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Overview of paediatric cataract in Malaysia

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ABSTRACT

Paediatric cataract is a leading cause of preventable childhood visual impairment in Malaysia. Despite a relatively strong healthcare system, delayed diagnosis and referral, particularly in rural areas, remain major challenges affecting visual outcomes. The condition may be congenital or acquired, with causes including genetic disorders, infections, metabolic diseases, and trauma. Surgical treatment, mainly lens aspiration with or without intraocular lens implantation, is effective, but visual prognosis depends on early intervention and adherence to amblyopia therapy. Malaysian studies show improved surgical outcomes, yet late presentation often leads to irreversible amblyopia. Strengthening screening programs and early referral systems is essential to reduce childhood blindness.

KEYWORDS:
Paediatric cataract; Malaysia; cataract surgery; amblyopia; visual outcomes

INTRODUCTION

Paediatric cataract constitutes a critical global health imperative, universally recognized as a leading cause of preventable childhood blindness. In alignment with the World Health Organization's mandate to eliminate avoidable visual impairment, addressing untreated lens opacities is of paramount importance, as they severely impede a child's sensory, cognitive, and educational development.[1,2]

Prevalence

Paediatric cataract is an important cause of avoidable childhood blindness in Southeast Asia, where disparities in healthcare access, socioeconomic conditions, and public health infrastructure contribute to variations in disease prevalence and treatment outcomes. The prevalence of paediatric cataract in Southeast Asia is estimated to range between 0.6 and 13.6 cases per 10,000 children, with higher burdens generally observed in lower-resource settings.[2-4] Available Malaysian hospital-based studies suggest that the prevalence of paediatric cataract in Malaysia is comparable to other Southeast Asian countries, with estimates generally ranging from 1 to 15 cases per 10,000 children.[5-8]

Causes

Unlike in developed countries, where hereditary and idiopathic causes predominate, paediatric cataract in low- and middle-income nations is frequently associated with preventable environmental and systemic factors.[2] The aetiology may be congenital or acquired, unilateral or bilateral, and often reflects the socioeconomic and healthcare conditions of the population.

One of the major causes in developing countries is congenital infection, particularly rubella infection during pregnancy. Maternal rubella remains an important public health problem in countries with incomplete immunization coverage, and congenital rubella syndrome commonly presents with cataract, hearing impairment, and cardiac defects. Other TORCH infections, including toxoplasmosis, cytomegalovirus, herpes simplex virus, and syphilis have also been implicated in congenital cataract formation.

Traumatic cataracts occur more frequently than in developed nations because children are often exposed to unsafe environments, inadequate supervision, hazardous play activities, agricultural tools, sharp objects, and occupational risks associated with child labour.[8,9] Boys are generally more affected than girls due to greater participation in outdoor and high-risk activities. The injuries frequently induce severe, concurrent structural damage to the anterior segment, significantly complicating surgical interventions. 69% of these paediatric patients exhibiting a presenting visual acuity of worse than 6/60, a factor that severely compromises their long-term visual prognoses and necessitates immediate, complex rehabilitative care.[8]

Late Presentation

Late presentation remains a major challenge in developing countries, including Malaysia, and is one of the principal causes of poor visual outcomes and preventable childhood blindness.[5-12] Early diagnosis and timely surgical intervention are essential because delayed treatment during the critical period of visual development can result in irreversible deprivation amblyopia, strabismus, nystagmus, and permanent visual impairment.

Delayed presentation is commonly associated with poor awareness among parents and caregivers regarding the signs and urgency of childhood cataract. Leukocoria, poor fixation, wandering eyes, and visual inattentiveness may not be recognized early, particularly in rural communities with limited health literacy. Financial difficulties, transportation barriers, long distances to tertiary eye centres, and shortages of paediatric ophthalmologists further contribute to delayed referral and treatment.[5-12]

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In Malaysia, delayed presentation of paediatric cataract continues to be reported despite improvements in tertiary ophthalmology services.[5-8] A ten-year review conducted at Hospital Pakar Universiti Sains Malaysia in Kelantan reported that delayed diagnosis and referral were persistent problems among paediatric cataract patients.[6] Muhd-Syafi et al noted that socioeconomic factors, reduced healthcare accessibility, and inadequate awareness among caregivers contributed significantly to late presentation.

Children who presented late frequently experienced poorer visual outcomes despite surgical intervention because amblyopia had already developed.[6] Likewise, studies from Hospital Kuala Lumpur and Hospital Malacca demonstrated that postoperative visual outcomes were strongly influenced by the timing of presentation and surgery.[5,7]

Surgical Intervention

The primary goal of surgery is to clear the visual axis to prevent irreversible deprivation amblyopia while ensuring long-term visual rehabilitation through optical correction and amblyopia therapy. Paediatric cataract surgery is more complex than in adults because of ongoing ocular development, smaller ocular dimensions, reduced scleral rigidity, highly elastic lens capsule, a stronger inflammatory response, and a higher risk of postoperative complications.[13-15]

Therefore, surgical timing, technique, and postoperative management must be carefully individualized based on age, laterality, and cataract density. The standard surgical approach is lens aspiration or phacoaspiration with or without intraocular lens (IOL) implantation. In infants under 6 months, many surgeons prefer leaving the child aphakic with contact lens or spectacle correction due to concerns about ocular growth and refractive unpredictability.

In children above the age of 2 years old, primary IOL implantation is more commonly performed. A critical component of paediatric cataract surgery is anterior vitrectomy, especially in younger children, to reduce the risk of visual axis opacification caused by posterior capsule opacification, which is far more common in children than in adults.[13,14]

In developing countries, barriers such as limited surgical expertise and lack of paediatric anaesthesia services can negatively affect surgical outcomes.[12-15] Nevertheless, advancements in microsurgical techniques, improved IOL design, and expanded paediatric ophthalmology training have significantly improved prognosis over the past two decades.

Postoperative Management

Postoperative care is equally important and includes intensive anti-inflammatory therapy, regular follow-up, refractive correction, and amblyopia management through patching or penalization therapy. Without strict adherence to postoperative amblyopia treatment, visual outcomes may remain suboptimal even after technically successful surgery. Long-term follow-up is required because children are at risk of complications such as glaucoma, visual axis opacification, retinal detachment, and IOL-related issues.

Visual Outcomes

In many developing countries, visual outcomes after paediatric cataract surgery are frequently suboptimal because children often present late, when amblyopia is already established.[16,17] Even when surgery is technically successful, long-term visual acuity may be limited by irreversible sensory deprivation. Studies from South Asia and Sub-Saharan Africa consistently report that a significant proportion of operated children achieve only moderate vision (6/18 to 6/60 or worse), particularly in cases of bilateral dense congenital cataracts.[12-14]

In Malaysia, visual outcomes are generally better than in many other developing countries due to improved access to tertiary eye care, availability of paediatric ophthalmologists, and more standardized surgical protocols.[5-8] Paediatric cataract surgery is primarily performed in tertiary centres such as Hospital Tuanku Azizah, Hospital Kuala Lumpur, Hospital Pakar Universiti Sains Malaysia, Universiti Malaya Medical Centre, and other major government hospitals with paediatric ophthalmology services. Factors influencing outcomes in Malaysia include age at surgery (earlier intervention leads to significantly better vision), type of cataract (unilateral congenital cataracts have worse prognosis than bilateral cases), consistency of amblyopia therapy follow-up and presence of complications such as PCO or glaucoma.[5-8]

Challenges

Challenges in Malaysia include delayed referral from primary care, variability in access to paediatric ophthalmology services in rural areas, and inconsistent follow-up compliance, particularly for amblyopia management. This non-compliance is frequently exacerbated by financial constraints, logistical challenges, and low health literacy prevalent in rural communities.[8]

However, improvements in healthcare infrastructure, expansion of ophthalmology training, and increased awareness among healthcare providers have contributed to better surgical outcomes over time. National eye health initiatives and newborn screening programs are also expected to improve early detection and timely surgical intervention in the future.

CONCLUSION

In Malaysia, visual outcomes following paediatric cataract surgery are promising, largely reflecting a more developed healthcare system. Nevertheless, late diagnosis and delayed intervention continue to be the primary factors associated with poor postoperative visual outcomes.

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ORIGINAL ARTICLE

Health-related quality of life of people living with HIV in a Malaysian state hospital during the COVID-19 pandemic

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ABSTRACT

Introduction: Assessing health-related quality of life (HRQOL) promotes understanding well-being of people living with HIV (PLHIV). This study aims to determine factors influencing HRQOL.

Materials and Methods: The cross-sectional study used a self-administered questionnaire among PLHIV receiving treatment in HIV clinic of a state hospital in Perlis, Malaysia. Potential subjects were approached in the waiting areas during routine clinic visits. The Malay questionnaire consists of WHOQOL-HIV BREF, EQ-5D-5L and EQ-VAS. Multiple linear regressions (MLRs) were used to identify independent predictors of HRQOL, and Spearman's correlations assessed the relationships between instruments.

Results: There were 88 participants in this study (mean age 43.5±13.1 years; 63.6% male). All were on antiretroviral therapy with undetectable viral loads. The mean overall WHOQOL score was 74.9±13.1 (on a 0–100 scale), EQ-5D index 0.90±0.13, and EQ-VAS 88.5±13.2. Each one-year increase in age was associated with a 3.3-point (β≈+3.3) higher WHOQOL score and middle-range household income of MYR3171-3970 (≈USD757-948 as of 1 USD=4.188 MYR) was linked to higher WHOQOL(β≈+8.7). In contrast, part-time employment corresponded to a lower WHOQOL(β≈–7.4). Having tertiary education and high income >MYR4850 (≈USD1158) were associated with lower EQ-VAS (β≈–10.3 and –16.0, respectively). An HIV transmission mode other than sex and intravenous drug use predicted significantly lower scores across all three HRQOL indicators. WHOQOL had a moderate positive correlation with EQ-5D (r=0.421) and a weaker correlation with EQ-VAS (r=0.265).

Conclusion: PLHIV in Perlis, Malaysia reported generally good HRQOL despite the COVID-19 pandemic. Higher age and moderate income were associated with better WHOQOL, whereas higher education and income paradoxically lowered self-rated health (EQ-VAS). Multi-dimensional assessment (WHOQOL, EQ-5D, EQ-VAS) revealed consistent trends and underscores the importance of holistic care for PLHIV in pandemic conditions.

KEYWORDS:
Quality of life, HIV infections, pandemics, health status, ambulatory care

INTRODUCTION

The COVID-19 pandemic affects people living with HIV (PLHIV)'s healthcare needs and mental wellbeing. PLHIV require lifelong medical management, making regular appointments essential to treatment adherence.[1] However, stay-at-home orders may interrupt medical treatment. Non-urgent medical follow-ups such as HIV may be postponed to minimise the overcrowding of hospitals. Moreover, being immunocompromised, PLHIV might have fear and anxiety about contracting COVID-19.[1] PLHIV could be harmed due to a strong stress response if they cannot adapt to the 'new normal' and succumb to the wrong coping mechanism. Besides the existing stigma separated from the community, physical distancing practices may further make PLHIV feel lonely and depressed.[1]

Health-related quality of life (HRQOL) is a patient-reported outcome reflecting the well-being and daily functioning.[2] To fully capture HRQOL in PLHIV, especially during COVID-19, we employed a combination of HIV-specific and generic measurement tools. The World Health Organisation Quality of Life (WHOQOL) questionnaire was adapted into anabbreviated version (WHOQOL-BREF), which was later developed into WHOQOL-HIV BREF, for PLHIV.[3] The WHOQOL-HIV BREF contains 31 items and has an extra five items specific to PLHIV.[4] The domains include physical needs, spirituality, psychological, environmental and social relationships.

In parallel, the EuroQOL-5 Dimension 5-Level (EQ-5D-5L) instrument provides a generic health status index.[5] It measures the five dimensions of life: mobility, self-care, usual activity, pain/discomfort and anxiety/depression. This yields a single utility value reflecting overall health, which is valuable for cost-effectiveness analyses and comparison across diseases.[6] In complement with EQ-5D-5L is the EuroQol Visual Analogue Scale (EQ-VAS). EQ-VAS records the respondents' self-perceived health on a vertical scale, with a value ranging from 0 to 100, on the health felt by patients on that day. Zero is the worst condition felt by patients and vice versa.

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The government's budget and human resources restrictions to combat any pandemic may impact other healthcare affairs, such as HIV/AIDS management. This is primarily because the same healthcare workers manage both diseases: the infectious disease (ID) team. By using all three instruments, a multidimensional profile of each patient's HRQOL can be obtained.[3] The WHOQOL-HIV BREF offers depth in quality-of-life domains specific to HIV, the EQ-5D-5L offers breadth and a standardised index of health, and the EQ-VAS captures the patient's subjective overall health in a single score. This combined approach is particularly important given the pandemic's potential impacts on both general health and the specific well-being of PLHIV. There is a lack of published studies investigating the three measures simultaneously on PLHIV in Malaysia. Therefore, this study aims to determine the factors influencing HRQOL among PLHIV during the COVID-19 pandemic, using these complementary tools, and to examine how the instruments' outcomes correlate with each other.

MATERIALS AND METHODS

This was a cross-sectional study using a self-administered questionnaire among adult patients receiving outpatient treatment in the Perlis state hospital HIV clinic. Patients who were unable to read Malay were excluded. Convenient sampling was employed on all patients during routine clinic visits from August 2021 to March 2022, capturing HRQOL during the later phases of the COVID-19 pandemic. The counsellors approached and introduced potential subjects (PLHIV) to the investigators in the waiting areas to be seen by the doctors. Those interested were invited to a private counselling room and briefed on the study before obtaining informed consent.

The Malay questionnaire consists of four sections: sociodemographics, clinical status, WHOQOL-HIV BREF (Malay version),[7] EQ-5D-5L and EQ-VAS (using the Malaysian population value set for EQ-5D scoring).[8] Sociodemographic data included age, gender, ethnicity, marital status, education, employment and monthly household income. Household income was categorised according to Malaysian national tiers: B40 (bottom 40%), M40 (middle 40%) and T20 (top 20%). For more detailed analysis, B40 was subdivided into B1–B4 income bands (with B1 as the lowest); however, due to sample size constraints, we combined all higher-income respondents into a single "M40&T20" category for regression models. Clinical variables (from medical records, confirmed by patients) included age at diagnosis, duration of HIV infection, WHO clinical stage, antiretroviral regimen type, duration on therapy, viral load and opportunistic infections. The survey took 10-15 minutes to complete. The study was registered in the Malaysian National Medical Research Register (NMRR-21-1549-60908) and approved by the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia prior to the conduct of the study.

Sample size was calculated using the population mean formulae.[9] Previous data indicate that the mean overall WHOQOL was 3.22±0.66,[5] and the population size of our HIV clinic is 200. If the Type I error probability and precision are 0.05 and 0.05, 49 samples were required. With an additional 20% dropout rate, the sample size is 62. The power of the study was 91.0% based on a minimum detectable effect (MDE) of 0.5 and n=62.[10] The data were analysed using SPSS version 20.0 (IBM Corp., Armonk, NY). Descriptive statistics were performed. Simple and multiple (stepwise inclusion of all variables) linear regressions (SLRs and MLRs) were conducted to identify the factors influencing WHOQOL, EQ-5D index and EQ-VAS scores. Spearman's rank correlations analysed the relationship between the three HRQOL measures. The strength of correlations was determined by r <0.3 as weak, 0.3-0.5 as moderate and >0.5 as strong.[11]

RESULTS

Of the 88 respondents recruited, all of them (100%) were free from any opportunistic infection, on a highly active antiretroviral therapy (HAART) regimen and had an undetectable viral load (<50 copies/mL) and WHO Stage I (asymptomatic) of HIV infection, indicating a well-controlled cohort. All participants in our sample were on highly active antiretroviral therapy. Participants had been diagnosed for a median of 6.5±3.5 years and were either on first- or second-line therapy. Most respondents were male (63.6%), Malay (76.1%), married (62.5%), secondary school leavers (51.1%), unemployed (44.3%), 77.3% had household income of less than MYR 2500 (bottom 40% or B40 group, ≈<USD 597) and contracted HIV through sex (47.7%). The mean age was 43.5±13.12 years, ranging from 21 to 68 years old. The mean WHOQOL score was 74.9±13.06 (on a 0–100 scale), with a domain mean score of 16.4±2.97 (physical health), 14.5±3.57 (spirituality), 14.4±2.48 (psychological health), 14.5±3.30 (environment) and 15.1±3.92 (social relationship), respectively, on a 4–20 domain scale.

The mean EQ-5D score was 0.9±0.13 (on a 0–1 utility scale). Most respondents had no problem in mobility (n=77, 87.5%), self-care (n=86, 97.7%), usual activities (n=80, 90.9%) and no pain/discomfort (n=71, 80.7%). While 58 respondents (65.9%) had no anxiety/depression, a sizable proportion of 24 respondents (27.3%) claimed slightly anxious or depressed as the best description of their health that day. The mean EQ-VAS (self-rated health) was 88.5±13.19 (0–100 scale), indicating generally high perceived health.

For linear regressions, B40 was dropped, and M40 and T20 were combined into a new income category of "M40&T20". In SLRs (Table I), several sociodemographic factors showed significant associations with HRQOL outcomes. For instance, ethnic Malay PLHIVs had higher scores in all three measures (WHOQOL, EQ-5D and EQ-VAS) compared to non-Malays (e.g., β for WHOQOL=+6.8 points, p=0.037). Having a tertiary education was significantly associated with a lower EQ-VAS (unadjusted β≈–8.0, p=0.014, versus no formal education). Retirees reported higher WHOQOL than those employed full-time. Notably, the mode of HIV transmission influenced HRQOL: patients whose infection route was "Others" (neither sex nor intravenous drug use) had significantly lower scores in all metrics (e.g., WHOQOL –6.8 points, p=0.037).

The MLR analysis (Table II) identified several significant predictors after controlling for overlapping factors.. Age remained a significant positive predictor of WHOQOL: each additional year of age was associated with a 3.3-point

Table I: Top 10 medicines returned by acquisition cost

Tablet	Quantity (Tab/Cap)	AC (RM)/Tab	Total AC (RM)	RP (RM)/Tab	Total RP (RM)
Trimetazidine 35mg MR (I)	4,475	0.30	1,351.00	1.62	7,249.50
Metformin 500mg (G)	17,041	0.08	1,344.53	0.16	2,726.56
Atorvastatin 20mg (G)	8,238	0.13	1,070.12	0.93	7,661.34
Ferrous Fumarate 200mg (G)	4,493	0.21	943.53	0.56	2,516.08
Clozapine 100mg (I)	754	0.91	687.20	3.75	2,827.50
Metoprolol Tartrate 100mg (G)	3,294	0.18	582.05	0.39	1,284.66
Pantoprazole 40mg (G)	3,003	0.19	557.66	3.4	10,210.20
Fenofibrate 145mg (I)	839	0.58	485.86	4.41	3,699.99
Calcitriol 0.25mcg (G)	1,837	0.26	477.44	1.58	2,902.46
Prazosin 2mg (G)	2,564	0.18	452.55	0.54	1,384.56

AC: Acquisition cost, RP: Retail price

increase in the WHOQOL score (adjusted β=3.3, 95% CI: 1.3 to 5.2, p=0.001). In contrast, age was not an independent predictor of EQ-5D or EQ-VAS in the final model. Education level and income impacted the self-rated health measure of EQ-VAS: having a tertiary education was associated with a 10.3-point lower EQ-VAS (95% CI: –16.2 to –4.4, p=0.001) compared to no formal education. Belonging to the highest income group (combined M40/T20, monthly income >MYR 4850) was also linked to a substantial decrease in EQ-VAS (–16.0 points) relative to the lowest-income group (B40) (p=0.023). Interestingly, an intermediate-income B40 subgroup (MYR 3171–3970) showed a positive association with WHOQOL (≈+8.7 points vs. lowest income, p=0.037), suggesting a non-linear income–QOL relationship.

Employment status was significant: participants working part-time had a WHOQOL score ≈7.4 points lower than those employed full-time (95% CI: –14.2 to –0.5, p=0.035), after adjustment. Finally, the mode of HIV transmission remained a consistent predictor: infection via routes other than sex or intravenous drug use negatively influenced WHOQOL, EQ-5D and EQ-VAS, resulting in lower scores across all HRQOL measures (adjusted β=–5.5 for WHOQOL, –0.10 for EQ-5D index and –12.2 for EQ-VAS; all p<0.05).

Correlation analysis (Table III) revealed that the overall WHOQOL was positively correlated with both generic measures. This association was moderate in strength with the EQ-5D index (r=0.421, p<0.001) and weak with the EQ-VAS (r=0.265, p=0.013). (By convention, r ≈0.3–0.5 indicates a moderate correlation.) The EQ-5D index and EQ-VAS had a smaller, non-significant correlation with each other (r=0.201, p=0.062).

At the domain level, higher WHOQOL physical domain scores were significantly associated with less problems in certain EQ-5D dimensions (e.g., fewer pain/discomfort issues, r=–0.294, p<0.01) and with better overall EQ-5D and EQ-VAS scores (r=0.380 and 0.323, respectively, p<0.01). Similarly, the spirituality domain showed a positive correlation with overall EQ-5D and EQ-VAS (both p<0.01) and a negative correlation with EQ-5D anxiety/depression (r=–0.300, p<0.01). Other WHOQOL domains (psychological, environment, social relationships) followed the pattern of higher QOL linked to fewer daily activity limitations, less pain/anxiety, and better EQ-5D/EQ-VAS scores. Notably, EQ-VAS had a significant inverse correlation only with the EQ-5D "usual activities" dimension (r=–0.252, p=0.016), suggesting that patients who reported more ability to engage in usual activities also felt healthier on the VAS scale.

DISCUSSION

Including various sociodemographic factors and the interaction between those factors revealed a more nuanced understanding of the HRQOL of PLHIV using MLR, as evidenced by the discrepancies in the predictive power of various factors from SLR to MLR. For example, ethnicity distinctions were associated with variations in HRQOL outcomes in SLR. However, after controlling for interrelated sociodemographics, ethnicity was no longer a determinant.

Increasing age emerged as a significant predictor of better WHOQOL in our study. This finding contrasts with the general expectation that ageing might worsen HRQOL due to declining health.12,13 In fact, our data suggest that older PLHIV in Perlis had higher quality-of-life scores (approximately +3 points on WHOQOL per year of age, holding other factors constant). This positive association aligns with evidence that long-term survivors develop effective coping mechanisms and resilience over time.[14] It is possible that older individuals have come to terms with their condition and benefit from stable routines in care, thereby reporting higher HRQOL.

Socioeconomic factors also played a nuanced role. Higher income generally facilitates better healthcare access and support, which would intuitively improve HRQOL.[15] Consistent with this, participants in the middle-income range (upper B40 tier) showed improved WHOQOL scores compared to the lowest-income group. However, intriguingly, those in the highest income bracket (M40/T20) reported lower self-rated health (EQ-VAS) despite presumably better material resources. One explanation could be that higher socioeconomic status is associated with greater health awareness and expectations, leading individuals to judge their health more critically.[16] Similarly, higher education (tertiary level) was linked to a lower EQ-VAS in our study. Educated patients might be more cognizant of their health limitations or more stressed by health-related issues, thus ranking themselves lower on the subjective health scale. These counterintuitive findings underscore that objective health status and subjective perceptions do not always align, and they highlight the value of using multiple instruments to capture these dimensions.

Employment status had a clear impact on HRQOL: being employed part-time was associated with notably worse WHOQOL scores compared to full-time employment. We suspect that part-time workers may experience financial insecurity or underemployment stress, which adversely affects their quality of life. Additionally, stigma in the workplace could disproportionately affect those in unstable job situations.[17] This suggests the need for workplace policies and support systems tailored to PLHIV, as stable employment appears to be protective for their QOL.

Our results confirmed that HIV transmission mode influences patients' well-being. Those infected via less common routes ("Others") had significantly lower scores across all HRQOL measures, even after controlling for other factors. This extends findings from earlier studies, which reported mixed effects of transmission route on mental and physical health.[18] In the Malaysian context, where HIV stigma remains pervasive, this category may arguably capture individuals who, fearing moral judgment and discrimination, choose not to disclose sexual or drug-related transmission routes. This reluctance to disclose underscores the deep-seated social stigma surrounding HIV in Northern Malaysia, a situation likely exacerbated by the social isolation and reduced access to peer support networks during the COVID-19 pandemic. Consequently, these individuals may carry a heavier psychological burden, lacking the community validation available to specific subgroups.

Finally, the correlations among WHOQOL, EQ-5D and EQ-VAS in our study provide insight into how these instruments converge and differ. WHOQOL-HIV BREF is an HIV-specific instrument[7] and theoretically more sensitive, hence the significant (albeit weak) correlations with other health indicators. The moderate correlation between WHOQOL and EQ-5D indicates that patients with better HIV-specific quality of life also tend to have better general health status. This is logical, as good physical health and functional ability (captured by EQ-5D) likely contribute to a higher quality of life. On the other hand, the weaker correlation with EQ-VAS suggests that the subjective health rating captures additional variability, e.g., momentary feelings or psychosocial factors, not fully accounted for by the more structured questionnaires. In fact, EQ-VAS had only a slight (non-significant) relationship with EQ-5D in our data, echoing that a single self-rated health score can diverge from multi-domain health indices.

While these measures are related, they are distinct constructs that capture different aspects of patient well-being. This highlights the need for a holistic approach to patient care that addresses all facets of health. As physical needs are met, PLHIV may experience less pain/discomfort and anxiety/depression, leading to an improvement in their overall EQ-5D and EQ-VAS. The spirituality domain's positive correlation with overall EQ-5D and EQ-VAS points to the potential protective role of spiritual well-being in enhancing quality of life and self-perceived health among HIV patients, especially in managing anxiety and depression.[19]

The findings on psychological health were consistent with the literature,[20] which indicates that good psychological health can reduce anxiety/depression and enhance overall EQ-5D and EQ-VAS. The environment domain suggests that a supportive environment can help reduce anxiety/depression and improve the overall EQ-5D of PLHIV. The social relationships domain's negative correlation with usual activities, pain/discomfort, and anxiety/depression emphasises the importance of social support in alleviating physical and psychological distress.[21] EQ-VAS only showed a negative correlation with usual activity. This suggests that the more usual activities PLHIV can engage in, the better their EQ-VAS. Together, these patterns reinforce that while all three tools measure aspects of health/quality of life, each instrument taps into distinct facets of a patient's experience. Hence, a multi-instrument approach provides a more comprehensive assessment than any single measure alone.

One strength of our study was the concurrent use of an HIV-specific HRQOL instrument alongside two generic health measures. The findings demonstrate the value of this multi-instrument approach. The WHOQOL-HIV BREF provided rich detail on domain-specific HRQOL, uncovering areas like spirituality and social relationships that influence perceived health. The EQ-5D-5L, in contrast, distilled health status into a single utility index and highlighted functional issues (e.g., pain or anxiety) that align with HRQOL. Meanwhile, the EQ-VAS captured patients' overall self-rated health, which can be influenced by momentary feelings or psychosocial factors. By integrating these tools, we gained a more comprehensive view than any single measure could offer. For instance, we observed that participants with high WHOQOL scores generally had high EQ-5D indices, indicating consistent reporting of good health. However, some high-HRQOL individuals gave lower EQ-VAS ratings, suggesting that subjective perception can differ from measured domains. Such insights are important: they remind us that a patient might score well on structured domains yet still feel "not so healthy" overall, or vice versa. Using multiple instruments also allowed cross-validation of results; the moderate correlations provide reassurance that all tools are capturing an underlying construct of HRQOL, even as each highlights different aspects. In practice, our approach highlights that holistic care for PLHIV should monitor both domain-specific quality of life and general health status. Interventions can then be tailored: e.g., if a patient has good clinical health (high EQ-5D) but low perceived health (EQ-VAS), psychological or social support might be needed. Conversely, if WHOQOL domains point to specific deficits (like poor social relationships), targeted community or counselling interventions can be implemented.

This study is not without its limitations. Considering our respondents were stable patients, it did not adequately reflect the health indicators of other patients with greater disease severity. The findings of this study open several avenues for future research. Longitudinal studies could provide insights into how WHOQOL, EQ-5D and EQ-VAS change over time in response to different interventions or changes in circumstances. Intervention studies could be designed, such as implementing programmes to enhance social relationships, provide a supportive environment or meet physical needs to address the factors influencing WHOQOL, EQ-5D and EQ-VAS. Expanding the study population to include PLHIV in other regions of Malaysia would determine if the findings hold true in different cultural or healthcare

contexts. Additionally, in-depth qualitative studies could provide a deeper understanding of the lived experiences of PLHIV.

The study's findings also have significant implications for policy advocacy. To enhance WHOQOL and EQ-VAS for PLHIV, policy efforts should aim to provide comprehensive support services that address not only medical needs but also the socioeconomic determinants of health. Future interventions could include programs tailored to improve employment opportunities for PLHIV, thereby addressing the association of part-time employment with decreased WHOQOL. Financial assistance programs could be revisited to provide additional support to those in lower-income brackets, mitigating the impact of economic constraints on quality of life.

The study indicates a need for targeted health education and psychological support services, particularly addressing modes of HIV transmission that are less common than sexual transmission and intravenous drug use. These modes seem to negatively impact all three health indicators, possibly due to associated stigma or lack of tailored support. Social inclusion should also be cultivated by reducing stigma and discrimination. These policies could address the factors influencing the WHOQOL, EQ-5D and EQ-VAS of PLHIV. Collaborative efforts with policymakers, healthcare providers and community organisations are essential for successful policy advocacy, especially in emphasising the inclusion of mental health services within the treatment plan for PLHIV, hence encouraging a biopsychosocial approach.

CONCLUSION

HIV patients in Perlis, Malaysia, had a good HRQOL amid the COVID-19 pandemic. An increase in age without working part-time increased WHOQOL only. An increase in income increased WHOQOL but decreased EQ-VAS. Mode of transmission other than sex and IVDU decreased all three health indicators. WHOQOL had significantly moderate correlations with EQ-5D but weakly correlated with EQ-VAS.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Cervical cancer survival rate after abdominal vs. laparoscopic radical hysterectomy in two government hospitals in Jakarta, Indonesia

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ABSTRACT

Introduction: Cervical cancer ranks among the top ten globally. Its five-year survival rate is 67.9% across all stages. In Indonesia, laparoscopic radical hysterectomy (LRH) is gaining traction but remains less common than abdominal radical hysterectomy (ARH). Limited research exists on cervical cancer survival rates in Indonesia. Our study compared ARH to LRH survival rates for cervical cancer patients.

