhan, Dr Ang Ee Lee, Dr Zainah bt Shaikh Hedra, Dr Rohani Abdul Jalil, Dr Chandran A/L Munusamy, Mr Kong Kian Keong, Dr Ling Hung Toh, Dr Janet Hii Lin Yee and Dr Chieng Chae Hee. We are also grateful to RCSI & UCD Malaysia Campus for their funding support.

FUNDING

This work was supported by funding from RCSI & UCD Malaysia Campus.

REFERENCES

1. Damanhuri NH, Ismail M, Jeganathan R, Karalasingam SD, Nasir MJM, Soelar SA, et al. Spontaneous preterm births in Malaysia: are there modifiable antenatal risk factors? Cureus 2024; 16(4): e59152.
2. World Health Organization. Kangaroo mother care: a practical guide. Geneva: WHO; 2003.
3. World Health Organization. WHO recommendations for care of the preterm or low birth weight infant. Geneva: WHO; 2022.
4. World Health Organization. Kangaroo mother care: implementation strategy for scale-up adaptable to different country contexts. Geneva: WHO; 2023.

5. World Health Organization. Kangaroo mother care: a transformative innovation in health care. Geneva: WHO; 2023.
6. SEA-URCHIN: South East Asia using research for change in hospitals 2011–2015 https://research.monash.edu/en/projects/sea-urchin-south-east-asia-using-research-for- change-in-hospital (Accessed on 20 November 2025)
7. Charpak N, Tessier R, Ruiz JG, Hernandez JT, Uriza F, Villegas J, et al. Twenty-year follow-up of kangaroo mother care versus traditional care. Pediatrics 2017; 139(1).
8. Malaysian Society for Quality in Health. https://www.msqh.com.my/web/ (Accessed on 20 November 2025)
9. Neoh SH. Report of the Malaysian National Neonatal Registry 2020: a study of critically ill babies in neonatal intensive care units. Kuala Lumpur: Perinatal Society of Malaysia; 2020.
10. StataCorp. Stata statistical software: release 13. College Station (TX): StataCorp LP; 2013.
11. Charpak N, Angel MI, Banker D, Bergh AM, Bertolotto AM, De Leon-Mendoza S, et al. Strategies for countrywide implementation of kangaroo mother care. Acta Paediatr 2020; 109(11): 2278-86.
12. Conde-Agudelo A, Díaz-Rossello JL. Kangaroo mother care to reduce morbidity and mortality in low birthweight infants. Cochrane Database Syst Rev 2016; (8).
13. Sivanandan S, Sankar MJ. Kangaroo mother care for preterm or low birth weight infants: a systematic review and meta-analysis. BMJ Glob Health 2023; 8(6).
14. Lundqvist A. Immediate skin-to-skin contact for very preterm and low birth weight infants. Stockholm: Karolinska Institutet; 2022.
15. Campbell-Yeo ML, Disher TC, Benoit BL, Johnston CC. Understanding kangaroo care and its benefits to preterm infants. Pediatr Health Med Ther 2015; 6: 15-32.
16. Charpak N, Tessier R, Ruiz JG, Uriza F, Hernandez JT, Cortes D, et al. Kangaroo mother care and brain structure in young adults born preterm. Acta Paediatr 2022; 111(5): 1004-14.
17. Foong WC, Foong SC, Ho JJ, Gautam D, Leong JJ, Tan PY, et al. Exploring factors influencing uptake of kangaroo mother care: interviews with parents. BMC Pregnancy Childbirth 2023; 23(1): 706.
18. Foong WC, Foong SC, Ho JJ, Tan PY, Leong JJ, Baskaran M. Factors influencing uptake of kangaroo mother care: interviews with healthcare workers. BMC Pregnancy Childbirth 2025; 25(1): 790.
19. Bergh AM, de Graft-Johnson J, Khadka N, Om'Iniabohs A, Udani R, Pratomo H, et al. Implementation of facility-based kangaroo mother care in Asia. BMC Int Health Hum Rights 2016; 16: 4.
20. Kenanga Purbasary E, Rustina Y, Budiarti T. Increasing confidence in implementing kangaroo mother care among young mothers. Compr Child Adolesc Nurs 2017; 40 Suppl 1: 1-7.
21. Siraneh Y, Berhane M, Abraham G, Feyissa GT, Morankar S. Compliance to kangaroo mother care best practice. JBI Evid Implement 2021; 19(3): 228-35.
22. Nghitanwa V. Perceptions on feasibility of kangaroo mother care implementation in Tsumeb district hospital, Namibia [Master thesis]. University of the Western Cape; 2012.
23. Gardner B, Rebar AL. Habit formation and behavior change. Oxford: Oxford University Press; 2019.
24. Salim N, Shabani J, Peven K, Rahman QS, Kc A, Shamba D, et al. EN-BIRTH validation study of kangaroo mother care. BMC Pregnancy Childbirth 2021; 21 Suppl 1: 231.
25. WHO KMC Study Group. Impact of immediate kangaroo mother care on survival of newborns 1.0 to <1.8 kg: protocol for randomized trial. Trials 2020; 21.
26. Mohammadi M, Bergh AM, Jahdi NS, Valizadeh L, Hosseini M, Hakimi S. Launching continuous kangaroo mother care in Iran. BMC Health Serv Res 2023; 23(1): 436.
27. Cai Q, Zhou Y, Hong M, Chen D, Xu X. Providers' experiences of kangaroo mother care in China: qualitative study. Front Public Health 2024; 12: 1419828.
28. Calibo AP, De Leon Mendoza S, Silvestre MA, Murray JCS, Li Z, Mannava P, et al. Scaling up kangaroo mother care in the Philippines. BMJ Glob Health 2021; 6(8).
29. Cavallin F, Trevisanuto D, Tiep TV, Diep NTN, Hao VT, Ngan DT, et al. Kangaroo mother care in Vietnam: national survey. Children (Basel) 2022; 9(11).
30. Jadaun AS, Dalpath SK, Trikha S, Upadhyay RP, Bhandari N, Punia JS, et al. Government initiative to increase kangaroo mother care in North India. Acta Paediatr 2023; 112 Suppl 473: 6-14.
31. Stikes R, Barbier D. Increasing use of kangaroo care using PDSA model. J Nurs Manag 2013; 21(1): 70-8.
32. Torres LM, Mazia G, Guenther T, Valsangkar B, Wall S. Monitoring implementation and scale-up of facility-based kangaroo mother care. J Glob Health 2021; 11: 14001.

Appendix 1: Questionnaire (edited)

Title of study: National survey on the implementation of Kangaroo Mother Care for premature infants in hospitals across Malaysia

Tajuk kajian: Kajian kebangsaan mengenai pelaksanaan Kangaroo Mother Care untuk bayi pramatang di hospital di seluruh Malaysia

1. By clicking either option, I am providing my consent and agreement accordingly. *
   Berdasarkan pilihan saya, saya mengakui saya telah memberikan persetujuan yang sewajarnya.]

   Mark only one oval.

   ☐ I agree to participate in the study. [Saya bersetuju untuk mengambil bahagian dalam kajian ini.]
   ☐ I do not agree to participate in the study. [Saya tidak setuju untuk mengambil bahagian dalam kajian ini.]
   Skip to section 5 (Thank you very much for taking the time and effort in filling up this form. Please click the "Submit" button. Terima kasih kerana meluangkan masa dan tenaga untuk melengkapkan borang kajian ini. Sila klik butang 'Submit'.)

Section B

Demographic data

Thank you for your participation which will help guide future strategies to assist in the implementation of KMC in hospitals. Please note that in this study, **KMC refers to prolonged skin-to-skin practices between mother (or surrogates) and baby after the 1st hour skin-to-skin contact in the labour room.**

Terima kasih di atas penyertaan anda dalam kaji selidik KMC yang akan membantu meningkatkan strategi penambahbaikan perlaksanaan KMC di hospital.(Untuk makluman anda, ***KMC dalam kaji selidik ini merujuk kepada amalan sentuhan kulit-ke-kulit yang berpanjangan antara ibu (atau pengganti) dengan bayi, selepas amalan sentuhan kulit-ke-kulit pada jam pertama selepas kelahiran di dalam dewan bersalin.***

2. Study ID *

   _____

Your designation (eg Matron/ Neonatologist/ Medical officer etc) *
Jawatan anda: Contoh Ketua Penyelia Jururawat, Neonatologis, Pegawai Perubatan, dsb.

3. In which state is your hospital located? *(Dimanakah lokasi hospital anda?)* *
   Mark only one oval.

   ☐ Perlis
   ☐ Kedah
   ☐ Kelantan
   ☐ Penang
   ☐ Perak
   ☐ Pahang
   ☐ Selangor
   ☐ Negeri Sembilan
   ☐ Melaka
   ☐ Terengganu
   ☐ Johor
   ☐ Sabah
   ☐ Sarawak

4. Number of live births in your hospital in Year 2023 *(Pada tahun 2023, berapakah kelahiran bayi hidup di hospital anda?)*

   _____

5. Number of babies born preterm in your hospital in Year 2023 *(Pada tahun 2023, berapakah kelahiran bayi pramatang di hospital anda?)*

_____

6. Does your hospital implement KMC practices? *(Adakah hospital anda mengamalkan amalan KMC?)* *

Mark only one oval.

- ☐ Yes, this is regular practice in the neonatal units (Ya, sentiasa diamalkan di unit neonat)
- ☐ Yes, this is sometimes done in the neonatal units (Ya, tetapi sekali-sekala di unit neonat)
- ☐ No, this is not done (Tidah, tak pernah amalkan) *Skip to question 16*
- ☐ Don't know (Tidak tahu) *Skip to question 16*

Section C: KMC implementation practices *(Amalan perlaksanaan KMC)*

7. Does your hospital have any of these to support KMC practices? (Please tick (√) all items that apply).*
Adakah hospital anda mempunyai mana mana yang berikutan untuk menyokong amalan KMC? (Sila tandakan (√) pada semua yang berkenaan)

Check all that apply.

- ☐ Yes. a written policy (Ya, ada polisi bertulis.)
- ☐ Yes, a guideline or protocol (Ya, ada garispanduan atau protokol)
- ☐ Yes, regular CME or hands-on teaching on the job on KMC (Ya, ada CME atau kursus berkenaan KMC sewaktu kerja dair masa ke semasa)
- ☐ No (Tiada)

8. In which part(s) of your hospital is/are KMC support provided? (please tick all items that apply) *
Di hospital anda, di manakah sokongan KMC disediakan? (Sila tandakan (√) pada semua yang berkenaan)

Check all that apply.

- ☐ Postnatal wards (Wad postnatal)
- ☐ Special care nursery or neonatal wards (Wad perawatan bayi) Mother's rooming in room (Bilik 'rooming-in' ibu)
- ☐ KMC room (Bilik KMC) NICU
- ☐ Maternal ICU or HDU (ICU atau HDU si ibu selepas bersalin)
- ☐ Other: _____

9. Which of the following groups of babies receive KMC in your hospital? (please tick all items that apply) *
Antara bayi-bayi yang disenaraikan dibawah, bayi yang mana menerima perawatan KMC di hospital anda? (Sila tandakan (√) untuk semua yang berkenaan)

Check all that apply.

- ☐ Term AGA (Cukup bulan AGA) Term SGA (Cukup bulan SGA)
- ☐ Preterm baby 34 weeks to 36 weeks and 6 days (Bayi pramatang 34 minggu hingga 36 minggu dan 6 hari)
- ☐ Preterm baby 32 weeks to 33 weeks and 6 days (Bayi pramatang 32 minggu hingga 33 minggu dan 6 hari)
- ☐ Preterm baby < 32 weeks and 6 days (Bayi pramatan kurang dari 32 minggu) Baby on tube feeding (Bayi yang memerlukan tube feeding)
- ☐ Baby on oxygen (Bayi yang memerlukan bantuan oksigen)
- ☐ Baby on CPAP (Bayi yang sedang menggunakan bantuan pernafasan CPAP)
- ☐ Baby on mechanical ventilator (Bayi yang sedang menggunakan bantuan pernafasan ventilator)
- ☐ Baby with central lines (Bayi yang ada "central lines")
- ☐ Other: _____

10. What facilities or support do your hospital have for KMC practices? (choose all that apply) *
Apakah kemudahan atau sokongan untuk amalan KMC yang sedia ada di hospital anda?(Sila tandakan (√) untuk semua yang berkenaan)

Check all that apply.

- ☐ KMC corner in the ward (Sudut KMC di wad)
- ☐ Allowance of KMC practices in mother's rooming-in rooms (Kebenaran untuk mengamal KMC di bilik rooming-in)
- ☐ Lazy chair (Kerusi malas)
- ☐ Bed/reclining chair or sofa (kerusi atau sofa bersandar)
- ☐ KMC binders (not bedsheets/big blanket) [pengikat/karung KMC, bukan cadar atau selimut panjang]
- ☐ Screens (Skrin)
- ☐ Front-button blouses (Baju berbutang depan) Changing room (Bilik tukar pakaian)
- ☐ KMC pamphlets (Risalah KMC)
- ☐ Having KMC as part of routine ward duties (Amalan KMC sebagai sebahagian tugasan harian)
- ☐ Other:

11. When KMC is provided, is this documented somewhere? (e.g. in the patient's notes) *
Apabila KMC dilakukan, adakah aktiviti ini dicatatkan? (Cth: seperti di dalam laporan pesakit)

Mark only one oval.

- ☐ Yes, all KMC activity is documented. (Ya, semua aktiviti KMC dicatatkan.)
- ☐ Yes, but only intermittently documented. (Ya, tetapi hanya kadang kadang dicatat.)
- ☐ No. (Tidak) *Skip to question 16*
- ☐ Don't know. (Tidak tahu) *Skip to question 16*

12. If only intermittently documented, could you let us know why?
Jika aktiviti KMC tidak selalu dicatatkan, bolehkah anda beritahu mengapa?

_____

_____

_____

_____

13. Where do the neonatal staff write down KMC practices that is done for the infants? (please tick all items that apply) *
Dimanakah kakitangan neonat menulis laporan aktiviti KMC untuk bayi? (Sila tandakan (√) untuk memilih semua yang berkenaan)

Check all that apply.

- ☐ Patients' observational notes (Laporan harian pesakit)
- ☐ Doctors' handover sheet (Lembaran penyerahan doktor)
- ☐ Nurses' handover sheet (Lembaran penyerahan jururawat)
- ☐ the Ward's Noticeboard (Papan notis wad)
- ☐ Other: _____

14. Do you have a census to document ongoing data collection of all KMC practice records in your hospital? *
Adakah hospital anda memperoleh data melalui bancian bagi semua rekod amalan KMC?

Mark only one oval.

- ☐ Yes (Ada)
- ☐ No (Tiada)
- ☐ Don't know (Tidak pasti)

Section D: Facilitating KMC implementation practices
Sokongan kepada amalan perlaksanaan KMC

15. What does your hospital need (or is still lacking) which makes KMC practice difficult to implement? (choose all that apply)*
Apakah sokongan yang diperlukan oleh hospital anda (atau masih berkurangan) yang menyebabkan amalan KMC susah diimplementasi?

Check all that apply.

- ☐ KMC corner in the ward (Sudut KMC di wad)
- ☐ Allowance of KMC practices in mother's rooming-in rooms (Kebenaran untuk mengamal KMC di bilik ibu)
- ☐ KMC room (Bilik KMC) Lazy chair (Kerusi malas)
- ☐ Bed/reclining chair or sofa (Kerusi atau sofa bersandar)
- ☐ KMC binders (not bedsheets/big blanket) [pengikat/karung KMC, bukan cadar atau selimut panjang]
- ☐ Screens (Skrin)
- ☐ Front-button blouses (Baju berbutang depan) Changing room (Bilik tukar pakaian)
- ☐ KMC pamphlets (Risalah KMC)
- ☐ Ward policy and protocol on KMC (Polisi dan protokol amalan KMC di wad)
- ☐ Recognising KMC as key performance index (Pengiktirafan KMC sebagai KPI)
- ☐ Other: _____

16. How many of the staff in the neonatal ward (including yourself) have been trained (formally or informally) to support KMC?*
Berapakah kakitangan di wad neonat (termasuk anda) yang pernah dilatih untuk KMC (secara formal dan bukan formal)?)

Mark only one oval.

- ☐ Most of them (Kebanyakan)
- ☐ Some of them (Sebahagian)
- ☐ Very few of them (Segelintir)
- ☐ Not sure (Tidak pasti)
- ☐ None of us are trained (Tiada)

17. Where did they get KMC training from? (tick (√) all that applies) *
Di manakah mereka menerima ilmu amalan KMC? (Sila tandakan (√) untuk kesemua yang berkenaan)

Check all that apply.

- ☐ Don't know/No one has been trained (Tidak tahu. Tiada antara kami dilatih)
- ☐ Workshops organised by Hospital Sultan Abdul Halim (Bengkel yang dianjurkan oleh Hospital Sultan Abdul Halim)
- ☐ Workshops organised by Hospital Seberang Jaya (Bengkel yang dianjurkan oleh Hospital Seberang Jaya)
- ☐ Workshops organised by Hospital Pulau Pinang (Bengkel yang dianjurkan oleh Hospital Pulau Pinang)
- ☐ Workshops organised by Hospital Sultanah Bahiyah (Bengkel yang dianjurkan oleh Hospital
- ☐ Workshops organised by Hospital Raja Permaisuri Bainun (Bengkel yang dianjurkan oleh Hospital Raja Permaisuri Bainun)
- ☐ Workshops organised by Hospital Raja Perempuan Zainab II (Bengkel yang dianjurkan oleh Hospital Raja Perempuan Zainab II)
- ☐ Workshops organised by Hospital Sibu (Bengkel yang dianjurkan oleh Hospital Sibu) Workshops organised by Hospital Kuching (Bengkel yang dianjurkan oleh Hospital Kuching)
- ☐ Workshops organised by PPUKM (Bengkel yang dianjurkan oleh PPUKM)
- ☐ Workshops organised by Penang Medical College (now RCSI & UCD Malaysia Campus) and KAMY (Bengkel yang dianjurkan oleh RUMC dan KAMY)
- ☐ SEA-URCHIN Project (South East Asia - Using Research for Change in Hospital-acquired Infection in Neonates Project) (Melalui projek SEA-URCHIN)
- ☐ Self-training using World Health Organisation (WHO) guidelines 2003 (Latihan kendiri dengan garis panduan WHO 2003)
- ☐ Self-training using WHO guidelines 2022 (Latihan kendiri dengan garis panduan WHO 2022)
- ☐ Other: _____

18. Would your hospital be interested to receive KMC support? *
Adakah hospital anda berminat untuk menerima sokongan KMC?

Mark only one oval.

- ☐ Yes (Ya)
- ☐ Maybe (Mungkin)
- ☐ No (Tidak)
  Skip to section 5 (Thank you very much for taking the time and effort in filling up this form. Please click the "Submit" button. Terima kasih kerana meluangkan masa dan tenaga untuk melengkapkan borang kajian ini. Sila klik butang 'Submit'.)

19. Please describe what support your hospital needs.
Sila nyatakan sokongan yang diperlukan oleh hospital anda

_____

_____

_____

_____

Thank you very much for taking the time and effort in filling up this form. Please click the "Submit" button.
Terima kasih kerana meluangkan masa dan tenaga untuk melengkapkan borang kajian ini. Sila klik butang 'Submit'.

Total corneal astigmatism magnitude and vector orientation in diabetic and non-diabetic Malay eyes

Afira Ahmad Suhaimi, MBBS[1,2], Muhammad Aizuddin Ahmad, DrOphth[1,2], Mohd Salami Ibrahim, PhD[1], Sumaiyah Adzahar, MPath[1], Khairidzan Mohd Kamal, MSurg (Ophthal)[3], Mohammad Hudzaifah Nordin, MMed (Ophthal)[1,2,3]

[1]Faculty of Medicine, Universiti Sultan Zainal Abidin, Kampus Perubatan, Kuala Terengganu, Terengganu, Malaysia, [2]Department of Ophthalmology, Hospital Sultan Zainal Abidin, Kuala Terengganu, Terengganu, Malaysia, [3]Department of Ophthalmology, Kulliyyah of Medicine, International Islamic University Malaysia, Kuantan, Pahang, Malaysia

ABSTRACT

Introduction: The influence of diabetes mellitus (DM) on total corneal astigmatism (TCA) remains incompletely understood. Using total keratometry (TK), this study characterised TCA magnitude and orientation in a Malay adult population and evaluated the influence of metabolic control and ocular parameters on TCA.