Materials and Methods: We reported a retrospective study that included 275 patients of all cervical cancer stages who met inclusion criteria from 2015 to 2019 in two of Jakarta's national teaching hospitals. The patients underwent ARH or LRH, radiotherapy, and chemotherapy and were observed for five years. Univariate and multivariate analyses were performed to investigate survival rates.

Results: 236 patients underwent ARH, and 39 patients underwent LRH. The median survival of LRH and ARH were 23.9 months and 29.6 months, respectively. The five-year survival rates of LRH and ARH patients were 75.0 % and 83.5%, respectively. The early-stage survival rate was higher than in the advanced stage (76.7% vs. 73.5%, p=0.006). Cox multivariate modelling determined that surgical approach (ARH vs. LRH) (HR: 2.3; 95% CI: 1.2 - 4.5; p = 0.01) and cancer stage (HR: 1.9; 95% CI: 1.18 – 2.92; p = 0.007) were significant factors.

Conclusion: The higher cancer stage resulted in a lower five-year survival rate. In this limited sample study, LRH demonstrated an inferior five-year survival rate compared to ARH.

KEYWORDS:
Uterine cervical neoplasms, survival, radical hysterectomy, laparoscopy, Indonesia

INTRODUCTION

Globally, cervical cancer is one of the ten most diagnosed cancers in the world. It is estimated that there were 662,301 (3.3%) new cases and 348,874 (3.5%) deaths in 2022. Of all the reported cases worldwide, 60% of all new cases were from Asia, with a 5-year prevalence of 1,186,812 (60,9%) cases.[1] In Indonesia, cervical cancer ranked third highest for incidence with 36,964 (9.0%) new cases and ranked fourth for mortality with 20,708 (8.5%) deaths in 2022.[2,3] According to national data from the Indonesian Society of Gynaecologic Oncology (INASGO), cervical cancer remains the leading cause of all gynaecologic cancer cases in Indonesia. Notably, the majority of patients fall within the middle age group (ages 36-55), with a predominant stage of IIIB and a histotype primarily identified as squamous cell carcinoma.[4]

The disparity in cervical cancer incidence and mortality between developed and developing countries remains substantial. In high-income settings, sustained reductions have been achieved through effective screening, follow-up, and timely treatment, whereas many low- and middle-income countries continue to face persistent barriers to implementing these measures.[5] In Indonesia, survival data are difficult to obtain because follow-up systems and patient compliance remain inadequate, and only limited studies have reported cervical cancer survival outcomes.[6] In addition, laparoscopic radical hysterectomy (LRH) is not routinely performed in Indonesia, likely due to the high proportion of patients diagnosed at an advanced stage and the greater cost and technical complexity of LRH compared with abdominal radical hysterectomy (ARH), with limited public insurance support in many hospitals.

Minimally invasive radical hysterectomy (including LRH) gained popularity because it can reduce perioperative morbidity and shorten recovery compared with open ARH. However, oncologic safety concerns were raised after the phase III Laparoscopic Approach to Cervical Cancer (LACC) randomized trial demonstrated inferior survival with minimally invasive radical hysterectomy versus open surgery in early-stage cervical cancer (4.5-year disease-free survival 86.0% vs 96.5%), with increased hazards for recurrence or death (HR 3.74) and overall mortality (HR 6.00).[7] Subsequent large observational cohorts, including Surgery in Cervical Cancer, Observational, Retrospective (SUCCOR), reported higher relapse and death rates after minimally invasive approaches than after open radical hysterectomy, reinforcing

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Table I: Patient characteristics divided by surgical procedure

Characteristics	Laparoscopy n (%)	Abdominal n (%)
n (%)	26 (17.8)	120 (82.2)
Age (y)		
<50	13 (50.0)	76 (63.3)
≥50	13 (50.0)	44 (36.7)
Parity		
Nulliparity	5 (19.2)	16 (13.3)
Primiparity	0 (0.00)	17 (14.2)
Multiparity	21 (80.8)	87 (72.5))
Cancer Stage		
Early stage	26 (66.6)	120 (50.8)
Tumour size		
< 2 cm	21 (80.8)	95 (79.2)
≥ 2 cm	5 (19.2)	25 (20.8)
Histotype		
SCC	20 (76.9)	74 (61.7)
Adenocarcinoma	6 (23.0)	38 (31.7)
Adenosquamous	0 (0.0)	8 (6.7)
Differentiation		
1	3 (11.5)	36 (30.0)
2	19 (73.1)	74 (61.7)
3	4 (15.4)	10 (8.3)
Lymph Node extraction		
(mean±SD)	21.92±8.96	18.62±8.9
Min-Max	4-37	0-43

Table II: The five-year survival rate of all-stage cervical cancer patients

Factors	aFive-year survival Rate	bp-value
All		
Laparoscopy	76.9%	0.942
Abdominal	76.7%	
Age (y)		
<50	82.5%	0.053
≥50	69.7%	
Parity		
Nulliparity	44.4%	0.803
Primiparity	88.9%	
Multiparity	80.7%	
Tumour size		
< 2 cm	81.9%	0.753
≥ 2 cm	80.0%	
Histotype		
SCC	75.0%	0.709
Adenocarcinoma	78.6%	
Adenosquamous	87.5%	
Differentiation		
1	73.3%	0.242
2	81.8%	
3	66.7%	

Notes: [a]Data are % (95% confidence interval); blog rank test; *p-value <0.05; SCC = squamous cell carcinoma.

Table III: Estimated hazard ratio of cervical cancer

Characteristics	Adjusted HR	95%CI HR	[a]p-value
Age (years)	1.94	0.978 – 3.83	0.58
Parity	0.83	0.25 – 2.80	0.77
Tumor size	2.02	0.98 – 4.15	0.06
Histotype	1.74	0.22 – 13.72	0.60
Differentiation	1.25	0.50 – 2.99	0.23
Lymph Node extraction	1.1	0.92 – 1.02	0.96
Surgical Approach	1.04	0.43 – 2.50	0.942

Notes: alog-rank test; *p-value < 0.05; CI = confidence interval; HR = hazard ratio

the need for real-world evaluation.[8] In light of this evidence, contemporary guidance and reviews describe open ARH as the standard approach for radical hysterectomy in cervical cancer, while ongoing work investigates whether specific techniques or carefully selected low-risk subgroups may mitigate risk.[9] Accordingly, this study aimed to compare oncologic outcomes between cervical cancer patients undergoing LRH and ARH in two centres.

MATERIALS AND METHODS

We conducted a retrospective cohort study of women with early-stage cervical cancer who received primary radical hysterectomy between 1 January 2015 and 31 December 2019. Early-stage disease was defined as FIGO (International Federation of Gynaecology and Obstetrics) stage IB2 or lower. Total sampling was used, including all eligible cases that met the study criteria during the study period. Demographic, clinicopathological, and treatment data were abstracted from medical records. Tumour stage and grade were assigned according to FIGO criteria. Inclusion criteria were early-stage cervical cancer treated initially between 1 January 2015 and 31 December 2019. Records with >50% missing clinical data or documented disease progression before definitive surgery were excluded.

All radical hysterectomies were performed by consultant gynaecological oncologists or by gynaecological oncology fellows under the direct supervision of a consultant gynaecological oncologist. Fellows participated only after meeting institutional competency milestones, and the supervising consultant was scrubbed for critical steps (e.g., parametrial dissection, pelvic lymphadenectomy, vaginal cuff closure) and responsible for intraoperative decision-making and final haemostasis.

We analysed the data using Statistical Package for the Social Sciences (SPSS), employing the Kaplan–Meier method to assess patients' five-year survival rates. The five-year survival rate was defined as the proportion alive 60 months after definitive surgery, counting death from any cause as the event and censoring patients at last contact or 31 January 2022, whichever occurred first. Additionally, logistic regression analysis was conducted where appropriate. We utilised the Cox proportional hazards regression model for univariate and multivariate analyses. The log-rank test was employed to compare prognostic factors in the multivariate analysis. Five-year survival was measured in all cases, survival curves were plotted using the Kaplan–Meier method, and results included the log-rank tests. All statistical analyses were considered significant at $p<0.05$.

This study was reviewed and approved by the Institutional Review Board and Ethics Committee of the Faculty of Medicine, University of Indonesia. Good clinical care guidelines were followed, and the principles of the Declaration of Helsinki were adhered to.

RESULTS

Of 801 records consisting of cervical cancer patients of all stages screened, 203 met the inclusion criteria for early-stage cervical cancer at initial diagnosis; however, some patients were subsequently upstaged to advanced disease based on postoperative histopathology and therefore proceeded to chemoradiation, and these cases were excluded because they no longer met the study criteria. After excluding 57 records due to inadequate follow-up or missing data and removing cases with documented progression before definitive surgery, 146 patients remained for analysis. We used total sampling of all eligible cases and followed patients for up to five years, with outcomes ascertained through 31 January 2022. The cohort comprised women treated between 1 January 2015 and 31 December 2019. Most were aged <50 years (60.9%), multiparous (74%), with squamous cell carcinoma (64.3%) and grade II differentiation (63.7%). Lymph nodes were assessed in 36% of patients. Among surgical approaches, 120 underwent ARH and 26 underwent LRH. Baseline characteristics are summarised in Table I.

The median survival for LRH and ARH was 23.9 months and 29.6 months, respectively. The shortest survival was one day (perioperative death), and the longest observed survival was five years. Across all stages, LRH and ARH patients' five-year survival rates were 75.0% and 83.5%, respectively (Table II). Log-rank testing with chi-squared analysis identified parity, cancer stage, and surgical approach as factors significantly associated with survival (Table II). Cox multivariate modelling indicated that the significant factors were parity (hazard ratio (HR) 0.5; $p<0.01$), cancer stage (HR 1.9; $p=0.007$), and surgical approach (HR 2.3; $p=0.01$) (Table III). Kaplan–Meier survival curves by surgical approach are shown in Figure 1.

DISCUSSION

In this two-centre retrospective cohort, we did not observe a statistically significant difference in overall survival between LRH and ARH. This finding suggests that, within our setting and case mix, LRH achieved oncologic outcomes comparable to open surgery. However, given the retrospective design and the relatively small LRH sample, the absence of statistical significance should be interpreted cautiously, because limited power and residual and residual confounding may mask modest between-group differences.

Our results should be interpreted in the context of an evolving and sometimes conflicting evidence base. High-profile evidence, most notable the randomized LACC trial, reported inferior disease-free and overall survival with minimally invasive radical hysterectomy compared with open surgery for early-stage cervical cancer.[10] In addition, large observational datasets and meta-analyses have reported increased risks of recurrence and death with minimally invasive radical hysterectomy overall.[11,12] Nonetheless, not all real-world studies demonstrated a survival disadvantage, and some multicentre series have reported similar long-term survival between open and minimally invasive approaches, particularly when stratified by tumour size and other risk features.

One plausible explanation for heterogeneity across studies is that technique-related factors may modify oncologic risk in minimally invasive surgery. The SUCCOR study reported

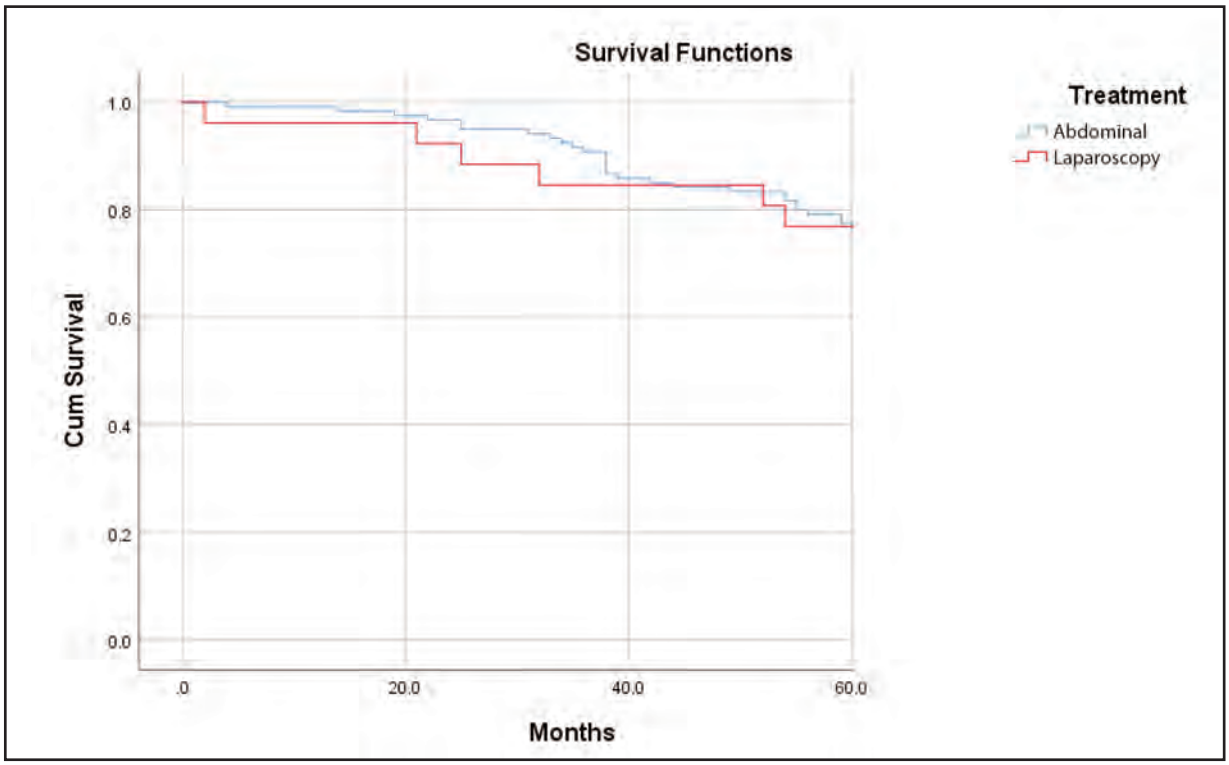

Fig. 1: Five-year survival rate by surgical approach

worse outcomes overall with minimally invasive radical hysterectomy, but suggested that avoiding uterine manipulators and adopting tumour-containment measures at colpotomy could yield outcomes close to open surgery.[13] The "No-look No-touch" technique—which involves vaginal cuff closure, avoidance of uterine manipulators, minimal handling of the cervix, and enclosing the excised organ in a bag—demonstrated progression-free survival and overall survival rates comparable to those of ARH.[14] Furthermore, Chiva et al.'s research indicated that the employment of uterine manipulators could increase the risk of recurrence by 2.76-fold (HR: 2.07; 95% CI: 1.35 to 3.15; p=0.001).[8] These observations support the interpretation that surgical approach alone may not fully explain differences in survival; rather, how minimally invasive radical hysterectomy is performed (and in which patients) may be critical. Finally, the potential impact of surgeon expertise was possibly not fully considered in the LACC trial. Research by Matsuo et al. demonstrated that surgeries performed at high-volume centres were linked to a reduced rate of recurrence and lower overall mortality compared to those conducted at low-volume centres.[15] Additionally, a study by Kim et al. suggested that surgeons who are at the initial stages of mastering minimally invasive radical hysterectomy (MIRH) had poorer progression-free survival (PFS) outcomes than those who are more advanced in their training (5-year PFS, late-stage 100% vs. early 78.2%; p=0.014).[16]

Tumour size and case selection are also frequently cited as effect modifiers. Some studies have suggested that any disadvantage of minimally invasive radical hysterectomy is more apparent in larger tumours, while carefully selected small-volume disease may have comparable outcomes.[17,18] In our cohort, the lack of significant difference between LRH and ARH may reflect selection of LRH for patients with more favourable prognostic features, centre-specific surgical practices, or perioperative pathways that reduce differences between approaches. These factors highlight the importance of reporting detailed operative technique, such as manipulator use, colpotomy method, vaginal cuff closure, and tumour characteristics (e.g. size cut-offs, lymphovascular invasion, and nodal status) when interpreting oncologic outcomes by surgical approach.

Lastly, practice patterns have changed substantially following publication of LACC, with marked reductions in minimally invasive radical hysterectomy rates in some settings. In Indonesia, where LRH adoption has been limited by cost, technical demands, and referral patterns, our findings contribute local data to a global debate and underscore a need for larger, methodically robust studies. Future work should prioritise adequate power, rigorous adjustment for confounding (or propensity-based methods), and explicit documentation of tumour-containment steps, as these may be key determinants of oncologic safety for minimally invasive approaches.

Although we explored several potential prognostic covariates (age, parity, tumour size, histotype, and differentiation), none showed a statistically significant association with overall survival in this early-stage surgical cohort, which is plausible for several reasons. First, case-mix restriction (FIGO ≤IB2) narrows the biological and clinical heterogeneity that often drives prognostic separation; even variables that are prognostic in broader populations can lose discriminatory value when the cohort is limited to surgically treated early-

stage disease. Second, the number of events is typically low in early-stage cohorts, so the study may be underpowered to detect modest effect sizes, particularly for subgroup comparisons (e.g., non-squamous histotypes). This is relevant because tumour size, grade, and histology have repeatedly been linked to outcomes in other settings: tumour size (including 2-cm interval cut points) has been reported as an independent prognostic factor after radical hysterectomy, with larger tumours correlating with other adverse features and the need for adjuvant therapy.[19] Differentiation/grade has also been associated with survival—especially in squamous cervical cancer—although its prognostic signal can be attenuated by interobserver variability and missingness in retrospective datasets.[20,21] For histotype, the literature is mixed: some early-stage series report similar survival between adenocarcinoma and squamous carcinoma after hysterectomy/lymphadenectomy (particularly in node-negative disease), while others find histology contributes to risk stratification; therefore, the lack of significance in our dataset may reflect small numbers in non-squamous categories rather than true equivalence.[21,22] Finally, age and parity may have limited direct prognostic impact once patients are selected for curative surgery; age often operates through comorbidity and treatment tolerance rather than tumour biology, and parity is more consistently associated with risk of developing cervical cancer than with post-treatment survival, which may explain why neither variable emerged as significant here.

This study has several important limitations inherent to its retrospective, medical-record-based design, including incomplete documentation and potential misclassification of clinicopathological variables. Although we used total sampling, a large proportion of screened records were excluded due to inadequate follow-up and missing data, which may introduce selection bias and reduce statistical power, particularly for the LRH arm. In addition, the LRH cohort was relatively small and likely influenced by access and reimbursement constraints (laparoscopy coverage being more limited during the study period), which may have resulted in systematic differences between patients selected for LRH versus ARH. Because the analysis was restricted to early-stage disease (FIGO ≤IB2), the findings may not be generalisable to more advanced stages or to settings with different case-mix and surgical pathways. Key operative and perioperative determinants of oncologic outcomes, such as colpotomy technique, uterine manipulator use, tumour containment steps, and granular measures of surgeon experience/volume were not consistently available and therefore could not be fully controlled for, leaving the possibility of residual confounding. Finally, lymph node assessment was performed in only a minority of patients, limiting interpretation of nodal risk stratification and adjustment, and the small number of events in an early-stage cohort may have limited our ability to detect modest prognostic effects of covariates beyond surgical approach.

CONCLUSION

In this two-centre retrospective cohort of women with early-stage cervical cancer (FIGO ≤ IB2) undergoing primary radical hysterectomy between 2015 and 2019, LRH demonstrated no statistically significant difference in overall survival compared with ARH in our setting. None of the other evaluated baseline clinicopathological variables (age, parity, tumour size, histotype, and differentiation) were significantly associated with survival, which may reflect the restricted early-stage case mix and limited event numbers. While these findings support LRH as a potentially comparable option to ARH in selected early-stage patients, larger studies with more events, robust control of confounding, and clearer documentation of key operative techniques are needed to confirm safety and define which patients and surgical practices yield equivalent outcomes.

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Trends and determinants of pertussis mortality in Sabah, Malaysia

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ABSTRACT

Introduction: Pertussis remains a major cause of infant morbidity and mortality despite widespread vaccination. Sabah, Malaysia, has consistently reported the nation's highest pertussis burden. This study described the epidemiology of pertussis and identified factors associated with mortality among confirmed cases in Sabah.

Material and Methods: A retrospective registry-based study was conducted using data from the Communicable Disease Control Information System (CDCIS) for all confirmed pertussis cases reported between January 2023 and December 2024. Sociodemographic, vaccination, and clinical variables were extracted. Univariable and multiple logistic regressions were performed to determine factors associated with death; variables with $p < 0.25$ were entered into the multivariable model. Adjusted odds ratios (aOR) with 95 % confidence intervals (CI) were reported.

Results: A total of 287 confirmed pertussis cases were recorded, including 35 deaths (case-fatality rate = 12.2 %). Most deaths occurred in infants < 2 months and among non-Malaysian or unvaccinated children. In the multivariable model, shortness of breath (aOR = 21.6; $p < 0.001$), cyanosis (aOR = 5.45; $p = 0.006$), fitting (aOR = 14.2; $p = 0.027$), and post-tussive vomiting (aOR = 136.0; $p = 0.004$) were independent predictors of death. Male sex was protective (aOR = 0.23; $p = 0.008$). Age, citizenship, and vaccination status were not statistically significant after adjustment. The model demonstrated good fit (Hosmer–Lemeshow $p = 0.807$; Nagelkerke $R^2 = 0.471$).

Conclusion: Pertussis mortality in Sabah remains high and is driven primarily by severe clinical manifestations, with additional influence from demographic and structural factors. Strengthening early clinical recognition, improving referral and intensive care capacity, and expanding preventive strategies particularly maternal vaccination and equitable immunisation for non-Malaysian populations are critical to reducing preventable deaths.

KEYWORDS:
Pertussis; whooping cough; mortality; risk factors; Sabah

INTRODUCTION

Pertussis, or whooping cough, is a highly contagious respiratory disease caused by *Bordetella pertussis*. Despite the availability of effective vaccines, it remains a major cause of infant morbidity and mortality worldwide. The World Health Organization (WHO) estimates more than 150,000 cases annually, with the greatest burden in low- and middle-income countries.[1] The global resurgence of pertussis has been attributed to waning immunity, suboptimal vaccine effectiveness, and gaps in immunisation coverage.[2,3]

In Malaysia, pertussis is a notifiable disease under the Prevention and Control of Infectious Diseases Act 1988. Although the National Immunisation Programme has achieved high coverage, cyclical outbreaks persist, particularly among infants too young to be vaccinated.[4] The COVID-19 pandemic further disrupted immunisation services, leading to delayed or missed childhood doses and increased susceptibility to outbreaks.[3,5]

Sabah, a state in East Malaysia, has recorded the highest national burden of pertussis in recent years, with major peaks in 2019 and 2023.[6] Most deaths occurred in infants under six months, consistent with global evidence that young infants are the most vulnerable.[7] Non-Malaysian populations are disproportionately affected, reflecting inequities in healthcare access and vaccination coverage.[8] Antenatal pertussis vaccination provides passive immunity to newborns and has been shown to reduce infant morbidity and mortality.[9] In Malaysia, this strategy was only introduced in 2024, leaving previous cohorts dependent on herd immunity and infant vaccination.[10]

Despite descriptive reports and outbreak investigations, limited studies have examined the determinants of pertussis mortality in Sabah. Existing evidence largely derives from high-income countries, where health systems differ significantly. Understanding local demographic, vaccination, and clinical determinants is essential to guide targeted interventions and reduce preventable deaths. Therefore, this study aimed to identify factors associated with pertussis mortality using all confirmed cases reported in Sabah between January 2023 and December 2024.

MATERIALS AND METHODS

This study was conducted in Sabah, a Malaysian state in northern Borneo with an estimated 3.4 million residents in 2022, distributed across 27 districts. Sabah shares extensive land and maritime borders contributing to its unique demographic and healthcare challenges. Pertussis is a

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notifiable disease, whereby all suspected cases are reported via the Communicable Disease Control Information System (CDCIS) to district health offices for investigation and surveiilance.

We performed a retrospective registry-based study of confirmed pertussis cases notified to CDCIS between 1st January 2023 and 31st December 2024. The study comprised descriptive and analytical epidemiology to identify factors associated with pertussis mortality. Data was extracted from CDCIS and linked investigation forms completed by district health teams. All confirmed cases with a documented outcome (alive or death) were included. Data completeness was assessed prior to analysis. Any missing or inconsistent variables identified in the CDCIS registry were cross-checked against the original case investigation forms maintained by district health offices. After verification, all variables included in the final analysis were complete, and no imputation was required. Informed consent was waived for this study.

A confirmed pertussis case was defined based on laboratory confirmation and/or epidemiological linkage. Pertussis deaths were defined as cases verified by the attending hospital or district health office and recorded as such in CDCIS. The primary outcome was pertussis status (alive or death). Independent variables included sociodemographic (age, gender and citizenship), vaccination status (complete, incomplete, or ineligible) and clinical features (shortness of breath (SOB), cyanosis, seizures, post-tussive vomiting, cough, fever, and runny nose)

Categorical variables were summarised as frequencies and percentages, and continuous variables as min, max and median (interquartile range). Simple logistic regression was first used to estimate crude odds ratios (cOR) and 95% confidence intervals (CI) for each independent variable. Variables with a p-value < 0.25 in bivariable analysis were considered for entry into the multiple logistic regression model.[11] The final multiple logistic regression model included these predictors, and results were presented as adjusted odds ratios (aOR) with 95% CI. Selection of variables for multiple logistic regression model was made by forward, backward and stepwise elimination. Confounder was further assessed using a ≥10% change-in-estimate rule with interaction terms were explored, and model diagnostics included variance inflation factors (VIF) for multicollinearity, the Hosmer–Lemeshow test for calibration. All analyses were performed using RStudio (version 2025.05.1, Build 513; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Epidemiological distribution

Figure 1 illustrates the weekly distribution of pertussis cases and deaths during the study period. Between January 2023 and December 2024, a total of 287 confirmed pertussis cases were reported. Of these, 35 deaths (12.2%) were recorded. Peaks in case notifications were observed between epidemiology weeks (EW) 10 and 27 of 2023, during which both incidence and mortality were highest. In 2024, reported cases declined substantially, although sporadic deaths continued to occur until EW 45.

Descriptive characteristics of pertussis cases

Table I summarises the sociodemographic, vaccination, and clinical characteristics of pertussis cases by outcome. In terms of age, 45.8% occurred in infants younger than 2 months, followed by those aged 2–<18 months (37.1%). Children aged ≥18 months accounted for only 17.1% of deaths. Females represented a larger proportion of deaths (68.6%) compared with survivors (52.4%). With respect to citizenship, non-Malaysian children comprised many deaths (80.0%), whereas Malaysians and non-Malaysians were more evenly distributed among survivors (49.6% vs 50.4%). Vaccination status showed 88.6% of deaths occurred among ineligible or unvaccinated infants, compared with 73.8% of survivors. In contrast, only 8.6% of deaths were reported among fully vaccinated children, compared with 25.0% of survivors.

Several clinical features distinguished deaths from survivors. SOB was the most prominent, affecting 68.6% of deaths compared with only 12.3% of survivors. Cyanosis was also more frequent among deaths (22.9% vs 7.1%), while seizures was reported in 8.6% of deaths compared with only 0.8% of survivors. Fever occurred in both groups but was slightly higher among deaths (71.4% vs 63.9%). In contrast, cough was present in all cases (100%), reflecting its role as a hallmark symptom, and thus did not differentiate between outcomes. Runny nose and post-tussive vomiting were uncommon overall and did not show meaningful differences between deaths and survivors.

Descriptive statistics of numerical variables

Table II presents the distribution of continuous variables stratified by outcome. The median age at diagnosis among deaths was 0.19 years (IQR 0.11–0.44), which was lower than that of survivors (0.29 years; IQR 0.15–2.29), reflecting the higher vulnerability of very young infants.

The duration of cough before diagnosis was shorter among deaths (median 4 days; IQR 2.0–7.0) compared with survivors (median 6 days; IQR 3.0–11.3), suggesting that children who died tended to present earlier in the disease course, possibly due to rapid progression of severe symptoms.

For logistical factors, the median distance of the cases' residence from the nearest government hospital was shorter among deaths (6.5 km; IQR 3.1–17.4) compared with survivors (10.2 km; IQR 6.0–23.6). Similarly, the median distance to the nearest government clinic was 3.0 km (IQR 1.3–7.1) among deaths and 3.8 km (IQR 1.9–8.1) among survivors. These findings indicate that proximity to healthcare facilities did not necessarily protect against fatal outcomes, and deaths still occurred even among those living nearer to hospitals and clinics.

Factors associated with pertussis mortality: Simple logistic regression

Table III presents the results of the simple logistic regression analysis examining factors associated with pertussis mortality in Sabah between 2023 and 2024. Among continuous variables, age and duration of cough before diagnosis was associated with mortality. Each additional year of age slightly reduced the odds of death (OR=0.78; 95% CI 0.60–1.02; p=0.072), while each additional day of cough prior

Table I: Descriptive analysis statistical results

Mortality	Yes (n, %) 35 (12.2)	No (n, %) 252 (87.8)	Total (n, %) 287 (100)
Age			
<2 months	16 (45.8)	75 (29.8)	91(31.7)
2-<18 months	13 (37.1)	102 (40.4)	115(40.1)
>18 months	6 (17.1)	75 (29.8)	81(28.2)
Gender			
Male11 (31.4)	120 (47.6)	131 (45.6)	
Female	24 (68.6)	132 (52.4)	156 (54.4)
Citizenship			
Non-Malaysian	28(80.0)	127 (50.4)	155 (54.0)
Malaysian	7 (20.0)	125 (49.6)	132 (46.0)
Vaccination status			
Ineligible/unvaccinated	31 (88.6)	186 (73.8)	217 (75.6)
Incomplete	1 (2.8)	3 (1.2)	4 (1.4)
Complete	3 (8.6)	63 (25.0)	66 (23.0)
Clinical symptoms			
Cough			
Yes	35 (100)	252 (100)	287 (100)
Cyanosis			
Yes	8 (22.9)	18 (7.1)	26 (9.1)
No	27 (77.1)	234 (92.9)	261 (90.9)
Shortness of breath			
Yes	24 (68.6)	31 (12.3)	55 (19.2)
No	11 (31.4)	221 (87.7)	232 (80.8)
Seizures			
Yes	3 (8.6)	2 (0.8)	5 (1.7)
No	32 (91.4)	250 (99.2)	282 (98.3)
Fever			
Yes	25 (71.4)	161 (63.9)	186(64.8)
No	10 (28.6)	91 (36.1)	101(35.2)
Runny nose			
Yes	0 (0.0)	5 (2.0)	5 (1.7)
No	35 (100)	247 (98.0)	282 (98.3)
Post-tussive Vomiting			
Yes	1 (2.9)	1 (0.4)	2 (0.7)
No	34 (97.1)	251 (99.6)	285 (99.3)

Table II: Descriptive statistics for numerical variable

Mortality	Yes (n=35)		No (n=252)		Total(n=287)	
variable	Min-Max	Median (IQR)	Min-Max	Median (IQR)	Min-Max	Median (IQR)
Age (year)	0.05-3.92	0.19 (0.11-0.44)	0.02-75	0.29 (0.15-2.29)	0.02-75	0.267 (0.15-2.03)
Duration of cough before diagnosis (day)	0-21	4 (2.00-7.00)	0-40	6 (3.00-11.25)	0-40	6 (3.0-10.5)
Distance of cases from nearby government hospital (km)	0.6-111.0	6.5 (3.10-17.40)	0.3-137.0	10.15 (6.0-23.6)	0.3-137	9.9 (5.65-23.6)
Distance of cases from nearby government clinic (km)	0.2-35.8	3 (1.25-7.05)	0.2-54	3.75 (1.87-8.10)	0.2-54	3.7 (1.55-8.05)

IQR: Inter quartile range (Q1-Q3)

to diagnosis decreased the odds of death by 8% (OR=0.92; 95% CI 0.86–0.99; p=0.018). In contrast, distance to the nearest hospital and government clinic were not significantly associated with mortality (p=0.874 and p=0.697, respectively).

Regarding categorical variables, infants aged <2 months had higher odds of death compared with those aged ≥18 months (OR=2.67; 95% CI 0.99–7.19; p=0.052), although this finding was not statistically significant. Male had lower odds of death compared with females (OR=0.50; 95% CI 0.24–1.07; p=0.076). Non-Malaysian children had nearly fourfold higher odds of death compared with Malaysians (OR=3.94; 95% CI 1.66–9.34; p=0.002).

For vaccination status, ineligible or unvaccinated infants had a significantly greater risk of death compared with fully vaccinated children (OR=3.50; 95% CI 1.03–11.84; p=0.044).

Clinical features strongly associated with mortality included cyanosis, SOB, and seizures. Cases presenting with cyanosis had almost fourfold higher odds of death (OR=3.85; 95% CI 1.53–9.70; p=0.004), those with SOB had 15-fold higher odds (OR = 15.55; 95% CI 6.94–34.84; p<0.001), and those with seizures had 12-fold higher odds of death (OR=11.72; 95% CI 1.89–72.81; p=0.008). Fever, runny nose, and post-tussive vomiting were not significantly associated with death.

Table III: Simple logistic regression of factors associated with pertussis death

Variable	Simple Logistic Regression	
	Crude OR (95% CI)	p-value
Age (year)	0.78 (0.6,1.02)	0.072**
Duration of cough before diagnosis (day)	0.92 (0.86,0.99)	0.018**
Distance of cases from nearby government hospital (km)	1.00 (0.99, 1.01)	0.874
Distance of cases from nearby government clinic (km)	0.99 (0.96, 1.06)	0.697
Age		
<2 months	2.67 (0.99,7.19)	0.052**
2-<18 months	1.59 (0.58,4.38)	0.367
>18 months	1	
Gender		
Male	0.5 (0.24, 1.07)	0.076**
Female	1	
Citizenship		
Non-Malaysian	3.94 (1.66,9.34)	0.002**
Malaysian	1	
Vaccination status		
Ineligible/unvaccinated	3.5 (1.03,11.84)	0.044**
Incomplete	7 (0.55,88.96)	0.134 **
Complete	1	
Clinical symptoms		
Cyanosis		
Yes	3.85 (1.53,9.7)	0.004**
No	1	
Shortness of breath		
Yes	15.55 (6.94,34.84)	<0.001**
No	1	
Seizures		
Yes	11.72 (1.89,72.81)	0.008**
No	1	
Fever		
Yes	1.41 (0.65,3.07)	0.383
No	1	
Runny nose		
Yes	0 (0,Inf)	0.989
No	1	
Post-tussive Vomiting		
Yes	7.38 (0.45,120.78)	0.161**
No	1	

**p-value of < 0.25: include in multiple logistic variable

Variables with p<0.25 were selected for inclusion in the multiple logistic regression model. The following variables were selected for the multiple logistic regression model: age, duration of cough before diagnosis, gender, citizenship, vaccination status, cyanosis, SOB, seizures, and post-tussive vomiting.

Factors associated with pertussis mortality: Multiple logistic regression

Table IV shows the multiple logistic regression analysis of factors associated with pertussis mortality. Shortness of breath (SOB) was the strongest predictor, where affected cases had 21.6-fold higher odds of death compared with those without SOB (aOR=21.6; 95% CI 8.05–65.4; p<0.001). Cyanosis was also associated with mortality (aOR=5.45; 95% CI 1.59–18.4; p=0.006). Likewise, seizures increased the odds of death more than fourteen-fold (aOR=14.2; 95% CI 1.43–180.0; p=0.027), while post-tussive vomiting, was associated with markedly elevated odds of death (aOR=136.0; 95% CI 3.69–5289; p=0.004), although this estimate should be interpreted cautiously due to the very small number of death cases and wide confidence interval.

Among demographic factors, male was significantly protective, with males showing 77% lower odds of death compared with females (aOR=0.23; 95% CI 0.07–0.64; p=0.008). Citizenship and vaccination status were not statistically significant after adjustment, although non-Malaysian children still had approximately threefold higher odds of death (aOR=2.90; 95% CI 0.88–11.0; p=0.094). Similarly, age was not a significant predictor, despite higher crude mortality among infants aged < 2 months.

The final model demonstrated good overall fit (Hosmer–Lemeshow p=0.807) and explained 47.1% of the variation in mortality (Nagelkerke R^2=0.471). No multicollinearity was detected. After adjustment for potential confounders, several clinical features remained significant predictors of death. Gender, vaccination status, and citizenship were identified as confounders: gender mainly confounded the associations of citizenship, vomiting, and seizures; vaccination status confounded the effects of citizenship, cyanosis, vomiting, and seizures; and citizenship strongly confounded the relationships between vaccination status, gender, and young age.

Table IV: Multivariable logistic regression of factors associated with pertussis death

Variable	Multiple Logistic Regression	
	Adjusted OR (95% CI)	p-value
Age		
<2 months	2.15(0.59, 8.68)	0.3
2-<18 months	0.53(0.14, 2.08)	0.3
>18 months	1	
Gender		
Male	0.23(0.07, 0.64)	0.008*
Female	1	
Citizenship		
Non-Malaysian	2.90(0.88, 11.0)	0.094
Malaysian	1	
Vaccination status		
Ineligible/unvaccinated	0.72(0.13, 4.54)	0.7
Incomplete	1.54(0.05, 37.0)	0.8
Complete	1	
Clinical symptoms		
Cyanosis		
Yes	5.45(1.59, 18.4)	0.006*
No	1	
Shortness of breath		
Yes	21.6(8.05, 65.4)	<0.001*
No	1	
Seizures		
Yes	14.2(1.43, 180)	0.027*
No	1	
Post-tussive Vomiting		
Yes	136(3.69, 5,289)	0.004*
No	1	

*p-value <0.05: significant level
AIC: 153.5. No multicollinearity among the variables was detected in the final model. Nagelkerke's R-squared: 47.1%. Hosmer-Lemeshow Goodness-of-Fit Test: 0.807.
Gender, vaccination status, and citizenship were identified as confounders. Gender confounded the effects of citizenship, post-tussive vomiting, and seizures. Vaccination status confounded the associations of citizenship, cyanosis, post-tussive vomiting, and seizures. Citizenship strongly confounded the relationship between vaccination status, gender, seizures, and young age.

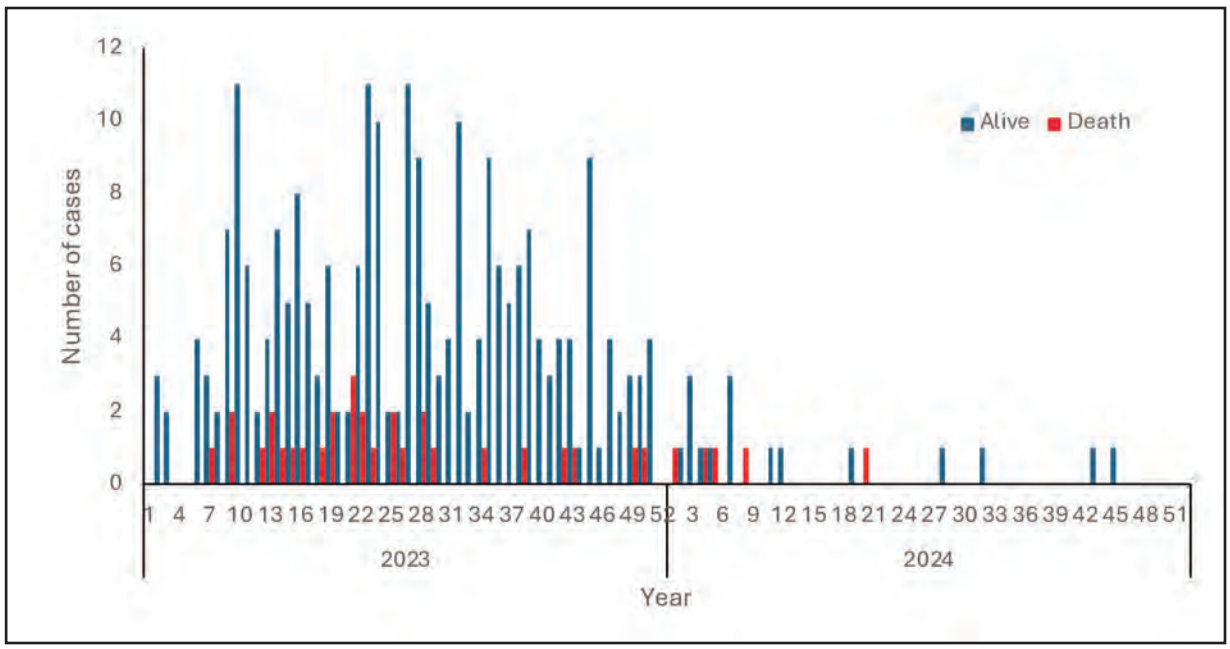

Fig. 1: Distribution of pertussis cases and mortality cases in Sabah according epidemiology week (EW) from 2023 until 2024

DISCUSSION

This study analysed all confirmed pertussis cases reported in Sabah between 2023 and 2024 and identified several factors associated with mortality. The overall case fatality rate (CFR) was 12.2%, which is substantially higher than CFRs reported in many high-income settings, where deaths are typically below 1% due to strong immunisation coverage and intensive care support.[1,2] These findings demonstrate the persistent burden of pertussis mortality in Sabah, consistent with global evidence showing that low- and middle-income countries continue to face disproportionate risk.[3]

Globally, there has been a resurgence of pertussis in recent years, driven by waning immunity, suboptimal vaccination uptake, and disruptions to immunisation programmes during the COVID-19 pandemic.[12] The pandemic disrupted routine childhood immunisation services worldwide, including in Malaysia, leading to delayed or missed vaccinations and altered health-seeking behaviours due to fear of COVID-19 exposure.[13] Similar to other regions, Sabah reported vaccination coverage below the 95% threshold required for herd immunity, contributing to increased pertussis susceptibility during and immediately after the pandemic years.[14]

Malaysia's National Immunisation Programme schedules pertussis vaccination via the hexavalent combination vaccine (diphtheria, tetanus, pertussis, polio, hepatitis B, and *Haemophilus influenzae* type b) administered at 2, 3, 5, and 18 months.[4] In recognition of inequities faced by non-Malaysian children, the Ministry of Health issued an exemption for polio vaccination fee in 2022, granting free hexavalent vaccination for all non-Malaysian children under seven years old.[15] These initiatives, combined with catch-up campaigns, contributed to the decline in pertussis incidence observed in 2024 following the 2023 epidemic peak.

In the present study, female infants had higher mortality compared with males. The adjusted model showed that males had significantly lower odds of death (aOR=0.23; 95% CI 0.07–0.64; p=0.008). Although evidence on sex differences in pertussis outcomes is limited, biological differences in immune regulation may contribute to this observation. Females typically develop stronger immune responses to infections and vaccination, influenced by hormonal and genetic factors.[16,17] However, stronger immune activation during severe respiratory illness may also increase inflammation and tissue damage. The observed protective association among males may reflect statistical variability due to the relatively small number of deaths. Further research in larger populations is needed to better understand this association.

Severe clinical symptoms particularly SOB, cyanosis, seizures, and post-tussive vomiting were strong predictors of death. These clinical features should not be interpreted as independent causal determinants of mortality, but rather as markers of advanced disease severity. Symptoms such as shortness of breath, cyanosis, and seizures likely reflect underlying respiratory compromise and systemic hypoxia preceding fatal outcomes. Thus, they function primarily as prognostic indicators for triage and escalation of care rather than primary etiological risk factors.[18,19]

In contrast, age, vaccination status and citizenship were not statistically significant after adjustment, although nearly half of the deaths occurred in infants younger than two months and most fatalities were among those ineligible or unvaccinated. This pattern reflects the influence of both biological vulnerability and structural inequities. Young infants remain immunologically immature and rely on maternal or herd immunity for protection. Global studies consistently show that under vaccinated infants, especially in lower-income settings, face the highest risk of severe disease and death.[9,20] In Sabah, the relationship between these factors is further shaped by contextual issues such as healthcare access, vaccination opportunities, and social determinants of health.[21,22] The association of citizenship and vaccination effects after adjustment may also reflect residual confounding from unmeasured structural variables not captured in surveillance data.

The persistence of high mortality despite proximity to health facilities suggests that delayed recognition and initiation of critical care, rather than geographic access alone, may underlie many deaths. Similar challenges have been observed in other low- and middle-income countries, where structural barriers such as transport limitations, healthcare costs, and fear of discrimination may impede timely care.[9,22]

Several limitations should be considered when interpreting these findings. The retrospective study design limits causal inference, while the CDCIS registry does not capture important variables such as socioeconomic status, household crowding, parental education, maternal vaccination history, healthcare access barriers, care-seeking delays, and underlying co-morbidities. The absence of these variables may have introduced residual confounding, particularly regarding the associations involving citizenship and vaccination status after adjustment. In addition, the relatively small number of deaths reduced statistical power and contributed to wide confidence intervals for some estimates, particularly post-tussive vomiting, where sparse data may have led to model instability and overestimation of effect size. Furthermore, the two-year study period may not fully capture the cyclical epidemic patterns characteristic of pertussis, limiting long-term trend interpretation and generalisability.

Despite these limitations, the use of comprehensive CDCIS surveillance data allowed complete case capture across Sabah and strengthened the validity of the findings. By combining descriptive and multivariable analyses, this study identified important clinical and sociodemographic predictors of pertussis mortality in a high-burden setting. Overall, pertussis mortality in Sabah reflects the combined effects of clinical severity, biological vulnerability, and structural inequities, underscoring the need for targeted interventions to strengthen early diagnosis, equitable vaccination access, and critical care management.

CONCLUSION

In conclusion, pertussis mortality in Sabah remains high, driven by both clinical severity and sociodemographic inequities. Policy responses must address both clinical management (early recognition, referral, and intensive

support) and prevention (strengthening immunisation) which has shown strong protective effects in other countries.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

ETHICS STATEMENT

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ORIGINAL ARTICLE

Ten-year review of paediatric cataract surgery outcomes at a tertiary referral centre

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ABSTRACT

Introduction: Paediatric cataract is a major cause of preventable childhood visual impairment, with surgical outcomes associated with several factors. This study aimed to investigate the post-operative visual outcomes, complications, and factors associated with poor visual outcomes in paediatric patients who underwent cataract surgery, one-year post-operation.

Materials and Methods: Retrospective study on paediatric patients who underwent cataract surgery in Hospital Raja Perempuan Zainab II, Malaysia from January 2014 until December 2023. The data was collected from medical records.

Results: 48 paediatric patients (65 eyes) were recruited. The mean age was 7.7 ±4.79 years. 32 (66.7%) males and 16 (33.3%) females. 17 patients had bilateral while 31 patients had unilateral cataract. 44 eyes (67.7%) had primary cataract, and 21 eyes (32.3%) had secondary cataract. Overall, 53.8% (35 eyes) achieved good visual outcomes of 6/12 or better, but outcome was better in primary cataracts with 56.8% achieved good vision compared to 47.6% in secondary cataracts. 52.4% (11 eyes) of the secondary cataracts was traumatic in nature, with male predominance (72.7%) and 72.7% (8 eyes) achieved good vision. Post-operative complication occurred in 18.5% (12 eyes), with posterior capsular opacification being the commonest. Overall, ocular and systemic comorbidities contributed to poor visual outcome. Specifically for traumatic cataracts, the factors leading to poor visual outcomes were significant corneal opacity and amblyopia. Implantation of posterior chamber IOL was significantly associated with good visual outcomes (60.7%).

Conclusion: Paediatric cataract surgery outcomes at our centre are comparable with previous studies, with posterior chamber IOL implantation give favourable results. Ocular and systemic comorbidities significantly elevate the risk of poor outcomes. Corneal scarring and amblyopia were common causes of poor vision in traumatic cataracts

KEYWORDS:
Malaysia; paediatric cataract; congenital cataract; lens aspiration; visual outcome

INTRODUCTION

Cataract is one of the leading causes of visual loss (22.3%) among paediatric population in Malaysia, aside from retinal disorders (20.8%).[1-3] Malaysia has one of the highest prevalence of paediatric cataract in Asia at 5.33 per 10,000 people, compared to its neighbours, Indonesia and Thailand, at 0.60 and 4.27 per 10,000 people, respectively.[4] Paediatric cataracts have various aetiologies such as idiopathic, drug induced, metabolic disorders, traumatic, intrauterine infection, and association with systemic abnormalities.[5] Acquired cataracts are also reported as relatively common in Asian children.[6,7]

Surgery at young age in paediatric cataract is challenging and have variable outcomes due to several factors. Particular challenges include a more elastic lens capsule, a smaller eye that can preclude intraocular lens (IOL) implantation, and quickly changing axial length, which makes determining IOL power more challenging.[8] There are several factors, including the laterality of cataracts, the presence of ocular and systemic comorbidities, the development of glaucoma after surgery, and the phakic condition of the eye, have been shown in prior research to influence the outcomes of patients after surgery.[9] One local study by Chew et al concluded that eyes with longer axial length was significantly associated with good visual outcome.[10] Some factors are preventable and addressing these will improve the patients' surgical outcome.

There are relatively few studies on paediatric cataract in Malaysia, and all published studies to date have been conducted at single centres.[10-13] The present study was designed to add to the limited literature on paediatric cataract in Malaysia. We aim to describe the demographics, clinical features, post-operative visual outcomes, complications, and factors associated with poor visual outcomes in paediatric patients who underwent cataract surgery, one-year post-operation in our tertiary institution.

MATERIALS AND METHODS

This is a retrospective record review of paediatric patients aged below 18 years old who underwent cataract surgery in Raja Perempuan Zainab II Hospital, Kelantan, Malaysia from January 2014 to December 2023. Purposive sampling was used and data were extracted from the Cataract Registry of National Eye Database, a Ministry of Health of Malaysia's

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website. The study obtained ethical approval from Medical Research and Ethics Committee of the Malaysian Ministry of Health (NMRR ID-24-00814-OLC (IIR)) and conducted in accordance with the Declaration of Helsinki.

The data included patients' socio-demographic characteristics, clinical characteristics, cataract surgery related information (including type of cataract surgery done, intraocular lens implantation, duration of surgery and complications), and visual outcomes. All data extracted were devoid of any patient identifier. Both digital and physical medical records were traced from the Opthalmology Clinic to complete any missing data. Patients with incomplete data or missing medical records were excluded from this study. Good visual outcome is defined by visual acuity at one-year post operation of 6/12 or better and poor visual outcome is visual acuity worse than 6/12.

IBM Statistical Package for the Social Sciences (SPSS) software version 28.0 was used for further analysis of the data collected. The visual outcomes at one-year post-operation and the factors associated with poor visual outcomes were analysed using logistic regression.

RESULTS

A total of 117 eyes (94 patients) underwent cataract surgery over ten-year period from January 2014 until December 2023. Only 65 eyes were included as others were excluded due to incomplete medical records. The demographic data, clinical and operative characteristic of the patient cohort are outlined in Table I. The mean age of patient in our study is 7.7 years (±4.79 years). Majority of the patients are male, 32 patients, 66.7% (41 eyes) are males and 16 patients, 33.3% (24 eyes) are females. This study was conducted at a hospital with significant majority of Malay community, thus 98.5% of the operated eyes belongs to this ethnic category. Thirty-one patients had unilateral cataract and 17 patients (34 eyes) had bilateral cataract. 44 eyes had primary cataract and 21 eyes had secondary cataract (11 eyes: traumatic cataract, five eyes: post vitrectomy cataract, five eyes: uveitic cataract). Most of the patients had no ocular comorbidities (72.3%) or systemic comorbidities (80%). The most common postoperative complication in this study is posterior capsule opacification, diagnosed in eight eyes (12.3%).

Table II shows the multiple logistic regression analysis done on the factors associated with poor visual outcome post paediatric cataract surgery. The presence of ocular and systemic comorbidities was shown to be significantly associated with poor postoperative visual outcomes. The odds of poor visual outcomes were 5.85 times greater for patients with ocular comorbidities and 4.78 times greater for those with systemic comorbidities compared patients with no comorbidities. In this study, thirteen patients have systemic comorbidities, including Down syndrome, congenital heart disease, global developmental delay and retroviral disease. All these findings were statistically adjusted for variables such as age, gender, cause of cataract, axial length of the eye, and duration of the surgical procedure.

Table III presents the demographic and clinical characteristics of paediatric patients with traumatic cataract (n = 11), including age distribution, gender, mechanisms of injury, and the location of the traumatic event, structural injuries associated with traumatic cataract, the timing of intraocular lens (IOL) implantation, the operation details and the visual outcomes. Among the 11 paediatric patients with traumatic cataract, the mean age was 9.1 years (± 4.13 years), with a predominance of boys (72.7%). Penetrating trauma was the most common mechanism of injury (72.7%), and the majority of injuries occurred at home (72.7%). While isolated lens injury was seen in only 18.2% of cases, the majority (81.8%) presented with multiple structural injuries, most commonly involving the lens, cornea, and iris together (36.3%). Primary IOL implantation during lens aspiration was performed in 63.6% of cases, whereas secondary implantation was required in 27.3%, and one patient remained aphakic. Notably, no patients underwent lens surgery within the first month post-injury; the timing was evenly distributed between 1–6 months and more than 6 months (45.5% each). At presentation, 90.9% of patients had a visual acuity worse than 6/60. By 1 year, 72.7% achieved a final visual acuity of 6/12 or better, while 18.2% remained worse than 6/60. The causes of poor postoperative visual outcomes included corneal scar with aphakia, amblyopia, and corneal scarring with exogenous endophthalmitis, each accounting for 9.1% of cases.

DISCUSSION

Primary cataracts (67.7%) were more common than secondary cataract (32.3%), which is consistent with previous studies.[6,10,11] A study conducted by Song et al in 2014 in an Ophthalmology Department of Shengjing Hospital over 10-year period involved 367 patients, 296 patients (80.7%) were diagnosed with primary cataract.[6] Among secondary cataracts, traumatic cases were predominant, 11 eyes, followed by post vitrectomy cataract (five eyes) and uveitic cataract (five eyes). Consistent with Song et al and Chew et al , traumatic cataract is the commonest cause of acquired cataract, which is preventable.[6,10] Song et al reported 61 (85.9%) patients with acquired cataract were traumatic cataract and Muhd-Syafi et al reported 40% of the acquired cataract were traumatic cataract whereas in this study noted a comparable percentage of 52.4% patients with traumatic cataract.[6,11]

Our study found a higher prevalence of male patients with paediatric cataract, 32 patients (66.7%), consistent with local and international studies.[6,7,10,11,14] Interestingly, a 2020 study by Ramadhon et al from Indonesia, a neighbouring Southeast Asian country, reported a higher prevalence of female patients (58.5%) compared to male patients (41.5%).15 Besides that, in this study, majority patients have unilateral cataract, 31 patients (64.6%) and 17 patients (35.4%) have bilateral cataract, consistent with local study reported by Muhd-Syafi et al.[11] Muhd-Syafi et al reported majority of unilateral cataract of 68.2% of the patients[11] Interestingly, two other studies by Song et aland Chew et al discovered that majority of patients have bilateral cataract with 65.9% and 69.2% respectively.[6,10]

Table I: The demographic data, clinical and operative characteristics of paediatric patients who underwent cataract surgery

Variables	Total n (%)	BCVA group		p-value
		Good vision n (%)	Poor vision n (%)	
Age, mean (SD)	7.7 (+4.79 years)	8.4 (+4.32 years)	7.0 (+5.26 years)	0.243[c]
Total	65 (100.0)	35 (53.8)	30 (46.2)	
Gender				
Male	41 (63.1)	21 (51.2)	20 (48.8)	0.579[a]
Female	24 (36.9)	14 (58.3)	10 (41.7)	
Ethnic Group				
Malay	64 (98.5)	34 (53.1)	30 (46.9)	1.000b
Indian	1 (1.5)	1 (100.0)	0 (0.0)	
Laterality				
Unilateral	31 (47.7)	16 (51.6)	15 (48.4)	0.730[a]
Bilateral	34 (52.3)	19 (55.9)	15 (44.1)	
Cause of Cataract				
Primary	44 (67.7)	25 (56.8)	19 (43.2)	0.487[a]
Secondary	21 (32.3)	10 (47.6)	11 (52.4)	
Axial Length				
22mm-25mm	34 (52.3)	21 (61.8)	13 (38.2)	0.352[a]
<22mm & >25mm	28 (43.1)	14 (50.0)	14 (50.0)	
IOL Implantation				
PCIOL	56 (86.2)	34 (60.7)	22 (39.3)	0.003[b]
Aphakia	7 (10.8)	0 (0.0)	7 (100.0)	
IOL in sulcus	2 (3.1)	1 (50.0)	1 (50.0)	
Ocular Comorbidity				
No	47 (72.3)	31 (66.0)	16 (34.0)	0.002[a]
Yes	18 (27.7)	4 (22.2)	14 (77.8)	
Systemic Comorbidity				
No	52 (80.0)	32 (61.5)	20 (38.5)	0.013[a]
Yes	13 (20.0)	3 (23.1)	10 (76.9)	
Duration of Operation (min)				
0-60	53 (81.5)	30 (56.6)	23 (43.4)	0.349[a]
>60	12 (18.5)	5 (41.7)	7 (58.3)	
Post-operative Complication				
No	53 (81.5)	33 (62.3)	20 (37.7)	0.010[b]
PCO	8 (12.3)	1 (12.5)	7 (87.5)	
Cornea Scar	1 (1.5)	0 (0)	1 (100)	
High refractive power	3 (4.6)	1 (33.3)	2 (66.7)	

[a]Chi-square test
[b]Fisher's exact test
[c]Independent t-test
BCVA= best corrected visual acuity, IOL=intraocular lens, PCIOL=Posterior chamber intraocular lens, PCO= Posterior Capsule Opacification

Table II: Factors associated with poor visual outcome post paediatric cataract surgery

	Simple logistic regression		Multiple logistic regression[a]	
	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age operation	0.94 (0.85, 1.04)	0.240		
Gender				
Male	1.33 (0.48, 3.69)	0.579		
Female	1			
Cause of Cataract				
Primary	1			
Secondary	1.45 (0.51, 4.11)	0.487		
Axial Length				
22mm-25mm	1			
<22mm & >25mm	1.62 (0.59, 4.45)	0.354		
Ocular Comorbidity				
No	1		1	
Yes	6.78 (1.92, 24.01)	0.003	5.85 (1.39, 24.68)	0.045
Systemic Comorbidity				
No	1		1	
Yes	5.33 (1.31, 21.76)	0.020	4.78 (1.04, 22.00)	0.016
Duration of Operation (min)				
0-60	1			
>60	1.83 (0.51, 6.50)	0.353		

[a]Backward method was applied
[a]No multicollinerity and no interaction
[a]Hosmer and Lemeshow Test, p-value=0.311

Table III: Demographic data of paediatric patients with traumatic cataract (n = 11), the mechanisms of injury, locations of event, structural injuries, operation details and the visual outcomes

Characteristics	No. (%)
Age range (years)	
1-6	3 (27.2)
7-12	4 (36.4)
13-17	4 (36.4)
Mean (SD): 9.1 years (+ 4.13 years)	
Gender	
Boys	8 (72.7)
Girls	3 (27.3)
Mechanism of injury	
Penetrating Trauma	8 (72.7)
Blunt trauma	3 (27.3)
Location of event	
At home	8 (72.7)
Elsewhere	
Tailor shop	1 (9.1)
Outdoor playground	2 (18.2)
Lens injury only	
Multiple structural injuries	
Lens and cornea	2 (18.2)
Lens and iris	1 (9.1)
Lens, cornea and iris	4 (36.3)
Lens, cornea, iris and sclera	1 (9.1)
Lens, cornea, iris and choroid	1 (9.1)
IOL implantation setting	
Lens aspiration and primary IOL	7 (63.6)
Secondary IOL	3 (27.3)
Aphakic	1 (9.1)
Time to lens surgery (months)	
Less than 1	0 (0.0)
Between 1 to 6	5 (45.5)
More than 6	5 (45.5)
	* 1 aphakic
Visual acuity at presentation	
6/12 or better	0 (0.0)
6/15 – 6/60	1 (9.1)
Worse than 6/60	10 (90.9)
Visual acuity 1 year postoperatively	
6/12 and better	8 (72.7)
6/15 – 6/60	1 (9.1)
Worse than 6/60	2 (18.2)
Causes of poor visual outcome	
Cornea scar and aphakia	1 (9.1)
Amblyopia	1 (9.1)
Cornea scar with exogenous endophthalmitis	1 (9.1)

IOL=Intraocular lens

For primary cataract, 56.8% had good visual outcome whereas 43.2% had poor visual outcome as shown in Table I, comparable to local and international studies where 44.1% to 85.0% of the patients with primary cataract achieved good postoperative outcome of 6/12 or better.[10,12,14] Chew et al reported that, at final review, 44.1% (49 out of 111) of subjects achieved a visual acuity of 0.3 LogMAR or better.[10] Ting et al reported a greater proportion of eyes with good visual outcomes, with 25 (71.4%) obtained best corrected visual acuity (BCVA) of 6/12 and better at 6 months after IOL implantation.[12] Another study by Lekskul et al in Thailand likewise found that 85% of patients had a good visual outcome of 6/12 or better.[14]

In this study, the most common cause of poor post operative outcome is posterior capsule opacification (PCO) which is seen in eight patients (12.3%) as shown in Table I, consistent with previous local studies where the rate of PCO ranged from 17.1% to 30.8%.10-12 Compared to adult eyes, paediatric eyes have more tendency for excessive post-surgical inflammation, which increases the rate of posterior capsule opacification (PCO) with high risk of amblyopia due to potential difficulties in compliance to visual rehabilitation post-operatively.[8]

Simple and multiple logistic regression showed that ocular and systemic comorbidity were significantly associated with poor visual outcome, with p-value of 0.016 and 0.045 respectively. This study concludes that patients with ocular comorbidity has 5.85 times more likely to develop poor vision. Patients with systemic comorbidity has 4.78 times more likely to develop poor vision post cataract surgery. There are no significant association of age, axial length, cause of cataract and duration of surgery with the poor visual outcome. The most commonly observed systemic comorbidity was Down syndrome, identified in four eyes, followed by

congenital heart disease and retroviral disease, each affecting two eyes. This finding is consistent with patterns observed in regional and international studies. A local study by Chew et al. conducted on the West Coast of Malaysia similarly highlighted Down syndrome as the most prevalent systemic comorbidity among paediatric patients with ocular conditions.[10] A systematic review by Munoz–Ortiz et al in 2022 reported that cataract is one of the most commonly associated condition in Down Syndrome ((10.9% of patients) 16. Similar study done in United Kingdom reports 5.4 % od patients diagnosed with cataract were diagnosed with Down Syndrome with the majority (61.5%) diagnosed during the neonatal period, highlighting the early onset of lens opacities in this population.[17] 18 (27.7%) eyes have ocular comorbidities, the commonest one being rhegmatogenous retinal detachment in six eyes (9.2%). This is consistent with a Japanese study done by Oshika et al in 2023 involving 457 eyes where the visual outcomes were influenced by systemic and ocular comorbidities, the laterality of the cataract, and the patient's age at surgery.[9]

In contrast to previous studies, this current study found no association between shorter or longer axial length with the visual outcome. The axial length in this study ranges from 15.37mm to 27.62 mm with a mean of 22.53mm +2.40mm. 34 eyes (52.3%) have normal axiL length, and 28 eyes (43.1%) have short or long axial length. In a study done at Hospital Kuala Lumpur, Malaysia, Chew et al found that eyes with longer axial lengths being associated with better visual outcomes at one-year post operation.10 In the study, most of the subjects (61.3%, 68/111) were aged one year and below, and the mean age at surgery was 33.14 months (±33.47 months). A possible explanation to relate the longer axial length with better visual outcome is, longer eyeballs are nearing its adult length, with less degree of lengthening compared to shorter eyeballs when reviewed at one year post operation. This association could possibly change if the paediatric patients were to be followed up for a longer duration, as most of the patients are aged below one year old at the time of operation with more potential for eyeball growth.18 Similar findings were found in another study by Zhou X. et al in 2022, who investigate the effect of pre-operative axial length on myopic shift three years following primary IOL implantation, concluded eyes with longer axial length has slower myopic shift.19 Our cohort, being older with a mean age of 7.7 years, may have had more stable axial lengths, reducing the confounding effect of myopic shift.. Additionally, the relatively smaller sample size in this study may have limited statistical power to detect subtle associations.