Materials and Methods: This cross-sectional study analysed 190 eyes (88 non-diabetic; 102 diabetic). TCA magnitude and axis were derived from TK obtained using swept-source optical coherence tomography (IOLMaster 700, Carl Zeiss Meditec, Germany) and decomposed into power-vector components; J0 (horizontal/vertical) and J45 (oblique). Corneal endothelial parameters were measured using specular microscopy (Topcon SP-1P, Japan). Group comparisons were performed using Welch's t-test. Within diabetic eyes, linear regression models identified independent predictors of TCA magnitude and orientation, adjusting for age, glycated haemoglobin (HbA1c), DM duration, cumulative metformin exposure, central corneal thickness, endothelial cell density, and white-to-white diameter.

Results: TCA magnitude did not differ significantly between diabetic and non-diabetic eyes (p = 0.066). Vector analysis demonstrated no significant between-group difference in J0 or J45, with substantial vector centroid overlap. In diabetic eyes, higher HbA1c was independently associated with greater TCA magnitude, while increasing age was independently associated with a shift towards more negative J0 values. DM duration and metformin exposure were not independently associated with TCA magnitude or vector components.

Conclusion: Diabetes status alone was not associated with systematic differences in TCA magnitude or orientation. Age and metabolic control were the strongest factors associated with TCA characteristics. Vector-based analysis provides a robust framework for astigmatism assessment in diabetic and non-diabetic eyes.

KEYWORDS:
Astigmatism, cornea, diabetes mellitus, metformin, keratometry, Malay population

INTRODUCTION

Diabetes mellitus (DM) is a systemic metabolic disorder that affects multiple ocular tissues, including the cornea, where it induces structural and biomechanical alterations involving endothelial cell density, stromal hydration, and connective tissue integrity.[1] This is particularly relevant in the Malay population, in whom the pooled prevalence of DM has been estimated at 15.25%, exceeding the Malaysian national average of 14.39%.[2] Such diabetes-related corneal changes may influence corneal curvature and astigmatism, with important implications for visual quality, refractive predictability, and surgical planning.[1,3-4]

Corneal astigmatism in diabetic eyes has predominantly been evaluated using anterior keratometry and conventional cylinder-axis notation.[1,5] However, these approaches incompletely characterise corneal optics, as they do not account for the posterior corneal curvature, which has been shown to meaningfully influence total corneal astigmatism (TCA).[5] The advent of swept-source optical coherence tomography (SS-OCT) has enabled measurement of total keratometry (TK), providing a more physiologically accurate representation of corneal astigmatism by incorporating both anterior and posterior corneal surfaces.[6-7]

Despite these advances, the relationship between diabetes and TCA remains incompletely defined. Prior studies have reported variable findings, with limited data specifically addressing astigmatism behaviour in diabetic populations and inconsistencies arising from differences in disease severity, metabolic control, and methodological approaches.[1,4] Moreover, most prior investigations have relied on separate analyses of astigmatism magnitude and orientation, without adopting vector-based methods.

Vector representation of astigmatism, first formalised by Thibos et al., is now widely recognised as the preferred framework for quantitative astigmatism analysis. This approach decomposes astigmatic error into two independent Cartesian components (J0 and J45), enabling magnitude and orientation to be analysed as continuous variables while avoiding axis-wrapping artefacts inherent to polar representations. Consequently, vector analysis permits valid averaging, hypothesis testing, and parametric modelling of astigmatism data.[8-9]

This article was accepted: 25 February 2026
Corresponding Author: Mohammad Hudzaifah Nordin
Email: hudzaifahnordin@unisza.edu.my

In addition, data examining the relationship between metabolic control, DM duration, cumulative metformin exposure, and corneal structural parameters such as central corneal thickness (CCT), endothelial cell density (ECD), and white-to-white diameter (WTW) with TCA magnitude and vector components remain limited, particularly in Malay populations.

Therefore, this study aimed to compare TCA magnitude and orientation between diabetic and non-diabetic eyes in a Malay adult population, and to determine whether systemic factors (age, DM duration, glycated haemoglobin [HbA1c], and cumulative metformin exposure) and ocular parameters (CCT, ECD, and WTW) are independently associated with TCA characteristics within diabetic eyes using a vector-based analytical framework.

MATERIALS AND METHODS

Study Design and Population

Participants were recruited from patients undergoing routine ophthalmic assessment at the Ophthalmology Clinic, Hospital Sultan Zainal Abidin (HoSZA) between January and June 2025. Eligible participants were Malay adults aged ≥18 years with reliable SS-OCT biometry, ECD measurements, and complete systemic data. Exclusion criteria included corneal pathology, previous corneal or intraocular surgery, ocular trauma, and media opacity that could compromise measurement quality. Only right eyes were included to avoid inter-eye correlation.

Demography, Systemic and Ocular Variables

A total of 190 participants were included in the analysis, comprising 88 non-diabetic individuals and 102 patients with DM. Diabetes status was determined based on documented clinical diagnosis, supported by random blood glucose and HbA1c measurements, obtained from the HoSZA General Medical Clinic or affiliated primary healthcare clinics.

Demographic variables included age and sex. Diabetes-specific variables comprised DM duration in years, cross-referenced using medical records and patient self-report. Only HbA1c values obtained within three months of ophthalmic assessment were included. Cumulative metformin exposure was calculated as the total prescribed metformin dose (mg) since treatment initiation, based on medical records and patient-reported adherence. Information regarding other diabetic treatment modalities, including insulin or combination therapy, was inconsistently documented in shared medical records, particularly for participants co-managed in primary healthcare clinics. Consequently, other treatment modalities could not be reliably stratified and were not included as a covariate in the analysis.

Ocular parameters included TCA, derived from TK measurement obtained using SS-OCT biometry with the IOLMaster 700 (Carl Zeiss Meditec, Germany). The device utilises telecentric keratometry with a 950-nm light source and acquires measurements along the visual axis by projecting 18 measurement points across three corneal zones (1.5, 2.5, and 3.5 mm), allowing calculation of the flattest and steepest keratometry values and TK. Measurements were accepted only when the device quality indicator signalled successful acquisition. Participants were instructed to fixate on the internal target and to blink immediately before each measurement to ensure tear-film stability. CCT and WTW were obtained during the same measurement session.[10]

ECD was measured using a non-contact Topcon SP-1P specular microscope (Topcon, Japan). Images were automatically centred, focused, and captured from the central, nasal and temporal cornea with full corneal exposure. All measurements were performed by a single trained operator.

Astigmatism Vector Analysis

TCA was expressed as magnitude in dioptres (D) and decomposed into power-vector components using Thibos notation.11 The horizontal/vertical component was defined as $J0 = -(C/2) \times \cos(2\alpha)$, representing astigmatism along the 0°/90° meridians, corresponding to with-the-rule (WTR) and against-the-rule (ATR) orientation. The oblique component was defined as $J45 = -(C/2) \times \sin(2\alpha)$. In these expressions, C denotes cylinder power and α denotes astigmatism axis in degrees.

Data Analysis

All statistical analyses were performed using Jamovi (version 2.6.26), an open-source statistical platform built on the R statistical computing environment (The jamovi project, 2025, https://jamovi.org). Statistical significance was defined as $p < 0.05$. All statistical tests were two-sided.

Continuous variables were assessed for normality using the Shapiro-Wilk test and visual inspection of histograms. Descriptive statistics are presented as mean ± standard deviation for approximately normally distributed variables and median with interquartile range (IQR) for non-normally distributed variables.

Comparisons between diabetic and non-diabetic eyes were performed using Welch's independent-samples t-test, selected a priori to account for unequal sample sizes and potential variance heterogeneity. Categorical variables were analysed using the χ^2 test of independence.

Within diabetic eyes, simple linear regression was initially used to screen associations between clinical variables and TCA magnitude and vector components (J0, J45). Variables of clinical relevance were subsequently entered into multiple linear regression models to identify independent predictors, while adjusting for age, sex, HbA1c, DM duration, cumulative metformin exposure, CCT, ECD, and WTW. Regression assumptions including linearity, homoscedasticity, normality of residuals, and absence of multicollinearity were verified. Model performance was assessed using the coefficient of determination (R^2). Due to a right-skewed distribution, cumulative metformin exposure was log-transformed prior to regression analysis to improve homoscedasticity.

Double-angle vector plots of J0 and J45 were generated using the R Editor module in Jamovi to visualise astigmatism orientation distributions and centroids.

Ethics Approval

This cross-sectional observational study was approved by the Universiti Sultan Zainal Abidin Human Research Ethics Committee (UniSZA/UHREC/2024/666) and supported by a DPU 1.0 Grant (UniSZA/2023/DPU1.0/42[RD053]). The study was conducted in accordance with the tenets of the Declaration of Helsinki.

RESULTS

Study Population and Baseline Characteristics

A total of 190 right eyes from a Malay cohort were analysed, comprising 88 non-diabetic eyes (46.3%) and 102 diabetic eyes (53.7%). The overall mean age was 69.30 ± 8.50 years (range 38 - 87 years), with no significant difference in age between groups (p = 0.551), confirming that the cohorts were well-balanced for age-related corneal analysis.

Baseline demographic and ocular characteristics are summarised in Table I. The two groups were comparable in age, sex distribution, ECD, and WTW. Diabetic eyes demonstrated significantly thinner CCT compared with non-diabetic eyes (p = 0.026). Diabetes-specific variables, including DM duration, HbA1c, and cumulative metformin exposure, were further summarised descriptively within the diabetic cohort only.

TCA Magnitude and Orientation Profile

TCA magnitude demonstrated a trend towards lower values in diabetic eyes compared with non-diabetic eyes; however, this difference did not reach statistical significance (p = 0.066).

Vector-based analysis revealed negative mean J0 values in both diabetic and non-diabetic eyes, indicating a predominance of ATR astigmatism in this predominantly older population. Mean J45 values were also negative in both groups, reflecting centroids oriented towards the 135° oblique meridian.

No statistically significant differences were observed between diabetic and non-diabetic eyes for either horizontal/vertical astigmatism orientation (J0) or oblique orientation (J45) component (p = 0.960 and p = 0.590, respectively), indicating no group-level association between diabetes status and TCA orientation.

Relationship Between Clinical Variables and TCA Magnitude in Diabetic Eyes

Within diabetic eyes, simple linear regression identified several variables associated with TCA magnitude. After multivariable adjustment, increasing age and higher HbA1c levels remained independently associated with greater TCA magnitude.

Variables that were significant in crude analysis, including DM duration and ECD, were no longer significant after adjustment, suggesting that their initial associations were

Table I: Demographic Profile, Diabetic and Ocular Parameters (N=190)

Variables	Non-Diabetics (n=88)	Diabetics (n=102)	p value
Age (years), mean ± SD	69.70 ± 9.60	69.00 ± 7.50	0.551
Sex, n (%)			0.120
Male	47 (53.4)	43 (42.2)	
Female	41 (46.6)	59 (57.8)	
TCA (TK) Magnitude (D), mean ± SD	1.21 ± 0.66	1.04 ± 0.63	0.066
Vector J0 (D), mean ± SD	–0.22 ± 0.59	–0.22 ± 0.50	0.960
Vector J45 (D), mean ± SD	–0.02 ± 0.29	–0.04 ± 0.27	0.590
CCT (µm), mean ± SD	531.20 ± 36.95	519.70 ± 33.63	**0.026**
ECD (cells/mm²), mean ± SD	2683.00 ± 521.00	2627.00 ± 458.00	0.430
WTW (mm), mean ± SD	12.00 ± 0.37	11.90 ± 0.39	0.220
DM duration (years), median (IQR)	-	9.00 (5.00-14.80)	-
HbA1c (%), mean ± SD	-	7.90 ± 1.80	-
Cumulative metformin dose (mg), median (IQR) (3.88–12.50 × 10^6)	-	7.31 × 10^6	
Log cumulative metformin dose, mean ± SD	-	13.10 ± 5.90	-

Statistical significance was defined as $p < 0.05$

Values are presented as mean ± SD or median (IQR), as appropriate. Continuous variables between non-diabetic and diabetic groups were compared using Welch's independent-samples t-test. Sex distribution was compared using the χ^2 test. DM-specific variables were summarised descriptively within the diabetic group only

Abbreviations: DM= Diabetes mellitus, HbA1c = glycated haemoglobin, IQR = Interquartile range, TCA = Total corneal astigmatism, TK = Total keratometry, D = Dioptres, CCT = Central corneal thickness, ECD = Endothelial cell density, WTW = White-to-white corneal diameter

Table II: Relationship of Clinical Variables with TCA Magnitude

TCA Magnitude (D)	Simple Linear Regression		Multiple Linear Regression	
(n=102)	Crude b[a] 95% CI	p value	Adj. b[b] 95% CI	p value
Age (years)	0.035 (0.020, 0.050)	**<0.001**	0.033 (0.017, 0.049)	**<0.001**
Sex (M-F)	–0.041 (–0.290, 0.209)	0.746		
DM duration (years)	0.002 (0.0004, 0.0039)	**0.016**		
HbA1c (%)	0.084 (0.0069, 0.161)	**0.035**	0.084 (0.007, 0.161)	**0.033**
Log metformin cumulative dose	–0.007 (–0.028, 0.014)	0.502		
CCT (µm)	–0.002 (–0.0059, 0.0014)	0.227		
ECD (cells/mm²)	0.00029 (0.00002, 0.00055)	**0.034**		
WTW (mm)	–0.301 (–0.611, 0.010)	0.057		

[a]Crude regression coefficient
[b]Adjusted regression coefficient; Model R^2 = 28.6%, Adjusted R^2 = 22.4%
Linear regression assumptions, including linearity and homoscedasticity, were met
Statistical significance defined as $p < 0.05$
Abbreviations: TCA = Total Corneal Astigmatism, D = Dioptres, DM= Diabetes mellitus, HbA1c = glycated haemoglobin, CCT = Central corneal thickness, ECD = Endothelial cell density, WTW = White-to-white corneal diameter

Table III: Relationship of Variables with J0 Orientation

J0 Astigmatism Component (D)	Simple Linear Regression		Multiple Linear Regression	
(n=102)	Crude b[a] 95% CI	p value	Adj. b[b] 95% CI	p value
Age (years)	–0.019 (–0.031, –0.006)	**0.004**	-0.022 (-0.035, -0.008)	**0.002**
Sex (M-F)	–0.041 (–0.290, 0.209)	0.746		
DM Duration (years)	–0.00025 (–0.0017, 0.0012)	0.725		
HbA1c (%)	0.031 (–0.032, 0.095)	0.329		
Log metformin cumulative dose	–0.009 (–0.026, 0.007)	0.262		
CCT (µm)	–0.002 (–0.005, 0.001)	0.134		
ECD (cells/mm²)	0.00003 (–0.00017, 0.00024)	0.807		
WTW (mm)	0.284 (0.039, 0.530)	**0.024**		

[a]Crude regression coefficient
[b]Adjusted regression coefficient; Model R^2 = 17.2%, Adjusted R^2 = 10.0%
Linear regression assumptions, including linearity and homoscedasticity, were met
Statistical significance defined as $p < 0.05$
Abbreviations: D = Dioptres, DM= Diabetes mellitus, HbA1c = glycated haemoglobin, CCT = Central corneal thickness, ECD = Endothelial cell density, WTW = White-to-white corneal diameter

attributable to confounding rather than independent effects. Cumulative metformin exposure was not associated with TCA magnitude in either crude or adjusted models. The final multivariable model explained approximately one-quarter of the variance in TCA magnitude (adjusted R^2 = 22.4%), consistent with the multifactorial nature of corneal astigmatism. Detailed regression results are outlined in Table II.

Relationship Between Clinical Variables and TCA Orientation (J0 and J45) in Diabetic Eyes

For the J0 component, representing horizontal/vertical astigmatism orientation (WTR/ATR), age remained independently associated with a shift towards more negative J0 values on multivariable analysis (Adj. b = –0.022 D/year; p = 0.002), reflecting an age-related transition towards ATR astigmatism (Table III).

Although WTW showed an association with J0 in univariable analysis, this relationship was no longer significant after adjustment. No systemic or ocular variables including age, HbA1c, DM duration, CCT, ECD, or metformin exposure were independently associated with the J45 component in either crude or adjusted analyses (all p > 0.05), suggesting that oblique astigmatism exhibits greater variability and weaker systemic associations.

Vector Distribution and Centroid Analysis

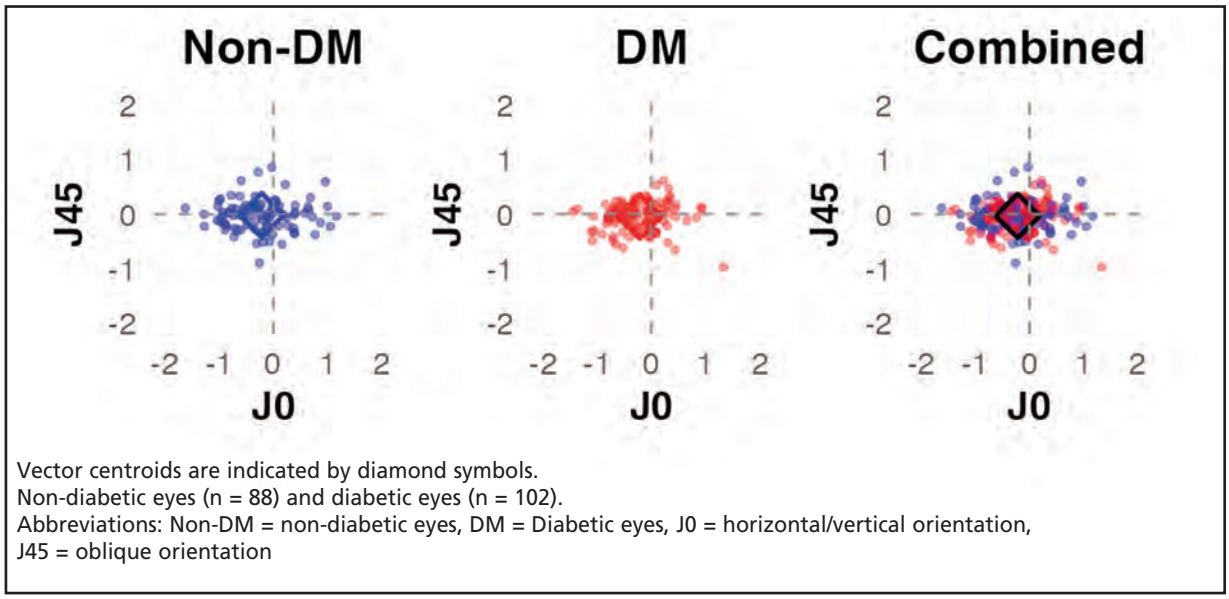
Double-angle vector plots demonstrated substantial overlap of J0 and J45 vector distributions and centroids between diabetic and non-diabetic eyes (Figure 1). This visual representation corroborated the statistical findings and confirmed the absence of a meaningful relationship between diabetes status and TCA orientation at a population level.

DISCUSSION

To our knowledge, this study is among the first to provide a vector-based characterisation of TCA in a Malay adult population, comparing diabetic and non-diabetic eyes. Our findings demonstrate that diabetes status alone does not systematically alter the TCA profile, while age and metabolic control (HbA1c) show statistically meaningful relationships with astigmatic orientation and magnitude, respectively. These findings suggest that corneal astigmatism is more strongly associated with age-related biomechanical remodelling and the prevailing metabolic environment than with the presence of diabetes itself.

Diabetes and TCA Magnitude

Diabetic eyes did not exhibit a statistically significant difference in TCA magnitude compared with non-diabetic eyes. This indicates that diabetes per se is less likely to be a dominant explanatory variable for TCA magnitude when



Vector centroids are indicated by diamond symbols.
Non-diabetic eyes (n = 88) and diabetic eyes (n = 102).
Abbreviations: Non-DM = non-diabetic eyes, DM = Diabetic eyes, J0 = horizontal/vertical orientation, J45 = oblique orientation

Fig. 1: Double Angle Plot of Non-Diabetic and Diabetic Eyes

assessed using TK. Importantly, this observation is consistent with prior work employing comparable keratometric methodologies, which similarly reported no meaningful magnitude difference between diabetic and non-diabetic eyes.[1]

Although earlier reports described higher anterior keratometric readings in diabetic patients, these often involved cohorts with poorer glycaemic control.[4,12] In contrast, the relatively well-controlled metabolic status of our diabetic cohort (mean HbA1c 7.9 ± 1.8%) and the use of TCA derived from TK, which incorporates posterior corneal power, may partly explain the absence of a significant magnitude difference. These findings suggest that any diabetes-related effect on TCA magnitude is likely modest and potentially masked by broader inter-individual variability.