Traumatic cataract

Traumatic cataract was the commonest cause of acquired cataract in this study. Similar to other studies, there is male preponderance of traumatic cataract.[13,20-21] The majority (72.7%) of the patients with traumatic cataract achieved good visual outcome of 6/12 or better at 1 year post-operation (Table V), comparable to studies in other countries, where 50.0%–80.0% of the patients had a good postoperative visual outcome of 6/12 or better.[22-24] A similar study done at another local centre only had 34.5% of patients with good outcome, and this was mainly attributed to significant corneal opacity and amblyopia, similar to this current study.[20]

Other studies have also shown that cornea scarring and amblyopia are common causes of poor outcome, contributing to 7.7% - 100% and 11.0% – 100% of poor visual outcome, respectively.[22-24] The outcome of traumatic cataract is unpredictable as it depends on the structures involved. Similar to other studies, penetrating injuries (72.7%) were more common than blunt injuries in this study, which tends to involve the cornea and cause scarring (Table IV).[21-25] The majority of injuries occurred at home (72.7%), highlighting the critical need for improved supervision and the creation of safer environments for children within the household.

There are several limitations in this study. Firstly, it was a retrospective study and conducted in a tertiary centre with mostly referred and complicated cases, which may affect final visual outcomes. Secondly, sample exclusion due to the missing or incomplete data led to a relatively smaller sample size in this study, which may affect the statistical analysis result. Future multicentre studies with bigger sample size produce a more robust study.

CONCLUSION

Our paediatric cataract surgery outcomes align with previous reports, with posterior chamber IOL implantation associated with better vision. Ocular and systemic comorbidities markedly increased the risk of poor outcomes, while corneal scarring and amblyopia were frequent causes of visual impairment in traumatic cases. The high rate of home-related injuries and delayed surgeries highlights the need for caregiver education and improved access to care. Future priorities include multicentre studies to enhance generalisability, along with long-term follow-up to track amblyopia progression, sustained visual outcomes, and refractive changes particularly in growing paediatric eyes.

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ORIGINAL ARTICLE

Genetic polymorphisms of *XRCC1* on cervical cancer susceptibility risk

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ABSTRACT

Introduction: Cervical cancer is the fourth most frequently diagnosed cancer and the fourth leading cause of cancer-related mortality among women worldwide. Genetic polymorphisms in DNA repair genes may influence susceptibility to cervical carcinogenesis. X-ray repair cross-complementing protein 1 (XRCC1), an important scaffolding protein in the base excision repair (BER) pathway, plays a crucial role in repairing DNA damage. This study investigated the association of XRCC1 Arg399Gln G>A (rs25487) and *XRCC1* Arg194Trp C>T (rs1799782) polymorphisms with cervical cancer susceptibility risk.

Materials and Methods: A total of 133 cervical cancer patients and 133 healthy female controls were enrolled. Genotyping of both polymorphisms was performed using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Genotype and allele frequencies were compared between groups using chi-square analysis, while logistic regression analysis was performed to determine Odds Ratios (ORs) with 95% confidence intervals (CI).

Results: A significant association was observed between XRCC1 Arg399Gln G>A (rs25487) polymorphism and cervical cancer susceptibility. The heterozygous GA genotype showed a significantly increased risk of cervical cancer (OR: 2.325, 95% CI: 1.380–3.918, p=0.002). In contrast, no significant association was identified between *XRCC1* Arg194Trp C>T (rs1799782) polymorphism and cervical cancer risk.

Conclusion: In conclusion, *XRCC1* Arg399Gln G>A (rs25487) polymorphism may contribute to cervical cancer susceptibility and could potentially serve as a future biomarker for early detection. Further large-scale studies involving multiple genes and polymorphisms are required to validate these findings.

KEYWORDS:
Cervical cancer, XRCC1 gene polymorphism, susceptibility risk

INTRODUCTION

Cervical cancer remains a major public health issue affecting women worldwide, particularly in low- and middle-income countries.[1] According to Global Cancer Statistics 2020, cervical cancer was ranked as the fourth most frequently diagnosed cancer and the fourth leading cause of cancer-related mortality among women, with approximately 604,000 new cases and 342,000 deaths globally.[1] In Malaysia, cervical cancer was reported as the third most common cancer among females, accounting for 6.2% of all female cancers after breast and colorectal cancers.[2] Persistent infection with high-risk Human Papillomavirus (HPV) is a well-established cause of cervical cancer and its precursor lesion, cervical intraepithelial neoplasia (CIN).[3,4] HPV is a non-enveloped double-stranded DNA virus comprising more than 100 genotypes, of which 13 are classified as high-risk and 5 as likely high-risk types.[5] Among these, HPV 16 and 18 are the most aggressive and frequently associated with cervical neoplasia due to their ability to integrate into the host genome.[5] Nevertheless, HPV infection alone is insufficient to induce cervical carcinogenesis because most infections are transient and self-limiting, while only a small proportion persist and progress to malignancy.[3,4,6] Therefore, other cofactors including environmental exposure, lifestyle factors, and host genetic susceptibility contribute significantly to cervical cancer development. Factors such as cigarette smoking, early and multiple childbirths, multiple sexual partners, immunosuppression, oral contraceptive use, and low socioeconomic status have been implicated in cervical cancer progression.

DNA repair mechanisms play a critical role in maintaining genomic integrity by repairing DNA damage induced by endogenous and exogenous factors. Failure of these repair pathways may result in apoptosis, uncontrolled cell proliferation, and carcinogenesis.[7] Several DNA repair pathways exist in human cells, including base excision repair (BER), nucleotide excision repair (NER), double-strand break repair (DSBR), and DNA mismatch repair (DMR). BER is particularly important in repairing oxidative DNA damage caused by reactive oxygen species. Genetic variations such as single nucleotide polymorphisms (SNPs), which represent the most common form of genetic variation, may alter DNA repair efficiency and influence susceptibility to various diseases including cancer.[6-8] SNPs in DNA repair genes may induce structural alterations in repair enzymes, thereby modulating cancer susceptibility.[8] X-ray repair cross-complementing protein 1 (XRCC1) is an important nonenzymatic scaffolding protein involved in BER and is

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encoded by the *XRCC1* gene located on chromosome 19p13.2.[9-11] *XRCC1* interacts with several proteins involved in BER, including DNA polymerase β, poly(ADP-ribose) polymerase (PARP), and DNA ligase III.[8] Polymorphisms in XRCC1 may impair protein interactions and reduce DNA repair efficiency, consequently increasing the risk of carcinogenesis.[10]

Numerous epidemiological studies have reported associations between *XRCC1* polymorphisms and several cancers including lung, gastric, breast, prostate, colorectal, pancreatic, head and neck, and gynaecological malignancies.[12-17] However, findings regarding the association between *XRCC1* polymorphisms and cervical cancer susceptibility remain inconsistent across different populations and ethnic groups.[17-20] Two commonly studied *XRCC1* SNPs are Arg194Trp C>T (rs1799782) and Arg399Gln G>A (rs25487). The *XRCC1* Arg194Trp polymorphism involves a C>T substitution resulting in an arginine-to-tryptophan amino acid change in exon 6, whereas XRCC1 Arg399Gln involves a G>A substitution causing an arginine-to-glutamine change in exon 10.[24] Several studies demonstrated significant associations between these polymorphisms and cervical cancer risk, as well as other malignancies such as thyroid cancer, skin carcinoma, and nasopharyngeal carcinoma.[18-20,25-30] Despite these findings, most studies were conducted outside Malaysia, and genetic associations identified in other populations may not be directly applicable to the Malaysian population due to ethnic diversity. To date, limited data are available regarding the distribution and impact of *XRCC1* polymorphisms among Malaysian cervical cancer patients. Therefore, this study was conducted to investigate the role of *XRCC1* Arg399Gln G>A (rs25487) and *XRCC1* Arg194Trp C>T (rs1799782) polymorphisms in modulating cervical cancer susceptibility risk among the local population.

MATERIALS AND METHODS

Study participants

This study was performed using archived DNA samples which had been previously extracted from peripheral blood samples of previous research study. The original research entitled "Roles of selected genetic variations and molecular alterations in Human Papillomavirus mediated cancer of uterine cervix" was carried out starting in August 2012 and completed in January 2016. The research study had received ethical approval from the Human Research Ethics Committee of Universiti Sains Malaysia (reference numbers: USMKK/PPP/JEPeM [253.3.(7)] and USM/JEPeM/14100325) as well as the Medical Research and Ethics Committee of Ministry of Health, Malaysia (reference numbers: KKM/NIHSEC/08/0804/P12-380, and KKM/NIHSEC/P15-1214). The study subjects were previously recruited from (i) Hospital Universiti Sains Malaysia, Kubang Kerian, Kelantan, (ii) Hospital Raja Perempuan Zainab II, Kota Bharu, Kelantan, and (iii) Hospital Sultan Ismail, Johor Bahru, Johor between August 2012 and January 2016.

The present study received ethical approval obtained from the Human Research Ethics Committee of USM (USM/JEPeM/21120779) which complies with the Declaration of Helsinki. A total number of samples used in this study were 133 cervical cancer patients and 133 normal female control. The selection criteria for cervical cancer cases were clinically and histopathologically confirmed cases of cervical cancer female and their age ranges between 18 to 70 years old. Subjects who have had a personal history of previous or concurrent malignancy, subjects diagnosed with metastatic cancer to the cervix, subjects who have prior treatment before undergoing surgery and those who were found to have a history of autoimmune or chronic infectious disease were excluded from this study. For the normal healthy female control group, the selection criteria were cancer-free healthy female volunteer who was age-matched to the case group, biologically unrelated to the case, and age range between 18 to 70 years old. Individuals with a family history of cervical cancer and those who were found to have a history of autoimmune or chronic infectious disease were excluded.

Genotyping of *XRCC1* Arg194Trp (rs1799782) and Arg399Gln (rs25487)

The DNA samples were previously extracted from a peripheral blood samples of the study subjects using commercial QIAamp DNA Mini Kit (QIAGEN). The genotyping of both SNPs *XRCC1* Arg194Trp (rs1799782) and Arg399Gln (rs25487) was performed by using PCR – restriction fragment length polymorphism (RFLP) technique. PCR reaction was performed in 20µl of the final volume containing 0.2µM of each forward and reverse primer, 50ng extracted genomic DNA, 2mM $MgCl_2$, 0.2mM dNTPs, 1.0 unit of Taq DNA polymerase and 1X of 5X Promega Green GoTaq™ Flexi Buffer. The PCR master mix for both SNPs was similar. Amplification was performed in Mastercycle thermocycler for the PCR reaction. The PCR condition started with an initial denaturation at 95°C for two minutes, followed by 30 cycles of denaturation at 95°C for 45 seconds, annealing at 58°C for 45 seconds (for *XRCC1* Arg194Trp rs1799782) and 54°C for 45 seconds (for *XRCC1* Arg399Gln rs25487), and extension at 72°C for 45 seconds, then a final extension at 72°C for five minutes. Next, PCR products were incubated for fast digestion for one hour at 37°C with the restriction enzyme *Pvull* (Fermentas, Vilnius, Lithuania) (for *XRCC1* Arg194Trp rs1799782) and restriction enzyme *Mspl* (Fermentas, Vilnius, Lithuania) (for *XRCC1* Arg399Gln rs25487) according to the manufacturer's instructions and subsequently analyzed by electrophoresis on a 2% agarose gel. After genotyping, the genotypes were categorized into three groups: homozygous wild type (major), heterozygous and homozygous variant (minor).

Statistical analysis

Statistical analysis was performed by using Statistical Package for the Social Sciences version 27.0 for statistical calculation. The genotype and allele frequencies for each SNPs of *XRCC1* were compared among cervical cancer patients and normal healthy controls using Pearson's chi-square (X^2) test or Fisher exact test. Next, the association of genotype and allele frequencies of *XRCC1* polymorphism (either singly and in combination) between cervical cancer patients and normal healthy controls were evaluated using logistic regression analysis by deriving odds ratio (ORs) and 95% confidence interval (CI) using unconditional logistic regression analysis. For all analyses, $p<0.05$ was considered as statistically significant.

Table I: Genotype and allele frequencies of XRCC1 Arg399Gln G>A (rs25487) in cervical cancer patients and controls

SNP	Model	Genotype	Cervical cancer patients (n=133)	Controls (n=133)	p-value
Arg399Gln G>A (rs25487)	Homozygous wild-type	GG	54 (40.6%)	78 (58.7%)	0.003*
	Heterozygous	GA	66 (49.6%)	41 (30.8%)	0.002*
	Homozygous variant	AA	13 (9.8%)	14 (10.5%)	0.541
	Dominant model	GG	79 (%)	55 (%)	0.003*
		GA + AA	54 (%)	78 (%)	
	Recessive model	GG + GA	120 (%)	119 (%)	0.841
		AA	13 (%)	14 (%)	
	Allele	G	174 (65.4%)	197(74.1%)	0.030*
		A	92 (34.6%)	69(25.9%)	

*p-value <0.05, statistically significant

Table II: Genotype and allele frequencies of XRCC1 Arg194Trp C>T (rs1799782) in cervical cancer patients and controls

SNP	Model	Genotype	Cervical cancer patients (n=133)	Controls (n=133)	p-value
Arg194Trp C>T (rs1799782)	Homozygous wild-type	CC	73 (54.9%)	68 (51.1%)	0.538
	Heterozygous	CT	54 (40.6%)	54 (40.6%)	1.000
	Homozygous variant	TT	6 (4.5%)	11 (8.3%)	0.210
	Dominant model	CC	73 (54.9%)	68 (51.1%)	0.537
		CT + TT	60 (45.1%)	65 (48.9%)	
	Recessive model	CC + CT	127 (95.5%)	122(91.7%)	0.210
		TT	6 (4.5%)	11 (8.3%)	
	Allele	C	200 (75.2%)	190(71.4%)	0.327
		T	66 (24.8%)	76(28.6%)	

*p-value <0.05, statistically significant

Table III: Risk association of XRCC1 Arg399Gln G>A (rs25487) with cervical cancer susceptibility

SNP	Model	Genotype	Cervical cancer patients (n=133)	Controls (n=133)	p-value
Arg194Trp C>T (rs1799782)	Homozygous wild-type	CC	73 (54.9%)	68 (51.1%)	0.538
	Heterozygous	CT	54 (40.6%)	54 (40.6%)	1.000
	Homozygous variant	TT	6 (4.5%)	11 (8.3%)	0.210
	Dominant model	CC	73 (54.9%)	68 (51.1%)	0.537
		CT + TT	60 (45.1%)	65 (48.9%)	
	Recessive model	CC + CT	127 (95.5%)	122(91.7%)	0.210
		TT	6 (4.5%)	11 (8.3%)	
	Allele	C	200 (75.2%)	190(71.4%)	0.327
		T	66 (24.8%)	76(28.6%)	

*p-value <0.05, statistically significant

Table IV: Risk association of XRCC1 Arg194Trp C>T (rs1799782) with cervical cancer susceptibility

SNP	Model	Genotype	Cervical cancer patients (n=133)	Controls (n=133)	OR (95% CI)	p-value
Arg194Trp C>T (rs1799782) (Ref)	Homozygous wild-type	CC	73 (54.9%)	68 (51.1%)	1.000	-
	Heterozygous	CT	54 (40.6%)	54(40.6%)	0.932 (0.564-1.538)	0.782
	Homozygous variant	TT	6 (4.5%)	11 (8.3%)	0.508 (0.178-1.449)	0.205
	Dominant model	CC	73 (54.9%)	68(51.1%)	0.860	0.539
		CT + TT	60 (45.1%)	65(48.9%)	(0.531-1.392)	
	Recessive model	CC + CT	127 (95.5%)	122(91.7%)	0.524	0.217
		TT	6 (4.5%)	11 (8.3%)	(0.188-1.461)	
	Allele	C	200 (75.2%)	190(71.4%)	0.825	0.327
		T	66 (24.8%)	76 (28.6%)	(0.561-1.212)	

*p-value <0.05, statistically significant

RESULTS

Genotype and allele frequencies of XRCC1 Arg399Gln G>A (rs25487) in cervical cancer patients and controls

The genotype and allele frequencies of XRCC1 Arg399Gln G>A (rs25487) in cervical cancer patients and controls are shown in Table I. Among the 133 cervical cancer patients, 66 (49.6%) showed heterozygous, 54 (40.6%) showed homozygous wild-type and 13 (9.8%) showed homozygous variant genotypes. In controls, the genotype frequencies were 78 (58.7%) for homozygous wild-type, 41 (30.8%) for heterozygous and 14 (10.5%) for homozygous variant. The heterozygous (GA) genotype was significantly higher in cervical cancer patients as compared to the controls. On the contrary, the homozygous wild-type (GG) was significantly higher in controls compared to the cervical cancer patients. The frequencies of G allele and A allele were 65.4% and 34.6% in cervical cancer patients and 74.1% and 25.9% in controls, respectively. Allele A was found to be significantly higher in cervical cancer patients (34.6%) compared to controls (25.9%) with a p-value <0.05.

Genotype and allele frequencies of *XRCC1* Arg194Trp C>T (rs1799782) in cervical cancer patients and controls

The genotype and allele frequencies of *XRCC1* Arg194Trp C>T (rs1799782) in cervical cancer patients and controls are shown in Table II. Out of the 133 cervical cancer patients, 73 (54.9%) showed homozygous wild-type, 54 (40.6%) showed heterozygous and 6 (4.5%) showed homozygous variant genotypes. In controls, the genotype frequencies were 68 (51.1%) for homozygous wild-type, 54 (40.6%) for heterozygous and 11 (8.3%) for homozygous variant. In cervical cancer patients, 75.2% showed C allele and 24.8% showed T allele, whereas in controls, 71.4% showed C allele and 28.6% showed T allele. No significant difference in the frequencies of these genotypes and alleles were found between cervical cancer patients and controls.

Risk association of *XRCC1* Arg399Gln G>A (rs25487) with cervical cancer susceptibility

Table III showed the associated risk of XRCC1 Arg399Gln G>A (rs25487) polymorphism with cervical cancer susceptibility. The heterozygous (GA) genotype showed significantly higher risk for cervical cancer susceptibility with OR: 2.325, 95% CI: (1.380-3.918) and p-value of 0.002. The homozygous variant (AA) showed higher risk values with OR: 1.341, 95% CI: 0.584-3.079, but were not statistically significant with p-value of 0.489.

Risk association of *XRCC1* Arg194Trp C>T (rs1799782) with cervical cancer susceptibility

Table IV shows the associated risk of XRCC1 Arg194Trp C>T (rs1799782) polymorphism with cervical cancer susceptibility. No significant risk association was found between the heterozygous and homozygous variant genotypes with cervical cancer susceptibility.

DISCUSSION

Study on the XRCC1 polymorphisms has become an area of interest for intensive research as the resultant functional alterations that impair the DNA damage cellular repair mechanism and genome stability, impose their possible role in cancer susceptibility risk. There are numerous studies done to investigate the role of XRCC1 polymorphism in cancer development including cervical cancer. However, most of the study pertaining to XRCC1 polymorphism and cervical cancer were conducted outside Malaysia. To the best of our available knowledge, there are no available reports on the association of XRCC1 polymorphism with cervical cancer in Malaysia. In our study, we investigated two commonest SNPs of *XRCC1* (XRCC1 Arg399Gln G>A (rs25487) and XRCC1 Arg194Trp C>T (rs1799782) and their association with cervical cancer susceptibility risk. We found a significant association of genetic polymorphism in *XRCC1* Arg399Gln G>A (rs25487) with cervical cancer susceptibility risk. Our study involved 133 cervical cancer patients and 133 healthy female control individuals revealed that carriers of heterozygous (GA) genotype of *XRCC1* Arg399Gln G>A (rs25487) showed significantly higher risk for cervical cancer susceptibility. Our findings on *XRCC1* Arg399Gln G>A (rs25487) association with cervical cancer risk are in agreement with other previous studies.

Studies found a significant association between XRCC1 Arg399Gln polymorphism and the risk of cervical carcinoma risk in both Caucasians and Asians.[24] In another study on XRCC1 Arg399Gln polymorphism by PCR-RFLP in 189 patients with advanced cervical cancer and 308 controls reveals patients with advanced cervical cancer having the Gln/Gln or Gln/Arg vs Arg/Arg genotype displayed a 1.726-fold increased risk of cervical cancer (95% confidence interval [CI]=1.158-2.572, p=0.007).30 The odds ratio for Gln/Gln vs Gln/Arg or Arg/Arg was 1.742 (95% CI=1.073-2.827; p=0.0236). They also found a significantly higher frequency of the *XRCC1* Arg399Gln allele in patients with cervical cancer than in controls, with OR=1.489 (95% CI=1.148-1.930, p=0.0026). Other studies also demonstrated a strong association of the *XRCC1* Arg399Gln polymorphism with an increased risk of cervical cancer.[25,26] In addition, study by Datkhile also in agreement with other findings where he found out *XRCC1* Arg399Gln were significantly increased in relation to the relative risk of cervical cancer (OR= 2.99; 95% CI= 1.60-5.56).7 Al-Harbi also found patients harbouring variant allele *XRCC1* Arg399Gln have approximately 1.5-fold increased risk to develop cervical cancer.[28]

On the other hand, our study observed no statistical association for *XRCC1* Arg194Trp C>T (rs1799782) with cervical cancer susceptibility risk. However, in other studies *XRCC1* Arg194Trp has been showed to be significantly associated with cervical cancer risk. A meta-analysis suggested *XRCC1* Arg194Trp was associated with significant cervical cancer risk (Trp/Trp vs Arg/Arg, OR = 2.21, 95% CI = 1.60–3.06; Arg/Trp vs Arg/Arg, OR = 1.23, 95% CI = 1.02–1.49; dominant model, OR = 1.36, 95% CI = 1.14–1.63; recessive model, OR = 2.06, 95% CI = 1.51–2.82).21 Besides, a significant association was found among XRCC1 Arg194Trp and cervical cancer (OR= 2.696; 95% CI= 1.181-6.154; p= 0.018, using an additive model), (OR=2.989; 95% CI= 1.078-8.283; p= 0.035, using a dominant model).29 A few other studies also discovered a positive association of the XRCC1 Arg194Trp with cervical cancer development risk.[25,26]

Genetic polymorphism of *XRCC1* was also found to be associated with various other cancers as well. A study found a statistical association between *XRCC1* Arg194Trp and

thyroid cancer risk with the homozygote genetic model (TT vs. CC: OR=1.815, 95% CI=1.115-2.953, p=0.016) and the recessive genetic model (TT vs. TC+CC: OR=1.854, 95% CI=1.433-2.399, p=<0.001).[25] A significant association was also found in similar study between *XRCC1* Arg399Gln polymorphism risk of thyroid cancer among Caucasians with allele genetic comparison (A vs. G: OR=0.882, 95% CI=0.794-0.979, p=0.136) and dominant genetic comparison (AA+AG vs. GG: OR=0.838, 95% CI=0.728-0.965, p=0.014).25 In addition, study also found XRCC1 Arg399Gln might be a risk factor for non-melanoma skin cancer in Asian populations, and the XRCC1 Arg194Trp might be a protective factor for patients with squamous-cell skin cancer cases.[27] Besides, a meta-analysis in a study noted *XRCC1* Arg399Gln is a potential predictor for susceptibility to nasopharyngeal carcinoma, especially for Asians.[26]

Although our study shows a significant association of one of the SNP studied XRCC1 Arg399Gln G>A (rs25487) with cervical cancer risk, there are a few limitations that needs to be highlighted. Firstly, our study examined the association of only two SNPs of XRCC1 with cervical cancer risk. Other SNPs or genes that are involved in all pathways of DNA repair were clearly not covered and this can be considered for the future study. DNA repair pathway mechanism is a very complex process and the molecular target focus for research study is massive and obviously our findings does not conclusive and representative of all. To get better clearer and broader picture, future research need to incorporate multiple genes studies involved in DNA repair pathway and its association in cervical cancer development. With the advent of massively parallel sequencing technologies such as whole genome sequencing or whole exome sequencing, this research question has a huge potential to be answered and the application in the research need to be considered. In addition, we acknowledge the limitation of the time for the research conducted, research budget as well as the limited research resources and skills. In addition, this study was conducted using achieved DNA samples that was extracted from peripheral blood of the previous researcher. Thus, there are limitations in getting the details of clinicopathological data that was conducted earlier due to missing data. Because of this limitation, we are not able to discuss further details on the other aspect particularly related to demographic background such as ethnic background, age, and other socio-demographic and salient clinical information of each participants.

The advances in SNP mapping utilizing high throughput DNA sequencing could facilitate the analysis of variants in DNA repair pathway. This may contribute to the advancement of knowledge on genetic predisposing factors related to cervical cancer susceptibility risk in Malaysian population. This, in turn may help to identify the high risk individuals with cervical cancer susceptibility risk genotype in the population and devise appropriate preventive strategies as well as incorporate this molecular genetic approach in the patient's clinical management. One of the significant aspect of this study on *XRCC1* in cervical cancer that would like to emphasize on the potential outlook of this study findings as this *XRCC1* genotype detection is expected to be a molecular marker for gynaecologic cancer screening according to meta-analysis by 18. This is a huge potential for the future diagnosis of cervical cancer as this can help treating physician to incorporate this genetic testing in the management of the cervical cancer. Future research need to be explored further for better understanding and implementation in our local population.

CONCLUSION

Our study demonstrated an association between genetic polymorphisms in one of DNA repair pathway (BER) gene *XRCC1* Arg399Gln G>A (rs25487) with susceptibility risk of cervical cancer patients. The positive association from this research study may be considered to be applied as a screening tool for early detection in cervical cancer patient in the future. However no significant association was observed for *XRCC1* Arg194Trp C>T (rs1799782) with cervical cancer susceptibility risk. Although a prospective study with a larger patient population and involvement of multiple SNPs and genes necessary to validate this findings, our findings provides preliminary data locally and opportunity for future study.

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ORIGINAL ARTICLE

The relationship between neutrophil to lymphocyte ratio and the success of hydrostatic reduction in patients with intussusception

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ABSTRACT

Introduction: Intussusception is a common emergency condition in children. Intussusception leads to inflammation, which is marked by an increase in acute inflammatory markers, including the Neutrophil-Lymphocyte Ratio (NLR). Reduction of sedation (SR) using air or fluid enema is considered safe and effective. We present examining the relationship between NLR and the success of hydrostatic reduction in patients with intussusception for 3 years.

Materials and Methods: A retrospective study was conducted from July 2021 to July 2024 in Yogyakarta, Indonesia, involving 41 children with intussusception who underwent hydrostatic reduction under sedation. Demographic, clinical, and laboratory data were collected from medical records, and NLR values were calculated from neutrophil and lymphocyte counts. Receiver operating characteristic (ROC), bivariate, and multivariate analyses were performed to evaluate the association between NLR and successful reduction.

Results: The average age of children who successfully underwent reduction was 25.5 months, compared to 9 months in those who failed. The proportion of children with bleeding stool in the successful reduction group was 28.6%, while it was 73.3% in the unsuccessful, with a p-value <0.05 (0.005). Bivariate analysis indicated that NLR is a significant predictor of successful reduction under sedation procedure with a p-value <0.05 (0.031). Children with NLR <1.73 had a success rate of 84.6%, with a p-value of <0.05 (0.036).

Conclusion: The success rate of hydrostatic reduction is higher in children with a low NLR. This study provides new insights into how NLR can predict the success of SR in children with intussusception.