HbA1c reflects integrated glycaemic exposure over the preceding three months and therefore represents the prevailing metabolic environment at the time of measurement. Elevated HbA1c levels are associated with hyperglycaemia-induced activation of polyol pathway, leading to intracellular sorbitol accumulation and osmotic stress within corneal tissues. In addition, accumulation of advanced glycation end products may alter collagen cross-linking changes in corneal biomechanics. These alterations may produce subtle curvature variability and contribute to astigmatic magnitude shift observed.[3,13]

Astigmatism magnitude exhibits substantial inter-individual dispersion in middle-aged and older populations, reflecting the combined effects of age-related corneal biomechanical remodelling and intrinsic anatomical heterogeneity.[5,14] This wide natural variability inflates error variance and reduces statistical power in magnitude-based cross-sectional comparisons, rendering them relatively insensitive to detecting subtle systemic influences such as diabetes-related effects on corneal toricity.[1] Accordingly, magnitude-only analyses may underestimate small but directionally specific corneal changes.

Although DM is frequently associated with increased CCT, our cohort demonstrated significantly thinner CCT in diabetic eyes. The median disease duration of approximately a decade suggests prolonged exposure to hyperglycaemia, which may induce degeneration of unmyelinated corneal nerves and reduce trophic support to the cornea, resulting in stromal and epithelial thinning.[4,13] Despite this structural difference, CCT was not independently associated with TCA magnitude or vector orientation after multivariable adjustment. This indicates that while diabetes-related corneal changes influence overall thickness, they do not meaningfully contribute to variability in astigmatic magnitude or orientation once age, metabolic control, and other ocular parameters are accounted for.

Collectively, these findings suggest that while TCA magnitude remains clinically relevant for refractive planning, it is not a discriminative marker for identifying diabetes-related corneal effects in cross-sectional analyses, where microstructural or transient metabolic influences may not translate into measurable differences in global corneal toricity.[3,4]

Vector Orientation of TCA (J0 and J45)

A major strength of this study is the application of vector-based astigmatism analysis, which overcomes the inherent limitations of conventional cylinder–axis notation for statistical modelling and group comparisons.

In both diabetic and non-diabetic eyes, mean J0 values were negative, indicating a predominance of ATR astigmatism consistent with the age profile of the cohort.[5,14] Crucially, no meaningful differences were observed between groups in either J0 or J45, and the substantial overlap of vector distributions and centroids on double-angle plots visually

corroborated these findings. This indicates the absence of systematic directional shift attributable to diabetes status.

These results indicate that diabetes does not systematically reorient TCA when assessed using TK and vector-based representation. This observed directional stability aligns with findings by Beato et al., who reported consistent keratometric behaviour between diabetic and non-diabetic eyes irrespective of diabetes duration or retinopathy stage.[1] Importantly, vector-based analysis further confirms that while apparent axis dispersion may be observed at the individual eye level, the population-level astigmatic centroid remains directionally stable across diabetes status, indicating preservation of the overall astigmatic phenotype.[8,14]

Relationships Between Clinical Variables and TCA in Diabetic Eyes

Within the diabetic cohort, HbA1c emerged as an independent variable associated with greater TCA magnitude, supporting the concept that current glycaemic control, rather than diabetes diagnosis alone, influences total corneal toricity. This relationship is biologically plausible, as fluctuations in glucose levels are known to induce transient refractive and topographic changes through alterations in stromal hydration and endothelial pump function.[3,13] This implies that while the presence of diabetes does not necessitate a change in surgical approach, the stability of glucose control at the time of biometry is paramount for refractive predictability.

In contrast, DM duration did not remain significant after multivariable adjustment, suggesting that its apparent effect is largely confounded by age and metabolic control. In the Malaysian context, delayed diagnosis and inconsistent longitudinal follow-up may further limit the precision of reported DM duration, reducing its statistical reliability as a predictor.[15]

Age remains the most consistent variable associated with vector orientation, independently related to a shift towards more negative J0 values. This finding reflects the well-established age-related transition towards ATR astigmatism, whereby age-driven biomechanical remodelling of the cornea shows a strong association with astigmatic orientation. As a result, the variance structure of vector profiles is largely governed by age effects, diminishing the relative contribution of disease-specific factors. Consequently, diabetes status alone did not differentiate vector profiles, as any potential diabetes-related influence appears modest when compared with the strong age-associated signal influencing corneal astigmatism orientation.[5,14]

No systemic or ocular variables were independently associated with the J45 component, consistent with the greater variability observed in oblique astigmatism. Unlike astigmatism magnitude or the J0 vector, J45 does not appear to follow a consistent biological pattern and demonstrates weak or absent associations with biometric and metabolic factors, as reported in prior studies.1,16 These findings support a cautious interpretation of J45 in both clinical assessment and epidemiological analysis in this Malay cohort.

Metformin Exposure and Corneal Astigmatism

Cumulative metformin exposure was not independently associated with TCA magnitude or vector components; however, short-term or transient corneal effects related to medication exposure cannot be excluded in a cross-sectional design. These findings reinforce the primacy of overall metabolic status, rather than specific pharmacological exposure in influencing corneal morphology.[3-4]

Implications for Cataract and Refractive Planning

From a cataract surgery perspective, these findings provide reassurance that TCA magnitude and orientation are broadly comparable between diabetes and non-diabetic eyes when measured using consistent technology. This supports the routine use of keratometric measurements without diabetes-specific adjustment. Nevertheless, the observed relationship between HbA1c and TCA magnitude highlights the importance of metabolic stability at the time of biometry acquisition to minimise transient refractive variability.[3,13]

LIMITATIONS

This study has several limitations. First, its cross-sectional design precludes causal inference between metabolic factors and corneal astigmatism behaviour. Systemic parameters were obtained at a single time point and may not fully capture temporal fluctuations in metabolic control that could influence corneal structure. Second, information regarding other diabetic treatment modalities, including insulin or combination therapy, was not consistently available across medical records, particularly for patients co-managed in primary care settings, and was therefore not included as a covariate.

Because medication modality was inconsistently documented, patients receiving insulin or combination therapy could not be reliably identified and treatment intensity was therefore not analysed. HbA1c was selected as the primary metabolic variable because it reflects integrated glycaemic exposure over the preceding three months and serves as a clinically relevant indicator of metabolic status independent of treatment regimen. Additionally, the modest R^2 values observed in the regression models indicate that a substantial proportion of variability in TCA remains unexplained, consistent with the multifactorial biomechanical nature of the cornea. As the diabetic cohort consisted predominantly of individuals with relatively well-controlled diabetes, inclusion of a larger proportion of poorly controlled diabetes may strengthen the observed associations. Finally, as the study population largely comprised older adults, the findings may not be generalisable to younger diabetic populations.

CONCLUSION

In this Malay adult population, diabetes status alone was not associated with systematic differences in TCA magnitude or orientation when assessed using TK and vector-based analysis. Age and metabolic control (HbA1c), rather than disease duration or metformin exposure, were the strongest factors associated with TCA characteristics. These findings support the use of vector-based analysis as a robust

framework for astigmatism assessment in both diabetic and non-diabetic eyes.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGEMENT

The authors thank Dr. Anas Rosedi for his support in conducting this research. The authors utilised Google Gemini for language editing and structural refinement, and NotebookLM for ensuring consistency in reference formatting and cross-checking citations. Following the use of these tools, the authors critically appraised all AI-generated suggestions and performed manual verification of all data and literature citations.

FUNDING

This study was funded by the Universiti Sultan Zainal Abidin DPU 1.0 Grant (UniSZA/2023/DPU1.0/42(RD053)).

REFERENCES

1. Beato JN, Esteves-Leandro J, Reis D, Matos R, Falcão M, Rosas V, et al. Agreement between IOLMaster® 500 and Pentacam® HR for keratometry assessment in type 2 diabetic and non-diabetic patients. Int J Ophthalmol 2020;13(6): 920-6.
2. Akhtar S, Nasir JA, Ali A, Asghar M, Majeed R, Sarwar A. Prevalence of type-2 diabetes and prediabetes in Malaysia: A systematic review and meta-analysis. PLoS One 2022; 17(1): e0263135
3. Kiziltoprak H, Tekin K, Inanc M, Goker YS. Cataract in diabetes mellitus. World J Diabetes 2019; 10(3): 140-53.
4. Mallareddy DV, Daigavane S. A comparative study of corneal topographical and central corneal thickness changes in diabetics and non-diabetics before and after phacoemulsification: A study protocol. F1000Research. 2023; 12: 1219.
5. Koch DD, Ali SF, Weikert MP, Shirayama M, Jenkins R, Wang L. Contribution of posterior corneal astigmatism to total corneal astigmatism. J Cataract Refract Surg 2012; 38(12): 2080-7.
6. Li X, Cao X, Bao Y. Comparison of total corneal astigmatism between IOLMaster and Pentacam. Biomed Res Int 2022: 936006.
7. Anjou M, Brezin A, Monnet D. Total keratometry measured with a swept-source optical biometer versus anterior keratometry: from planning to postoperative results. J Refract Surg 2023; 39(4): 257-64.
8. Thibos LN, Wheeler W, Horner D. Power vectors: an application of Fourier analysis to the description and statistical analysis of refractive error. Optom Vis Sci 1997; 74(6): 367-75.
9. Elkadim M, El-Shehawy A. Novel Microsoft Excel spreadsheet calculator for vector analysis of mass astigmatism data and comparison between Alpins and Thibos methods. Delta J Ophthalmol. 2022; 23(4): 292-7.
10. Lei CS, Lin X, Ning R, Yu J, Huang X, Li K, et al. Repeatability and interobserver reproducibility of a swept-source optical coherence tomography for measurements of anterior, posterior, and total corneal power. Ophthalmol Ther 2023; 12(6): 3263-79.
11. Thibos LN, Horner D. Power vector analysis of the optical outcome of refractive surgery. J Cataract Refract Surg 2001; 27(1): 80-5.
12. Sonmez B, Bozkurt B, Atmaca A, Irkec M, Orhan M, Aslan U. Effect of glycemic control on refractive changes in diabetic patients with hyperglycemia. Cornea 2005; 24(5): 531-7.
13. Salvador-Roger R, Albarrán-Diego C, Garzón N, García-Montero M, Muñoz G, Micó V, et al. Revisiting Javal's rule: a fresh and improved power vector approach according to age. Graefe's Arch Clin Exp Ophthalmol 2024; 262(1): 249-60.
14. Piñero DP, Caballero MT, Nicolás-Albujer JM, de Fez D, Camps VJ. A new approach for the calculation of total corneal astigmatism considering the magnitude and orientation of posterior corneal astigmatism and thickness. Cornea. 2018; 37(6): 720-6.
15. Simpson RG, Moshirfar M, Edmonds JN, Christiansen SM. Laser in-situ keratomileusis in patients with diabetes mellitus: a review of the literature. Clin Ophthalmol. 2012; 6: 1665-74.
16. Ismail H, Saminathan TA, Lourdes TGR, Hasani WSR, Majid NLA, Yusoff MFM. Prevalence of diabetes mellitus and its associated factors among adults in Malaysia: findings from the National Health and Morbidity Survey 2019. IIUM Med J Malaysia 2025; 24: 1-10.
17. Muzyka-Woźniak M, Oleszko A, Grzybowski A. Measurements of anterior and posterior corneal curvatures with OCT and Scheimpflug biometers in patients with low total corneal astigmatism. J Clin Med 2022; 11(23): 6921.

ORIGINAL ARTICLE

Prevalence and determinants of Tuberculosis Preventive Treatment (TPT) completion in Latent Tuberculosis Infection (LTBI) among TB contacts in Selangor, from January 2022-December 2024: National TB Registry (NTBR)

Ideris Izanna, MD[1], Mohamad Ikhsan Selamat, MMed[1], Mariam Mohamad, MCommHlth[1], Siti Hasmah Ilias, DrPH[2]

[1]Department of Public Health Medicine, Faculty of Medicine, Universiti Teknologi MARA, Selangor, Malaysia, [2]Tuberculosis/Leprosy Unit, Selangor State Health Department, Malaysia

ABSTRACT

Introduction: Tuberculosis (TB) remains a major public health challenge globally and in Malaysia, where TB incidence reached 113 per 100,000 population in 2022. Latent tuberculosis infection (LTBI) affects an estimated 30% of exposed individuals, with 5-10% at risk of progression to active disease if untreated. Tuberculosis preventive treatment (TPT) effectively reduces this risk. However, completion rates remain suboptimal. In Malaysia, data on TPT completion among TB contacts, particularly at the state level, are limited. This study aimed to determine the prevalence and identify determinants of TPT completion in LTBI among TB contacts in Selangor.

Materials and Methods: A cross sectional study was conducted using secondary data from National Tuberculosis Registry (NTBR). LTBI among TB contacts who initiated TPT in Selangor between January 2022 until December 2024 were included. Multiple logistic regression analysis was performed to identify determinants of TPT completion.

Results: A total 1832 LTBI among TB contacts who initiated TPT were analyzed. The prevalence of TPT completion was 77.2% (95% CI 75.2, 79.1). Higher odds of TPT completion were observed among individuals aged 15- 24 years (aOR 2.128; 95% CI 1.280, 3.539) and 25-34 years (aOR 1.720; 95% CI 1.160, 2.551), those of Indian ethnicity (aOR 1.763; 95% CI 1.159, 2.680) and others ethnicities (aOR 2.290; 95% CI 1.157, 4.259), and those residing within 5km of a health facility in Kuala Langat (aOR 11.738; 95% CI 2.377, 57.958). In contrast, lower odds of completion were observed in LTBI among TB contacts residing in Kuala Selangor (aOR 0.149; 95% CI 0.031, 0.717) and those living more than 10km from a health facility (aOR 0.147; 95% CI 0.061, 0.350).

Conclusion: TPT completion in LTBI among TB contacts in Selangor is influenced by sociodemographic and health system-related factors, with substantial locality variation. Targeted intervention adapted to local health system and service delivery conditions, together with strengthened LTBI surveillance and data quality within the NTBR, are essential to improve TPT completion and support TB prevention efforts in Malaysia.

KEYWORDS:
TPT completion, Latent tuberculosis infection, tuberculosis contacts

INTRODUCTION

Tuberculosis (TB) continues to cause a major public health threat globally and in Malaysia.[1] In 2023, it regained its status as the leading cause of death from a single infectious agent, exceeding COVID-19 after three years.[2] Malaysia has classified into middle income country with upper moderate TB epidemiological classification.[3] TB incidence rate in Malaysia was increased to 113 per 100,000 population in 2022 as compared to 97 per 100,000 population per year in 2021.[4] It was estimated 30% of individuals exposed to *M. tuberculosis* will develop LTBI as supported by Fox, G. J., et al (5). And if left untreated, 5-10% will progress to active TB.[1,6] Those who having contact with TB cases are a well-recognized group that is likely to benefit from TPT. TPT has been demonstrated to effectively prevent the progression from LTBI to active diseases by eliminating replicating *mycobacteria*. Globally, according to Treatment Asia Group (7), TPT coverage among household contacts increased markedly, reaching 21% in 2023 compared to less than 1% in 2015 and 5% in 2019. The administration of TPT has been shown to effective in reducing the risk of progression from latent TB infection (LTBI) to active disease by 60-90% in individuals who complete the treatment regimen.[8]

However, despite the established effectiveness, TPT uptake and completion in LTBI among TB contacts remain suboptimal in many settings. The efficacy is dependent on patient adherence throughout the course of treatment and the completion of entire course.[9] Study by Alsdurf et al[10] revealed that only 18.8% of individuals eligible for TPT completed the treatment. According to a meta-analysis involving 58 study in India by Sagili KD et al[11], reported LTBI prevalence was 41%, TPT initiation 91% and TPT completion was 65%. In recent cluster-randomized trial held in China by Chen, et al[12] reported 87.1% completed TPT. In addition, a cross sectional study in USA involving 1,221 subjects have higher TPT completion with 94% among other studies.[13]

This article was accepted: 16 February 2026
Corresponding Author: Mohamad Ikhsan Selamat
Email: mohamadikhsan@uitm.edu.my

Among risk factors contributing to TPT completion reported in previous literature worldwide includes sociodemographic factors (age, citizenship, gender), social and environmental factors (category contact, diagnosis and treatment completion of index case and screening test for LTBI), TPT-related factors (interval of initiation TPT, drug regimen, presence of side effect of treatment) and healthcare system related factors (healthcare supervision). Factors that discourage adherence causing failure in TPT completion and increasing the risk of progression to active TB. In cases where the immune system fails to control the latent infection, this can lead to severe, fulminant forms of TB, including sepsis.[14]

In Malaysia, TPT has been integrated into National TB Control Program and the enrolment to TPT was 56.1% in 2019. Despite these promising outcomes, there still limitation in recent and specific data on TPT completion in LTBI among TB contacts in Malaysia. This gap is particularly pronounced in Selangor, the most populous and urbanized state, which accounted for highest TB burden with 5,071 cases in 2018,[15] and contributed up to total 20% of total TB mortality in Malaysia.[16-18] There is lack of recent and comprehensive state level data on prevalence and determinants of TPT completion limits the ability to design targeted interventions to improve treatment adherence and outcomes. Addressing this gap, the presents study will generate critical evidence on the prevalence and identify the determinants of TPT completion in LTBI among TB contacts in Selangor. The findings of this study are anticipated to inform targeted intervention strategies to improve TPT initiation, adherence and completion. This study also aims to provide valuable input to strengthen the implementation of LTBI surveillance system in NTBR and guide policymakers in ensuring that data quality is closely monitored and periodically reviewed by the respected team. These efforts will help align national surveillance practices with both national and global TB elimination goals, thereby supporting Malaysia's commitment to achieve TB elimination objectives.

MATERIALS AND METHODS

Study Design

This is a cross-sectional study utilizing secondary data acquired from the National Tuberculosis Registry (NTBR) obtained from Tuberculosis/ Leprosy Unit, Selangor State Health Department.

Locations and Study Population

The study was carried out in LTBI patients among TB contacts started on TPT in Selangor who were registered in NTBR from January 2022 until December 2024. From *Manual Sistem Maklumat Jangkitan TIBI Laten (LTBI) Kebangsaan 2020*[19], TPT is defined as treatment for LTBI, a drug regimen that prevents the progression of LTBI to TB disease; while LTBI as a person who has been exposed to a TB-positive index case and is confirmed positive by IGRA / TST or both, without any lesions indicating TB on chest X-ray, and does not exhibit any symptoms of active TB; and TB contacts are any person who was exposed to a case of TB.

Data Collection

The inclusion criteria encompassed all individuals diagnosed as LTBI among TB contacts in Selangor who started on TPT from January 2022- December 2024. NTBR is a surveillance system database of all TB, TB contacts and LTBI cases with status of treatment. Module from NTBR used includes database on TBIS 10A1: *Daftar Kes TB Daerah*, TBIS 101C: *Pemeriksaan Kontak* and LTBIS 401A: *Senarai daftar kes LTBI*. The NTBR dataset used in this study does not include specific variable identifying incarceration status. TB contacts registered in correctional facilities are recorded within the routine surveillance system; however, incarceration status could not be distinguished in this analysis. The exclusion criteria were patients who died during TPT course, change of diagnosis during TPT course, diagnosed with TB during the TPT course, or still undergoing TPT, individuals transferred out from Selangor before completed treatment, duplicated data and those missing data > 20%. All missing data greater than 20% were managed according to pairwise deletion while missing data in independent variables less than 20% were managed using listwise deletion. The study included all patients who met the eligibility criteria by using universal sampling. To safeguard the privacy and confidentiality of the subjects, a unique identification number assigned for each participant.

Sample Size

The sample size was determined using OpenEpi for a single population proportion based on the largest sample size identified in a study by Chen, H et al[12], which reported aOR 2.09, 95% confidence interval (CI), 80% power, percent of exposed to outcome= 87.1%. The minimum sample size required for this study was 490 after as estimated 20% was added to the final sample size estimates to account for potential incomplete data.

Operational Definition

The outcome of TPT for LTBI was not defined by WHO. However, the treatment outcome operational definitions employed in the study were based on *Manual Sistem Maklumat Jangkitan TIBI Laten (LTBI) Kebangsaan 2020* [19] and *Management of Tuberculosis (4th ed.)*.[20] The operational definition for TPT outcome in this study was as follows:

1. Completion treatment: LTBI patient who has completed treatment within the scheduled duration as outlined in the guidelines for LTBI infection management
2. Non completion treatment: LTBI patient who has loss to follow up and interrupted treatment for two consecutive months or more.