KEYWORDS:
Intussusception, pediatric surgery, neutrophile lymphocyte ratio, hydrostatic reduction with sedative

INTRODUCTION

Intussusception is a medical emergency in which one part of the intestine slides into and partially folds within another, leading to a bowel obstruction.[1] This condition is often referred to as "telescoping" because the way the segments fit together resembles the structure of a telescope.[2] Typically, intussusception affects the small intestine. This condition is a serious medical condition and a type of bowel obstruction. While it can occur at any age, it is most frequently seen in children aged 3 months to 3 years.[1,3,4]

Obstruction that occurs in the case of intussusception will increase intraluminal pressure and cause an inflammatory reaction, which subsequently increases the risk of perforation of the intestinal wall and leads to peritonitis or sepsis.[1,3,4] In recent decades, the role of neutrophils in chronic inflammation has been widely studied. Neutrophil are the first line defense mechanism in human body, which will go to the sites of ongoing inflammation, where they actively propel the inflammatory response. The neutrophil will secrete serine proteases and neutrophil extracellular traps (NETs), alongside with cytokines.[5]

The treatment of colonic intussusception is usually managed by first reducing the telescoped section. If the reduction procedure failed to resolve the intussusception or if there has been a perforation or sepsis, then performing a surgical resection is necessary.[1,3,6] Some studies had been shown that the inflammation that happened in intussusception has a significant effect on the need of surgery.[2,4,6,7] The use of the Neutrophil-Lymphocyte ratio (NLR) as an inflammatory marker has been explored in various clinical settings, including those with gastrointestinal (GI) obstruction.[8]

The NLR is simply the number of neutrophils divided by the number of lymphocytes. Under physiologic stress, the number of neutrophils increases, while the number of lymphocytes decreases.[9–15] However, the relationship between NLR and the success of hydrostatic reduction in pediatric intussusception remains unclear. Therefore, this study aimed to evaluate the relationship between NLR and the success of hydrostatic reduction in patients with intussusception.

MATERIALS AND METHODS

Study Design and Patients

A retrospective study was conducted from July 2021 to July 2024 in Yogyakarta, Indonesia. The study evaluated children diagnosed with intussusception who underwent hydrostatic reduction under sedation. A total of 41 pediatric patients

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were included in this study. Patients with incomplete medical record were excluded from the analysis. The outcome of hydrostatic reduction was classified as successful or failed reduction and was subsequently analyzed in relation to NLR levels.

Data Collection

Demographic and clinical characteristics, including age, sex, vomiting, bloody stool, abdominal distension, pseudoportio, location of intussusception, duration of symptoms, and NLR values, were collected from medical records. Laboratory findings obtained before the reduction procedure were used to calculate NLR values by dividing the absolute neutrophil count by the absolute lymphocyte count. The success of hydrostatic reduction under sedation was recorded and compared according to patients' NLR levels.

Statistical Analysis

The data collected were analyzed using Statistical Package for the Social Sciences (SPSS) software. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the relationship between NLR and the success of hydrostatic reduction in patients with intussusception. The optimal cutoff value of NLR was determined using the Youden index. Bivariate and multivariate analyses were also performed to identify factors associated with successful reduction. A p-value of <0.05 was considered statistically significant.

RESULTS

We had a total of 41 patients in the sample. The group with successful reduction was older than the group with unsuccessful reduction (25.5 months vs. 9 months), with a significant difference. The proportion of bloody stools in the successful reduction group (28.6%) was lower compared to the unsuccessful group (73.3%), with a significant difference. Patients with a lower NLR value have better outcomes compared to those with a higher NLR value ($p<0.05$).

On the other hand, no significant differences ($p>0.05$) were observed based on sex, vomiting, abdominal distension, pseudoportio, duration of symptoms (Table I).

The ROC analysis (Figure 1) results showed that NLR is a significant predictor of reduction success ($p=0.031$). The AUC value of 0.723 indicates moderate discriminatory ability of NLR in predicting the success of reduction. Optimal cutoff point using the Youden index method was found to be an NLR of 1.195, with a sensitivity of 50.0% and specificity of 90.0%.

Based on Table II, patients with a low NLR had a higher success rate in reduction (93.8%) than high NLR (60.0%), with a significant difference ($p=0.028$). The RR value of 1.56 means that patients with a low NLR are 1.56 times more likely to experience a successful reduction.

Variables that are significant in the bivariate test are continued in multivariate analysis using the backward method, which is excluding one by one the variables that are not significant (Table III). In the final step, the significant variables were found to be NLR ($p=0.045$, adj. RR=1.57) and bloody stool ($p=0.016$, adj. RR=1.09).

DISCUSSION

The patient characteristics (Table I) indicate that age tends to be a factor in experiencing intussusception, particularly at 9 months, along with the presence of bloody stools and pain located on the right side ($p<0.05$). However, characteristics such as sex, vomiting, abdominal distension, pseudoparalysis, pain duration, and NLR did not show significant results ($p>0.05$).

Intussusception is defined as the invagination of one part of the bowel into another.[1] It is also recognized as the second most common cause of acute abdominal pain in preschool children, after constipation.[3] Intussusception has the classical clinical presentation of colicky abdominal pain and vomiting with signs of red currant jelly stools and abdominal lump in a child less than 2 years. In addition, doughnut and pseudo-kidney sign on abdominal ultrasound are diagnostic features of intussusception.[16–19] These findings are important as they may help in the early identification of disease severity and progression.

The ROC curve analysis shows that NLR can be a significant predictor for measuring reduction success in patients with intussusception, with an AUC value of 0.723 (>0.5). The optimal cutoff point of NLR at 1.195 has a sensitivity of 50% and specificity of 90.9%. Based on these results, patients with a low NLR had a reduction success rate 1.56 times higher compared to those with a high NLR, with a p-value <0.05 (Table II). These findings are consistent with previous predictions, where a high NLR is expected to indicate a higher level of inflammation in the body, which in turn can affect the success of the reduction.

In Table III, both NLR and the presence of bloody stool were significant predictors for the need of surgery. Patients with a low NLR had a reduction success rate 1.57 times higher compared to those with a high NLR, while patients without bloody stool had a reduction success rate 1.09 times higher compared to those with bloody stool. Taken together, these findings suggest that both the level of inflammation in the body and patient's clinical manifestations may play an important role in determining the need for surgical intervention.

NLR is a well-recognized marker of the inflammatory response, where an increase in NLR is known to be a sign that active inflammation is occurring.[5] During intussusception, this inflammatory process increases the risk of intestinal wall perforation and causing peritonitis or sepsis.[1,3,4] The inflammation that occurs will also create edema in the intestinal wall and make the intussusception folds more difficult to reduce with hydrostatic reduction.10 As a result, a higher NLR may indicate a more severe inflammatory response, which could make non-surgical reduction less likely to succeed.

The findings in this study are in line with previous research. In a study by Delgado-Miguel et al. (2023) of 511 pediatric patients who had ileocolic intussusception, reported that high NLR values indicate a high level of intestinal inflammation and may anticipate the need for surgical treatment of ileocolic intussusception in children.[7] Similarly, Chen et al. (2021), in a study of 115 patients with intussusception found that NLR value, CRP level, neutrophil

Table I: Baseline Characteristics of the Patients

Characteristics		Success (n = 30)	Failed (n = 11)	Total (n = 41)	p-value
Age (months)	Median (min–max)	25.5 (0-60)	9 (6-72)	24 (0-72)	0.002*
Sex Male	16 (53.3%)	7 (63.6%)	23 (56.1%)	0.726	
	Female	14 (46.7%)	4 (36.4%)	18 (43.9%)	
Vomit	Yes	17 (56.7%)	10 (90.9%)	27 (65.9%)	0.064
	No	13 (43.3%)	1 (9.1%)	14 (34.1%)	
Bloody stool	Yes	10 (33.3%)	9 (81.8%)	19 (46.3%)	0.006*
	No	20 (66.7%)	2 (18.2%)	22 (53.7%)	
Abdominal distension	Yes	6 (20.7%)	6 (54.5%)	12 (30.0%)	0.056
	No	23 (79.3%)	5 (45.5%)	28 (70.0%)	
Location	Right	30 (100.0%)	8 (72.7%)	38 (92.7%)	0.015*
	Left	0 (0.0%)	3 (27.3%)	3 (7.3%)	
Pseudoportio	Yes	0 (0.0%)	2 (18.2%)	2 (4.9%)	0,067
	No	30 (100.0%)	9 (81.8%)	39 (95.1%)	
Duration (hours)	Median (min – max)	48 (24-168)	48 (24-168)	48 (24-168)	0,988
NLR	Mean ± SD	1.48 ± 0.90	2.16 ± 0.89	1.67 ± 0.94	0,039*

*Statistically significant at p=0.05

Table II: NLR Predicted Success for Reduction of Intussusception

	Success (n = 30)	Failed (n = 11)	p-value	RR	95% CI
NLR <1.195	15 (93.8%)	1 (6.3%)	0.028*	1.56	1.11-2.20
NLR >1.195	15 (60.0%)	10 (40.0%)			

*Statistically significant at p=0.05

Table III: Multivariate analysis

Variable	Step 1 p-value	Step 2 p-value	Step 3	
			p-value	Adj. RR (CI 95%)
NLR	0.089	0.051	0.045*	1.57 (1.08-2.27)
Age	0.250	0.171		
Bloody stool	0.144	0.079	0.016*	1.09 (1.02-1.16)
Location	0.999			

*Statistically significant at p=0.05

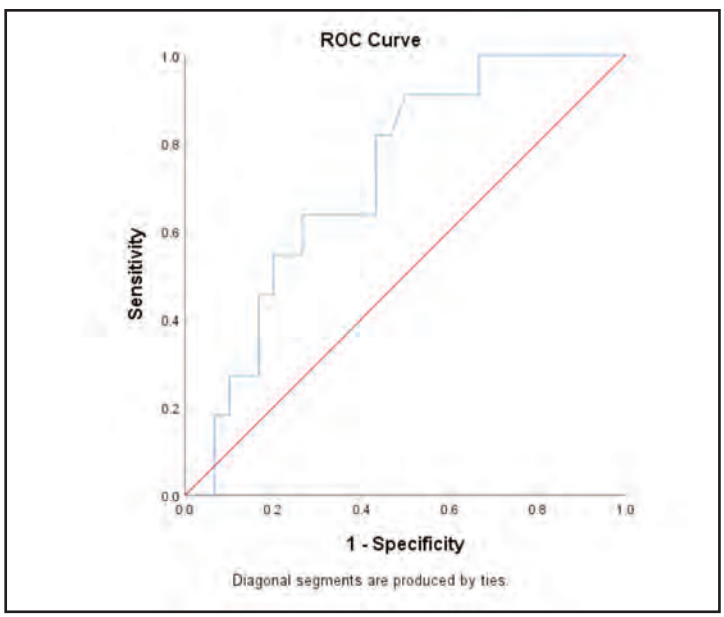

Fig. 1: ROC curve of NLR predicting successful hydrostatic reduction

count, and lymphocyte-CRP ratio have significant correlation with the need for surgical treatment of ileocolic intussusception.[2] In addition, a study conducted by Zhu et al. (2023) in 136,347 patients who underwent surgery at Sichuan University West China Hospital also stated that the prognostic model scores were significantly higher in the High-NLR group. The High-NLR group had a higher proportion of emergency cases (27.0% vs. 1.7%; p<0.001), higher intraoperative transfusion rates (11.7% vs. 2.4%; p<0.001), and chronic comorbidities such as chronic heart failure, cardiomyopathy, hemiplegia, paraplegia, and paralytic syndrome. This is in-line with research indicating that NLR values can be a prognostic factor in determining a patient's condition.[19]

Consistent with these findings, Putranto and Pramesta (2023) reported that NLR can be a reliable indicator for predicting surgical outcomes in 150 patients with GI obstruction at Cipto Mangunkusumo Hospital, Jakarta. They found that patients with a higher NLR have a greater risk of morbidity and mortality postoperatively. A higher NLR may indicate more intense systemic inflammation, which may potentially affect the success of recovery after major medical procedures.[14]

Although this study had a small sample size, our findings were consistent with previous studies that used larger samples. Therefore, further studies with larger sample sizes are needed to confirm these findings and minimize potential bias. Finally, the novelty of this study lies in the use of an Indonesian population to provide locally relevant evidence and broaden the existing literature on pediatrics intussusception.

CONCLUSION

The success rate of hydrostatic reduction is higher in children with a low NLR. This study provides new insights into how NLR can predict the success of SR in children with intussusception.

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ORIGINAL ARTICLE

Evaluation of vision-related quality of life and its associated factors in patients with diabetic vitreoretinal disease post trans pars plana vitrectomy using visual functioning questionnaire-25

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ABSTRACT

Introduction: Diabetic vitreoretinal disease often requires trans pars plana vitrectomy (TPPV) to preserve useful vision. Its impact on patients' vision-related quality of life (VRQoL) has not been fully detailed locally, especially Kelantan. We evaluated post-operative changes in VRQoL, using the validated Malay version National Eye Institute-Visual Functioning Questionnaire-25 (NEI-VFQ-25) questionnaire, and identified pre-operative and clinical factors associated with 3-months post TPPV NEI-VFQ-25 scores.

Materials and Methods: In this prospective cohort study, 85 patients with type 1 or 2 diabetic vitreoretinal disease undergoing first TPPV at Hospital Pakar Universiti Sains Malaysia and Hospital Raja Perempuan Zainab II were recruited between December 2023 and December 2024. Demographic data, systemic and ocular profiles were reviewed and recorded. VRQoL was assessed pre-operatively and at 3-months post TPPV using the NEI-VFQ-25 questionnaire. Factors associated with VRQoL at 3-months post TPPV were analysed using linear regression analysis.

Results: A total 85 patients completed 3 months follow-up post TPPV. NEI-VFQ-25 composite score significantly improved from 49.28±13.98 pre-operatively to 57.45±12.30 at 3-months post TPPV (mean difference 8.16; 95% Confidence Interval 7.13-9.20; p<0.001). In univariate analyses, employment, hyperlipidaemia, diabetic nephropathy, pre-operative blindness status, tertiary education level and pre-operative NEI-VFQ-25 score were the significant factors associated with 3-months post TPPV VRQoL (p<0.05). In multivariable regression, secondary and tertiary education level, presence of other comorbid and pre-operative NEI-VFQ-25 score were the significant factors (p<0.001).

Conclusion: TPPV yields significant improvements in VRQoL by 3 months. Patients' pre-operative VRQoL, as well as higher education levels and presence of other comorbid are among the strongest determinants of post-operative VRQoL, emphasising the value of early intervention and patient counselling.

KEYWORDS:
Diabetic vitreoretinal disease, pars plana vitrectomy, vision-related quality of life, VFQ-25, linear regression.

INTRODUCTION

Diabetes mellitus remains a prominent global health concern, ranking among the top ten non-communicable causes of morbidity and mortality.[1] In 2019, an estimated 463 million adults worldwide had diabetes, and this number is projected to reach 700 million by 2045.[2,3] A significant complication of diabetes is diabetic retinopathy (DR), characterized by progressive retinal microvascular damage due to sustained hyperglycaemia.[4] Over two decades, nearly all patients with type 1 diabetes and around 60% of type 2 diabetes patients develop some stage of DR. This disease progresses from mild non-proliferative diabetic retinopathy (NPDR), characterized by microaneurysms, to moderate and severe forms displaying more extensive retinal haemorrhages, venous beading, and intraretinal microvascular anomalies. Advanced stages, termed proliferative diabetic retinopathy (PDR), involve neovascularization with or without haemorrhages and can evolve into advanced diabetic eye disease (ADED), featuring complications like retinal detachment, vitreous haemorrhage, and macular anomalies.

In Malaysia, DR is prevalent in approximately 51.6% of diabetic patients, with 28.1% experiencing vision-threatening PDR and 26.7% developing maculopathy.[5] Then, up to 15.0% of eyes had vision threatening DR needing laser or surgery at their first visit.[6] Notable risk factors for DR progression include longer diabetes duration, hypertension, and systemic complications such as nephropathy and peripheral neuropathy.[5] Data from the Early Treatment Diabetic Retinopathy Study (ETDRS) indicate a cumulative five-year incidence of diabetic vitrectomy at approximately 5.3%, with frequent follow-up examinations and timely scatter panretinal photocoagulation, primarily due to non-clearing vitreous haemorrhage and retinal detachment.[7] Poor glycaemic and metabolic control notably elevates the likelihood of requiring surgical intervention.[8] Chronic hyperglycaemia plays a central role in DR development via multiple metabolic pathways including the polyol pathway,

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advanced glycation end-products, protein kinase C activation, and the hexosamine pathway. These biochemical changes initially result in retinal vessel dilation and altered blood flow, subsequently causing pericyte loss, endothelial apoptosis, and capillary occlusion. Retinal ischemia elevates vascular endothelial growth factor, exacerbating vascular permeability and retinal damage.[9] Concurrently, chronic low-grade inflammation, driven by increased leukocyte adhesion and elevated cytokines such as tumour necrosis factor-α, interleukin-6, and chemokines, further deteriorates the retinal microvasculature and barrier function.[9] Neuronal apoptosis and mitochondrial dysfunction are additional factors significantly contributing to retinal neurodegeneration and DR progression.[9] Trans pars plana vitrectomy (TPPV) is a standard surgical intervention employed to manage severe vitreoretinal complications of diabetes such as retinal detachments and vitreous haemorrhages, significantly enhancing postoperative visual acuity and visual functioning.[10,11] Studies have demonstrated that TPPV effectively improves vision-related quality of life (VRQoL), particularly in general vision, near and distance activities, and social and emotional scale (domains).[12-14] The National Eye Institute Visual Functioning Questionnaire-25 (NEI-VFQ-25) has been validated extensively to evaluate these patient-centred outcomes across diverse populations.[15-17] Despite its effectiveness, TPPV carries potential risks, including retinal tears, haemorrhages, and postoperative complications such as cataracts and glaucoma.[10]

Therefore, assessing VRQoL and associated factors following TPPV, especially within local Malaysian contexts, is essential. This study addresses the critical need for region-specific observational data regarding TPPV outcomes on visual acuity and quality of life (QoL) among diabetic vitreoretinal patients, filling a gap crucial for clinical decision-making and patient counselling.

MATERIALS AND METHODS

Study Design

A prospective cohort study was conducted at Ophthalmology Clinic, Hospital Pakar Universiti Sains Malaysia and Hospital Raja Perempuan Zainab II between December 2023 and December 2024. Approval for the study was obtained from the Human Research Ethics Committee of Universiti Sains Malaysia (JEPeM Code: USM/JEPeM/23110908) and in accordance with the tenets of Declaration of Helsinki. National Medical Research Register approval number: NMRR ID- 23-03058-NYY (IIR).

Patient Selection and Data Collection

A total of 85 patients were enrolled in this study. All of them underwent first TPPV with the indication of diabetic vitreoretinal disease with underlying diabetes mellitus (type 1 & 2). All of them aged over 18 years old.

Patients who are less than 18 years old, undergoing more than once TPPV, reoperation of TPPV within 3 months, unable to complete questionnaire with assistance of doctors, undergoing TTPV with indications other than diabetic vitreoretinal disease, those with retinal disease affecting the macula (e.g., inherited retinal diseases, pathologic myopia), those with ophthalmologic conditions other than diabetic vitreoretinal disease such as ocular inflammation (e.g., uveitis), ocular malignancy, or any media opacity that obscure fundus view, those who have been diagnosed with depression or any mental health issues, those with cognitive dysfunctions such as, dementia, Alzheimer's disease or memory lost, those with physical disabilities such as, post lower limbs amputation or post trauma, and those with concurrent terminal illness, such as cancer were excluded from this study.

Patients were classified as having diabetic vitreoretinal disease with tractional retinal detachment (TRD), either with or without vitreous haemorrhage, or as combined TRD and rhegmatogenous retinal detachment (RRD), also with or without vitreous haemorrhage.

All patients were screened for inclusion and exclusion criteria during an interview session. A written informed consent was obtained after an explanation of the nature and consequences of the study. Demographic data, including age, gender, marital status, race and occupation were collected. Systemic history including history of co-morbidity such as hypertension, hyperlipidaemia, diabetic nephropathy, type of vitreoretinal disease and laterality. Only one principal investigator conducted the session to minimize errors. Distance best corrected visual acuity (BCVA) was recorded using Snellen's chart at 6 meters for both eyes. Blindness is defined as BCVA of poorer than 3/60 in the better eye with best possible correction.[18]

Previous documentation of clinical presentation, eye examinations and investigations were collected from the medical records. Patients were referred to Ophthalmology Clinic for eye examinations if there were no previous eye examinations before.

National Eye Institute-Visual Functioning Questionnaire-25

In this study, the NEI-VFQ-25 questionnaire was used to assess the VRQoL. The questionnaire consists of 25 vision-targeted questions covering 11 vision-related scales, along with an additional single-item general health rating question. The NEI-VFQ-25 generates vision-targeted scales, including global vision rating, difficulty with near and distance vision activities, limitations in social functioning due to vision, role limitations due to vision, dependency on others due to vision, mental health symptoms due to vision, driving difficulties, limitations with peripheral and colour vision, and ocular pain. To overcome the language barrier, the questionnaire was translated into the national language of each respective country, including a Malay version for the Malaysian population.

The NEI-VFQ-25 scoring process, with or without optional items, involves two steps: Step 1 involves re-coding of the answer to a new value according to the Table I. All items are scored so that a higher score represents better functioning. Each item is then converted to a 0 to 100 scale, where the lowest score is 0, and the highest possible score is 100 points. Step 2 involves calculating scale scores. Items within each scale are averaged together to create the 12 scale scores. Table II indicates which items contribute to each specific scale. Items left blank (missing data) are not taken into account when calculating the scale scores. Each subscale item was given 5- and 6- points on the Likert scale, and the higher

score for each subscale represents better functioning. This two-step process ensures a standardised and consistent approach to scoring the NEI-VFQ-25, allowing for accurate interpretation and comparison of results.

In this study, the principal investigator administered the previously Malay translated and validated questionnaires face to face, on one-to-one approach in the consultation room of the ophthalmology clinic. To ensure a comfortable and patient-friendly environment, all interviews were conducted in a quiet room, free from interruptions. Each question was explained to the patient and after proper understanding of the question; the patient's answers were recorded. If difficulty comprehending the question aroused, a relative or caregiver present helped to explain the question to the patient. The NEI-VFQ-25 questionnaire took approximately 20 minutes. Pre-operatively, the NEI-VFQ-25 questionnaire was done within 1 week before operation, whereas 3-months post TPPV, the NEI-VFQ-25 questionnaire was done within 2 weeks. To minimise errors while conducting the study, the same questionnaire was used for the purpose of all measurements in the study, a single interviewer performed the task of asking the questions to minimise variation, and the questionnaire was conducted face to face, one on one approach.

Statistical Analysis

All relevant data such as age, race, gender, marital status, history of systemic diseases, and ocular profile from the case report form as well as NEI-VFQ-25 questionnaires were analysed using Statistical Package for Social Sciences (SPSS) version 26. All data were rechecked to avoid wrong data entry and missing data.

Descriptive statistics were used to analyse the demographic data, clinical profiles and distribution of the VRQoL scores pre- and post-TPPV, and of each scale of NEI-VFQ-25. Paired t-test was used to compare the VRQoL score between pre-operative and at 3-months post TPPV.

Simple and multiple linear regression analysis was conducted to determine the factors associated with NEI-VFQ-25 composite score including all the demographic factors, systemic comorbidities, and ocular profile. A p-value less than 0.05 was considered statistically significant.

RESULTS

A total of 85 patients with diabetic vitreoretinal disease planned for TPPV were enrolled in this study. The mean age of the patients is 60.73±9.79 years old. There was a male preponderance of slightly more than half (51.8%) among the patients. Among the subjects, 41 patients (48.2%) had tertiary education, and 43 patients (50.6%) were employed. Out of the total, 59 patients (69.4%) have other systemic comorbidities, which included stroke (7 patients, 8.24%), chronic obstructive pulmonary disease (10 patients, 11.76%), ischaemic heart disease (7 patients, 8.24%), cancer (5 patients, 5.88%), bronchial asthma (12 patients, 14.12%), and allergic rhinitis (18 patients, 21.18%). There was a slightly higher number of patients with bilateral diabetic vitreoretinal disease (56.5%). Most of the subjects were not blind (91.8%). Out of the total, 47 patients (55.3%) have TRD only, with those having vitreous haemorrhage consists of 8 patients (9.41%), 38 patients (44.7%) have both TRD and RRD, with those having vitreous haemorrhage consists of 5 patients (5.88%). Out of the overall patients, only 1 (1.2%) had post TPPV complication, which was secondary high intraocular pressure which resolved after 1 month. The socio-economic data and clinical profiles of patients with diabetic vitreoretinal disease is shown in Table III.

All 85 patients completed the interview for VRQoL using NEI-VFQ-25 pre-operatively and at 3-months post TPPV. General vision scale demonstrated increasing number of patients for good subscale from 10 (11.8%%) patients pre-operative to 31 (36.5%) patients at 3-months post TPPV. As for distance and near activities scales, there were reduction in number of patients for subscale extreme difficulty from 27 (31.8%) patients pre-operative to 8 (9.4%) patients at 3-months post TPPV and from 17 (20.0%) patients pre-operative to 7 (8.2%) patients at 3-months post TPPV, respectively. Both colour vision and peripheral vision scales showed increasing number of patients for subscale little difficulty from 31 (36.5%) patients pre-operative to 50 (58.8%) patients at 3-months post TPPV, and from 10 (11.8%) patients pre-operative to 50 (58.8%) patients at 3-months post TPPV, respectively.

VRQoL improved markedly at 3-months post TPPV (Table IV). The mean composite NEI-VFQ-25 score rose from 49.28±13.98 pre-operatively to 57.45±12.30 at 3-months post TPPV. Nearly all vision-targeted scales showed significant gains-most notably general vision, peripheral vision, and mental health, each $p<0.001$, while general health remained unchanged and ocular pain improved only slightly.

As peripheral vision and social functioning scales violated normality, Wilcoxon signed-rank tests were applied. Both scales shifted upward: median peripheral vision improved significantly from 50.00 to 75.00 ($Z = -7.27$; $p<0.001$), and social functioning increased from a median of 50.00 to 66.67 ($Z = -5.89$; $p<0.001$). These nonparametric confirmations reinforce that TPPV produces consistent patient-perceived benefits across even skewed QoL measures.

The associated factors affecting the NEI-VFQ-25 score at 3-months post TPPV were analysed using linear regression analysis. In a simple linear regression model, tertiary education level, employment, hyperlipidaemia, diabetic nephropathy, pre-operative blindness status, pre-operative NEI-VFQ- 25 score were significant factors associated with 3-months post TPPV NEI-VFQ-25 score. For the factors with p-value <0.25 during simple linear regression model and factors clinically meaningful were included in the multiple linear regression analysis: age, education level, occupation, hypertension, hyperlipidaemia, diabetic nephropathy, presence of other comorbid, laterality, pre-operative blindness status, type of vitreo-retinal disease and pre-operative NEI-VFQ-25 score. However, only secondary education level, tertiary education level, presence of other comorbid and pre-operative NEI-VFQ-25 score were the significant associated factors affecting 3-months post TPPV NEI-VFQ-25 score during multiple linear regression model.

Table I: Step 1: Scoring key of NEI-VFQ-25

Item Numbers	Original Response Category(a)	Recorded Value:
1,3,5,15c(b)	1	100
	2	75
	3	50
	4	25
	5	0
	1	100
	2	80
	3	60
	4	60
	5	60
	6	0
17,18,19,20,21,22,23,24,	1	0
25,A11a,A11b,A12,A13	2	25
	3	50
	4	75
	5	100
A1, A2	0 to 10	0 to 100

Footnotes:
(a) Precoded response choices as printed in the questionnaire.
(b) Item 15c has four-response levels, but is expanded to five-levels using item 15b.
Note: If 15b=1, then 15c should be recoded to "0". If 15b=2 or 3, then 15c should be recoded to missing.
(c) "A" before the item number indicates an optional item from the Appendix. If optional items are used, the NEI-VFQ developers encourage users to use all items for a given sub-scale.
This enhances the comparability of sub-scale scores across studies.
(d) Response choice "6" indicates the person does not perform the activity because of non-vision related problems. If selected, the item is coded as "missing."

Table II: Step 2: Averaging of items to generate NEI-VFQ-25 scales

Scale	Number of items	Items to be averaged (after recoding per Table II)
General Health	1	1
General Vision	1	2
Ocular Pain	2	4, 19
Near Activities	3	5, 6, 7
Distance Activities	3	8, 9, 14
Vision Specific:		
Social Functioning	2	11, 13
Mental Health	4	3, 21, 22, 25
Role Difficulties	2	17, 18
Dependency	3	20, 23, 24
Driving	3	15c, 16, 16a
Colour Vision	1	12
Peripheral Vision	1	10

Education level was a strong positive determinant of VRQoL. Compared with primary education, tertiary education had a 5.43 higher score of post TPPV NEI-VFQ-25 score, while secondary schooling had a 4.32 higher score of post TPPV NEI-VFQ-25 score, after controlling for presence of other comorbid and pre-operative NEI-VFQ-25 score. Those with presence of other comorbid had 3.69 points higher score post TPPV NEI-VFQ-25 score compared to those without, after controlling for education level and pre-operative NEI-VFQ-25 score. Whereas for pre-operative NEI-VFQ-25 score, 1 unit increase of score would increase 0.77 score in post TPPV NEI-VFQ-25 score, after controlling education level and presence of other comorbid (Table V).

The model met the assumptions of Multiple Regression analysis and accounted for 91.3% of the variability in the 3-months post TPPV NEI-VFQ-25 score. There is no multicollinearity problem. There is a significant interaction between other comorbid with pre- op VFQ- 25 score. p-value <0.05 is statistically significant

These results show that higher education, with presence of other systemic illness and level of pre-operative NEI-VFQ-25 score, predict a better post TPPV NEI-VFQ-25 score. Targeting these modifiable factors- through patient education, metabolic optimization, and early surgical referral- may maximize VRQoL gains after TPPV.