Below are the operational definition for those met the exclusion criteria:

1. Still on treatment: LTBI patient on TPT who are still receiving treatment up to the 12th month of the treatment period
2. Transferred out: LTBI patient on TPT who move out of Selangor state during treatment course
3. Died during TPT course: LTBI patient who dies for any reason during course of treatment
4. Treatment failed: LTBI patient who has developed active TB during treatment or within 18 months post treatment
5. Change of diagnosis during TPT course by treating doctor

In this study, the dependent variable was the TPT outcome. It was categorized as a dichotomous variable, either TPT completion or TPT non-completion. Those who not evaluated (or no TPT outcome) was not included as TPT non-completion as this will lead to inaccurate data that limits efforts to control and eliminate TB. This group has higher risk to develop drug - resistant later on. For independent variable, age categories were classified according to the US CDC surveillance groupings, while ethnicity analysis was limited to Malaysian citizens, excluding all non-citizen participants.

Data Analysis

All statistical analyses were performed by using Statistical Package for the Social Sciences (SPSS) Version 29.0. Descriptive statistics were used to describe the study population's characteristics. All independent variables were in categorical and presented in frequency and percentage (%). Then inferential statistics were carried out to determine the factors associated with TPT completion in LTBI among TB contacts. Simple Logistic Regression (SLogR) analysis was performed to examine crude associations between sociodemographic factors (age, gender, ethnicity, citizenship, locality), social and environmental factors (category contact, diagnosis TB in index case based on anatomical location, screening test), TPT- related factors (type of treatment facility started TPT, interval time between diagnosis LTBI and initiation TPT) and healthcare system-related factor (distance from place of residence to treatment facility). Only variables with a p-value <0.25 in SLogR were selected for Multiple Logistic Regression (binary) analysis to obtain the adjusted Odds Ratio (aOR). A backward likelihood ratio (LR) approach was applied to derive the final multivariable model. Variables were subsequently removed based on statistical non-significance while assessing potential confounding effects and model stability. Variables that did not meaningfully alter the adjusted effect estimates of retained predictors were excluded from the final model. Collinearity diagnostics were assessed, and no evidence of multicollinearity was identified. Records with missing information on category of contact were retained in the analysis, as this variable was not included in the final multivariable model. Excluding these records would have resulted in unnecessary loss of sample size and reduced statistical power. A complete case analysis excluding records with missing category of contact (n=1095) was additional conducted as a sensitive analysis to assess the robustness of the findings. A p value of 0.05 with a 95% confidence interval was used to indicate statistical significance in all analyses. The Hosmer-Lemeshow test was used to assess the model's reliability and goodness- of-fit. A p-value greater than 0.05 indicates that the model fits the data well.

Ethics approval

This study was conducted according to the guidelines of the Declaration of Helsinki and approved by Faculty Ethics Review Committee, Faculty of Medicine, MARA University of Technology (UiTM) (Ref. 100- FPR (PT.9/10) (FERC-EX-25-02) and The Medical Research and Ethics Committee, Ministry of Health Malaysia (NMRR ID-25-00523-PNC (IIR). This study utilized secondary data and did not contain any patient-identifying information. As all cases were anonymized, informed consent was not obtained from individual patients. Official permission also was granted by the Director of Selangor State Health Department prior to data collection.

RESULTS

From January 2022 to December 2024, 3,128 LTBI among TB contacts started TPT recorded in the National TB Registry in Selangor. After excluding cases still on treatment (n=252), treatment failure (n=3), duplicated data (n=138) and records with incomplete data on TPT outcome incomplete data on TPT outcome (n=913), 1,832 cases of LTBI among TB contacts who started TPT in Selangor were included in the main analysis. Of these, 1,095 cases had complete information on all covariates and were included in the sensitivity analyses. Using the total number of LTBI cases who initiated TPT in Selangor (n=1,832), the prevalence of TPT completion was 77.2% (95% CI 75.2, 79.1). The flow diagram of data extraction was summarized in Figure 1.

Characteristics of TPT completion in LTBI among TB contacts in Selangor

As shown in Table I, highest frequency of TPT completion are those participants under age group 35- 44 years old, male, citizen, Malay ethnic, Hulu Langat locality and rural residence. This classification of residence was based on Household Income Selangor, 2019.[21] About 95.4% of participants has no comorbid DM and all the participants are not people living with HIV (PLHIV) patients. For social and environmental factors, majority participants are from category contact Close/ Family/ Household and the diagnosis of TB in index case based on anatomical location was Pulmonary TB. 85.7% had positive screening test by using Tuberculin Skin Test (TST). For TPT- related factors, the majority of TPT initiation was made at health clinic and the interval time between diagnosis of LTBI and initiation TPT was <2 weeks (89.3%). For healthcare system- related factors, most of participants stay 5-10km distances from treatment facility.

Determinants of TPT completion in LTBI among TB contacts in Selangor

The study variables were analyzed using SLogR for univariate analysis and multiple logistic (binary) regression, as shown in Table II. In univariate analysis, all variables except the diagnosis of index case (based on an atomical location) were the factors potentially associated with TPT completion. The following potential confounders were included in the model: gender, citizenship, residence, category contact, screening results LTBI, types of treatment facility initiate TPT and the interval time between diagnosis LTBI and initiation TPT, did not remain statistically significant in the multivariable model and were subsequently removed during the backward selection process.

After adjusting with other potential confounders, compared to reference group, the patients aged 15-24 years old and 25-34 years old had 2.13 and 1.72 times the odds of TPT completion (aOR 2.13; 95% CI 1.28, 3.54, p= 0.004; and (aOR 1.72; 95% CI 1.16, 2.55, p= 0.007) respectively. Ethnicity also found to be determinants of TPT completion. Indian and 'Others' ethnic has higher odds TPT completion compared to Malay ethnic with aOR 1.76; 95% CI 1.16, 2.68 and aOR

Table I: Characteristics of individuals with TPT completion status in LTBI among TB contacts in Selangor from January 2022- December 2024 (N=1832)

Variable	TPT Completion n (%)	TPT non- completion n (%)	Total (n=1832) n (%)[a]
Age (years)			
<5	113 (8.3)	19 (4.6)	132 (7.5)
5-14	175 (12.9)	43 (10.5)	218 (12.3)
15-24	207 (15.3)	60 (14.6)	267 (15.1)
25-34	245 (18.1)	108 (26.3)	353 (20.0)
35-44	262 (19.3)	75 (18.3)	337 (19.1)
45-54	175 (12.9)	57 (13.9)	232 (13.1)
55-64	126 (9.3)	32 (7.8)	158 (8.9)
>65	54 (4.0)	16 (3.9)	70 (4.0)
Gender			
Male	729 (51.6)	229 (54.8)	958 (52.3)
Female	685 (48.4)	189 (45.2)	874 (47.7)
Citizenship			
Citizen	1220 (86.3)	380 (90.9)	1600 (87.3)
Non-citizen	194 (13.7)	38 (9.1)	232 (12.7)
Ethnic[b]			
Malay	884 (72.5)	275 (72.6)	1159 (72.5)
Chinese	190 (15.6)	42 (11.1)	232 (14.5)
Indian	117 (9.6)	47 (12.4)	164 (10.3)
Others	28 (2.3)	15 (4.0)	43 (2.7)
Locality			
Hulu Langat	370 (26.2)	99 (23.7)	469 (25.6)
Klang	338 (76.5)	104 (24.9)	442 (24.1)
Petaling	240 (17.0)	38 (9.1)	278 (15.2)
Gombak	195 (13.8)	52 (12.4)	247 (13.5)
Kuala Selangor	100 (7.1)	12 (2.9)	112 (6.1)
Sabak Bernam	62 (4.4)	29 (6.9)	91 (5.0)
Hulu Selangor	45 (3.2)	14 (3.3)	59 (3.2)
Sepang	43 (3.0)	26 (6.2)	69 (3.8)
Kuala Langat	21 (1.5)	44 (10.5)	65 (3.5)
Residencec			
Rural	936 (66.2)	302 (72.2)	1238 (67.6)
Urban	478 (33.8)	116 (27.8)	594 (32.4)
Category contact			
Close/ Family/ Household	589 (72.8)	236 (66.3)	825 (70.8)
Social/ Institutional/ Workplace	220 (27.2)	120 (33.7)	340 (29.2)
Diagnosis of index case (based on anatomical location)			
Pulmonary TB	716 (93.2)	305 (92.7)	1021 (93.1)
Extrapulmonary	52 (6.8)	24 (7.3)	76 (6.9)
Screening results LTBI			
TST[d] positive	1191 (84.4)	377 (90.2)	1568 (85.7)
IGRA[e] test positive	150 (10.6)	25 (6.0)	175 (9.6)
Both TST and IGRA positive	70 (5.0)	16 (3.8)	86 (4.7)
Types of treatment facility initiate TPT			
Health Clinic	1273 (91.8)	332 (80.6)	1605 (89.2)
Government Hospital	113 (8.1)	25 (6.1)	138 (7.7)
Private Hospital	1 (0.1)	55 (13.3)	56 (3.1)
Interval time between diagnosis LTBI and initiation TPT			
<2 weeks	1262 (89.3)	312 (74.6)	1574 (85.9)
>2 weeks- 2 months	110 (7.8)	36 (8.6)	146 (8.0)
>2 months- 2 years	42 (3.0)	70 (16.7)	112 (6.1)
Distance from place of residence to the health facility			
<5km	472 (33.4)	91 (21.8)	563 (30.7)
5-10km	576 (40.7)	195 (46.7)	771 (42.1)
>10km	366 (25.9)	132 (31.6)	498 (27.2)

[a]Within total sample
[b]Ethnicity among Malaysian citizen only
[c]Residence: Rural residence including Hulu Langat, Klang, Kuala Selangor, Sabak Bernam, Hulu Selangor and Kuala Langat, Urban residence including Petaling, Gombak and Sepang; based on Household Income Selangor, 2019 (Department of Statistics Malaysia, 2020)
[d]TST Tuberculin Skin Test (or Mantoux test)
[e]IGRA Interferon-Gamma Release Assay

Table II: Univariate and Multivariable analysis results of determinants of TPT completion in LTBI among TB Contacts in Selangor from January 2022- December 20224 (N=1832)

Variable	Simple Logistic Regression		Multiple Logistic Regression	
	Crude OR[a] (95% CI)	p value	Adjusted OR[b] (95% CI)	p value
Age (years)				
<5	0.587 (0.339, 1.018)	0.058	0.620 (0.334, 1.153)	0.131
5'-14	0.858 (0.563, 1.308)	0.477	1.612 (0.945, 2.747)	0.079
15-24	1.013 (0.689, 1.489)	0.949	2.128 (1.280, 3.539)	**0.004***
25-34	1.540 (1.094, 2.168)	0.013*	1.720 (1.160, 2.551)	**0.007***
35-44	Reference		Reference	
45-54	1.138 (0.767, 1.687)	0.521	1.205 (0.768, 1.891)	0.418
55-64	0.887 (0.557, 1.413)	0.614	1.694 (0.955, 3.005)	0.072
>65	1.035 (0.560, 1.913)	0.912	1.169 (0.592, 2.309)	0.652
Gender				
Male	Reference			
Female	0.878 (0.706, 1.093)	0.246*		
Citizenship				
Citizen	Reference			
Non-citizen	0.629 (0.436, 0.907)	0.013*		
Ethnic				
Malay	Reference		Reference	
Chinese	0.711 (0.495, 1.019)	0.063*	0.990 (0.652, 1.503)	0.962
Indian	1.291 (0.897, 1.859)	0.169	1.763 (1.159, 2.680)	**0.008***
Others	1.722 (0.907, 3.271)	0.097*	2.290 (1.157, 4.529)	**0.017***
Locality				
Hulu Langat	Reference		Reference	
Klang	1.15 (0.842, 1.571)	0.38	1.607 (0.771, 3.347)	0.205
Petaling	0.592 (0.394, 0.890)	0.012*	0.381 (0.110, 1.323)	0.129
Gombak	0.997 (0.683, 1.454)	0.986	0.651 (0.252, 1.678)	0.374
Kuala Selangor	0.448 (0.237, 0.849)	0.014*	0.149 (0.031, 0.717)	**0.018***
Sabak Bernam	1.748 (1.067, 2.864)	0.027*	0.536 (0.146, 1.971)	0.348
Hulu Selangor	1.163 (0.613, 2.204)	0.644	0.495 (0.138, 1.780)	0.282
Sepang	2.260 (1.323, 3.859)	0.003*	1.636 (0.409, 6.555)	0.487
Kuala Langat	7.831 (4.450, 13.780)	<0.001*	1.898 (0.594, 6.071)	0.28
Residence				
Rural	Reference			
Urban	0.752 (0.591, 0.957)	0.02*		
Category contact				
Close/ Family contact/ Household	Reference			
Social/ Institutional/ Workplace	1.361 (1.040, 1.781)	0.025*		
Diagnosis of index case (anatomical location)				
Pulmonary TB	Reference			
Extrapulmonary TB	1.083 (0.656, 1.790)	0.754		
Screening results LTBI				
TST positive	Reference			
IGRA test positive	0.527 (0.339, 0.817)	0.004*		
Both TST & IGRA positive	0.722 (0.414, 1.258)	0.25		
Types of treatment facility initiate TPT				
Health Clinic	Reference			
Government Hospital	0.848 (0.541, 1.330)	0.473		
Private Hospital	210.889 (29.077, 1529.531)	<0.001*		
Interval time between diagnosis LTBI and initiation TPT				
<2 weeks	Reference			
>2 weeks- 2 months	1.324 (0.891, 1.967)	0.165*		
>2 months- 2 years	6.741 (4.509, 10.078)	<0.001*		
Distance from place of residence to the health facility				
<5km	0.569 (0.432, 0.751)	<0.001*	0.526 (0.265, 1.044)	0.066
5-10km	Reference		Reference	
>10km	1.065 (0.824, 1.377)	0.629	0.147 (0.061, 0.350)	<0.001*
Interaction Distance*Locality				
<5km*Kuala Langat			11.738 (2.377, 57.958)	0.003*

OR= Odds Ratio, aOR= Adjusted OR, CI= Confidence Interval, LTBI= latent tuberculosis infection, TPT= Tuberculosis preventive treatment
Statistical test used [a]Crude OR (Simple Logistic Regression), [b]Ajdusted OR (Multiple Logistic Regression)
The Cox & Snell R2 value is 0.123, indicating the proportion of variance explained by the model. The Hosmer-Lemeshow test, (p= 0.31), suggesting good model fit. Classification: 79% and area under the ROC curve (AUC) is 72.1% (95% CI: 69.2, 75.1), p-value <0.001). Backward LR Multiple Logistic Regression Model was applied. Constant value: -0.747 and the model assumption is met. There is no multicollinearity and interaction.
Significant values are in bold

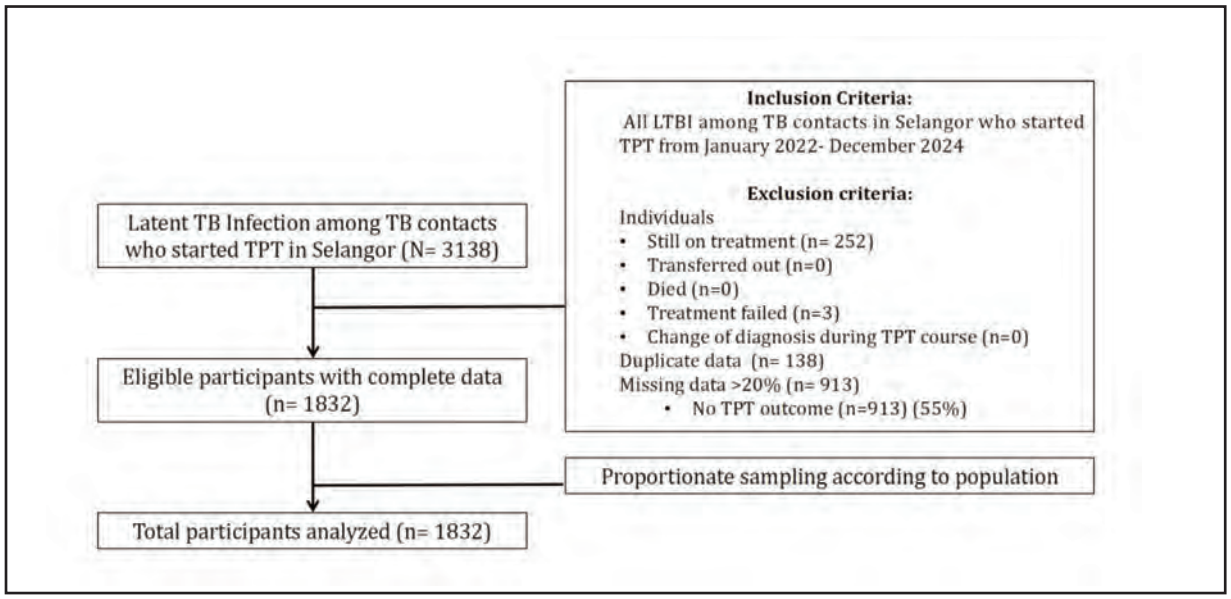


Fig. 1: Flow chart of data retrieval and extraction

2.29; 95% CI 1.16, 4.53 respectively. For locality, Kuala Selangor district has much lower odds of TPT completion with aOR 0.15; 95% CI 0.03, 0.72, compared to Hulu Langat district. Distance to health facility also affected TPT completion. LTBI individuals whom the distance from place of residence to the health facility >10km showing 0.147-time odds of TPT completion (aOR 0.147; 95% CI 0.061, 0.350). And lastly, the factor of interaction between distance and locality also found to be determinant of TPT completion. LTBI individuals who stay in Kuala Langat and the distance from residence place to health facility less than 5km has higher odds of TPT completion as compared to reference group with aOR 11.738; 95%CI 2.377, 57.958. The prediction of this model was 72.1% (95% CI:69.2, 75.1, p-value <0.001).

Overall, the direction and magnitude of effect estimates were broadly comparable between the main analysis and the sensitivity analysis, although some variables demonstrated reduced statistical significance in the smaller complete case dataset.

DISCUSSION

Based on our best knowledge, this is the first study to explore prevalence and determinants of TPT completion in Selangor using NTBR database. The present study found that TPT completion was 77.2% (95% CI 75.2, 79.1). This proportion is slightly lower that TPT completion rates in other studies.[12, 22-23]

After adjustment for potential confounders, age group, ethnicity, locality, distance to health facility and the interaction between distance and locality were significantly associated with TPT completion in LTBI among TB contacts in Selangor. Sensitivity analyses yielded largely consistent effect estimates, supporting the robustness of the main findings. The main analysis was therefore prioritized for interpretation, as it maximized available data and improved model stability without introducing additional sources of bias.

Age group

Previous studies have consistently reported age as an important determinant TPT adherence and compliance, although the direction of association varies across settings. In this study, younger age was significantly associated with higher odds of TPT completion. Compared with individuals aged 35-44 years old, those age 15-24 years and 25-34 years demonstrated significantly higher odds of TPT completion. Similar age-related patterns have been reported in other settings, where younger individuals demonstrated higher adherence and completion of TPT, likely due to fewer competing health conditions and stronger engagement with follow-up mechanism.[9,12,24] This finding suggests that working-age adults in the mid-life group may face greater barriers to treatment completion than younger individuals. Several factors may explain this association. First, individuals age 35-44 years often experience greater competing demands related to employment and childcare responsibilities, which may limit their ability to attend follow up visits consistently. Second, younger adults may exhibit higher responsiveness to health messaging, appointment reminders, and counselling particularly when concerns about future health and work capacity are emphasized. Third, younger contacts may be more frequently engaged through structured contact investigation processes and clinic based follow up systems that facilitate adherence.

Ethnicity

In this study, ethnicity emerged as important factor influencing TPT completion in LTBI among TB contacts in Selangor. Ethnic differences in TB or LTIB treatment outcomes have been reported previously and are often as proxies for underlying social, cultural and healthcare access factors rather than intrinsic behavioral differences.[25-26] Our analysis found that Indian participants and those classified under other ethnic groups demonstrating significantly higher odds of TPT completion compared with Malay participants. Possible explanations include differences in family support structures, health literacy and engagement with healthcare services across communities. Additionally, the observed

ethnic differences may be partly attributable to residual confounding by unmeasured socioeconomics factors, including occupation type, population mobility and urban density among Malaysian citizens.

Locality (district)
Variation in TPT completion across localities is likely to reflect differences in local health system capacity and the effectiveness of programmatic implementation, consistent with the TPT cascade framework, which highlights setting-specific barriers across multiple stages of care.[28] Locality based heterogeneity in TB outcomes within Selangor has been previously documented, with urban districts such as Petaling exhibiting distinct socioeconomic characteristics and disease burden profiles that may influence treatment engagement and continuity of care.[18,27] Similar locality or district level variation has also been reported in Sabah, where incomplete LTBI preventive treatment was significantly associated with region of residence, reflecting disparities in healthcare accessibility, workforce distribution and local socioeconomic conditions.[29] In contrast, a study by Musaazi et al[30], reported higher TPT completion among individuals initiating treatment at rural facilities compared with urban health centers, demonstrating that the role of service delivery context in shaping treatment adherence and influence the treatment completion. In the present study, locality was significantly associated with TPT completion with markedly lower odds observed in LTBI among TB contacts residing in Kuala Selangor compared with the reference district. This finding reinforces the influence of district level health system and contextual factors on preventive therapy outcomes. Differences in service availability, healthcare workforce capacity and the effectiveness of defaulter tracing systems may partly explain these patterns. Furthermore, population mobility related to employment and commuting, as well as variability in clinic workflows may affect patient engagement. The clinic may have different counselling quality, documentation practices and follow up mechanisms. Overall, these findings emphasize the importance of implementing district-level, context-responsive strategies to overcome local barriers and enhance TPT completion.

Distance to health facility from the place of residence
Access-related barriers, including challenges in reaching screening, diagnostic and treatment services have been consistently associated with poor completion of preventive therapy in high an intermediate incidence settings.[28] In the present study, distance to the treatment facility was a strong determinant of TPT completion, with LTBI among TB contacts residing more than 10km from a health facility demonstrating substantially lower odds of completion compared to those living 5-10km away, while a similar trend was observed among those residing within 5km. Longer travel distances increase transportation costs and time burden, contributing to miss appointments and treatment interruptions, while opportunity costs related to work and family responsibilities may further discourage repeated clinic visits. In addition, individuals living farther from healthcare facilities maybe more likely to change care locations or to be lost to follow up, compromising continuity of preventive therapy. These findings are consistent with previous studies demonstrating that geographic access barriers are strongly associated with poor TPT completion.[10,25,31]

Interaction between distance and locality
A significant interaction between distance and locality was observed, with LTBI among TB contacts residing within 5km of a health facility in Kuala Langat exhibiting substantially higher odds of TPT completion compared with the reference group. This finding suggests that the effect of geographic proximity may be shaped by local health system and service delivery conditions, whereby proximity to healthcare services may have greater benefit in certain district or locality. The observed association may reflect local service delivery characteristics, such as more efficient clinic workflows, stronger follow up mechanisms, or targeted community outreach in Kuala Langat. However, the wide confidence interval (CI) indicates potential small cell effects, and the estimate should therefore be interpreted with caution. Accordingly, this interaction appears to represent a facility or district level pathway rather than an effect that can be generalized across settings. These findings align with programmatic management framework for TPT which emphasizes that the impact of geographic access varies according to local health-system organization and service delivery.[28]

The strength of our study is that this is the first population-based analysis in Selangor to examine the prevalence and determinants of TPT completion in LTBI among TB contact using National TB Registry data. The large registry-based dataset enhances statistical power and reflects real world programmatic conditions, improving the generalizability and practical relevance of the findings or TB control planning. The inclusion of sociodemographic and healthcare access-related determinants including district-level locality, distance to health facilities and their interaction, provides insight into health-system heterogeneity within Selangor. Furthermore, the use of multivariable logistic regression with prior simple logistic regression and supporting sensitivity analyses improved internal validity and demonstrated the robustness of the findings despite missing data.

Several limitations should be considered. This study relied on secondary data analysis that were not designed for research purposes, and certain important determinants such as detailed socioeconomic status and incarceration status were not captured in the NTBR dataset. Preventive therapy delivered within correctional facilities may follow different adherence dynamics compared to community settings due to structured supervision and restricted mobility. The inability to distinguish incarcerated individuals may therefore limit generalizability and introduce residual confounding.

In addition, a substantial proportion of cases (n=913) were excluded due to missing TPT outcome data within the registry system. Although exclusion was necessary to ensure accurate outcome classification, this may introduce selection bias if the missing data were related to treatment adherence. Despite sensitive analysis to assess the robustness of findings, residual bias may remain. And the differences in data completeness across districts may also have influences the locality geographical findings. Furthermore, some interaction estimates demonstrated wide confidence intervals, likely reflecting small cell sizes in specific locality-distance subgroups, resulting in limited statistical precision.

Finally, the cross-sectional design precludes causal inference and some associations particularly interaction effects may reflect local health system or facility level factors. Despite this limitation, the consistency of results across sensitivity analyses and the population- based dataset reinforce the robustness and public health relevance of the findings.

CONCLUSION

In conclusion, this population-based study demonstrates that TPT completion in LTBI among TB contacts in Selangor is determined by combination of sociodemographic and health system-related factors including age, ethnicity, locality and distance to health facilities with evidence that effects vary according to local health system and service delivery conditions. The observed locality and access-related disparities demonstrate the importance of addressing structural and service delivery barriers that influence engagement and continuity of preventive therapy. These findings support the implementation of district level, context-adapted programmatic interventions, including strengthening patient follow up and defaulter tracing systems, improving service accessibility in underserved areas, and optimizing TPT service delivery in line with local health system capacity and operational realities.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGEMENTS

We express our gratitude to the Director General of Health Malaysia for granting us permission to publish this study. We would like to extend our appreciation to the Selangor Health State Department for allowing us to conduct this research. We would like to express our gratitude to the Department of Public Health Medicine, Faculty of Medicine, UiTM for the support during the study.

FUNDING

This study received no funding.

REFERENCES

1. Ministry of Health Malaysia. National strategic plan to end tuberculosis (2021–2030). Putrajaya: Disease Control Division, TB/Leprosy Sector, Ministry of Health Malaysia; 2021.
2. World Health Organization. Global tuberculosis report 2024. Geneva: WHO; 2024.
3. Teo AKJ, Morishita F, Islam T, Viney K, Ong CWM, Kato S, et al. Tuberculosis in older adults: challenges and best practices in the Western Pacific region. Lancet Reg Health West Pac 2023; 36: 100770.
4. Fadzil FA, Ramli SR, Neoh HM. Tuberculosis in Malaysia: disease timeline, epidemiology, control initiatives and outlook. Malays J Pathol 2025; 47(1): 13-23.
5. Fox GJ, Dobler CC, Marais BJ, Denholm JT. Preventive therapy for latent tuberculosis infection—the promise and the challenges. Int J Infect Dis 2017; 56: 68-76.
6. Houben RM, Dodd PJ. The global burden of latent tuberculosis infection: a re-estimation using mathematical modelling. PLoS Med 2016; 13(10): e1002152.
7. Treatment Action Group, Stop TB Partnership. Tuberculosis research funding trends 2005–2022. New York: Treatment Action Group; 2023. Available from: https://www.treatmentactiongroup.org/resources/tbrd-report/tbrd-report-2023/. Accessed 15 Jan 2026.
8. World Health Organization. Latent tuberculosis infection: updated and consolidated guidelines for programmatic management. Geneva: WHO; 2018.
9. Liu C, Jing R, Li S, Zhang W, Dong Y, Dong H, et al. Predictors of tuberculosis preventive treatment completion in college students: a high adherence study in China. Infect Drug Resist 2025; 18: 2581-8.
10. Alsdurf H, Hill PC, Matteelli A, Getahun H, Menzies D. The cascade of care in diagnosis and treatment of latent tuberculosis infection: a systematic review and meta-analysis. Lancet Infect Dis 2016; 16(11): 1269-78.
11. Sagili KD, Muniyandi M, Shringarpure K, Singh K, Kirubakaran R, Rao R, et al. Strategies to detect and manage latent tuberculosis infection among household contacts of pulmonary TB patients in high TB burden countries: a systematic review and meta-analysis. Trop Med Int Health 2022; 27(10): 842-63.
12. Chen H, Zhang H, Cheng J, Sun D, Wang Q, Wu C, et al. Adherence to preventive treatment for latent tuberculosis infection in close contacts of pulmonary tuberculosis patients: a cluster-randomized controlled trial in China. Int J Infect Dis 2024; 147: 107196.
13. Levine S, Fraulino D, Krupka P, Velamakanni S. Latent tuberculosis infection in the outpatient general medicine clinic: efficacy of a nurse-run electronic directly observed treatment program. Prev Med Rep 2023; 35: 102321.
14. Health Technology Assessment Section, Ministry of Health Malaysia. Programmatic management of latent tuberculosis infection. Putrajaya: Medical Development Division, Ministry of Health Malaysia; 2019.
15. Ministry of Health Malaysia. Annual report 2018: TB control programme in Malaysia. Kuala Lumpur: Ministry of Health Malaysia; 2019.
16. Kaur K, Said S, Norkhadijah S, Lim PY. Risk factors of unfavourable TB treatment outcomes in Hulu Langat, Selangor. Malays J Med Health Sci 2022; 18: 52-60.
17. Mohidem NA, Osman M, Hashim Z, Muharam FM, Mohd Elias S, Shaharudin R. Association of sociodemographic and environmental factors with spatial distribution of tuberculosis cases in Gombak, Selangor, Malaysia. PLoS One 2021; 16(6): e0252146.
18. Suhairi MH, Mohamad M, Isa MR, Sherzkawee A, Ismail N. Risk factors for tuberculosis-related death among adults with drug-sensitive pulmonary tuberculosis in Selangor, Malaysia from 2013 to 2019: a retrospective cohort study using surveillance data. BMJ Open 2024; 14(2): e080144.
19. Bahagian Kawalan Penyakit, Kementerian Kesihatan Malaysia. Manual sistem maklumat jangkitan tibi laten (LTBI) kebangsaan (Edisi kedua). Putrajaya: Kementerian Kesihatan Malaysia; 2020. Available from: https://www.moh.gov.my. Accessed 30 June 2025.
20. Malaysian Health Technology Assessment Section. Management of tuberculosis. 4th ed. Putrajaya: Ministry of Health Malaysia; 2021. Available from: https://www.moh.gov.my. Accessed 15 Jun 2025.
21. Department of Statistics Malaysia. Household income and basic amenities survey report by state and administrative district, Selangor, 2019. Putrajaya: Department of Statistics Malaysia; 2020. Available from: https://www.dosm.gov.my. Accessed 30 May 2025.
22. Sugishita Y, Goto C, Sakamoto T, Sugawara T, Ohkusa Y. Risk factors affecting the failure to complete treatment for patients with latent tuberculosis infection in Tokyo, Japan. J Infect Chemother 2020; 26(11): 1129-33.

23. Felisia F, Triasih R, Nababan BWY, Sanjaya GY, Dewi SC, Rahayu ES, et al. High tuberculosis preventive treatment uptake and completion rates using a person-centered approach among tuberculosis household contacts in Yogyakarta. Trop Med Infect Dis 2023; 8(12): 520.
24. An Y, Khun KE. Factors associated with incomplete tuberculosis preventive treatment: a retrospective analysis of six-years programmatic data in Cambodia. Sci Rep 2024; 14(1): 18458.
25. de Aguiar RM, da Silva Vieira MAM, de Almeida IN, de Paula Ramalho DM, Ruffino-Netto A, Carvalho ACC, et al. Factors associated with non-completion of latent tuberculosis infection treatment in Rio de Janeiro, Brazil: a non-matched case control study. Pulmonology 2022; 28(5): 350-7.
26. Shariff NM. Impact of ethnic disparities on the treatment outcomes of HIV-negative drug-resistant tuberculosis patients in Kuala Lumpur, Malaysia: a call for a culturally-sensitive community intervention approach. J Glob Antimicrob Resist 2019; 19: 234-40.
27. Mohd Zaini NNN, Abdul Rasam AR, Ahmad CB. Socio-economic characteristics of urban tuberculosis areas in Petaling, Selangor: a current spatial exploratory scenario. IOP Conf Ser Earth Environ Sci 2022; 1067(1): 012041.
28. Oxlade O, den Boon S, Menzies D, Falzon D, Lane MY, Kanchar A, et al. Tuberculosis preventive treatment in high- and intermediate-incidence countries: research needs for scale-up. Int J Tuberc Lung Dis 2021; 25(10): 823-31.
29. Mohamed AF, Shafei MN, Wan Mohammad WMZ, Teo R, Min Hui AS. Factors associated with incomplete latent tuberculosis infection preventive treatment in Sabah, Malaysia. PeerJ 2025; 13: e19736.
30. Musaazi J, Kiragga A, Kambugu A, Castelnuovo B, Kamya MR. Increased uptake of tuberculosis preventive therapy among people living with HIV following the 100-days accelerated campaign: a retrospective review of routinely collected data at six urban public health facilities in Uganda. PLoS One 2023; 18(2): e0268935.
31. Lwevola P, Izudi J, Kimuli D, Komuhangi A, Okoboi S. Low level of tuberculosis preventive therapy incompletion among people living with human immunodeficiency virus in eastern Uganda: a retrospective data review. J Clin Tuberc Other Mycobact Dis 2021; 25: 100269.

Transforming patient care: The QWIC system to optimise waiting times and efficiency in surgical outpatient clinics in Malaysia

Ramizah Mohd Shariff, MBBS[1], Abdul Aziz Harith, MPH[2], Tee Sze Chee, MMed(Surg)[1], Mohammad Shukri Jahit, MMed(Surg)[1]

[1]Surgical Department, National Cancer Institute, Ministry of Health Malaysia, Putrajaya, Malaysia, [2]Medical Division, Pahang State Health Department, Ministry of Health, Kuantan, Pahang Malaysia

ABSTRACT

Introduction: Waiting time at surgical outpatient clinics in Malaysian hospitals has become a critical concern, impacting patient satisfaction and overall healthcare efficiency. Many facilities face challenges leading to extended waiting periods for surgical consultations and procedures. These delays not only affect patient outcomes but also contribute to increased anxiety and frustration among patients. Implementing innovative solutions, such as advanced queue management systems, can play a significant role in operational workflows and reducing wait time. Thus, this study aims to determine the efficiency of waiting time using the Queue Won't Intimidate Customer (QWIC) system towards surgical outpatient clinics at the National Cancer Institute (NCI).

Materials and Methods: Data were collected retrospectively through a cross-sectional design over a six-month period, from April 1 to September 31, 2021, following the implementation of the QWIC system on 3 surgical clinics (bariatric clinic, general surgery (GS) clinic, and Upper gastrointestinal (UGI) clinic) under NCI. The Ministry of Health (MOH) established an acceptable waiting time benchmark of 60 minutes or less.

Results: The most efficient clinic was GS (98.9%), followed by UGI (96.2%) and bariatric (83.4%). Based on logistic regression analysis, bariatric clinic (COR: 18.72, 95% CI: 6.51-51.28, p < 0.001; AOR: 15.33, 95% CI: 5.32-44.13, p <0.001) and new surgical cases (COR: 3.19, 95% CI: 1.96-5.22, p < 0.001 and AOR: 2.56, 95% CI: 1.42-4.52, p = 0.001) are strongly associated with longer waits. UGI clinic also show increased waiting times (COR: 3.67, 95%CI: 1.23:10.94, p = 0.020; AOR: 3.34, 95% CI: 1.12-10.02, p = 0.031). Conversely, consultation durations over 60 minutes and attendance status did not significantly affect waiting times.

Conclusion: The QWIC System represents a significant advancement in managing patient appointments and consultations within surgical clinics. Overall, types of surgical clinic and case status were key factors influencing waiting times in surgical clinics.

KEYWORDS:
Waiting time, surgical clinics, outpatient, patients care, efficiency

INTRODUCTION

Prolonged waiting times in hospitals for consultations with physicians at surgical outpatient clinics have become a significant concern, impacting patient care and satisfaction globally.[1-3] The issue of long waiting times at outpatient clinics in public hospitals is not a recent occurrence but rather a persistent concern among healthcare professionals. As healthcare systems strive to provide timely and effective services, prolonged waiting times can significantly hinder patient outcomes, leading to increased anxiety and dissatisfaction.[4-5] Recent studies highlight the adverse effects of long wait times, an indication that patients often experience delays that can detract from their overall health experiences.[6] Other factors influencing patient satisfaction on waiting time were identified, including age under 20 years, literate, expectation versus actual waiting time.[1,7] Thus, understanding the complexities of waiting times is essential for improving healthcare delivery and enhancing patient satisfaction.

Several factors contributed to the prolonged waiting times encountered at surgical outpatient clinics. Insufficient staffing level including trainee, inefficient appointment scheduling, and limited availability of operating rooms are among the primary issues that hinder timely patient access.[8-9] Additionally, a mismatch between patient demand and available healthcare resources often leads to significant backlogs, prolonging the time patients must wait before seeing a physician.[8] Administrative inefficiencies, including poor communication between departments and a lack of coordination among healthcare providers, further exacerbate these delays.[10-12] These systemic issues not only affect the patient experience but can also lead to adverse health outcomes, underscoring the necessity for comprehensive reforms within healthcare systems.

In response, certain countries have set appropriate waiting time for patient to be serve at clinic such as South Africa who set 60 minutes at specialised hospitals.[12] A study on hospitals in five countries revealed that Australia, Canada, New Zealand, the United Kingdom, and the USA experienced average wait times of two hours or more.[7] Repeatedly, the stress of prolonged waiting time has resulted in aggressive tendencies by patients.[7] Patients' satisfaction could be enhanced through the implementation of real-time

This article was accepted: 20 February 2026
Corresponding Author: Abdul Aziz Harith
Email: drazizkpaskkm@gmail.com

information dissemination in hospital experiencing significant queuing issues.[6]

In Malaysia, the average waiting time from registration to meet a doctor in hospital outpatient departments is 60 minutes[11], meanwhile primary health clinics recorded 41 minutes.14 Patients have expressed numerous concerns about prolonged wait times at outpatient clinics. The important concern are the prolonged wait time for a doctor's appointment and the punctuality of healthcare workers themselves. For instance, a doctor's punctuality can contribute to prolonged waiting times, especially when their consultation duration is too short. Overseas studies have shown that patients are willing to wait an average of between 30 and 45 minutes to see a doctor.[8-9] When the number of patients waiting for consultation surpasses the rate of service delivery, queues form Healthcare in Malaysia is always in a state of "excess demand". Overcrowding in outpatient clinics is a common occurrence. A high number of patients, a shortage of staff, malfunctioning equipment, constrained facilities (such as shared consultation rooms with multidisciplinary teams), and a disorganised system are among the factors contributing to lengthy waiting times.[10-11]

Although prolonged waiting time is an issue in Malaysia, the Ministry of Health (MOH) acknowledged this emerging issue in 2008 and proposed incorporating "waiting time" as a key performance indicator (KPI) in general surgery clinical services, as it reflects the efficacy of healthcare services.[2-3] Thus, MOH has implemented several initiatives aimed at reducing waiting times for surgical outpatient consultations. Recent strategies include optimising appointment scheduling to improve patient flow, enhancing staffing levels to meet the growing demand for surgical services, and streaming operational processes within healthcare facilities.

Nevertheless, the appointment system at surgical outpatient clinics of NCI did not adhere to staggered appointment times prior this study. The system operated on a "first come, first served" principle, resulting in overcrowding and a backlog of cases at the clinic. This imposes a direct burden on the entire process. Following the audit of clinic waiting times, researchers identified several modifiable factors that could reduce the waiting duration. Therefore, a novel queue system has been suggested to address the potentially alterable or unpredictable variables. This system is referred to as the QWIC (Queue Won't Intimidate Customer) system.

MATERIALS AND METHODS

Study Design

This study employed a retrospective cross-sectional design using secondary data collected from the surgical outpatient clinics of National Cancer Institute (NCI), Malaysia. The data collected was within 6 months of study period starting 1 April until 31 September 2021. The surgical clinics comprise of bariatric clinic, general surgery clinic, and upper gastrointestinal clinic.

Study Participants

Inclusion Criteria

- *Scheduled Surgical Patients:* All surgical patients with pre-scheduled appointment are included in this study. This to ensures a focus on individuals who have a planned visit to the surgical clinics.
- *Outpatient Surgical Clinic Visits:* Patient must visit outpatient surgical clinics during the designated study period, allowing for consistent data collection and analysis related to scheduled care.

Exclusion criteria

- *Physician-Specific Appointments:* Patients who seek appointments specifically with a particular physician are excluded from the study to maintain a uniform patient population and reduce variability in data.
- *Walk-in Patients:* Individuals who present themselves at the clinics without a prior appointment, referred to as 'walk-in' patients, will not be included. This ensures that only scheduled visits are considered.
- *Multi Discipline Appointments:* Patients with appointments form two or more medical disciplines on the same day will be excluded. This helps maintain focus on a single specialty and reduces complexity in patient management.
- *Special Consultations:* Patients scheduled for special consultations, such as central line care, are excluded from this study.