DISCUSSION

Patients with diabetic vitreoretinal disease frequently endure severe visual impairment, which profoundly compromises daily activities, social engagement, emotional health, and overall quality of life.[19] TPPV is a well- established surgical intervention to address advanced complications such as TRD and non- clearing vitreous haemorrhage, preserving or restoring functional vision.[10] However, patient-reported outcomes, particularly VRQoL measured by the NEI-VFQ-25, have received comparatively less attention in Malaysian populations. This study demonstrates that TPPV yields significant and clinically meaningful improvements in

Table III: Socio-Demographic Data and Clinical Profiles of Patient with Diabetic Vitreoretinal Disease, (n=85)

Variables	n (%)
Age (years) [mean (SD)]	60.73 (9.79)
Gender	
Male	44 (51.8)
Female	41 (48.2)
Race	
Malay	75 (88.2)
Non- Malay	10 (11.8)
Education Level	
Primary	14 (16.5)
Secondary	30 (35.3)
Tertiary	41 (48.2)
Occupation	
Unemployed	42 (49.4)
Employed	43 (50.6)
Hypertension	
Present	50 (58.8)
Absent	35 (41.2)
Hyperlipidaemia	
Present	22 (25.9)
Absent	63 (74.1)
Diabetic nephropathy	
Present	12 (14.1)
Absent	73 (85.9)
Other co- morbid(s)	
Present	59 (69.4)
Absent	26 (30.6)
Laterality	
Unilateral	37 (43.5)
Bilateral	48 (56.5)
Pre-operative blindness status	
unilateral blindness	0 (0.0)
bilateral blindness	7 (8.2)
not blind	78 (91.8)
Post-TPPV blindness status	
unilateral blindness	0 (0.0)
bilateral blindness	7 (8.2)
not blind	78 (91.8)
Types of Vitreoretinal Disease	
TRD only	47 (55.3)
TRD and RRD	38 (44.7)

TRD: tractional retinal detachment, RRD: rhegmatogenous retinal detachment,
TPPV: trans pars plana vitrectomy

Table IV: Mean Vision Related Quality of Life based on NEI-VFQ-25 Score in Patients with Diabetic Vitreoretinal Disease

NEI-VFQ-25 Scale	NEI-VFQ-25 Score		Mean difference (95% CI)	t-statistic (df)	p-value
	Pre-operative Mean (SD)	At 3-months post TPPV Mean (SD)			
Composite Score	49.28 (13.98)	57.45 (12.30)	8.17 (7.13, 9.20)	15.68 (84)	<0.001
Scale score					
General health	46.18 (13.98)	47.12 (14.76)	0.94 (-0.35, 2.23)	1.45 (84)	0.152
General vision	44.53 (17.97)	59.64 (18.12)	15.12 (12.61, 17.62)	12.02 (84)	<0.001
Ocular pain	66.91 (16.22)	68.38 (15.74)	1.47 (0.19, 2.75)	2.29 (84)	0.024
Distance activity	46.27 (17.03)	53.82 (15.84)	7.55 (5.85, 9.24)	8.85 (84)	<0.001
Near activity	46.13 (15.49)	57.55 (11.81)	11.42 (9.88, 12.97)	14.70 (84)	<0.001
Driving	25.88 (22.59)	30.49 (22.59)	4.61 (2.49, 6.73)	4.32 (84)	<0.001
Colour vision	59.71 (24.12)	66.76 (20.91)	7.06 (4.22, 9.89)	4.95 (84)	<0.001
Peripheral vision	44.12 (16.21)	64.71 (15.57)	20.59 (17.24, 23.93)	12.23 (84)	<0.001
Mental health	49.76 (16.78)	60.76 (14.59)	11.00 (9.69, 12.31)	16.72 (84)	<0.001
Social Functioning	53.82 (22.11)	61.06 (20.23)	7.23 (5.37, 9.10)	7.70 (84)	<0.001
Role difficulties	50.67 (18.07)	60.22 (12.72)	9.55 (7.73, 11.37)	10.43 (84)	<0.001
Dependency	57.43 (18.76)	64.11 (14.69)	6.69 (4.82, 8.56)	7.12 (84)	<0.001

SD: standard deviation
NEI- VFQ- 25: National Eye Institute- Visual Function Questionnaire- 25
TPPV: trans pars plana vitrectomy
Paired t-test, p- value <0.05 is statistically significant

Table V: Factors Associated with Vision Related Quality of Life based on NEI-VFQ-25 among Patients with Diabetic Vitreoretinal Disease

Factors	Simple Linear Regression		Multiple Linear Regression	
	Bb (95% CI)	p-value	Adj. Bc (95% CI)	p-value
Age (year)	-0.19 (-0.46, 0.08)	0.160		
Gender				
Male	2.59 (-2.73, 7.90)	0.340		
Female				
Race				
Malay	1.75 (-4.20, 7.71)			
Non- Malay	0.560			
Education level				
Primary				
Secondary	-0.52 (-6.11, 5.06)	0.853	4.32 (1.69, 6.95)	0.020
Tertiary	9.14 (4.19, 14.10)	<0.001	5.43 (2.76, 8.10)	<0.001
Occupation				
Unemployed				
Employed	6.00 (0.82, 11.12)	0.024		
Hypertension				
Yes				
No	1.28 (-4.14, 6.70)	0.640		
Hyperlipidaemia				
Yes				
No	8.30 (2.48, 14.12)	0.006		
Diabetic nephropathy				
Yes				
No	17.19 (10.50, 23.87)	<0.001		
Presence of other comorbid				
No				
Yes	1.34 (-4.45, 7.13)	0.650	3.69 (1.86, 5.52)	<0.001
Laterality				
Bilateral				
Unilateral	4.82 (-0.46, 10.10)	0.073		
Pre-operative blindness status				
Unilateral blindness				
Bilateral blindness				
Not blind	20.47 (11.85, 29.09)	<0.001		
Type of vitreoretinal disease				
TRD and RRD				
TRD only	-2.84 (-8.17, 2.49)	0.293		
Pre-operative NEI-VFQ-25 score	0.83 (0.76, 0.89)	<0.001	0.77 (0.71, 0.84)	<0.001

[b]Crude regression coefficients
[c]Adjusted regression coefficient
CI: Confidence Interval
TRD: tractional retinal detachment, RRD: rhegmatogenous retinal detachment
NEI-VFQ-25: National Eye Institute- Visual Function Questionnaire- 25

VRQoL at 3-months post TPPV, and identifies key demographic, ocular, and systemic factors that independently shape postoperative VRQoL.

We observed that the mean composite NEI-VFQ-25 increase of 8.17 points (95% CI, 7.13-9.20; p<0.001), exceeding the minimal clinically important difference of 4-6 points for this instrument.[12,13] The largest gains occurred in the General Vision (Δ15.12; p<0.001), Peripheral Vision (Δ20.59; p<0.001), and Mental Health (Δ11.00; p<0.001) scales, underscoring that TPPV not only enhances central acuity but also restores broader aspects of visual function and emotional well-being.[20] Comparable magnitude improvements have been reported by Abu-Ameerh et al. in a Jordanian cohort.[12] The improvement also reported by Okamoto et al. following vitrectomy for PDR.[20] Smaller gains in Ocular Pain scale and non-significant changes in General Health scale are expected, as diabetic retinal disease is typically painless and systemic health perceptions evolve more slowly than vision-specific domains.[20]

In the univariate model, pre-operative blindness status found to be one of the strong predictors of post TPPV VRQoL. Okamoto et al. demonstrated that in PDR patients undergoing vitrectomy, better pre-operative BCVA was associated with larger gains in both composite and scale NEI-VFQ-25 scores at follow-up, underscoring that residual vision confers greater perceived benefit.[20] Cusick et al. similarly found strong correlations between central visual function measures (including BCVA) and the near- and distance-activities scales of the NEI-VFQ-25 in diabetic cohorts, indicating that even modest preserved vision translates into meaningful functional improvements.[21] In a cross-sectional study from Jordan, Abu-Ameerh et al. reported that patients with less severe baseline visual impairment experienced more pronounced VRQoL enhancement after vitrectomy than

those starting with profound vision loss.[12] In the simple regression, pre-operative blindness was significantly associated with post TPPV NEI-VFQ-25 scores, but this effect vanished in the multiple regression once key factors (notably the pre-operative NEI-VFQ-25 score) were included. This pattern indicates confounding- the univariate relationship between blindness and outcome was not independent, but rather driven by baseline visual function. Patients who were blind pre-operatively had very low baseline NEI-VFQ-25 scores, and that pre-operative NEI-VFQ-25 proved to be a stronger predictor of post TPPV VRQoL. Thus, when pre-operative NEI-VFQ-25 score was added to the model, it attenuated the apparent effect of the pre-operative blindness status. This phenomenon is well-recognized: a factor can seem significant in isolation but lose significance when a correlated, more explanatory variable is included. A study shows intensive diabetes mellitus control delays the onset and slows the progression of DR, nephropathy and neuropathy.[22] Besides, optimal systemic control is integral to DR management. In our univariate model, absence of hyperlipidaemia (B=+8.30; p=0.006) was associated with better post TPPV VRQoL. This effect likely reflects the protective impact of systemic cardiovascular risk factor control on retinal perfusion and surgical prognosis.[23]

Whereas in the multivariate model, pre-operative NEI-VFQ-25 score emerged as one of the strongest independent predictors of post TPPV VRQoL in our cohort: patients with higher NEI-VFQ-25 scores before surgery tended to have higher NEI-VFQ-25 scores after surgery, even after adjusting for the other factors. In other words, those who perceived better visual functioning and QoL at baseline also reported better QoL outcomes at 3-months post TPPV. This makes intuitive sense- baseline NEI-VFQ-25 reflects the degree of visual disability prior to surgery, which inherently limits the maximum achievable postoperative score. A patient starting from a very low NEI-VFQ-25 (severely impaired QoL pre-operative) can certainly improve substantially, but may still not reach the same absolute post TPPV NEI-VFQ-25 score as someone who began with a moderately higher baseline. Our finding aligns with prior observations in the literature. This finding is consistent with multiple studies highlighting the critical role of baseline visual function in shaping patient-reported outcomes after vitreoretinal surgery.[12,21] Its significance in the model highlights the prognostic value of baseline VRQoL- patients who start off with less visual disability tend to end up with better QoL scores after intervention.

Several mechanisms likely underlie this phenomenon. First, ceiling and floor effects of the NEI-VFQ-25 mean that individuals with extreme baseline deficits have limited scope for measurable improvement, whereas those with some remaining sight can register larger relative gains.[15] Second, preserved preoperative vision enables better engagement in daily activities- reading, mobility, and social interaction- which are directly captured by NEI-VFQ-25 scales, thus amplifying perceived QoL.[20,21] Third, early surgical intervention before the onset of blindness may prevent irreversible retinal damage, allowing patients to recover functional vision that supports independence and psychosocial well-being. These insights emphasize the importance of timely referral for TPPV in diabetic vitreoretinal disease, ideally before patients reach the threshold of legal blindness. Clinicians should counsel patients about the prognostic significance of their current visual status: maintaining residual vision not only preserves functional capacity but also maximizes postoperative QoL outcomes. Education influenced VRQoL outcomes substantially: compared with primary- educated patients, those with secondary schooling scored 4.32 points higher and those with tertiary education 5.43 points higher at 3-months post TPPV. This parallels broader health literature linking higher education to better health-related QoL, likely reflecting superior health literacy, treatment adherence, and self- management skills.[24] In DR, patients with greater educational attainment may better understand the rationale for pre- and post-operative care, leading to enhanced visual rehabilitation and adaptive coping strategies.

Interestingly, the presence of other comorbid (e.g., stroke, chronic obstructive pulmonary disease, heart disease) was associated with a +3.69 points higher NEI-VFQ-25 score ($p<0.001$)- a seemingly paradoxical result, since additional illnesses typically degrade QoL. We postulate that several mechanisms may explain this "reverse comorbidity effect." First, patients with multiple comorbidities often have more frequent healthcare contacts, leading to enhanced patient education, closer monitoring, and timelier interventions ("intensity of care" hypothesis).[25] Second, a response- shift phenomenon may occur: chronically ill patients recalibrate their internal standards and values, perceiving vision improvements more positively despite overall health challenges.[26] Third, selection bias is possible: those who survive and qualify for surgery despite multiple comorbidities may inherently possess greater resilience or functional reserve, thus achieving better subjective outcomes than healthier counterparts ("survivor bias" effect).[27] Future prospective work is needed to disentangle these complex interactions. There is a significant interaction between other comorbid and pre-operative NEI-VFQ-25 score, whereby presence of other comorbid might affect the pre-operative NEI-VFQ-25 score.

Our data reinforce that TPPV confers pronounced VRQoL benefits, particularly when performed before profound impairment of VRQoL. Baseline VRQoL assessment via NEI-VFQ-25 should be incorporated into surgical planning to inform expectations and personalize follow-up care. Educational interventions tailored to lower-literacy patients may help bridge outcome gaps. Besides, attention to the unique needs of multimorbid patients can exploit response shifts and healthcare engagement to maximize patient satisfaction and function.

Our limitations comprise the single-region tertiary hospital setting, which may limit generalizability, and the snapshot review of the VRQoL rather than capturing changes over time. Longer-term data are needed to evaluate VRQoL trajectories and the durability of gains. Qualitative studies could probe the nuanced experiences of patients with multiple comorbidities to validate the response-shift and care-intensity hypotheses.

CONCLUSION

TPPV leads to substantial and clinically meaningful improvements in VRQoL among Malaysian patients with diabetic vitreoretinal disease. Patients' pre-operative NEI-VFQ-25 score, higher educational attainment, and optimal systemic health independently predict better postoperative outcomes. A holistic care model- combining early surgical referral, targeted education, rigorous systemic risk factor management, and attention to the psychosocial context- is essential to optimize patient- reported outcomes in this population.

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CONFLICT OF INTEREST

The authors confirm that this article's content has no conflict of interest.

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ORIGINAL ARTICLE

Sixteen years of cochlear implant surgery in cochleovestibular malformation and cochlear nerve deficiency: Insights from northern Malaysia

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ABSTRACT

Introduction: Congenital sensorineural hearing loss associated with cochleovestibular malformations (CVM) and/or cochlear nerve deficiency (CND) presents distinct surgical and audiological challenges. Patients with CVM face elevated risks of intraoperative cerebrospinal fluid (CSF) gushers and aberrant facial nerve courses, while those with CND have historically been viewed as poor candidates for cochlear implantation (CI) due to concerns regarding neural sufficiency. This study aims to bridge this gap by evaluating the surgical safety and audiological outcomes of CI in a focused cohort of patients with CVM and CND at a tertiary referral centre in northern Malaysia.

Materials and Methods: A retrospective cohort study was conducted on 20 cases with CVM and/or CND performed between January 2009 and December 2024 at Hospital Sultanah Bahiyah, Kedah, Malaysia. The study population included patients with radiologically confirmed CVM classified according to the Sennaroglu classification and CND. Surgical outcomes, including the incidence of CSF gushers, were analysed by Fisher's exact test following stratification into high-risk and low-risk gusher group. Primary audiological outcomes were assessed using the aided average pure tone audiometry (PTA), analysed longitudinally using a linear mixed-effects model. Secondary functional audiological outcomes were evaluated by comparing pre-implantation and 12-month post-implantation Categories of Auditory Performance-II (CAP-II) scores using the Wilcoxon signed-rank test.

Results: The cohort was predominantly prelingual (90.0%). Surgical analysis revealed a shift in technique over the 16-year period, moving from cochleostomy to round window insertion. Intraoperative CSF gushers were encountered in 12 of 20 ears (60%). We found no statistically significant difference in the incidence of gushers between the "high risk" group (enlarged vestibular aqueduct and incomplete partition type II) and to the "low risk" group (p=0.559). There were no incidences of facial nerve injury. In terms of audiology outcome, the linear mixed-effects model revealed a highly significant improvement in aided PTA over time for all ears (p<0.001). Crucially, comparing CND versus non-CND ears revealed no statistically significant difference in outcomes, with both groups following a parallel trajectory of auditory improvement. Functional analysis confirmed that these gains translated into real-world benefits, with CAP-II scores improving significantly from a median of 2.0 pre-operatively to 4.5 at 12 months (p=0.003).

Conclusion: Cochlear implantation is a safe and effective intervention for children with CVM and/or CND. Our findings indicate that the risk of intraoperative CSF gushers extends beyond specific high-risk groups, underscoring the need for broad surgical readiness across the spectrum of malformations. The audiological outcomes observed, irrespective of the presence of CND, support the expansion of CI candidacy to this challenging population, provided there is requisite surgical expertise and thorough family counselling.

KEYWORDS:
Cochlear implants; Inner ear; Cerebrospinal fluid; Cochlear nerve; Audiology

INTRODUCTION

Congenital sensorineural hearing loss (SNHL) affects 1.5 to 3 in every 1,000 newborns.[1] A proportion of these cases, approximately 20%, are associated with structural anomalies of the inner ear, known as cochleovestibular malformations (CVM).[2] For cases of severe-to-profound sensorineural hearing loss (SNHL), cochlear implantation (CI) is the gold standard of care to restore auditory function.[3,4] In Malaysia, the Ministry of Health (MOH) National CI Programme was established in 2008 to address this need.[5] According to the programme's 10-Year Report (2008-2018), a total of 413 surgeries were performed across ten satellite hospitals nationwide.[5] However, the national data indicates that most of these recipients (91.5%) presented with normal inner ear anatomy, with cases of cochlear malformation or nerve hypoplasia representing a small minority of the national cohort.[5]

However, CI in patients with CVM involves various surgical challenges. The anomalous development of the bony

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labyrinth can lead to an aberrant course of the facial nerve, difficulties in electrode placement, and, most notably, an increased risk of intraoperative cerebrospinal fluid (CSF) leakage, commonly termed a "gusher".[6,7] A CSF gusher, defined as a profuse, pulsatile egress of CSF upon opening the inner ear, occurs due to an abnormal communication between the subarachnoid space and the perilymph.[8] These events not only complicate the surgical procedure but also increase the risk of postoperative morbidity, including meningitis.[9] To navigate this complex surgical landscape, meticulous preoperative planning is essential. High-resolution computed tomography (HRCT) and magnetic resonance imaging (MRI) are vital for diagnosis and surgical road-mapping.[10,11] The imaging-based classification system proposed by Sennaroglu et al. is the globally accepted standard for categorizing CVM, providing a crucial link between specific developmental anomalies and the potential intraoperative challenges a surgeon is likely to encounter.[7,12] In addition to the anatomical challenges posed by CVM, a separate and equally critical consideration is the integrity of the neural pathway itself: cochlear nerve deficiency (CND). This condition has a reported prevalence ranging from 33% to 39% in cases of unilateral SNHL.[13,14] CND is radiologically classified according to the Birman classification, which categorizes the condition based on MRI visualization of the cochlear nerve and CT assessment of the bony cochlear aperture, ranging from normal morphology to hypoplasia or complete aplasia of the nerve.[15] Historically considered a contraindication for CI, recent literature presents a wide spectrum of results.[16,17]

Globally, the assessment of CI outcomes relies on various assessments designed to capture both the physiological restoration of hearing and the functional acquisition of auditory skills. While the aided pure tone audiometry (PTA) thresholds remain the fundamental test for determining sound detection thresholds and verifying device function, there has been increasing emphasis on functional outcomes that reflect real-world performance. Validated scales, most notably the Categories of Auditory Performance-II (CAP-II) and Speech Intelligibility Rating (SIR), are universally adopted to track the longitudinal trajectory of auditory development.[18,19] These standardized measures are essential not only to monitor individual progress, but also to facilitate comparison across different international centres and diverse patient populations.

CI outcomes in Malaysia have generally been positive, with major centres like Universiti Kebangsaan Malaysia (UKM) and University Malaya Medical Centre (UMMC) reporting excellent long-term functional results in the general population.[20,21] However, specific data regarding the management and outcomes of the sub-population with CVM and/or CND remains underreported in our region. This study aims to address these gaps by presenting a 16-year experience from a tertiary referral centre in northern Malaysia. Our analysis includes both CVM and CND. The primary objective was to retrospectively evaluate the surgical approaches, intraoperative findings, and postoperative complications. Secondarily, we aimed to correlate specific malformations with the incidence of CSF gushers and to evaluate audiological improvements.

MATERIALS AND METHODS

This study was conducted as a retrospective, single-centre, observational chart review. The reporting of this study was structured to adhere to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cohort studies.[22] The study protocol received approval from the National Medical Research Registry (NMRR) of Malaysia (NMRR ID-25-04235-JKH). Given the retrospective nature of the data analysis and the de-identification of patient information, the requirement for individual patient consent was waived by the committee.

The study was performed at Hospital Sultanah Bahiyah, a tertiary referral public hospital in northern Malaysia with an established cochlear implant programme. A comprehensive review was conducted of all CI surgeries performed between January 1, 2009, and December 31, 2024. The inclusion criteria for this study were all patients who underwent cochlear implantation during the specified period and who had radiologically confirmed evidence of CVM or CND on preoperative imaging. Diagnosis was established through a combination of HRCT of the temporal bones and MRI of the internal auditory meatus (IAM) and brain. Patients with normal inner ear anatomy, hearing loss secondary to labyrinthitis ossificans, or those with incomplete medical, surgical, or radiological records were excluded. For patients who underwent bilateral CI, each ear was treated as an independent case for the analysis of radiological findings and intraoperative surgical outcomes.

Relevant information was extracted from patient medical records, operative logs, audiological files, and the Picture Archiving and Communication System (PACS) for radiological images. All preoperative imaging studies (HRCT and MRI) were reviewed. Cochleovestibular malformation (CVM) was diagnosed based on radiological abnormalities of the cochlea and/or vestibular structures on HRCT and MRI. Diagnostic criteria included abnormal cochlear morphology (reduced number of turns, absent or deficient modiolus, cystic configuration), enlarged vestibule or vestibular aqueduct (midpoint diameter >1.5 mm), and dysplastic or aplastic semicircular canals (SCC).12 The identified anomalies were classified according to the Sennaroglu classification, which includes categories such as incomplete partition type I (IP-I), incomplete partition type II (IP-II), cochlear hypoplasia (CH), and enlarged vestibular aqueduct (EVA).[12] The status of the cochlear nerve (e.g., normal, hypoplastic, aplastic) was also documented. Anomalies were noted as being isolated or occurring in combination with other malformations.

Pre-operative variables collected were patient demographics of age at the time of implantation and radiological findings as mentioned above. Intraoperative surgical information collected included cochlear access (cochleostomy or round window membrane insertion), CSF gusher, other intraoperative difficulties and electrode insertion. A "gusher" was defined as a profuse, pulsatile, and rapid flow of CSF upon opening the inner ear, while "leak" was defined as a less vigorous, gentle flow of the fluid.[8] Medical records were then reviewed for any documented immediate or delayed postoperative complications, including but not limited to wound infection, seroma, device failure or migration,

Table I: Surgical details and intraoperative complications

Surgical details	n	Rate (%)
Technique		
Insertion route		
Cochleotomy	7	35.0
Round window	13	65.0
Electrode insertion		
Complete	18	90.0
Partial	2	10.0
Intraoperative complications		
CSF gusher		
Absent	8	40.0
Present	12	60.0
Facial nerve injury		
Absent	20	100
Present	0	0

Abbreviations: CSF, cerebrospinal fluid.

Table II: Distribution of cochleovestibular malformations in the study cohort and gusher rate (n=24)

Types of malformations Cochleovestibular malformations (Sennaroglu)	n (%)	Co-existing anomalies	CSF gusher n (%)
Cochlear hypoplasia	2 (13.30)	1 hypoplastic nerve, 1 EVA	1 (50)
IP I	4 (26.70)	3 hypoplastic nerve, 1 EVA	3 (75)
IP II	7 (46.70)	1 hypoplastic nerve, 6 EVA	6 (85.70)
EVA	2 (13.30)	Not applicable	2 (100)
Cochlear nerve deficiency (CND)		Co-existing anomalies	
Isolated hypoplastic nerve	3 (37.50)	Not applicable	0 (0)
Hypoplastic nerve related with CVM	5 (62.50)	3 IP-I, 1 IP-II, 1 CH	4 (57.14)

Abbreviations: CH, cochlear hypoplasia; CND, cochlear nerve deficiency; CSF, cerebrospinal fluid; CVM, cochleovestibular malformation; EVA, enlarged vestibular aqueduct; IP, incomplete partition.

Table III: Incidence of intraoperative CSF gusher stratified by anomaly risk group

Anomaly type	With CSF Gusher	No CSF Gusher	Total
High-Risk Group (EVA & IP-II)	8	1	9
Low-Risk Group (IP-I, CH)	4	2	6
Total	12	3	15

Abbreviations: CH, cochlear hypoplasia; CSF, cerebrospinal fluid; EVA, enlarged vestibular aqueduct; IP, incomplete partition.

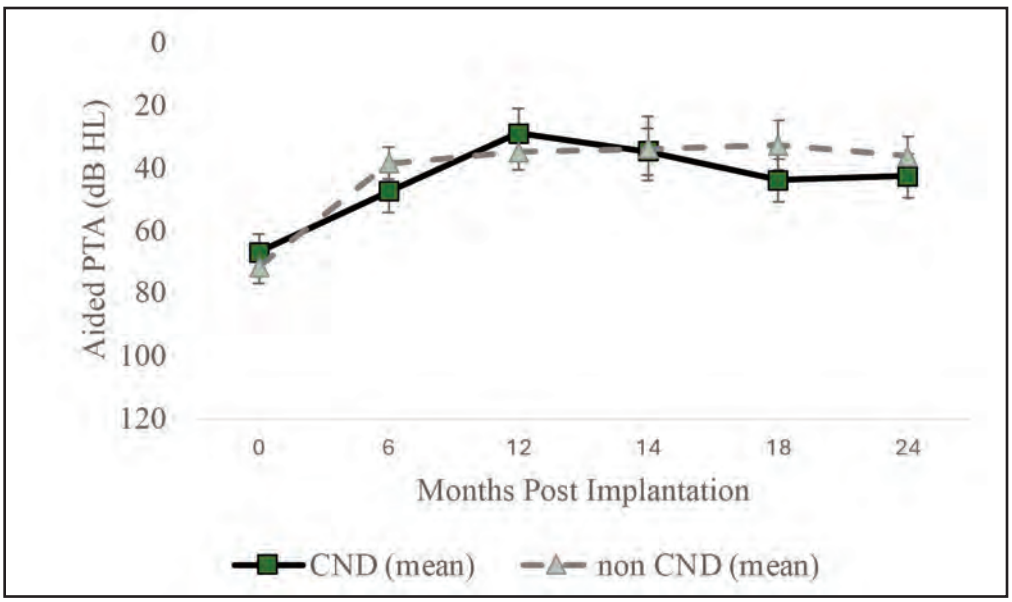

Fig. 1: Longitudinal comparison of aided pure tone average (PTA) between the cochlear nerve deficiency (CND) and non-CND groups. Data points represent the mean aided PTA at each follow-up interval. Error bars indicate the standard error of the mean. Both groups exhibit a significant and parallel improvement in hearing thresholds over time ($p<0.001$), with no significant difference between groups ($p > 0.05$).

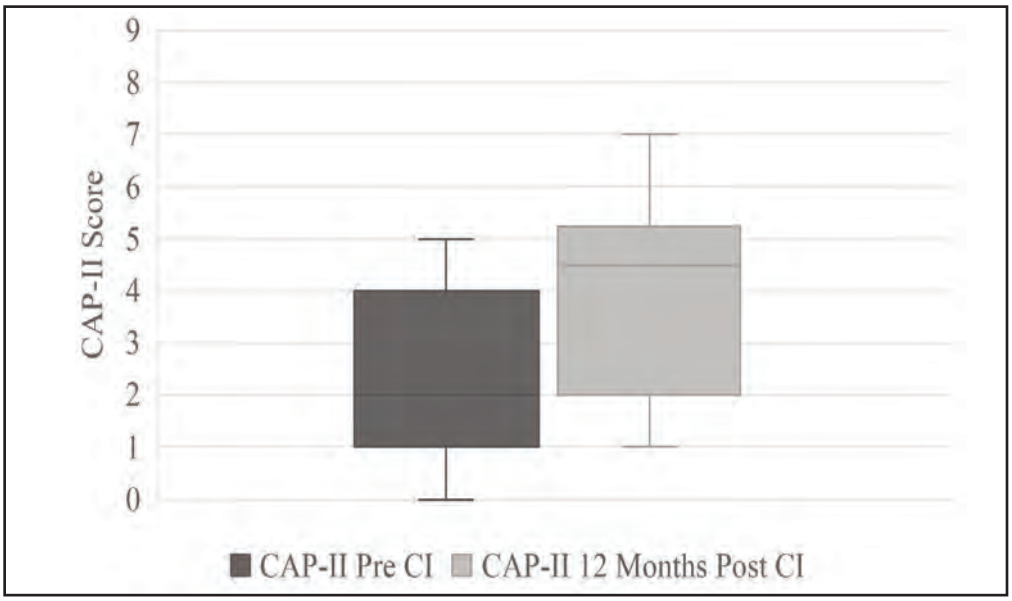

Fig. 2: Comparison of Categories of Auditory Performance-II (CAP-II) scores pre-implantation and 12 months post-implantation. The box plot illustrates the significant improvement in functional auditory performance following cochlear implantation (p=0.003, Wilcoxon signed-rank test). The horizontal line within the box represents the median score, while the box edges represent the interquartile range

persistent CSF leakage, and meningitis. Audiological outcomes were assessed using average aided pure tone audiometry (PTA) thresholds across four frequencies (500 Hz, 1 kHz, 2 kHz, and 4 kHz) in dB HL during follow-up visits up to 24 months. Functional auditory performance was evaluated using CAP-II scores obtained preimplantation and 12 months post implantation.

All data were analysed using SPSS Statistics for Windows, Version 29.0.2.0.[20] To assess the association between anatomical risk and CSF gushers, cases with only CND were first excluded. The remaining patients were stratified into a high-risk group (EVA & IP-II) and a low-risk group (IP-I and CH). A Fisher's exact test was used to determine the significance of this association. To analyse the longitudinal aided PTA data, the unit of analysis was the operated ear. A linear mixed-effects model was employed. The model included time (follow up months) and CND status (CND vs non-CND) and their interaction term as fixed effects, with a random intercept for each subject. For the functional CAP-II score analysis, the unit of analysis was the individual patient. To ensure independence of data, bilateral cases were considered as a single observational unit. A Wilcoxon signed-rank test was used to compare the paired pre- and post-implantation CAP-II scores. A p-value of < 0.05 was considered statistically significant.

RESULTS

Over the 16-year study period, a total of 20 CI cases met the inclusion criteria. This included 20 operated ears from 16 patients. There were 4 patients who underwent bilateral CI at different setting, with each ear considered as individual cases. Most patients were prelingual (n=18, 90.0%). There were only 2 syndromic cases, which included a single case of CHARGE syndrome and Down syndrome each. Age of implantation ranged between 8 months to 53 months old and 6 to 16 years old for prelingual and postlingual cases respectively.

A review of the surgical records revealed an evolution in the preferred technique for cochlear access over the study period. Prior to 2020, promontorial cochleostomy was the standard approach. From 2020 onwards, a deliberate shift was made towards round window insertion as the primary technique, reflecting a centre-wide adoption of principles aimed at less traumatic surgery and structural preservation.

Regarding electrode insertion, a successful full insertion of the electrode array was achieved in 18 of the 20 patients (90.0%) as shown in Table I. The two cases of partial electrode insertion both occurred in patients with an IP-I malformation. No other significant intraoperative difficulties, such as an aberrant facial nerve requiring a change in surgical approach, were documented in the operative reports.