Study Instrument

The QWIC System (Figure 1) is designed to optimise patient flow and enhance the consultation experience in surgical clinics. By standardising appointment times and streaming processes, the QWIC System aims to reduce waiting times and improve overall efficiency in patient care. The QWIC system incorporates several key features:

1) Staggered appointment scheduling
2) Patient ownership (dedicated patient lists for each consultation times)
3) Timekeeping and real-time tacking of consultation times
4) Maximising consultation room utilization during clinic sessions
5) Adequate manpower allocation on the floor during clinic hours

Step 1: Staggered Appointment System

The staggered appointment system efficiently schedules patient visits, aiming to optimize the use of consultation rooms and medical staff while minimizing patient wait times. Key components include:

1. Staggered Appointments:
- Appointments are scheduled at short intervals (60 minutes for new cases and 30 minutes for follow-ups) to spread patient arrivals throughout the day, reducing congestion and facilitating a smoother patient flow.
- Patients are scheduled the day prior to their designated consultation room with the assigned doctor.
2. Timekeeping:
- The QWIC system tracks consultation durations with predefined timeframes. A visible digital timer ensures adherence to schedules and optimizes clinic flow.
- Consultation Time for New Cases

o Bariatric and Upper GI Cases: Each new patient consultation is allocated 60 minutes to ensure through assessment and discussion.

- General Surgery Cases: New consultations are allotted 30 minutes to address patient needs effectively.
- Consultation Time for Follow-Up Cases
- Bariatric and Upper GI Cases: Follow-up consultations are scheduled for 30 minutes, allowing adequate review of patient progress and ongoing management.
- General Surgery Cases: Follow-up visits are set for 15 minutes, focusing on essential updates and care continuity.

3. Time from Registration to Vitals Examination
- The waiting period between registration and the vitals examination is waived, allowing patients to move promptly into the next stage of their visit without unnecessary delays.

4. Queue Time
- The queue time officially begins only after the vitals examination, ensuring that patients are acknowledged and ready for their consultations, thereby minimising idle waiting periods.

5. Doctor Queueing:
- Doctors are placed in a queue rather than nurses, enabling them to manage their caseloads effectively. Patients are registered and placed in a virtual queue, with doctors moving between consultation rooms to see patients in order.

6. Patient Ownership:
- Each patient is assigned to a specific doctor, ensuring continuity of care.
- The assigned doctor is responsible for the patient's treatment plan and follow-ups, allowing for better awareness and management of case backlogs.

Step 2: Enhanced Capacity and Flexibility

The administration has taken steps to increase consultation room availability, significantly improving the efficiency of the staggered appointment system:

1. Increased Consultation Rooms:
- Additional rooms allow for more patients to be seen simultaneously, enhancing flexibility and reducing bottlenecks.

2. Reallocation of Shared Rooms:
- Moving shared rooms to another building ensures dedicated space for the primary discipline, reducing scheduling conflicts and creating a focused environment.

Step 3: Staffing Enhancements

To support the success of the QWIC system, the clinic has increased nursing and medical staff at the surgical clinics:

1. Dedicated Nursing Staff:
- Nurses focus on specific tasks, reducing errors and bottlenecks while improving patient care.

2. Additional Medical Doctors:
- The supply of doctors is proportionate with the scheduled patients and allocated consultation rooms

Data Analysis

This research used Statistical Package for Social Sciences (SPSS) version 25 for data management and analysis. The continuous data analysis was represented as mean and standard deviation (SD) for a normal distribution. The association between the independent and dependent variables was determined using the Chi-square test. Concurrently, performed multiple logistic regression to verify the significant risk factors associated with prolonged waiting times.

Ethics approval

This study was registered and approved by the National Medical Research Registry (NMRR ID-22-00005-6GC(IIR) and the Medical Research and Ethic Committee (MREC), respectively. This research was conducted with highest ethical principles as outlined in the Declaration on Helsinki and Malaysian Good Clinical Practice Guideline.

RESULTS

A total of 1134 patients attended surgical clinics at the NCI during the six months of study period. Meanwhile, 287 (25.3%) patients visited Bariatric clinic, 358 (31.6%) patients visited GS clinic and 466 (41.1%) patients visited UGI clinic.

Across the surgical clinics at the NCI, the bariatric clinic received highest percentages of new surgical cases (26.4%) while the GS clinic reports the lowest (17.0%) (Table I). Most cases across all clinics are follow-ups, with the GS clinic having the largest share (83.0%) and the Bariatric clinic reveals the lowest percentages of punctual attendees (28.8%), while the GS clinic ranks highest at 41.0%. A substantial majority of patients at all clinics arrived after their schedules appointment time, with the Bariatric clinic exhibiting the highest rate (71.2%).

The average waiting time at surgical clinics was 24.9 minutes. The Bariatric clinic has a mean waiting time of 36.1 minutes (SD = 35.19), whereas the GS clinic exhibits the shortest mean waiting time of 14.7 minutes (SD = 11.12). The UGI clinic has an average waiting time of 23.9 minutes (SD = 21.35). Majority of patients in all clinics attended to within 60 minutes, with GS (98.9%) and UGI (96.3%) demonstrating exceptionally high rates. The Bariatric clinic exhibits a lower rate of 83.4%. Bariatric patients exhibit the highest proportion, at 16.6%, of those waiting over 60 minutes.

The average consultation duration for the Bariatric clinic is 44.4 minutes (SD = 40.58), which is significantly longer than the GS clinic's average of 26.1 minutes (SD = 24.29) and the UGI clinic's average of 28.9 minutes (SD = 23.54). This indicates that the Bariatric clinic manages more complicate or extensive assessments. The GS clinic exhibits the highest proportion of consultations, with 39.9% lasting under 15 minutes. Both GS and UGI exhibit comparable distributions for consultations lasting 16-30 minutes. The Bariatric clinic shows the highest proportion of consultations lasting 31-60 minutes (32.8%) , whereas 22.3% of its patients have consultations exceeding 60 minutes, in contrast to merely 7.3% in the GS clinic.

Majority of patients (93.7%) attended surgical clinics waited 60 minutes of less for their appointments, while only 6.3% experienced waits exceeding this duration. This difference is statistically significant ($p < 0.001$), highlighting the general efficiency of the surgical clinics. Looking at the breakdown of the clinic, the Bariatric clinic shows that 83.4% of patients waited 60 minutes or less, with 16.6% exceeding this time.

This suggests a higher percentage of longer waits compared to the overall average. In contrast, the GS clinic demonstrates impressive efficiency, with 98.9% of patients waiting 60 minutes or less and only 1.1% waiting longer. The UGI clinic also performs well, as 96.2% of its patients are seen within 60 minutes, with 3.8% waiting longer (Table I).

The waiting times by surgical case status indicates that 87.1% of new cases waited 60 minutes or less, whereas 12.9% experienced longer wait times ($p < 0.001$), suggesting that new cases generally endure longer waiting times than follow-up cases (Table II). In fact, a higher percentage of follow-up patients (95.6%) waited 60 minutes or less, with only 4.4% exceeding that duration. Regarding attendance status, patients who arrived punctually experienced a waiting time of 60 minutes or less in 94.3% of cases, while only 5.7% waited longer, but the p-value indicates that the difference is not statistically significance ($p = 0.535$). Meanwhile, patients who arrived after their scheduled appointment, 93.4% experienced a wait time of 60 minutes or less, while 6.6% waited longer. This suggests that arriving late does not have substantial impact on waiting times in a statistically significant manner.

Patients with consultations under 15 minutes encountered the shortest waiting time, with 96.9% waiting 60 minutes or less and merely 3.1% surpassing this duration ($p=0.002$). In the 16-30 minutes consultation group, 94.0% of individuals waited 60 minutes or less, while 6.0% experienced longer waiting times. For patients whose consultations lasted 31-60 minutes, 92.9% experienced waiting time of 60 minutes or less, whereas 7.1% waited longer. Significantly, patients with consultations exceeding 60 minutes experienced 87.6% waiting 60 minutes or less, while 12.4% waited longer. This. Signifies a correlation between prolonged consultation durations and increased waiting times.

Table III identified factors associated with waiting time experienced by patients who visited surgical clinics at NCI. The bariatric clinic has a strong association with >60 minutes waiting time (COR: 18.72, 95% CI: 6.51-51.28, $p < 0.001$; AOR: 15.33, 95% CI: 5.32-44.13, $p <0.001$). In contrast to the GS clinic, bariatric clinic patients were significantly more likely to experience the longer waiting time. A moderate association observed between the UGI clinic and waiting time (COR: 3.67, 95%CI: 1.23:10.94, $p = 0.020$; AOR: 3.34, 95% CI: 1.12-10.02, $p = 0.031$).

Furthermore, surgery outcomes are strongly correlated with new cases compared follow-up cases (COR: 3.19, 95% CI: 1.96-5.22, $p < 0.001$ and AOR: 2.56, 95% CI: 1.42-4.52, $p = 0.001$). Nevertheless, no correlation was found between attendance on-time or past time the appointment time. Meanwhile, consultation duration yields mixed results. An initial correlation exists (COR:4.4, 95% CI: 1.98-9.76, $p < 0.001$) for consultations more than 60 minutes; however, upon adjusting for additional variables, the correlation was no longer significant (AOR=1.55, 95% CI: 0.71-3.39, $p = 0.264$). Consulting sessions of 31-60 minutes initially demonstrate a significant association (COR: 2.36, 95%CI: 1.12-4.94, $p = 0.023$) but lose significance in the adjusted model (AOR: 1.25, 95%CI: 0.56-2.77, $p = 0.573$). Following adjustment, 16-30 minutes consultations were not statistically significant (AOR: 1.48, 95%CI: 0.60-3.64, $p = 0.384$).

DISCUSSION

Overall, the data suggests that waiting times are generally efficient across the surgical clinics at NCI, particularly in the GS clinic. As more than 90% of patients experience wait times was less than 60 minutes, demonstrating the adherence to the Ministry of Health Malaysia's benchmark. However, notable variations do exist across different clinic types and patient categories which still meet the desired waiting time. New cases tend to experience longer waits compared to follow-up cases, and consultation duration significantly influences waiting times (8). Attendance status appears not to have a significant effect on waiting time outcomes, indicating that other factors may contribute to the overall efficiency of the clinics.

The bariatric clinic exhibits elevated rates of new cases, extended consultation and waiting durations, and a considerable proportion of patients arriving after their scheduled appointments. The GS clinic shows the shortest waiting and consultation durations, yet it also possesses the highest proportion of extremely short consultations (under 15 minutes). Between the two, the UGI clinic stands out due to its significant predominance of follow-up cases. The findings indicate possible disparities in patient complexity, operational efficiency, and differing practices or patient demographics across the three clinics under surgical department, National Institute of Cancer. These findings align with a recent study who identified similar challenges in specialised surgical cases, which could be the complexity of cases and execution of a management plan.[15] Previous study also has highlighted similar pattern prominence, which is the additional detailed patient educations that mostly require multidisciplinary care components pose unique challenges in managing bariatric patients.[16]

By implementing structured time allocations and streamlining processes, the QWIC system has shown significant efficiency in managing patients at surgical outpatient clinics at the NCI. Nevertheless, the surgical department must determine the department's service priority to forecast the number of patients coming to the surgical clinic so that the QWIC system is sustainable. According to the study, the percentage of new cases in the Bariatric clinic was higher than in the GS clinic and UGI clinic. This aligns with findings from recent studies[17-18] that highlight the increasing demand for bariatric procedures due to rising obesity rates. Nevertheless, the majority of patients in the bariatric clinic experience wait times of less than 60 minutes. However, the proportion exceeding this threshold (16.6%) is concerning, as multivariate analysis reveals that patients at the bariatric clinic are 15 times more likely to experience prolonged waiting time. Another research emphasises that extended wait times can negatively affect patient satisfaction and compliance.[19] Another finding in the Bariatric clinic was that a substantial proportion of consultations in the Bariatric clinic extend beyond 60 minutes (22.3%), which was consistent with the findings from previous researches20-21,

Table I: Patient characteristics across different type of clinics (N=1134)

Variables	Patient, n (%)		
	Bariatric clinic (n=287)	GS clinic (n=358)	UGI clinic (n=466)
Status of surgical case			
New case	78 (26.4)	63 (17.0)	10.8 (23.1)
Follow-up	217 (73.6)	308 (83.0)	360 (76.9)
Attendance status			
On-time	85 (28.8)	152 (41.0)	185 (39.5)
Past-time	210 (71.2)	219 (59.0)	283 (60.5)
Waiting time (mins)			
Mean (standard deviation)	36.1 (35.19)	14.7 (11.12)	23.9 (21.35)
<60 minutes	246 (83.4)	367 (98.9)	450 (96.2)
>60 minutes	49 (16.6)	4 (1.1)	18 (3.8)
Consultation time (mins)			
Mean (standard deviation)	44.4 (40.58)	26.1 (24.29)	28.9 (23.54)
<15	54 (18.4)	143 (39.9)	156 (33.5)
16-30	75 (26.1)	107 (29.9)	135 (29.0)
31-60	94 (32.8)	82 (22.9)	136 (29.2)
>60	64 (22.3)	26 (7.3)	39 (8.4)

Table II: Distribution of waiting times in surgical clinics by patient characteristics (N=1134)

Variables	Waiting time, n (%)		p valuea
	<=60mins	>60mins	
Overall Surgical clinics	1063 (93.7)	71 (6.3)	
Surgical clinics			
Bariatric clinic	246 (83.4)	49 (16.6)	<0.001
GS clinic	367 (98.9)	4 (1.1)	
UGI clinic	450 (96.2)	18 (3.8)	
Status of surgical case			
New case	217 (87.1)	32(12.9)	<0.001
Follow-up	846 (95.6)	39 (4.4)	
Attendance status			
On-time	398 (94.3)	24 (5.7)	0.613
Past appointment time	665 (93.4)	47 (6.6)	
Consultation duration			
<15mins	342 (96.9)	11 (3.1)	0.002
16-30 mins	298 (94.0)	19 (6.0)	
31-60 mins	290 (92.9)	22 (7.1)	
>60mins	113 (87.6)	16 (12.4)	

[a] Chi-square test

Table III: Logistic Regressions of factors associated with waiting time among patients visiting surgical clinics at National Cancer Institute

Variables	Simple logistic regression			Multiple logistic regression		
	COR	95% CI	p	AOR	95% CI	p
Types of clinics						
GS clinic			Ref			Ref
Bariatric clinic	18.72	6.51-51.28	<0.001	15.33	5.32-44.13	<0.001
UGI clinic	3.67	1.23-10.94	0.020	3.34	1.11-10.02	0.031
Status of surgical case						
Follow-up			Ref			Ref
New case	3.19	1.96-5.22	<0.001	2.56	1.45-4.52	0.001
Attendance status						
On-time			Ref			Ref
Past appointment time	1.17	0.70-1.94	0.536	0.88	0.51-1.52	0.656
Consultation duration						
<15mins			Ref			Ref
>60mins	4.40	1.98-9.76	<0.001	1.55	0.71-3.39	0.264
31-60 mins	2.36	1.12-4.94	0.023	1.25	0.56-2.77	0.573
16-30 mins	1.98	0.93-4.23	0.077	1.48	0.60-3.64	0.384

COR= Crude odd ratio, AOR= Adjusted crude ratio, CI = Confidence interval, Ref = reference

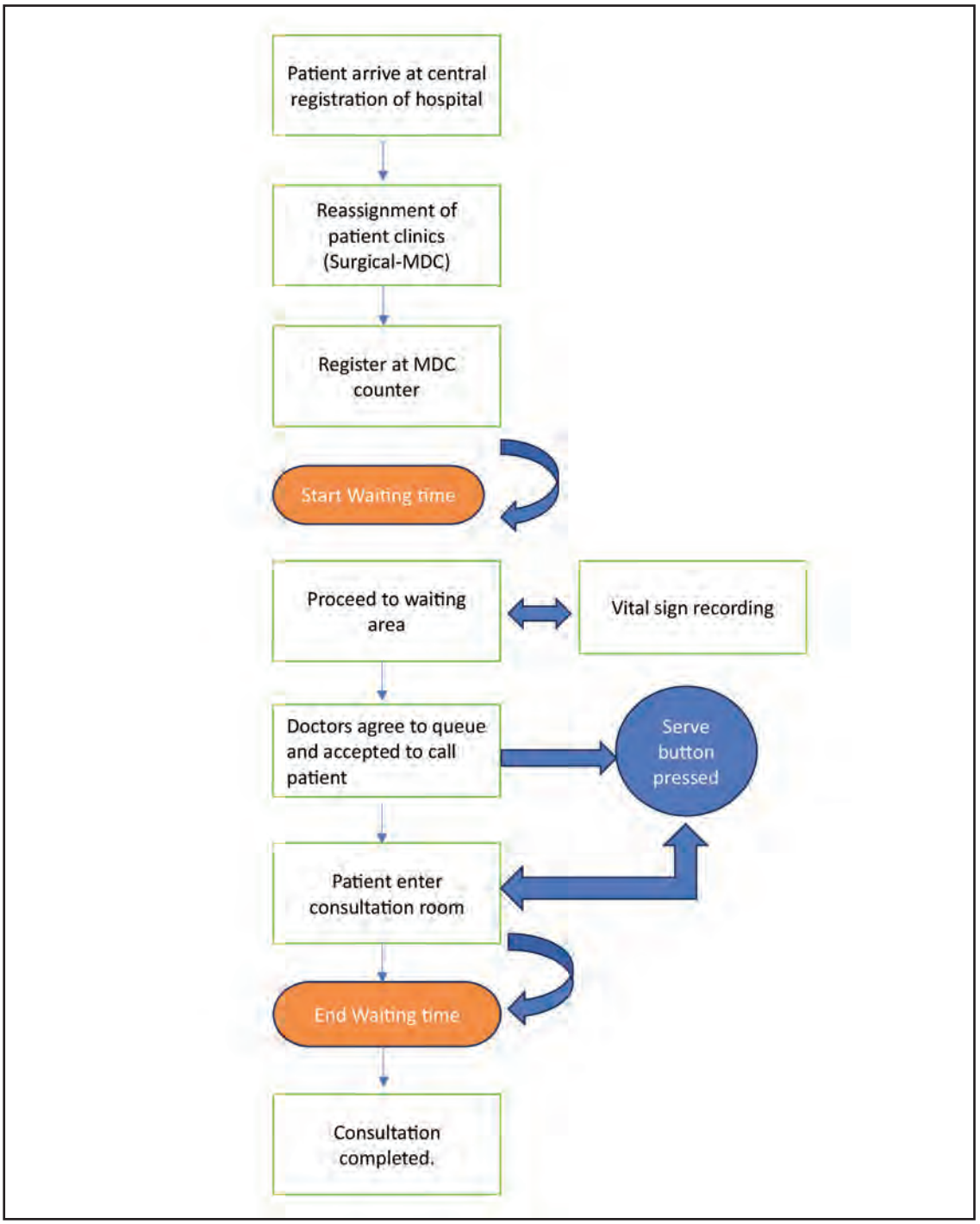


Fig. 1: Patient's Flow Chart of QWIC System at National Cancer Institute

who reported that comprehensive pre-operative evaluations in Bariatric surgery necessitate extended consultations.

In addition to the discipline, the type of cases (new or follow-up cases) represents a significant factor influencing patient waiting times within healthcare settings. Effectively managing these cases in a structured manner has the potential to enhance and reduce overall waiting times. The present analysis indicates that new cases consistently exhibit prolonged waiting times when compared to follow-up appointments, with this difference reaching statistical significance. This finding was consistent with another study who emphasised that the extended duration required for the initial assessment of new patients is a primary contributor to prolonged waiting times.[22] Such assessments typically involve detailed reviews of medical history, comprehensive physical examinations, and the development of treatment plans, all of which contribute to the extended wait. Furthermore, other studies also observed that the initial consultation phase places additional demands on time, as it requires a thorough evaluation of the patient's condition.[8] These findings collectively suggest that optimising the initial assessment

process by assigning senior surgical doctor for improving patient flow and reducing waiting times. the analysis revealed that attendance status-whether patients adhered to their scheduled appointment times or arrived beyond the designated time-did not exhibit a statistically significant impact on extended waiting times. This finding challenge traditional assumptions that punctuality and adherence to scheduled appointment times directly influence clinic flow. Previous research suggests that appointment adherence is commonly believed to affect clinic operations and management strategies, as delays can often lead to cascading disruptions throughout the daily schedule.[23] For instance, a further analysis of patient attendance at a bariatric clinic in this study revealed that over 65% of patients arrived beyond their scheduled appointment time. This behaviour resulted in significant disruptions to the clinic's ability to maintain an orderly flow of appointments, ultimately affecting overall clinic efficiency and patient wait times. While clinical settings often emphasise punctuality, these results suggest that other systematic factors may exert a more significant influence on waiting times and clinic management. The findings from this study highlight significant disparities in patient characteristics and clinic performance metrics across the three types of surgical clinics. The implications of these findings suggest a need for Bariatric clinic to evaluate their operational efficiencies and patient flow processes. Building a streamlined process for complex consultation is a requisite step. Additionally, implementing differentiated time allocation for new versus follow-up cases would be an important improvement to consider.

CONCLUSION

The QWIC System represents a significant advancement in managing patient appointments and consultations within surgical clinics. By implementing structured time allocations and streamlining processes enhanced patient satisfaction and clinical efficiency. Addressing the differences through targeted interventions and resource allocation could lead to improved patient experience and more efficient operations across all surgical expertise. Future research should explore patient truth satisfaction who attend surgical clinics to get dual feedback on improving the queue system at the clinic. Thus, this approach could be implemented in other surgical clinics at tertiary hospitals, which received an almost similar burden of patient flow.

CONFLICT OF INTEREST

All authors have no conflict of interest to declare and no competing interests on this study.

ACKNOWLEDGEMENTS

All authors would like to express our sincere gratitude to all staff (nurses, medical assistants, and healthcare assistants) at surgical clinics at the National Cancer Institute of Malaysia who contributed to the data collection and success of this study. Additionally, we are grateful to the National Cancer Institute Director for encouragement and support for this research. Not to forget, the authors also would like to express utmost gratitude to the Director General of Health Malaysia for authorising the publication of this research.

FUNDING

All authors would like to declare that this study did not receive any research funding.

REFERENCES

1. Alrasheedi KF, Al-Mohaithef M, Edrees HH, Chandramohan S. The Association Between Wait Times and Patient Satisfaction: Findings From Primary Health Centers in the Kingdom of Saudi Arabia. Health Serv Res Manag Epidemiol. Jan-Dec 2019
2. Zhang H, Ma W, Zhou S, Zhu J, Wang L, Gong K. Effect of waiting time on patient satisfaction in outpatient: An empirical investigation. Medicine (Baltimore). Oct 6 2023;102(40)
3. Morales J, Silva-Aravena F, Saez P. Reducing Waiting Times to Improve Patient Satisfaction: A Hybrid Strategy for Decision Support Management. Mathematics. 2024;12(23):3743
4. Oudhoff JP, Timmermans DRM, Knol DL, Bijnen AB, van der Wal G. Waiting for elective general surgery: impact on health related quality of life and psychosocial consequences. BMC Public Health. 2007/07/19 2007;7(1):164. doi:10.1186/1471-2458-7-164
5. Wu B, Wang HJ, Yang XP, Zhong ZH. The Influence of Preoperative Waiting Time on Anxiety and Pain Levels in Outpatient Surgery for Breast Diseases. J Patient Saf. Mar 1 2024;20(2):105-109.
6. Zhang H, Ma W-M, Zhu J-J, Wang L, Guo Z-J, Chen X-T. How to adjust the expected waiting time to improve patient's satisfaction? BMC Health Services Research. 2023/05/08 2023;23(1):455.
7. The Charter of Patient Rights and Responsibilities - Revised: June 2022 (The Scottish Government, October 2022) (2022).
8. Kagedan DJ, Edge SB, Takabe K. Behind the clock: elucidating factors contributing to longer clinic appointment duration and patient wait time. BMC Health Services Research. 2021/01/26 2021;21(1):87.
9. Helbig M, Helbig S, Kahla-Witzsch HA, May A. Quality management: reduction of waiting time and efficiency enhancement in an ENT-university outpatients' department. BMC Health Serv Res. Jan 31 2009;9:21.
10. Mwanswila MJ, Mollel HA, Mushi LD. Outcome evaluation of technical strategies on reduction of patient waiting time in the outpatient department at Kilimanjaro Christian Medical Centre-Northern Tanzania. BMC Health Serv Res. Jul 9 2024;24(1):785.
11. Pillay DI, Ghazali RJ, Manaf NH, et al. Hospital waiting time: the forgotten premise of healthcare service delivery? Int J Health Care Qual Assur. 2011;24(7):506-22.
12. National Guideline on Management of Patient Waiting Time in Clinics, Community Health Centers, and Outpatient Departments of Public Hospitals of South Africa (2023).
13. Hazilah Abd Manaf N. Inpatient satisfaction: an analysis of Malaysian public hospitals. International Journal of Public Sector Management. 2012;25(1):6-16.
14. Ahmad BA, Khairatul K, Farnaza A. An assessment of patient waiting and consultation time in a primary healthcare clinic. Malays Fam Physician. 2017;12(1):14-21.
15. Ahmad, N. A., Hamid, M. T. A., Ghani, N. A., Hasim, H., & Rohana, J. (2020). Challenges in specialized surgical cases: A study of patient waiting times and operational efficiency in Malaysian tertiary care. Asian Journal of Surgery, 43(1), 55-62.
16. Kumar, S., Merchant, S., & Reynolds, R. (2019). Evaluating waiting times and operational efficiency in surgical outpatient clinics: A comparative analysis of case complexity. Journal of Health Management, 21(3), 278-291
17. Smith, B. D., Johnson, R. K., & Williams, P. A. (2021). Increasing demand for bariatric procedures: Analysis of trends and contributing factors. Obesity Surgery International, 29(4), 542-558.
18. Lee, S. J., Wong, C. K., Tan, M. H., Razak, N. A., & Ibrahim, S. (2021). Factors influencing waiting times in surgical oncology clinics: Analysis of consultation duration and patient flow efficiency. Malaysian Journal of Medical Sciences, 28(4), 112-125.

19. Petel, A. R., Davidson, M. B., & O'Connor, S. J. (2024). Impact of extended waiting times on patient satisfaction and treatment compliance in specialized clinics. Healthcare Management Review, 37(2), 183-197.
20. Garcia, R. F., Nguyen, T. P., & Hernandez, L. M. (2022). Comprehensive pre-operative evaluations in bariatric surgery: Time requirements and clinical implications. Bariatric Surgical Practice and Patient Care, 17(1), 76-91.
21. Thompson, K. R., & Lee, W. S. (2022). Duration analysis of consultations in bariatric surgery: Factors influencing extended clinical encounters. Journal of Patient-Centered Research and Outcomes, 14(3), 298-312.
22. Wilson, J. R., Martinez-Garcia, A., & Thompson, K. L. (2023). Extended duration requirements for initial assessment of new patients in surgical consultations: A retrospective analysis. Journal of Surgical Management, 45(3), 217-231.
23. Chen, X. Y., Roberts, P. L., & Kim, J. H. (2022). The influence of appointment adherence on clinical operations and management strategies: A systematic review. BMC Health Services Research, 22(4), 367-382.

Serum kisspeptin levels in women with polycystic ovary syndrome: A systematic review and meta-analysis

Salmon Charles Siahaan, MD[1,2,3], Ashon Sa'adi, MD[1], Hendy Hendarto, MD[1,3], Budi Santoso, MD[1], Sri Ratna Dwiningsih, MD[1], Jimmy Yanuar Anas, MD[1,2], Relly Yanuari Primariawan, MD[1], Muhammad Yohanes Ardianta Widyanugraha, MD[1], Arif Tunjungseto, MD[1,2]

[1]Department of Obstetrics and Gynecology, Faculty of Medicine, Airlangga University, Surabaya, Indonesia, [2]Department of Obstetrics and Gynaecology, Airlangga University Hospital, Universitas Airlangga Faculty of Medicine, Surabaya, Indonesia, [3]School of Medicine Universitas Ciputra, Surabaya, Indonesia

ABSTRACT

Introduction: Kisspeptin is a key regulator of the hypothalamic–pituitary–gonadal axis and has been implicated in the pathophysiology of polycystic ovary syndrome (PCOS). However, reported associations between kisspeptin levels and PCOS have been inconsistent.

Materials and Methods: A systematic search of PubMed, Scopus, and Web of Science was performed from inception to August 2025 for studies comparing serum kisspeptin concentrations between PCOS patients and controls. Data extraction was conducted independently by two reviewers. A random-effects meta-analysis was used to calculate pooled standardized mean differences (SMD) with 95% confidence intervals (CI). Heterogeneity was assessed using the Q statistic and I^2 index. Meta-regression was performed to examine BMI as a predictor of kisspeptin levels.

Results: Twenty studies involving 670 participants were included. Pooled analysis demonstrated significantly higher serum kisspeptin levels in PCOS patients compared with controls (SMD = 0.511; 95% CI: 0.376–0.646; $p < 0.001$; I^2 = 0%). Meta-regression revealed that BMI significantly moderated the association, with overweight/obese PCOS patients showing the greatest elevation in kisspeptin concentrations (β = 0.756; 95% CI: 0.483–1.029; $p < 0.001$).

Conclusion: Serum kisspeptin levels are elevated in women with PCOS, particularly among those with overweight/obese BMI, suggesting a possible interaction between metabolic status and reproductive neuroendocrine regulation. These findings support the potential of kisspeptin as a biomarker for PCOS and highlight the need for further research into its mechanistic role and clinical applicability.

KEYWORDS:
Body mass index, kisspeptin, polycystic ovary syndrome

INTRODUCTION

Polycyclic ovary syndrome (PCOS) is a frequent endocrine disorder that happens in women at the age of reproductive life which is estimated to reach 6-20 percent around the world based on the diagnostic standards that flow on the Rotterdam, NIH, and AE-PCOS criteria.[1] The disease has a wide variable clinical characteristic with a central feature of chronic anovulation, hyperandrogenism and the ovarian character of massive cysts seen on ultrasound imaging.[1-2] Metabolic imbalances, such as insulin resistance, being overweight/obese, dyslipidemia, and increased chances of developing type 2 diabetes mellitus are also associated with PCOS.[1,3] Despite its high rate of prevalence and multifactorial phenotype, its pathophysiological mechanisms are not fully described, which reduces the ability not only to make an adequate diagnosis but also to implement effective treatment options accordingly.

The neuropeptide, kisspeptin, encoded by KISS1 has gained more and more acceptance as a central modulator of the hypothalamicpituitarygonadal (HPG) axis through its activating effect on gonadotropin-releasing hormone (GnRH) release.[4] When kisspeptin binds to its receptor, GPR54 (also called KISS1R), expression is facilitated on GnRH neurons, which in turn stimulates the release of luteinizing hormone(LH) and follicle-stimulating hormone (FSH).[4-5] This signaling cascade is necessary to not only the induction of puberty, but required to sustain reproductive capacity as well. As a result, impairment of kisspeptin-GPR54 signaling is the basis of a range of reproductive pathologies, such as hypogonadotropic hypogonadism, precocious puberty, and infertility.[4-5] Considering the primary position of GnRH in the process of ovarian functioning, deviations either in the levels or the activity of kisspeptin will account for the hormonal and ovulatory disturbances that dominate this complicated clinical picture of PCOS.

Several studies have investigated serum kisspeptin levels in women with PCOS, aiming to elucidate its potential role in the disorder's pathogenesis.[6-7] However, the results have been inconsistent: some studies report elevated kisspeptin concentrations in PCOS patients, possibly reflecting increased GnRH pulse frequency and LH hypersecretion, while others find no significant differences or even reduced levels, suggesting altered feedback mechanisms. These discrepancies may stem from differences in study populations, diagnostic criteria, assay methodologies, and confounding factors such as body mass index (BMI), insulin resistance, and androgen levels. Such heterogeneity highlights the need for a

This article was accepted: 16 February 2026
Corresponding Author: Salmon Charles Siahaan
Email: charlessiahaan.obgyn@gmail.com

systematic synthesis of the evidence to better understand the relationship between kisspeptin and PCOS.[6,8]

A comprehensive meta-analysis can quantitatively assess the existing data, address variability among studies, and provide more precise estimates of the association between kisspeptin levels and PCOS. By pooling data from multiple studies, this approach may clarify whether kisspeptin is consistently altered in PCOS and explore potential modifiers of this relationship, such as BMI, assay technique, or regional differences. Understanding this relationship is not only relevant to elucidating PCOS pathophysiology but may also inform the development of novel diagnostic biomarkers and therapeutic targets. This systematic review and meta-analysis therefore aims to evaluate and synthesize current evidence on serum kisspeptin levels in women with PCOS compared to healthy controls.

MATERIALS AND METHODS

This study followed the PRISMA 2020 guidelines for conducting and reporting systematic reviews and meta-analyses. The review protocol was developed a priori and registered in PROSPERO to ensure transparency and reduce potential for bias.

Studies were considered eligible if they:

1. Included reproductive-age women with diagnosed PCOS (Rotterdam, NIH, or AES criteria) and a healthy control group;
2. Reported serum or plasma kisspeptin levels;
3. Employed observational study designs (case-control or cross-sectional);
4. Reported data sufficient to compute effect sizes (means with SD or equivalent).

Excluded were: animal or in vitro studies, reviews, conference abstracts without full texts, and studies lacking necessary quantitative data.

We systematically searched PubMed, Scopus, Web of Science, and Cochrane Library from inception to 2025. Search terms included variations of ("kisspeptin" OR "metastin") AND ("PCOS" OR "polycystic ovary syndrome"). Citation lists of relevant articles and reference lists were manually screened for additional studies.[9]

Titles and abstracts were screened independently by two reviewers. Full texts of potential studies were assessed for eligibility. Discrepancies were resolved by consensus or a third reviewer. The study selection process is summarized using a PRISMA flow diagram.

Reviewer independently extracted data into a standardized form, including: author, publication year, country, sample sizes, age, BMI, diagnostic criteria, kisspeptin measurement method (e.g., ELISA), and mean ± SD levels. Any discrepancies were discussed and resolved.

Study quality was assessed using the Newcastle–Ottawa Scale (NOS) for observational studies. Criteria included selection of participants, comparability of groups, and ascertainment of exposure/outcome.[10]

We calculated pooled standardized mean differences (SMDs) with 95% confidence intervals using a random-effects model. Heterogeneity was evaluated using the I^2 statistic. Pre-specified subgroup analyses were conducted based on BMI category, diagnostic criteria used, and assay method. Sensitivity analyses and assessment of publication bias (funnel plot, Egger's test) were also performed.[11-12]

RESULTS

A total of 1,591 records were identified from databases (n = 1,506) and trial registers (n = 85). Additional records were obtained from websites (n = 12), organizations (n = 5), and citation searching (n = 2). After removing duplicates, 740 records were screened by title and abstract, with 451 reports sought for retrieval. Of these, 257 reports were assessed for eligibility, resulting in the inclusion of 16 new studies (2 reports). Combined with the 17 studies (5 reports) from the previous version of the review, the final analysis included 18 studies (21 reports). Figure 1 shows the PRISMA flow diagram for study selection.

The heterogeneity test ($Q_e(20) = 36.76$, $p = 0.013$) indicates statistically significant variability in effect sizes across the included studies, suggesting that the observed differences are unlikely to be due to sampling error alone. This finding implies the presence of potential moderators or study-level characteristics influencing the effect size. The pooled effect size was statistically significant ($t(20) = 5.27$, $p < 0.001$), confirming a robust overall association between the studied variables across all included datasets.

The pooled effect size was estimated at 0.586 (95% CI: 0.354 to 0.818), indicating a moderate and positive association between the variables of interest. The 95% prediction interval ranged from –0.160 to 1.331, suggesting that while most future studies are xpected to yield positive effects, there remains the possibility of obtaining negligible or even negative effects under certain conditions (Table I).

The between-study standard deviation (τ) was 0.340, and the between-study variance (τ^2) was 0.115, pointing to notable dispersion of true effect sizes. The I^2 statistic was 45.78% (95% CI: 7.00% to 74.74%), reflecting moderate heterogeneity, while the H^2 value of 1.844 suggests that the total variability is approximately 1.84 times greater than what would be expected from sampling error alone. These heterogeneity metrics reinforce the conclusion from the Q test that variability among studies warrants further exploration, potentially via meta-regression or subgroup analyses (Figure 2).

The residual heterogeneity test ($Q_e(19) = 12.32$, $p = 0.871$) was not statistically significant, indicating that the variability in effect sizes remaining after accounting for the moderator is consistent with sampling error alone. This suggests that the included moderator explains most of the between-study variance. The pooled effect was statistically significant ($t(19) = 7.92$, $p < 0.001$), reflecting a consistent and substantial association across studies. The moderation test ($F(1, 19) = 33.71$, $p < 0.001$) confirmed that the moderator variable had a statistically significant influence on the effect size estimates.

Table I: Meta-Analytic estimates of the review

	Estimate	95% CI		95% PI	
		Lower	Upper	Lower	Upper
Pooled effect	0.586	0.354	0.818	-0.16	1.331
τ	0.34	0.101	0.636		
τ^2	0.115	0.01	0.405		
I^2	45.777	6.997	74.735		
H^2	1.844	1.075	3.958		

Table II: Effect Size Meta-Regression Coefficients

	Estimate	Standard Error	95% CI		t	df	p
			Lower	Upper			
Intercept	0.187	0.086	0.007	0.366	2.18	19	0.042
BMI Category (Overweight and Obese I-II)	0.756	0.13	0.483	1.029	5.806	19	< .001

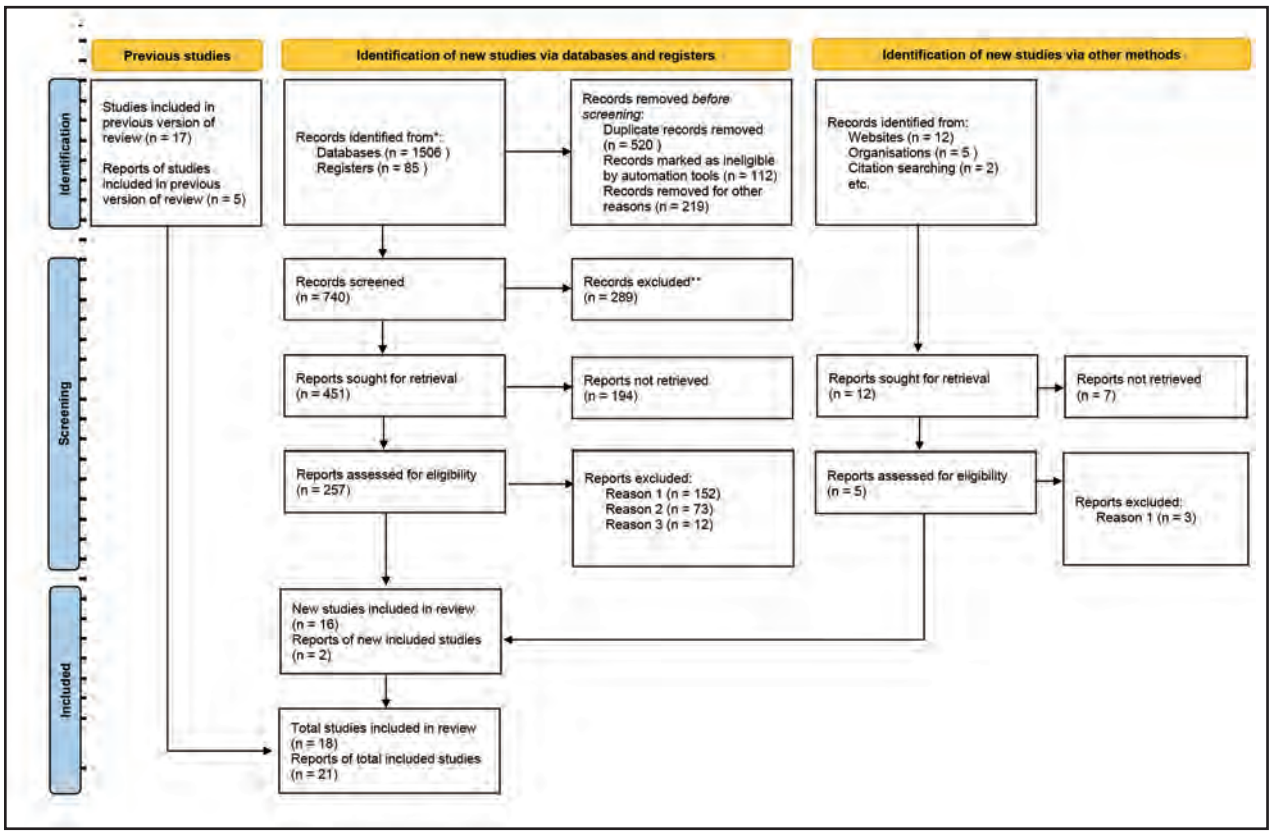


Fig. 1: PRISMA Flow Diagram

The pooled effect size was 0.511 (95% CI: 0.376 to 0.646), indicating a moderate positive association between the variables under study. The 95% prediction interval matched the confidence interval (0.376 to 0.646), implying that future studies under similar conditions are expected to yield effect sizes within this range, with minimal risk of extreme deviation.