Secondarily, the analysis of functional outcomes via CAP-II score was performed at the patient level. This analysis was performed in 14 patients, after the exclusion of 2 cases with incomplete CAP-II data. The Wilcoxon signed-rank test confirmed that the improvement in CAP-II scores from pre-implantation (median = 2) to 12 months post-implantation (median = 4.5) was statistically significant (p=0.003). This indicates that the objective hearing gains translated into meaningful, real-world improvements in auditory performance across the diverse range of complex cases.

Intraoperatively, no cases of facial nerve injury were recorded. CSF gusher was encountered in 12 of the 20 patients (60%). Major postoperative complications were confined to one patient with IP-II who had experienced an intraoperative gusher, who developed a CSF leak and subsequently bacterial meningitis but recovered fully with medical therapy.

The distribution of various anomalies with gusher rate is detailed in Table II. Among the 15 patients with CVM according to Sennaroglu classification, the most frequently

observed malformation was IP-II, accounting for 7 cases (46.7%). This was followed by IP-I in 4 cases (26.7%). The remaining CVM consisted of CH and isolated EVA. All cases of CND were radiologically classified as hypoplastic, and one-third of these were isolated findings.

The rate of CSF gusher varied across the different types of CVM. The highest rates were observed in patients with EVA, where 100% of cases experienced a gusher, and in patients with IP-II, with an 85.7% incidence.

To assess the relationship between anomaly type and CSF gushers, the cohort was stratified into a high-risk group (comprising patients with EVA and IP-II) and a low-risk group (comprising patients with IP-I and CH). The incidence of intraoperative CSF gusher was not statistically significant between the high-risk group and the low-risk group (p=0.559, Fisher's exact test) (Table III).

Of the 20 cases in the initial cohort, 1 were lost to follow-up and did not have post-implantation PTA data available. Therefore, statistical analyses of PTA outcomes were performed on the remaining 19 cases who had complete pre- and post-operative datasets.

To analyse the longitudinal trajectory of audiological outcome, a linear mixed-effects model was performed with aided PTA as the dependent variable. The model included fixed effects for time (in months), risk group (CND vs non-CND), and their interaction, with a random intercept for each patient. This statistical analysis performed revealed three key findings. First, there was a significant improvement in hearing thresholds over time for all patients in the cohort ($p<0.001$). Second, there was no statistically significant difference in the overall aided PTA between the CND and non-CND groups. Third, the interaction between group and time was not significant, indicating that both groups followed a similar, parallel trajectory of improvement over the 24-month follow-up period. This suggests that the rate of objective auditory improvement was comparable, regardless of the presence of CND.

DISCUSSION

This 16-year retrospective review provides valuable insights into the surgical management and outcomes of cochlear implantation (CI) in a diverse cohort of patients with CVM and/or CND from a regional centre in northern Malaysia. Our findings complement the broader National MOH CI Programme 10-Year Report (2008-2018).[5] While the national report identified normal inner ear anatomy in nearly 95% of prelingual recipients, our study focused exclusively on the remaining complex minority, specifically those with CVM and/or CND who presented distinct surgical and audiological challenges. Our findings underscore that meticulous preoperative planning is essential, and they help to refine our understanding of surgical risk and expand the boundaries of CI candidacy. Beyond simply reporting outcomes, this study offers a unique perspective from a regional centre in northern Malaysia, contributing to the global understanding of these complex cases.

CVMs are diagnosed radiologically according to the classification proposed by Sennaroglu.[7] The Sennaroglu classification categorizes CVMs according to the stage of embryologic arrest and associated surgical implications.[7] As encountered in our cohort, IP-I, IP-II, CH and EVA were identified. IP-I is characterised by a cystic cochlea lacking internal architecture, with complete absence of the modiolus and interscalar septa, typically associated with a dilated vestibule.[7] In contrast, IP-II demonstrates cystic fusion of the middle and apical cochlear turns with a preserved basal turn and is commonly associated with EVA.[7] CH refers to a cochlea that is smaller than normal with varying degrees of internal structural deformity.[7] It is typically characterised by reduced cochlear turns (often fewer than 2½ turns) and diminished overall dimensions on CT or MRI.[7] Lastly, EVA is diagnosed when the vestibular aqueduct diameter exceeds 1.5 mm at the midpoint between posterior labyrinth and operculum, in the background of normal cochlea, vestibule and SCC.[7] The status of the cochlear nerve was assessed on MRI, with hypoplasia defined as a smaller calibre nerve compared to the facial nerve, and aplasia defined as absence of a visible nerve within the internal auditory canal.7 Diagnostic criteria for other CVMs are not detailed here as they were not observed in our cohort.

The National MOH Report cited a low overall complication rate of 5.57%, with CSF gushers noted as an intraoperative finding rather than a major complication.[5] In stark contrast, our focused cohort of complex anomalies revealed a gusher incidence of 60%. While previous literature has often stratified risk based on specific anomalies, our analysis of this cohort revealed no statistically significant difference in the incidence of CSF gushers between the "high-risk" group (EVA & IP-II) and the "low-risk" group (IP-I & CH).[8,23,24] Nevertheless, cases of EVA and IP-II had the highest and second highest rate of CSF gushers in our cohort respectively. In IP-II, a deficient modiolus creates a wide, patent communication between the cochlea and the CSF-filled internal auditory canal.[23] Similarly, EVA is frequently associated with a patent and enlarged cochlear aqueduct, providing another direct conduit for CSF.[25] The lack of statistical significance in our risk stratification analysis must be considered along with two important factors. First, the small sample size (n=15) possibly limits the statistical power of the study, increasing the likelihood of a Type II error where a true difference fails to reach the threshold of significance. Second, and clinically more important, is the unexpectedly high incidence of gushers (66.7%) within the "low-risk" group. This was primarily driven by patients with IP-I. While typically considered lower risk than IP-II or EVA, IP-I is characterized by the absence of the cribriform plate, which creates a direct, low-resistance pathway for CSF to enter the cochlea.[7] Consequently, our data suggests that the risk of a gusher is not confined to specific "high-risk" categories but is a constant challenge across the spectrum of major CVM. Therefore, surgeons should maintain a high index of suspicion and prepare for a gusher in all cases of CVM. Literature describes various techniques of CSF gusher management, such as tight packing of the cochleostomy or round window niche with temporalis muscle, fascia, fat tissue or fibrin glue immediately following electrode insertion.[8,26] Interestingly, in our centre, we do not routinely perform any

packing. The fact that only one patient in our high-risk group developed a postoperative CSF leak suggests that a snug fit of the electrode array alone can effectively arrest the fluid egress, rendering the use of any packing unnecessary in most cases.

An important insight from our data is the clear link between anatomy, intraoperative events, and postoperative complications. The confinement of all major complications (persistent CSF leak and meningitis) exclusively to patients with IP-II malformations demonstrates a clear pathophysiological cascade. As mentioned by Sennaroglu et al., third window defect of EVA transmitting CSF pressure into the cochlea leads to a high probability of a high-pressure intraoperative gusher.[7] It is more challenging to seal such a CSF gush than managing a low-pressure ooze. Consequently, the imperfect seal then creates a persistent fistula between the non-sterile middle ear and the sterile subarachnoid space, serving as a direct pathway for bacteria and placing the patient at a significantly elevated risk for life-threatening meningitis.[9] This suggests that preoperative identification of IP-II is of importance not only for managing the gusher but, more critically, for mitigating the risk of severe postoperative morbidity. Interestingly, our study discovered a shift in surgical technique over the last decade, moving from promontorial cochleostomy to round window CI electrode insertion. This not only reflects global trends towards atraumatic and less invasive methods, but it also holds specific advantages in dysplastic cochlea.[27] In cases of IP-II or EVA where a gusher is anticipated, the round window approach avoids the drilling of cochlear bone, thereby reducing the risk of inadvertent injury to an aberrant facial nerve a common anomaly in this population.[9,28] Although our sample size is insufficient to statistically compare gusher rates between approaches, the absence of facial nerve injuries in our cohort supports the safety of this surgical strategy. Importantly, our study decouples this intraoperative surgical challenge from the audiological success. Despite a high incidence of CSF gushers, our data demonstrated significant improvements in both aided PTA and CAP-II scores. This supports the view that a CSF gusher is an intraoperative event to be managed, rather than a negative prognostic indicator for long-term hearing outcomes, provided a secure seal is achieved. The profound audiological benefits demonstrated in our cohort strongly support the argument that this predictable and manageable surgical risk is justified.

To assess the benefit of CI, we utilized the aided PTA as one of our audiological outcomes. While speech perception scores are often considered the gold standard, aided PTA was selected given that some of our patients are cases of bilateral CI in different period of life. While the National MOH Report utilized aided thresholds to categorize performance (≤40dBHL vs >40dBHL), we employed a linear mixed-effects model to track longitudinal continuous data at the ear level rather than the patient level.[5] Analysing at the ear level allowed us to isolate the specific impact of the anatomical anomaly on hearing thresholds in individual ear. The most compelling finding of our study and the one with the most significant clinical implication relates to the outcomes in patients with CND. Historically, CND has been viewed with caution or even considered a contraindication for CI due to concerns that the hypoplastic nerve would fail to transmit electrical stimulation effectively stimulation.17 In our study, when comparing the CND and non-CND groups, there was no statistically significant difference in aided PTA outcomes. Crucially, the interaction between the group (CND vs non-CND) and time was not significant. This indicates that both groups followed a parallel trajectory of improvement over the 24-month follow-up period. This suggests that the presence of a radiologically hypoplastic nerve does not inherently limit the rate of auditory learning or neural adaptation in the first two years post-implantation. These findings align with emerging evidence suggesting that children with CND can achieve comparable performance and should not be considered an absolute contraindication for CI.[29] Indeed, other studies have found that children with CNH can achieve performance comparable to their matched counterparts, especially with longer CI usage.[17] Therefore, CND should not be an absolute barrier to implantation. Instead, these excellent outcomes support the expansion of CI candidacy to this population, provided there is requisite surgical expertise and thorough family counselling regarding variable outcomes.

While aided PTA measures auditory detection, it does not necessarily reflect function as in how the patients uses hearing in daily life. To address this, we analysed the Categories of Auditory Performance-II (CAP-II) scores.18 Unlike the ear-level analysis used for aided PTA, CAP-II was analysed at the patient level, treating bilateral cases as a single unit to reflect the patient's overall functional ability. The significant increase in CAP-II scores confirms that the audiological detection measured by PTA translates into meaningful, real-world benefits. It demonstrates that even in distinctively complex cases such as those involving high-risk gushers, anatomical distortions, or nerve deficiency, patients are not just "hearing" sound but are developing the requisite listening behaviours to interact with their environment.

Our findings contribute to the growing body of evidence regarding cochlear implant safety and audiological efficacy within the Malaysian context. Landmark longitudinal studies by Goh et al. from UKM and Konting et al. from UMMC have previously established that the general paediatric CI population in Malaysia achieves high rates of oral communication and mainstream education integration.[20,21] While these studies primarily characterized the general population, recent local data indicates that this positive trend extends to the distinctively complex demographic of CVM and CND. Notably, Misron et al. at Hospital Sultan Ismail reported significant improvements in CAP-II and Meaningful Auditory Integration Scale (MAIS) scores within their CVM cohort, while Abdullah et al. at UKM observed similar significant gains in CAP-II and SIR scores among children with CVM and/or CND.[17,30] Supporting these findings, the statistically significant improvement in aided PTA and CAP-II scores observed in our cohort validates that with appropriate surgical planning, even patients with complex anatomy can achieve functional outcomes comparable to their peers.

Looking forward, there is a clear need for prospective, multi-centre research within the region to overcome the statistical

limitations inherent to single-centre retrospective reviews. The establishment of a collaborative national registry for complex CI cases encompassing both MOH and university hospitals would provide the necessary sample size to perform more detailed analyses of specific malformation subtypes. Most importantly, any future studies must incorporate standardized, long-term audiological and speech outcome measures. This will be essential for building a comprehensive understanding of the relationship between inner ear anatomy, surgical complexity, and the success of auditory rehabilitation in this challenging and deserving patient population.

CONCLUSION

This 16-year review from northern Malaysia demonstrates that cochlear implantation is a safe and effective intervention for patients with CVM and/or CND. Meticulous preoperative radiological evaluation is of vital importance. However, our findings highlight that the risk of intraoperative CSF gushers extends beyond classically defined high-risk groups, necessitating proactive surgical readiness for this complication across the spectrum of CVM. Most importantly, this study reinforces the evolving consensus that CI candidacy can and should be extended to anatomically complex cases, including those with CND, provided there is the requisite surgical expertise and a framework for thorough, realistic preoperative counselling for patients and their families.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there is no actual or potential conflict of interest in relation to this article.

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ORIGINAL ARTICLE

Prevalence of metabolic associated fatty liver disease (MAFLD) and its associated factors among type 2 diabetes mellitus (T2DM) in primary care settings in Kuantan, Pahang

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ABSTRACT

Introduction: Metabolic associated fatty liver disease (MAFLD) is a common comorbidity in type 2 diabetes mellitus (T2DM) and is associated with adverse hepatic and metabolic outcomes. Early detection in primary care is limited by restricted access to imaging, highlighting the need for practical non-invasive screening tools. This study aimed to determine the prevalence of MAFLD using the Fatty Liver Index (FLI) and identify associated factors among T2DM patients in Kuantan, Pahang.

Materials and Methods: A cross-sectional study was conducted among T2DM patients aged ≥18 years selected through systematic random sampling from primary care clinics. Sociodemographic and clinical data were obtained from interviews and medical records. FLI, calculated using BMI, waist circumference, triglycerides, and gamma-glutamyl transferase, was used to estimate hepatic steatosis, with MAFLD defined as FLI ≥60. Data were analysed using SPSS version 29, and multiple logistic regression was used to identify independent predictors.

Results: Among 430 participants, MAFLD prevalence was 51.2% (n=220). Patients with MAFLD were younger (56.4 vs. 61.5 years, p<0.001), had shorter diabetes duration (6 vs. 8 years, p=0.011), and poorer glycaemic control (HbA1c ≥7%: 64.5% vs. 48.2%, p<0.001). Prevalence was highest among Indians (61.9%), followed by Malays (53.7%) and Chinese (35.1%) (p=0.008). Multivariable analysis demonstrates younger age (AOR=0.974; 95% CI: 0.956–0.992) and poor glycaemic control (AOR=2.016; 95% CI: 1.326–3.065) were independently associated with MAFLD.

Conclusion: MAFLD prevalence was high among T2DM patients in primary care. Younger age and poor glycaemic control were independently associated with MAFLD. Routine FLI screening may support early identification of high-risk patients and timely intervention.

KEYWORDS:
Fatty Liver Index; MAFLD; Type 2 Diabetes Mellitus; Prevalence; Malaysia

INTRODUCTION

Metabolic associated fatty liver disease (MAFLD) is a clinically defined condition characterised by hepatic steatosis alongside metabolic dysfunction, such as overweight/obesity, dyslipidaemia, or type 2 diabetes mellitus (T2DM). This redefinition, transitioning from the previous non-alcoholic fatty liver disease (NAFLD) framework, emphasises inclusion based on metabolic criteria rather than solely excluding alcohol or other liver diseases.[1] The change was endorsed by the Asian Pacific Association for the Study of the Liver (APASL) and national societies, including the Malaysian Society of Gastroenterology and Hepatology (MSGH).[2,3]

In 2023, an international consensus introduced the term metabolic dysfunctional associated steatotic liver disease (MASLD) to standardise nomenclature and replace NAFLD.[4,5] MASLD is defined as hepatic steatosis occurring in the presence of at least one cardiometabolic risk factor, excluding significant alcohol intake and other liver diseases. Given the close alignment between the concepts of MAFLD and MASLD, the MAFLD framework remains clinically relevant and was therefore adopted in the present study.

Beyond terminology, the clinical and public health burden of metabolically driven fatty liver disease is substantial. Globally, MAFLD affects more than 1 billion individuals. In the population with T2DM, meta-analyses indicate that nearly 65% have MAFLD, putting them at a heightened risk for advanced fibrosis, cirrhosis, hepatocellular carcinoma, and cardiovascular mortality.[6–9] In Malaysia, the National Health and Morbidity Survey (NHMS) 2023 reported a national MAFLD prevalence of 28.2%, with higher rates observed among urban and overweight adults.[9,10] Recent evidence from 2020 to 2025 further demonstrates a substantial burden among high-risk Malaysian populations, including hemodialysis cohorts and hospital-based T2DM patients, where MAFLD prevalence ranges from 43% to 45%, and 22–26% meet criteria for advanced fibrosis.[11,12] Despite these concerning trends, there remains a paucity of local data describing the burden of MAFLD specifically within primary care settings, where most T2DM patients receive long-term follow-up and where opportunities for early detection are greatest.

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Thus, this study was conducted to determine the prevalence of MAFLD and its associated factors among patients with T2DM attending government primary care clinics in Kuantan, Pahang. By examining the burden of MAFLD in a real-world primary care population, this study aims to strengthen local epidemiological evidence and inform targeted screening strategies to support earlier identification of high-risk individuals.

MATERIALS AND METHODS

Population, Setting and Sample Size Calculation

This cross-sectional study was conducted from April 2024 to April 2025 at government health clinics in Kuantan, Pahang. The inclusion criteria comprised Malaysian citizens aged 18 years and older with a diagnosis of T2DM, registered in the National Diabetes Registry (NDR) and attending routine follow-up at least twice yearly. Individuals with known chronic liver diseases such as hepatitis B or C, autoimmune hepatitis, Wilson's disease, hepatocellular carcinoma, or decompensated liver failure were excluded. Pregnant women, individuals who consume alcohol and vulnerable populations, including prisoners or aggressive respondents, were excluded.

The required sample size was determined to be 430, calculated based on an expected prevalence of 63.2% for MAFLD among T2DM patients from a previous study in China.[13] This calculation was made with a 95% confidence interval, a precision of 5%, and a 20% allowance for non-response. Simple random sampling was used to select respondents from the five clinics with high T2DM burden. Patients were randomly selected from the NDR using Excel to minimise selection bias.

Data Collection and Study Instruments

Data was collected using a structured, interviewer-administered questionnaire and validated measurement tools. The questionnaire covered socio-demographic information (age, sex, ethnicity, education, household income), clinical history (duration of diabetes, smoking status), and physical activity using the validated Malay short-form International Physical Activity Questionnaire (IPAQ-M). Anthropometric measurements, including weight, height, body mass index (BMI), and waist circumference (WC), were obtained using standard SECA equipment to ensure accuracy and consistency. Venous blood samples were obtained for routine diabetes monitoring (HbA1c, fasting lipid profile, and liver function tests), with gamma-glutamyl transferase (GGT) explicitly measured for this study. Fatty liver status was determined using the FLI, which incorporates WC(cm), BMI (kg/m²), GGT (U/L), and triglycerides (mg/dL). The formula is as follows:

$$FLI = \frac{(e0.953\times\ln(TG)+0.139\times BMI+0.718\times\ln(GGT)+0.053\times WC-15.745)}{(1+e0.953\times\ln(TG)+0.139\times BMI+0.718\times\ln(GGT)+0.053\times WC-15.745)} \times 100$$

An FLI score ≥60 was used to indicate steatosis in this study. FLI was chosen for its practicality and suitability for large-scale screening in primary care, where imaging modalities such as ultrasonography or transient elastography are not routinely available. In ultrasound-based validation studies, this cut-off showed good diagnostic performance, with a sensitivity of 80.3%, specificity of 87.3%, and substantial agreement with ultrasonography (κ=0.65).[14,15]

Data Analysis

All data were analysed using SPSS version 29. Descriptive statistics were used to summarise socio-demographic, clinical, and biochemical characteristics. Continuous variables were reported as mean ± standard deviation (SD) or median (interquartile range, IQR), while categorical variables were presented as frequencies and percentages. Bivariate analyses were conducted to examine associations between MAFLD and potential predictors. Multiple logistic regression was performed to identify independent factors associated with MAFLD, and adjusted odds ratios with 95% confidence intervals were reported. A p-value < 0.05 was considered statistically significant.

RESULTS

Sociodemographic and clinical characteristics of respondents. Four hundred thirty adults with type 2 diabetes mellitus in Kuantan, Pahang, were included in this study. The general characteristics of the respondents at baseline are presented in Table I. Most respondents were female (59.5%, n=246) with a mean age of 58.89 years, and the majority were Malay (72.3%, n=311). The median duration of diabetes was 7 years (IQR: 10), and anthropometric measurements indicated a high prevalence of obesity (mean BMI 28.7 kg/m²; mean waist circumference 91.36 cm). More than half had secondary education (52.3%, n=225), and most were from the B40 income group (82.3%, n=354). Most of the respondents were non-smokers (87.7%, n=377) and had low physical activity (54.4%, n=234).

Table II illustrates 56% of respondents had HbA1c levels ≥7%, indicating poor glycaemic control. The median ALT was 31 U/L (IQR: 20), while mean AST and GGT levels were 22.36 U/L (SD=10.001) and 41.14 U/L (SD=37.162), respectively. Although triglyceride (mean 129.53 mg/dL, SD=72.99) and HDL cholesterol levels (mean 56.55 mg/dL, SD=18.51) were generally favourable, LDL cholesterol remained high (mean 104.43 mg/dL, SD=44.42).

Prevalence of Metabolic Associated Fatty Liver Disease (MAFLD) among Type 2 Diabetes Mellitus (T2DM) patients.

Figure 1 presents the prevalence of metabolic associated liver disease (MAFLD) among type 2 diabetes mellitus (T2DM) patients attending primary care settings in Kuantan, Pahang. In this study, 51.2% (n=220) of the respondents were detected to have MAFLD. This finding indicates the prevalence of MAFLD was notably high in this population.

Factors associated with Metabolic Associated Fatty Liver Disease (MAFLD) among T2DM patients.

In Table III, the bivariate analysis identified several factors associated with MAFLD. Respondents with MAFLD were significantly younger than the non-MAFLD group (56.4 vs. 61.4 years, p < 0.001). Ethnicity was also a significant factor (p=0.008), with Indians exhibiting the highest prevalence (61.9%, n=26). MAFLD was additionally associated with a

Table I: Sociodemographic characteristics of respondents

Variable	n (%)
Age (years)	Mean = 58.89, SD = 0.575
Male	174 (40.5%)
Female	256 (59.5%)
Race	
Malay	311 (72.3%)
Chinese	77 (17.9%)
Indian	42 (9.8%)
Duration of DM (years)	Median = 7.0, IQR = 10
BMI (Kg/m²)	Mean =28.79, SD = 6.444
Waist Circumference (cm)	Mean = 91.36, SD = 19.449
Education Level	
Primary School	112 (26.0%)
Secondary School	225 (52.3%)
College/University	93 (21.6%)
Household Income	
B40 (<RM3,900/month)	354 (82.3%)
M40 (RM3,900–RM7,599/month)	60 (14.0%)
T20 (>RM7,599/month)	16 (3.7%)
Smoking Status	
Yes	53 (12.3%)
No	377 (87.7%)
Physical Activity Level	
Low	234 (54.4%)
Moderate	147 (34.2%)
High	49 (11.4%)

SD: standard deviation; IQR: interquartile range

Table II: Clinical parameters of respondents

Variables	n (%)
HbA1c (%)	
HbA1c <7%	189 (44.0%)
HbA1c ≥7%	241 (56.0%)
ALT (U/L)	Median = 31.00, IQR = 20
AST (U/L)	Mean = 22.36, SD = 10.001
GGT (U/L)	Mean = 41.14, SD = 37.162
Triglyceride (mg/dl)	Mean = 129.525, SD = 72.988
HDL (mg/dl)	Mean = 56.546, SD = 18.510
LDL (mg/dl)	Mean = 104.430, SD = 44.422

SD: standard deviation; IQR: interquartile range

shorter duration of diabetes (p=0.011) and poor glycaemic control, with 58.9% (n=142) of individuals with HbA1c ≥7% affected (p < 0.001).

The multivariable logistic regression analysis (Table IV) shows age and glycaemic control remained independently associated with MAFLD after adjustment for potential confounders. Increasing age was inversely associated with MAFLD (AOR=0.974, p=0.005), indicating a higher likelihood of MAFLD among younger patients with T2DM. In contrast, poor glycaemic control (HbA1c ≥ 7%) was associated with approximately a two-fold increase in the odds of MAFLD (AOR=2.016, p=0.001).

DISCUSSION

In this study, 51.2% of respondents had MAFLD, accounting for half of the T2DM patients in Kuantan, Pahang. This finding highlights a considerable metabolic burden within the local diabetic population and reflects the emerging recognition of MAFLD as the hepatic manifestation of metabolic dysfunction. The high prevalence observed in our setting underscores the need for heightened awareness and early screening for MAFLD in primary care, where most diabetic patients receive long-term follow-up and lifestyle counselling.

Compared with our observed prevalence, recent evidence suggests the global burden of MAFLD is generally lower, with a pooled adult prevalence of around 38–39%.[4,6,16–18] However, when comparing with the individuals with T2DM specifically, published prevalence figures tend to be substantially higher than in the general population. A recent meta-analysis reported a global prevalence of MAFLD among T2DM of approximately 65.33%, with the highest prevalence in the Eastern European region.[17] Moreover, K. E. Chan et al. (2022) also reported that patients with diabetes have nearly four times higher odds of developing MAFLD compared to non-diabetics (OR 3.80; 95% CI 2.65–5.43).[19] Our study reaffirmed the previous findings that patients with diabetes mellitus have a higher risk of getting MAFLD. The prevalence of MAFLD in our cohort was 51.2%, substantially higher than

Table III: Factors associated with MAFLD among Type 2 Diabetes Mellitus patients in primary care settings in Kuantan, Pahang

	Non-MAFLD (n=210)	MAFLD (n=220)	MAFLD (%)	p-value (2-sided)
Age	m:61.5±11.13	m:56.4±12.13	-	<.001*
Gender				0.434
Female	129	127	57.7%	
Male	81	93	42.3%	
Race				0.008*
Malay	144	167	75.9%	
Chinese	50	27	12.3%	
Indian	16	26	11.8%	
Educational Status				0.488
Primary School	60	52	23.6%	
Secondary School	105	120	54.5%	
College/University	45	48	21.8%	
Household Income				0.602
B40 (<RM3900/Month)	173	181	82.3%	
M40(RM3900RM7599/Month)	31	29	13.2%	
T20 (> RM 7599/Month)	6	10	4.5%	
Smoking Status				0.254
No	188	189	85.9%	
Yes	22	31	14.1%	
Physical Status				0.620
Low	111	123	55.9%	
Moderate	72	75	34.1%	
High	27	22	10.0%	
Duration of DM	8.00 (IQR:4-16)	6.00 (IQR: 3 -10.75	-	0.011*
HbA1c status				<0.001*
HbA1c <7%	111	78	35.5%	
HbA1c ≥7%	99	142	64.5%	

IQR: interquartile range; m: mean; * significant p-value<0.05

Table IV: Multiple logistic regression predicting associated factors of MAFLD among T2DM patients

Predictor	B	Wald	AOR	95% CI	p-value
Age (years)	–0.026	7.813	0.974	0.956 – 0.992	0.005*
Race (overall)	—	4.251	—	—	0.119
Chinese vs Malay	–0.477	2.938	0.620	0.359 – 1.071	0.086
Indian vs Malay	0.305	0.757	1.356	0.683 – 2.694	0.384
Duration of DM (years)	–0.030	3.799	0.970	0.941 – 1.000	0.051
HbA1c ≥7% (vs <7%)	0.701	10.750	2.016	1.326 – 3.065	0.001*

AOR: Adjusted odd ratio; CI: confidence interval; * significant at p- value <0.05

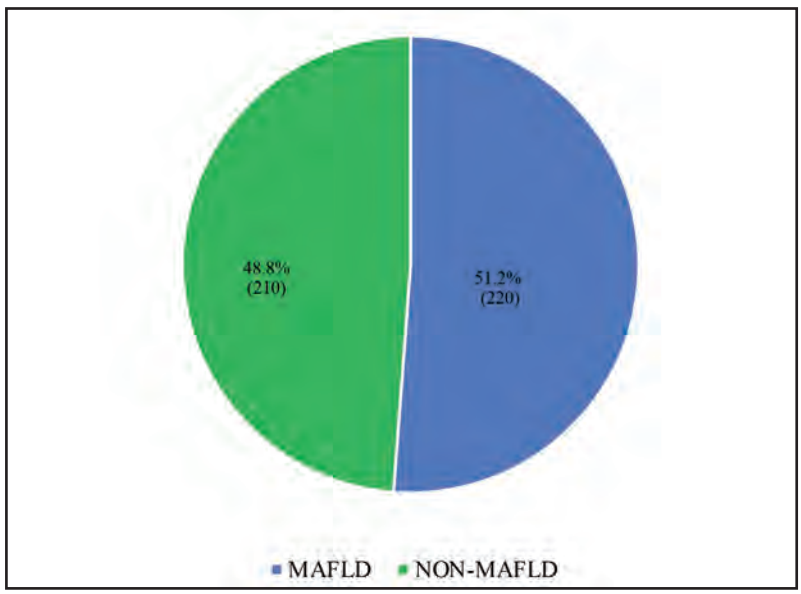

Fig. 1: Prevalence of metabolic associated fatty liver disease (MAFLD) among type 2 diabetes mellitus (T2DM) in primary care settings in Kuantan, Pahang (N= 430)

the 28.2% reported in the general Malaysian population. This finding is particularly noteworthy, as our respondents exhibited more favourable metabolic profiles, including a lower average BMI (27.04 kg/m² vs national 32.5 kg/m²), triglyceride levels (129.53 mg/dL vs national 165.63 mg/dL), as were their liver enzymes: ALT (31.00 vs. national 41.07), AST (22.36 vs. national 29.68), and GGT (41.14 vs. national 62.33). However, glycaemic control was suboptimal, with 56% of participants having HbA1c ≥7%, compared with a national mean of 6.04%. As our cohort consisted exclusively of patients with T2DM, a recognised high-risk group for fatty liver disease, the elevated prevalence observed was expected.9 The coexistence of T2DM and MAFLD has important clinical implications, as it significantly increases the risk of advanced liver fibrosis, cardiovascular disease, and renal complications. Poor glycaemic control may further accelerate hepatic steatosis and fibrosis progression through worsening insulin resistance and metabolic dysfunction.[17,20,21] These findings highlight the importance of incorporating early MAFLD screening and timely metabolic optimisation into routine primary care diabetes management to reduce future hepatic and systemic complications.