The between-study standard deviation (τ) and variance (τ^2) were both estimated at zero, with upper confidence bounds of 0.231 and 0.053, respectively, suggesting negligible heterogeneity after accounting for the moderator. Similarly, the I^2 statistic was 0% (95% CI: 0% to 28.17%), and H^2 was 1.00 (95% CI: 1.00 to 1.39), further confirming the absence of meaningful residual variability across studies. These results indicate that the observed effects are highly consistent once the moderator is included in the model.

The omnibus test for the moderator variable "BMI Category" was statistically significant ($F(1, 19) = 33.71$, $p < 0.001$), based on the Knapp and Hartung adjustment. This indicates that BMI category explains a substantial proportion of the variance in effect sizes across studies (Table II and Figure 3).

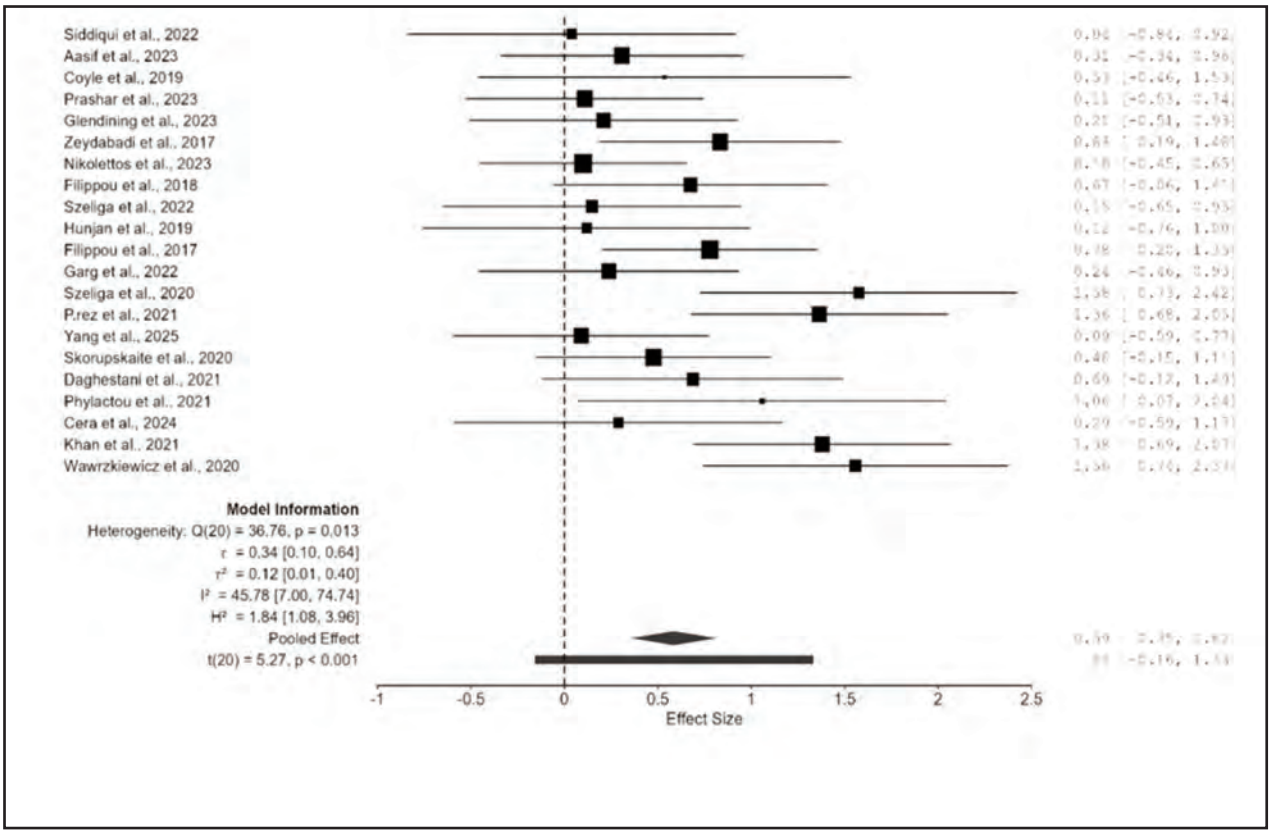


Fig. 2: Forest Plot[13-33]

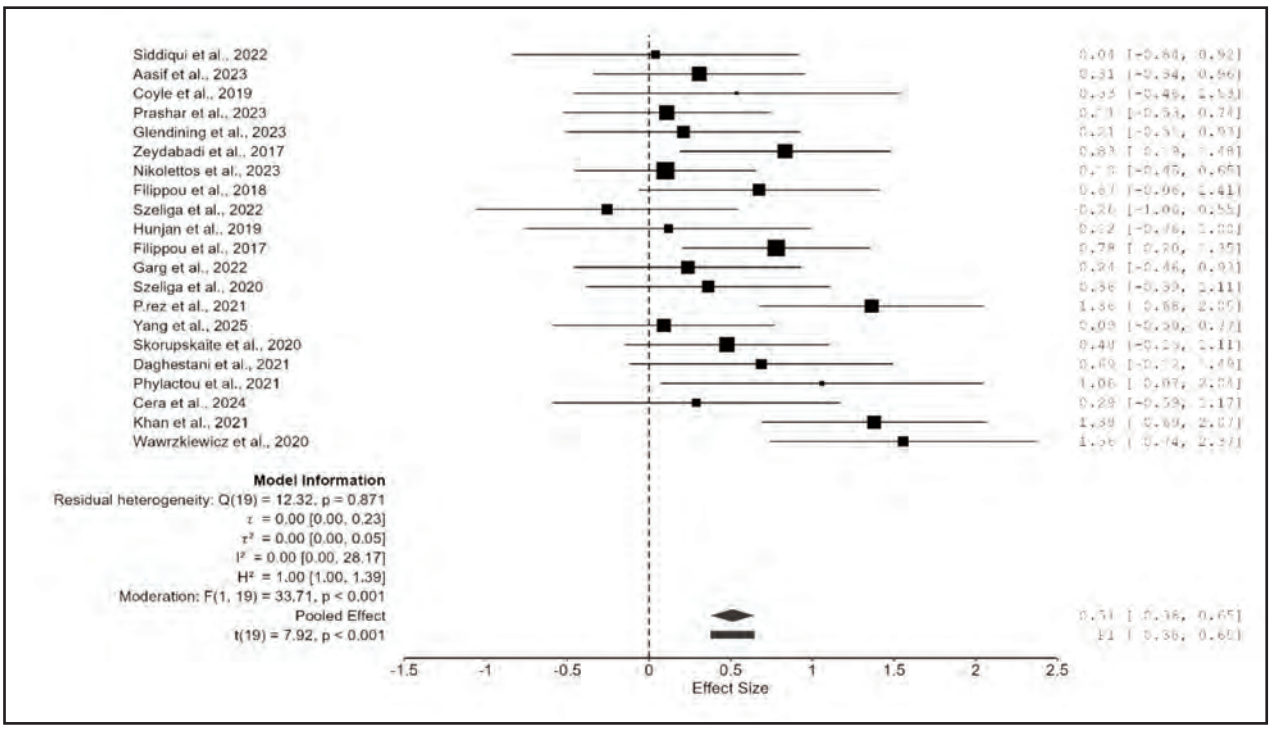


Fig. 3: Forest Plot of Regression Effect[13-33]

The intercept represents the estimated effect size for the reference BMI category (presumably normal weight), which was 0.187 (SE = 0.086, 95% CI: 0.007 to 0.366, t(19) = 2.18, p = 0.042), indicating a small but statistically significant positive effect in this group.

For the overweight, obese I, and obese II BMI category, the coefficient was 0.756 (SE = 0.130, 95% CI: 0.483 to 1.029, t(19) = 5.806, p < 0.001). This suggests that overweight or obese status is associated with an effect size approximately 0.76 units higher than the reference category, representing a substantial and statistically robust increase.

These findings imply that BMI category is an important moderator, with overweight/obese individuals showing markedly larger effect sizes compared to those in the reference group. The strength and precision of the estimates, coupled with the absence of residual heterogeneity in the prior analysis, suggest that BMI category may fully account for the between-study variability observed in the unmoderated model.

DISCUSSION

This meta-regression was informative to show that polycystic ovary syndrome (PCOS) moderates its relationship with circulating levels of kisspeptin based on the body-mass index (BMI) category. Women with PCOS in the overweight/obese range of the BMI scale had significantly higher kisspeptin concentrations than women in the reference (normal weight) group. A coefficient of 0.756 denotes the strong statistically significant increase in Greek points in the levels of kisspeptin in obese women and suggests a possible interaction between adiposity and hypo- pituitary-gonadal (HPG) regulation in PCOS. Raising support to the emerging evidence that metabolic status and especially excess adiposity may cause the potentiation of neuroendocrine changes in PCOS, these findings are consistent with our previous works. The biological possibility of such an outcome lies in the versatile role of kisspeptin in regulatory functions of the reproductive and metabolic processes.[5] Kisspeptin acts via its effect on the release of gonadotropin-releasing hormone (GnRH) to affect the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), both of which are commonly disregulated in PCOS.5 The role of overweight/obese and obesity in reduced insulin sensitivity, hyperinsulinemia, and abnormal leptin signaling and all of them can alter kisspeptin neuron activity has been previously reported.[3] The consequent rise in kisspeptin in the overweight/obese PCOS women could thus represent a compensatory upregulation as a reaction to changed metabolic signals or indeed an escalation of the reproductive endocrine imbalance that derails PCOS.[29] Individually, however, clinically the findings indicate why the inclusion of BMI as a critical stratification factor in assessment of kisspeptin levels is critical in PCOS research and treatment. The increased kisspeptin levels in overweight/obese women with PCOS may also be a predictor of metabolically worsened phenotype that should be treated by both reproductive and metabolic care. Further investigation is needed to establish whether kisspeptin would be a causative variable or merely an effect of the metabolic/reproductive interplay in PCOS and whether specific kisspeptin signaling manipulation may constitute a therapeutic option, especially in overweight/obese individuals.

Building upon the established correlation between adiposity and neuroendocrine dysfunction, the clinical application of these findings offers a transformative perspective on managing the multifaceted challenges of PCOS. For patients facing subfertility, the identification of kisspeptin as a potential biomarker provides a clearer window into the GnRH pulse frequency disturbances that drive chronic anovulation and LH hypersecretion.[5,16] Clinically, this suggests that kisspeptin levels could eventually guide the timing or selection of ovulation induction therapies, moving toward a more precision-based reproductive model. Furthermore, the strong moderation effect of BMI directly addresses metabolic disorders by confirming that overweight/obese status significantly potentiates these hormonal shifts ($\beta = 0.756$). This underscores the necessity of integrated care where weight management is not merely an adjunct but a primary intervention to recalibrate the HPG axis. Addressing these underlying metabolic drivers can simultaneously improve body image issues by reducing the physical manifestations of the syndrome, such as weight gain and androgen-related symptoms, which are often exacerbated by the interplay of hyperinsulinemia and kisspeptin signaling. Ultimately, recognizing kisspeptin as a bridge between metabolic status and reproductive health empowers clinicians to move beyond symptom management toward targeted interventions that address the disorder's fundamental pathogenic drivers.

CONCLUSION

This meta-regression analysis indicates that BMI status significantly influences circulating kisspeptin levels in women with PCOS, with overweight/obese individuals exhibiting markedly higher concentrations compared to their normal-weight counterparts. These findings suggest that adiposity may exacerbate neuroendocrine alterations in PCOS, potentially through metabolic–reproductive axis interactions. Recognizing BMI as a moderating factor is essential for both research interpretation and clinical assessment, and future studies should explore whether kisspeptin elevation in overweight/obese PCOS represents a compensatory mechanism or a pathogenic driver amenable to targeted intervention.

CONFLICT OF INTEREST

There are no potential conflicts of interest to disclose.

FUNDING

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

REFERENCES

1. Meng Y, Zhao T, Zhang R, Zhu X, Ma C, Shi Q. Global burden of polycystic ovary syndrome among women of childbearing age, 1990–2021: a systematic analysis using the global burden of disease study 2021. Frontiers in Public Health 2025; 26: 13.

2. Fahs D, Salloum D, Nasrallah M, Ghazeeri G. Polycystic Ovary Syndrome: Pathophysiology and Controversies in Diagnosis. Diagnostics 2023; 13(9): 1559.
3. Gholinezhad M, Gholsorkhtabaramiri M, Esmaeilzadeh S, Ghanbarpour A. Insulin resistance and adverse metabolic profile in overweight/obese and normal weight of young women with polycystic ovary syndrome. Caspian journal of internal medicine 2018; 9(3): 260–7.
4. Popa SM, Clifton DK, Steiner RD. The Role of Kisspeptins and GPR54 in the Neuroendocrine Regulation of Reproduction. Caspian Journal Of International Medicine 2008; 70(1): 213–38.
5. Xie Q, Kang Y, Zhang C, Xie Y, Wang C, Liu J, et al. The Role of Kisspeptin in the Control of the Hypothalamic-Pituitary-Gonadal Axis and Reproduction. Frontiers in Endocrinology 2022; 13: 925206.
6. Zheng Z, Ma Y, Shi Y, Xu Y. Associations between kisspeptin hormone level and its genetic polymorphisms with polycystic ovary syndrome. International Journal of Gynecology & Obstetrics 2025;
7. Mei H, Doran J, Kyle V, Yeo SH, Colledge WH. Does Kisspeptin Signaling have a Role in the Testes? Frontiers in Endocrinology 2013; 4.
8. Deswal R, Narwal V, Dang A, Pundir CS. The Prevalence of Polycystic Ovary Syndrome: A Brief Systematic Review. Journal of Human Reproductive Sciences 2020; 13(4): 261–71.
9. 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. British Medical Journal 2021; 372(71)
10. Schiavo JH. PROSPERO: An International Register of Systematic Review Protocols. Medical Reference Services Quarterly 2019; 38(2): 171–80.
11. Deeks JJ, HIggins JP, Altman DG, McKenzie JE, Veroniki AA. Chapter 10: Analysing data and undertaking meta-analyses | Cochrane. Cochrane.org 2024;
12. Lin L, Chu H. Quantifying publication bias in meta-analysis. Biometrics 2017; 74(3): 785-94.
13. Siddiqui S, Mateen S, Ahmad R, Moin S. A brief insight into the etiology, genetics, and immunology of polycystic ovarian syndrome (PCOS). Journal of Assisted Reproduction and Genetics 2022; 39(11): 2439-73.
14. Aasif A, Alam R, Ahsan H, Khan MM, Khan A, Khan S. The role of kisspeptin in the pathogenesis of a polycystic ovary syndrome. Endocrine Regulations 2023; 57(1): 292-303.
15. Coyle C, Campbell RE. Pathological pulses in PCOS. Molecular and Cellular Endocrinology 2019; 498: 110561.
16. Prashar V, Arora T, Singh R, Sharma A, Parkash J. Hypothalamic Kisspeptin Neurons: Integral Elements of the GnRH System. Reproductive Sciences 2023; 30(3): 802-22.
17. Glendining KA, Campbell RE. Recent advances in emerging PCOS therapies. Current Opinion in Pharmacology 2023; 68: 102345.
18. Zeydabadi NS, Ramezani TF, Zadeh-Vakili A. The Role of Kisspeptin in Female Reproduction. International Journal of Endocrinology and Metabolism 2017; 22; 15(3): e44337.
19. Nikolettos K, Nikolettos N, Vlahos N, Pagonopoulou O, Asimakopoulos B. Role of leptin, adiponectin, and kisspeptin in polycystic ovarian syndrome pathogenesis. Minerva Obstetricia e Ginecologia 2023; 75(5): 460-7.
20. Filippou P, Homburg R. Is foetal hyperexposure to androgens a cause of PCOS? Hum Reprod Update 2018; 23(4): 421-32.
21. Szeliga A, Rudnicka E, Maciejewska-Jeske M, Kucharski M, Kostrzak A, Hajbos M, et al. Neuroendocrine Determinants of Polycystic Ovary Syndrome. International Journal of Environmental Research and Public Health 2022; 19(5): 3089.
22. Hunjan T, Abbara A. Clinical translational studies of kisspeptin and neurokinin B. Semin Reprod Med 2019; 37(3): 119-24.
23. Filippou P, Homburg R. Is foetal hyperexposure to androgens a cause of PCOS? Human reproduction update 2017; 23(4): 421–32.
24. Garg A, Patel B, Abbara A, Dhillo WS. Treatments targeting neuroendocrine dysfunction in polycystic ovary syndrome (PCOS). Clinical Endocrinology 2022; 8: 97(2).
25. Szeliga A, Podfigurna A, Bala G, Meczekalski B. Kisspeptin and neurokinin B analogs use in gynecological endocrinology: where do we stand? Journal of Endocrinological Investigation 2019; 43(5): 555–61.
26. Pérez-López FR, Lía O, López-Baena MT, Santabárbara J, Savirón-Cornudella R, Pérez-Roncero G. Circulating kisspeptin and anti-müllerian hormone levels, and insulin resistance in women with polycystic ovary syndrome: A systematic review, meta-analysis, and meta-regression. European Journal of Obstetrics & Gynecology and Reproductive Biology 2021; 260: 85–98.
27. Yang Q, Jia S, Tao J, Zhang J, Fan Z. Multiple effects of kisspeptin on neuroendocrine, reproduction, and metabolism in polycystic ovary syndrome. J Neuroendocrinol 2025; 37(2): e13482.
28. Skorupskaite K, George JT, Veldhuis JD, Millar RP, Anderson RA. Kisspeptin and neurokinin B interactions in modulating gonadotropin secretion in women with polycystic ovary syndrome. Hum Reprod 2020; 35(6): 1421-31.
29. Daghestani MH, Warsy A, El-Ansary A, Omair MA, Hassen LM, Alhumaidhi EMH, et al. Adverse effects of selected markers on the metabolic and endocrine profiles of obese women with and without PCOS. Front Endocrinol (Lausanne) 2021; 12: 665446.
30. Phylactou M, Clarke SA, Patel B, Baggaley C, Jayasena CN, Kelsey TW, et al. Clinical and biochemical discriminants between functional hypothalamic amenorrhoea (FHA) and polycystic ovary syndrome (PCOS). Clin Endocrinol (Oxf) 2021; 95(2): 239-52.
31. Cera N, Pinto J, Pignatelli D. What do we know about abnormally low prolactin levels in polycystic ovary syndrome? A narrative review. Rev Endocr Metab Disord. 2024; 25(6): 1127-38.
32. Khan SH, Chaudhry N. Beyond GnRH, LH and FSH: The role of kisspeptin on hypothalamic-pituitary gonadal (HPG) axis pathology and diagnostic consideration. J Pak Med Assoc 2021; 71(7): 1862-9.
33. Wawrzkiewicz-Jałowiecka A, Kowalczyk K, Trybek P, Jarosz T, Radosz P, Setlak M, et al. In search of new therapeutics—Molecular aspects of the PCOS pathophysiology: Genetics, hormones, metabolism and beyond. Int J Mol Sci 2020; 21(19): 7054.

Acknowledgement
March Issue 2026

The Editorial Board of The Medical Journal of Malaysia gratefully acknowledge the following individuals for reviewing the papers submitted for publication:

1. Aina Mariana Abdul Manaf
2. Astri Khairana Wardhani
3. Awal Prasetyo
4. Azarinah Izaham
5. Chai Har Loo
6. Cheng Wei Li
7. Elaheh Ainy
8. Glen Alvin
9. Hannan Shahabuddin
10. Haris Abdul Rahman
11. Kwai Meng Pong
12. Kwang-Sheng Ng
13. Lailatul Imtikhan
14. Mahayuddin Abdul Manap
15. Mohd Azmi Bin Suliman
16. Muhd Syafi Abd Bari
17. Muri Mohd Zain
18. Nazimah Idris
19. Noor Azlin Azraini Che Soh
20. Nor Azam Kamaruzaman
21. Saiyidah Adila Adibi
22. Salwana Abu Bakar
23. Sharif Ahmad
24. Shelva Meena Gurusamy
25. Siti Aishah Abdul Aziz
26. Syadwa Abdul Shukor
27. Teck Hock Toh
28. Tim Aung
29. Wulan Fadinie