In this study, multivariable logistic regression analysis demonstrated that age and glycaemic control were independently associated with MAFLD among patients with T2DM. Notably, MAFLD was more prevalent among younger adults with T2DM, with a mean age of 56.4 years. While earlier population-based studies have consistently shown that MAFLD becomes more common with advancing age, more recent diabetic cohorts demonstrate an emerging shift whereby MAFLD increasingly affects younger individuals.[13,22–25] Similar observations have emerged in Malaysia, where MAFLD patients were nearly a decade younger than the global average but experienced a higher burden of metabolic comorbidities.[9] Our findings were consistent with this emerging trend, as each 1-year increase in age was associated with a 2.6% reduction in the odds of MAFLD (AOR 0.974; 95% CI 0.956–0.992; p-value=0.005). This shift toward younger-onset MAFLD among T2DM patients likely reflects earlier development of metabolic risk factors, rising early-onset diabetes, and prolonged lifetime exposure to hyperglycaemia and dyslipidaemia. Such early metabolic derangement accelerates hepatic fat accumulation and fibrosis progression. In contrast, older patients may represent a survivor group or may have progressed to more advanced liver disease, where steatosis becomes less detectable using FLI. For future T2DM populations, this trend is concerning as it increases the lifetime risk of advanced liver disease, cardiovascular complications, and long-term healthcare burden, underscoring the need for earlier screening and tighter metabolic control in primary care.

Poor glycaemic control further compounded this risk. Individuals with HbA1c ≥7% had almost twice the odds of developing MAFLD (AOR 2.016; 95% CI 1.326–3.065; p-value=0.001), highlighting the key role of persistent hyperglycaemia in driving hepatic steatosis. Pathophysiologically, prolonged elevation in glucose levels exacerbates insulin resistance, stimulates de novo lipogenesis, increases hepatic free fatty acid influx, and promotes inflammatory liver injury. Similar associations have been demonstrated across other diabetic cohorts, where higher HbA1c levels were consistently observed among MAFLD cases compared to non-MAFLD T2DM patients and international evidence has reinforced the strong link between sustained hyperglycaemia and disease severity.[22,26–29] Taken together, the combination of younger age and poor glycaemic control suggests a shift towards a more metabolically aggressive form of MAFLD in T2DM patients, underscoring the importance of early metabolic intervention to reduce hepatic injury and prevent future progression.

Other demographic factors, including gender and race, did not show a significant association with MAFLD in this study. Despite reports of higher MAFLD prevalence among males with T2DM, we found no significant sex differences, indicating a high metabolic burden in both genders. Although Indian ethnicity in Malaysia is associated with higher visceral fat and cardiometabolic risk, it lost significance after adjustments. This implies that metabolic disturbances have a greater impact than ethnic background on liver fat accumulation after diabetes develops. Apart from that, longer diabetes duration showed a borderline inverse association with MAFLD (AOR 0.970; p=0.051), which contrasts with recent evidence linking prolonged diabetes with greater hepatic steatosis and fibrosis.[12,30] This finding is likely affected by the high rate of poor blood sugar control in our group, as over half of the participants had an HbA1c level of 7% or higher. Chronic hyperglycemia is a stronger driver of hepatic fat accumulation than diabetes duration. The limited range of diabetes duration in our study may have limited our ability to detect a clear association, likely explaining the weaker association between diabetes duration and MAFLD in our cohort compared with previous studies.

Physical activity, smoking, socioeconomic status, and education were not significantly associated with MAFLD in our study, differing from previous research. Earlier studies consistently reported that lower physical activity and smoking increase the risk of NAFLD/MAFLD.[31–33] This difference might be attributable to limitations of the IPAQ questionnaire, which relies on self-reported data and may overlook key differences. Similarly, smoking lost its significance after adjustments, despite its known role in promoting hepatic steatosis and fibrosis.[8,34] The more pronounced influence of metabolic factors, particularly adiposity and HbA1c, may have overshadowed the effects of these lifestyle factors. Nonetheless, physical inactivity and smoking remain critical determinants of metabolic health. Therefore, lifestyle counselling should continue to be emphasised in routine diabetes care. Additionally, socioeconomic status and education were not associated with MAFLD in our cohort, in contrast to studies that have linked higher income or urban living to a greater risk and lower education to a lower risk.[24,35,36] The possible reason for these findings is the relatively similar urban population served by primary care clinics in Kuantan. Modern eating habits, easy access to high-calorie foods, and sedentary lifestyles are common across all income and education levels, which may reduce the usual differences seen between socioeconomic groups. As a result, the absence of significant differences in demographic, lifestyle, or socioeconomic factors likely reflects the strong influence of overall metabolic burden in individuals with T2DM.

The findings from this study have important implications for diabetes care in Malaysian primary care settings. The high burden of MAFLD among individuals with T2DM, together with the strong influence of poor glycaemic control, highlights the need for earlier screening and more aggressive metabolic intervention before fibrosis and liver-related complications develop. Screening for fatty liver disease should not rely solely on liver enzymes, as many patients with MAFLD may have normal ALT levels. Instead, simple non-invasive tools such as the FLI, abdominal obesity measures, and routine metabolic profiling can be incorporated into routine diabetes follow-up assessments, particularly among younger patients with poor HbA1c control who already demonstrate significant metabolic risk. These findings are especially relevant in Malaysia, given rapid urbanisation, increasingly sedentary lifestyles, and widespread access to energy-dense foods and sugary beverages, which may help explain the lack of significant socioeconomic differences observed in our cohort. In line with the 2023 international consensus, the Malaysian Society of Gastroenterology and Hepatology has adopted the term MASLD to emphasise the central role of metabolic dysfunction in fatty liver disease. Our findings further support this concept, as poor glycaemic control emerged as a major contributor to fatty liver disease among patients with T2DM. Integrating this understanding into routine diabetes care may facilitate earlier identification of high-risk individuals and enable timely intervention to reduce progression to fibrosis, cirrhosis, and other metabolic complications.[39]

This study provides insight into MAFLD among patients with T2DM in primary care, where most long-term diabetes management occurs. The use of the FLI, based on routinely available parameters, supports its practicality for large-scale screening. However, the study has several limitations including steatosis was assessed using FLI without imaging confirmation, and the intermediate range (FLI between 30–59) may underestimate prevalence. In addition, the single-district primary care setting may limit generalisability. Future longitudinal studies incorporating imaging modalities and fibrosis assessment, including transient elastography and FIB-4, are recommended.

CONCLUSION

MAFLD was highly prevalent among patients with T2DM in Kuantan, reflecting a substantial local metabolic burden. Younger age and poor glycaemic control were independently associated with MAFLD, underscoring the importance of early screening and proactive metabolic optimisation. Integrating MAFLD assessment into routine diabetes care within primary care settings is crucial to mitigate the growing dual burden of diabetes and fatty liver disease in Malaysia.

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ETHICAL APPROVAL

This study was approved by the Research and Ethical Committee of the researchers' institution (IREC number 1073) and NMMR (NMRR ID-24-00035-876 (IIR)). All respondents had given their written consent. Those who refused to participate received the same standard of care as those who agreed.

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Non-specific orbital inflammation: Clinical and histopathological insights from a 6-year single-centre Malaysian cohort

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ABSTRACT

Introduction: Non-specific orbital inflammation (NSOI), formerly known as idiopathic orbital inflammatory disease (IOID), is a rare, exclusion-based orbital disorder with diverse clinical manifestations. This study evaluates the demographic patterns, clinical features, histopathological profiles, and treatment outcomes of NSOI cases managed at a tertiary referral centre in Malaysia.

Materials and Methods: A six-year retrospective review was conducted at a tertiary referral centre in northern Malaysia, involving 36 patients diagnosed with NSOI between January 2018 and December 2023. Diagnosis was based on clinical features, exclusion of systemic and infectious causes through serology, and supportive imaging or biopsy findings. Only cases with histopathological confirmation and immunohistochemical staining negative for lymphoma, carcinoma, and other malignancies were included. Data included demographics, clinical presentation, imaging and histopathological findings, serologic evaluations, and treatment modalities. Outcomes were assessed based on symptom resolution, radiologic improvement, recurrence, and treatment response.

Results: Most patients were male (61.1%), with a mean age of 43.6 years. Unilateral involvement predominated (77.8%). Common presentations included periorbital swelling (69.4%), ophthalmoplegia (22.2%), conjunctival mass (22.2%), and proptosis (19.4%). Imaging revealed frequent involvement of the lacrimal gland (45.8%), extraocular muscles (37.5%), and conjunctiva (37.5%). The main histopathological findings included reactive lymphoid hyperplasia (40%), granulomatous inflammation (20%), and chronic inflammation (23.3%). Of the 36 patients, 19 received medical treatment, with 84.2% given systemic corticosteroids, while the remaining 17 patients were managed conservatively without any medical treatment, and they remained clinically stable throughout follow-up with no evidence of disease progression. Among treated cases, recurrence occurred in 25%, predominantly in males.

Conclusion: NSOI shows varied clinical and anatomical patterns. Corticosteroids remain the mainstay of treatment, but conservative management is appropriate in stable, non-progressive cases when close monitoring and diagnostic exclusion are assured. These findings support individualised therapeutic strategies and long-term follow-up.

KEYWORDS:
Non-specific orbital inflammation, orbital pseudotumor, idiopathic orbital inflammation, IOID, myositis

INTRODUCTION

Non-specific orbital inflammation (NSOI), previously referred to as idiopathic orbital inflammatory disease (IOID) or orbital pseudotumor, is a non-infectious, exclusion-based inflammatory disorder of the orbit.[1] It ranks the third most common orbital inflammatory condition after thyroid eye disease and orbital lymphoma.[1,2] Although considered benign, NSOI poses diagnostic and therapeutic challenges due to its variable presentation and overlap with other orbital pathologies.[3]

NSOI may involve a wide range of orbital tissues, including the lacrimal gland, extraocular muscles, conjunctiva, optic nerve sheath, and orbital fat.[1,2] Imaging, particularly magnetic resonance imaging (MRI), is essential for assessing disease extent and excluding mimickers.[4] Histopathological evaluation (HPE), while not routinely performed, plays a pivotal role in confirming diagnosis and subclassifying inflammation, especially in cases of recurrence, steroid-refractory disease, or diagnostic uncertainty.[1,3,5]

Systemic corticosteroids remain the cornerstone of treatment, with close observation considered in patients with stable, non-vision-threatening disease.[1,6] Despite its clinical relevance, data on NSOI from Southeast Asia remain limited. This study characterises the clinical spectrum, diagnostic strategies, and treatment outcomes of NSOI at a Malaysian tertiary referral centre.

MATERIALS AND METHODS

This retrospective study analysed 36 patients diagnosed with NSOI at the Oculoplastic Clinic of Hospital Sultanah Bahiyah, a tertiary referral centre serving northern Peninsular Malaysia, between January 2018 and December 2023. The diagnosis was established through clinical

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assessment, serological exclusion of systemic and infectious aetiologies, and corroborative imaging or biopsy findings. Only patients with HPE and immunohistochemical staining negative for lymphoma, carcinoma, and other malignancies were included. The study was approved by the hospital administration and conducted in accordance with the Declaration of Helsinki. Informed written consent was obtained from all participants.

Medical records were reviewed to extract demographic data, clinical features, imaging and histopathological findings (where available), serologic test results for systemic and infectious mimickers, treatment modalities, and clinical outcomes. Patients were stratified by disease course into acute (< 2 weeks), subacute (2-6 weeks), and chronic (> 6 weeks) groups. NSOI was further classified by anatomical involvement (e.g., lacrimal gland, extraocular muscles, orbital fat, conjunctiva) and orbital location (anterior, diffuse, posterior, apical) based on imaging and HPE. Descriptive statistics were used to summarise demographic data, clinical characteristics, imaging findings and treatment outcomes.

RESULTS

Most of the confirmed NSOI patients enrolled in this study were males (61.1%), with a mean age of 43.61 ± 15.39 years. Eight patients had bilateral eye involvement. Most patients had a chronic disease course, presenting with symptoms lasting more than 6 weeks. Periorbital swelling was the most common presenting complaint, while conjunctival injection, eye pain, and diplopia were reported less frequently (Table I). Visual acuity remained unaffected in all patients, with no reported cases of vision loss. The most common features observed at presentation were ophthalmoplegia (22.2%), conjunctival mass (22.2%), and proptosis (19.4%).

The categorisation of NSOI cases in this study was based on the anatomical structures affected, as determined by imaging, and the pathological processes identified through HPE. Imaging studies were performed in 24 patients, with the majority undergoing computed tomography (CT) and one undergoing MRI, while biopsies were conducted in 30 patients. The most involved structures on imaging were the lacrimal gland (45.8%), extraocular muscles (37.5%), and conjunctiva (37.5%). Among the anatomical subtypes observed, anterior involvement predominated, as detailed in Table II. HPE revealed microscopic features of lymphoid hyperplasia in over half of the cases (53.4%), compared to granulomatous inflammation in 20% of cases (Table III). IgG4 immunostaining was performed in two biopsied cases, both of which were negative.

Of the 36 patients, 19 received medical treatment, while 17 were managed conservatively with close observation and no active medical therapy. Systemic corticosteroids were the first-line treatment in the majority of treated patients (84.2%). Oral prednisolone was initiated at 0.5-1 mg/kg/day (maximum 80 mg) and tapered weekly by 5-10 mg, with adjustments based on clinical response. In selected cases with more extensive orbital or optic nerve involvement, intravenous methylprednisolone (1 g/day for 3 consecutive days) was administered at presentation, followed by oral prednisolone 1 mg/kg/day with a similar tapering regimen. Topical corticosteroids were prescribed for patients with localised conjunctival masses. Due to concerns regarding psychiatric comorbidity, one patient received non-steroidal anti-inflammatory therapy instead of systemic corticosteroids.

In steroid-refractory cases or those with disease recurrence, steroid-sparing immunomodulatory therapy was initiated, including methotrexate (starting at 15 mg weekly), azathioprine (starting at 150 mg daily), or a combination of both, with doses adjusted according to clinical response. One patient with perineural optic nerve involvement extending to the orbital apex showed a suboptimal response despite prolonged corticosteroid therapy and required the addition of methotrexate. Two other patients with extensive orbital and bilateral lacrimal gland involvement experienced recurrence after an initial remission and were subsequently treated with azathioprine and methotrexate, respectively.

In contrast, those treated conservatively comprised patients with small, stable eyelid masses, chronic lid swelling or proptosis persisting for months to years without redness, pain, or visual impairment. All remained clinically stable or slightly improved over the observation period, without evidence of progression.

DISCUSSION

NSOI is a diagnosis of exclusion, characterised by idiopathic inflammation of orbital tissues in the absence of systemic or infectious causes.[2,6-8] This retrospective series represents the most detailed characterisation of NSOI in Malaysia to date and contributes valuable data from Southeast Asia, where published literature remains limited. Unlike most Western and regional reports that describe a female predominance in the fifth decade of life,[1,2,9,10] our cohort was predominantly male, with a younger mean age of 43.6 years. Notably, two paediatric cases (ages 8 and 12) were identified, highlighting the need to consider NSOI in children and adolescents. Although rare, paediatric presentations have been reported, with variable features ranging from isolated orbital inflammation to systemic overlap syndromes.[11,12]

Consistent with existing literature, our cohort demonstrated predominantly unilateral cases and a wide spectrum of clinical manifestations. The lacrimal gland was the most involved structure, aligning with prior reports of dacryoadenitis-type NSOI as a common presentation.[10,13,14] Conjunctival and extraocular muscle involvement were equally prevalent, further highlighting the anatomical heterogeneity and diagnostic complexity of the condition.[9] Although all patients maintained good visual acuity, two were radiologically diagnosed with optic neuritis and optic perineuritis, underscoring the need for comprehensive optic nerve function testing beyond Snellen acuity. The presence of ophthalmoplegia despite otherwise normal anterior segment and fundus examinations reinforces the importance of thorough clinical and radiologic evaluation to exclude mimickers such as thyroid eye disease, cranial nerve palsies, orbital apex syndrome, and cavernous sinus or brainstem pathology.[3,4,6,7,15]

Table I: Demographic profile and clinical characteristics of NSOI (n = 36)

Variables	n (%)
Age (years)	
Mean ± SD: 43.61 ± 15.39 (range: 8-71)	
Gender	
Male	22 (61.1)
Female	14 (38.9)
Race	
Malay	28 (77.8)
Chinese	5 (13.9)
Indian	3 (8.3)
Disease Course	
Acute	8 (22.2)
Subacute	4 (11.1)
Chronic	24 (66.7)
Laterality	
Unilateral	28 (77.8)
Bilateral	8 (22.2)
Presenting Symptoms	
Periorbital swelling	18 (50.0)
Conjunctival injection	4 (11.1)
Eye pain	3 (8.3)
Diplopia	3 (8.3)
Clinical Signs at Presentation	
Ophthalmoplegia	8 (22.2)
Conjunctival mass	8 (22.2)
Proptosis	7 (19.4)
Optic neuropathy (RAPD)	1 (2.8)
Chemosis	2 (5.6)
Palpable periorbital mass	2 (5.6)
Ptosis	1 (2.8)
Treatment	
Yes	19 (52.8)
Systemic corticosteroid	16 (84.2)
- Oral corticosteroid (initial treatment)	14 (73.7)
- Intravenous corticosteroid (initial treatment)	2 (10.5)
Topical corticosteroid	2 (10.5)
Immunomodulators	3 (15.8)
NSAIDS	1 (5.3)
No (Observation only)	17 (47.2)
Recurrence	
Treated group	9 (47.4)
Non-treated group	-

RAPD, relative afferent pupillary defect; NSAID, non-steroidal anti-inflammatory drug

Table II. Imaging-based characteristic of NSOI (n = 24)

Subtype of NSOI	n (%)
Tissue-specific subtype	
Lacrimal gland (Dacryoadenitis)	11 (45.8
Extraocular muscles (Myositis)	9 (37.5)
Optic nerve (Optic Neuritis)	1 (4.2)
Optic nerve sheath (Optic Perineuritis)	1 (4.2)
Orbital mass	3 (12.5)
Orbital fat	1 (4.2)
Conjunctiva	9 (37.5)
Eyelid	4 (16.7)
Lacrimal sac and duct	2 (8.3)
Anatomical subtype	
Anterior	18 (75.0)
Diffuse	4 (16.7)
Posterior	1 (4.2)
Apical	1 (4.2)
Dacryoadenitis	7 (29.2)
Myositis	5 (20.8)

Table III: Histopathological features observed in NSOI cases (n=30)

Histopathological Features	n (%)
Reactive lymphoid hyperplasia	12 (40.0)
Benign lymphoid hyperplasia	4 (13.4)
Granulomatous inflammation	6 (20.0)
Chronic inflammation	7 (23.3)
No obvious inflammation	1 (3.3)

Imaging is the cornerstone of NSOI diagnosis,16 particularly in our patients who declined biopsy due to concerns about surgical procedures and operative risks. CT was the primary modality used, given its accessibility and ability to delineate anatomical involvement, supporting diagnosis in cases where histopathological confirmation was not feasible. MRI offers superior soft tissue contrast and is especially useful for evaluating optic nerve involvement, orbital apex pathology, and intracranial extension,[4,16] but was not routinely performed due to cost and availability constraints.

Excluding infectious, autoimmune, and systemic causes is essential before diagnosing NSOI, given its nature as a diagnosis of exclusion.[3,5-7,17] However, the definitive diagnosis often relies on HPE analysis, especially when clinical and imaging findings are inconclusive.[1,2,15] Lymphoid hyperplasia was the predominant finding in our cohort, with reactive subtypes more common than benign forms. While both reflect lymphoid proliferation, reactive hyperplasia typically indicates a polyclonal inflammatory response, whereas benign hyperplasia may show organised follicular architecture, occasionally mimicking low-grade lymphoma.18 Granulomatous and chronic inflammation were also observed. The latter referred to non-specific infiltrates lacking defining features, possibly representing early-stage disease, treated lesions, or diagnostically indeterminate inflammation.[1]

Recent literature suggests that up to 50% of biopsy-proven NSOI cases may represent IgG4-related orbital disease (IgG4-ROD), a distinct clinicopathological entity with systemic implications. Despite increasing global recognition, reported cases from Malaysia remain limited, with the first case published in 2018 and only a few subsequent reports. This scarcity may reflect underdiagnosis, restricted access to IgG4 testing, or a genuinely lower local prevalence. In Malaysia, the diagnosis of IgG4-ROD is often hindered by broader healthcare resource limitations, while definitive confirmation remains further challenged by the restricted availability and high cost of histopathology and IgG4-specific immunohistochemistry services. In the absence of routine testing and comprehensive epidemiological data, the true burden remains uncertain. Future studies incorporating standardised immunohistochemistry are warranted to enable accurate subclassification of NSOI and guide long-term management strategies.

Management of NSOI is progressively expanding beyond corticosteroids to incorporate anti-metabolites (e.g., methotrexate, azathioprine), biologic and molecular therapies (including rituximab, TNF-α inhibitors, and IL-6 blockade) and emerging small-molecule treatments such as JAK inhibitors.1 While these approaches reflect a shift toward more targeted therapy, their use remains largely off-label and is supported primarily by limited observational data.[1]

In our cohort, systemic corticosteroids remained the first-line therapy, consistent with established treatment paradigms for NSOI.[3,5,6,21] Immunomodulatory agents, particularly azathioprine and methotrexate, were used in steroid-refractory cases, as previously reported, particularly those with dacryoadenitis, myositis, or perineuritis—subtypes frequently associated with recurrence.[3,5,7,21] Notably, findings from a French cohort report suggest that a cellular histological pattern and orbital fat involvement may be risk factors for corticosteroid failure, even in patients receiving high-dose therapy.[22] These features were observed in some of our refractory cases, supporting the need for early identification of high-risk patterns to guide escalation of immunosuppression. Although less commonly used, biologic agents, low-dose orbital radiotherapy, and surgical intervention remain potential options for refractory disease.[1,3,23]

Nearly half of our patients were managed conservatively due to indolent non-progressive disease, supported by negative serologic investigations and absence of visual disturbances. Their clinical phenotype, small lid mass or chronic, painless lid swelling or proptosis persisting for months to years without visual compromise or inflammatory signs, likely represents a less aggressive variant of idiopathic orbital inflammatory disease, typically involving anterior or localised regions with minimal functional impairment and no optic nerve involvement. This observation supports prior reports suggesting that NSOI may be self-limiting in selected cases.[24] However, conservative management should only be considered when imaging or biopsy excludes serious pathology, serologic screening is negative, and close follow-up is feasible. Identifying predictors of indolent NSOI, such as anatomical subtype, disease duration, and inflammatory markers, remains an important area for future research.

CONCLUSION

This study reinforces the broad clinical spectrum and heterogeneity of NSOI. While corticosteroid therapy remains the mainstay of treatment, not all patients achieve complete resolution, and some experience recurrence or persistent low-grade inflammation. Indolent cases may remain stable without intervention, suggesting that observation is reasonable when diagnostic confidence is high and follow-up is assured. Future studies should aim to identify predictors of disease activity, treatment response, and recurrence to optimise individualised management strategies.

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ORIGINAL ARTICLE

Gender representation across surgical specialties in Malaysia

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ABSTRACT

Introduction: Although female enrolment exceeds 50% in many undergraduate medical programmes worldwide, surgeons remain overwhelmingly male despite studies reporting better outcomes by female surgeons. We aimed to characterise gender representation across surgical specialties in Malaysia.

Materials and Methods: We performed a cross-sectional study, extracting data of all surgical specialties from the Malaysian Specialist Register up to 30th September 2023. Gender proportions were assessed using the UNESCO Gender Parity Index (GPI), GPI<1 indicating fewer females. Gender parity was considered present at GPI 0.97-1.03. Disparities were categorised as extreme (<0.5,>1.5), intermediate (0.5-0.89, 1.11-1.5), and close to parity (0.9-0.96,1.04-1.1). Number of years post-specialisation for each surgeon were calculated.

Results: 5236 surgeons were included. Only one specialty (Obstetrics & Gynaecology, GPI=1.03) showed parity and two specialties (Breast & Endocrine, GPI 2.67 and Ophthalmology, GPI 1.27) had more female surgeons. The other thirteen specialties showed various degrees of male predominance. Most GPI values trended higher when younger surgeons were included in the calculation, indicating greater female representation in recent years.

Conclusion: Most surgical specialties in Malaysia show extreme gender inequity. Further work is needed to identify root causes and improve trends. Future efforts should further examine gender disparities and strengthen measures such as mentorship, supportive policies, transparent processes, and inclusive cultures, to advance equity in surgery.

KEYWORDS:
Female Surgeons, Gender Parity, Inequity, Surgical Training, Women in Surgery

INTRODUCTION

The persistent underrepresentation of women in global surgical specialties has become an issue of concern in the healthcare sector, despite the near-parity in female enrolment in undergraduate medical programmes[1-3] and evidence supporting the positive impact of female surgeons on outcomes.[4-6] Although trends worldwide show an increasing number of women pursuing medical education, significant gender disparities persist within surgical specialties due to systemic and cultural barriers.[7]

Studies from the United States and the United Kingdom have shown gradual increases in female surgical representation, though progress varies across specialties and parity remains distant in several fields.[8-9] Worldwide, fewer than one-third of surgeons are women.[10] Across Asia, similar trends have been observed, with countries such as China[11] and Japan[12] also reporting lower female participation in surgical specialties.

Within Malaysia, surgical training follows a pathway of medical school, housemanship and postgraduate specialty training through local or international programmes. Despite an increasingly gender-balanced medical workforce, women remain underrepresented in most surgical fields. For subspecialties requiring longer training, greater on-call demands or historically strong male dominance, more gender gap is present.

Despite the aforementioned studies, there remains a notable gap in research examining gender disparities across surgical specialties in Asia.[13-14] Our study seeks to fill this gap with the objective to characterise gender representation across surgical specialties in Malaysia. Results of our study can be used to inform targeted interventions aimed at achieving greater gender equity in these crucial medical fields.

MATERIALS AND METHODS

A cross-sectional study examined all surgical specialties documented in the Malaysian Specialist Register (SR) from 1st July 2017 until 30th of September 2023. The SR is a publicly available database established by the Malaysian Medical Council pursuant to the enactment of the Medical (Amendment 2012) Act 1971. It serves as a repository of information pertaining to specialists since its inception on 1st July 2017. This database contains information on various disciplines, qualifications, and geographic distribution of medical and surgical specialists practising within Malaysia.15 As the data used in this study were limited to non-identifiable variables such as gender and specialty, and no individual could be identified from the dataset, ethical approval was not required.

Gender-related information for registered surgeons across all surgical specialties listed on the SR website were extracted. This encompassed the following specialties: Breast and Endocrine Surgery, Cardiothoracic Surgery, Colorectal

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Table I: Gender Parity Index (GPI) of all surgical specialties in Malaysia on 30th September 2023

Surgical Specialty	Female (F)	Male (M)	Total (N)	Gender Parity Index (GPI)	GPI Classification
Breast and Endocrine Surgery	48	18	66	2.67	Extreme disparity (>1.5)
Ophthalmology	460	362	822	1.27	Intermediate disparity (1.11-1.5)
Obstetrics and Gynaecology	650	632	1282	1.03	Parity (0.97-1.03)
Paediatric Surgery	27	45	72	0.60	Intermediate disparity (0.5-0.89)
Otorhinolaryngology	192	352	544	0.55	Intermediate disparity (0.5-0.89)
Plastic Surgery	32	77	109	0.42	Extreme disparity (<0.5)
General Surgery	131	602	733	0.22	Extreme disparity (<0.5)
Upper Gastrointestinal Surgery	4	23	27	0.17	Extreme disparity (<0.5)
Neurosurgery	21	144	165	0.15	Extreme disparity (<0.5)
Colorectal Surgery	10	71	81	0.14	Extreme disparity (<0.5)
Thoracic Surgery	1	9	10	0.11	Extreme disparity (<0.5)
Orthopaedic Surgery	101	913	1014	0.11	Extreme disparity (<0.5)
Hepatobiliary Surgery	3	46	49	0.07	Extreme disparity (<0.5)
Urology	5	134	139	0.04	Extreme disparity (<0.5)
Cardiothoracic Surgery	3	85	88	0.04	Extreme disparity (<0.5)
Vascular Surgery	1	34	35	0.03	Extreme disparity (<0.5)

Table II: Pearson Correlation between Years-Post Specialisation and Gender Parity Index (GPI) of all surgical specialties in Malaysia

Surgical Specialty	Pearson correlation coefficient	p-value
Breast and Endocrine Surgery	-0.72	0.01 *
Ophthalmology	-0.94	0.01 *
Obstetrics and Gynaecology	-0.94	0.01 *
Paediatric Surgery	-0.88	0.01 *
Otorhinolaryngology	-0.94	0.01 *
Plastic Surgery	-0.96	0.01 *
General Surgery	-0.88	0.01 *
Upper Gastrointestinal Surgery	-0.77	0.01 *
Neurosurgery	-0.76	0.01 *
Colorectal Surgery	-0.81	0.01 *
Thoracic Surgery	-0.673	0.05
Orthopaedic Surgery	-0.919	0.01 *
Hepatobiliary Surgery	-0.71	0.01 *
Urology	-0.86	0.01 *
Cardiothoracic Surgery	-0.87	0.01 *
Vascular Surgery	-0.66	0.01 *

Surgery, General Surgery, Hepatobiliary Surgery, Neurosurgery, Obstetrics and Gynaecology, Ophthalmology, Orthopaedic Surgery, Otorhinolaryngology, Paediatric Surgery, Plastic Surgery, Thoracic Surgery, Upper Gastrointestinal Surgery, Urology, and Vascular Surgery. Only surgeons registered on or before 30th September 2023 were included, thereby providing a snapshot of gender proportions within Malaysia up to that date. No data cleaning, recoding, or duplicate exclusion was required, as all analyses were conducted using the dataset as provided.

The number of female and male surgeons in each specialty was obtained. The Gender Parity Index (GPI) was calculated for each specialty to assess gender disparities by dividing the number of females by the number of males, rounded up to two decimal places. This methodology was uniformly applied across all surgical specialties listed on the SR. A GPI value below 1 indicates a predominance of male surgeons while GPI value above 1 suggests a preponderance of female surgeons. We then categorised the severity of disparities as follows: GPI values below 0.5 or above 1.5 were classified as

extreme disparities, while intermediate disparities were those that fell between 0.5 to 0.89 or 1.11 to 1.5. GPI ranges 0.9 - 0.96 and 1.04 - 1.1 were considered close to parity. Gender parity was considered present at GPI range 0.97-1.03.[16]

The surgical specialties were then ranked based on their GPI values and summarised in a table, with statistical measures such as mean, median, interquartile range, and standard deviation derived. In addition to gender-related data, the number of years post-specialisation for each surgeon were calculated by subtracting their year of first specialist qualification from 2023. Figures illustrating the relationship between GPI and number of years post-specialisation for each surgical specialty were generated based on this data. Descriptive analysis was used to characterise our results. Data was described as median, interquartile range and range. The average GPI by years post-specialisation across decades for surgical specialties was calculated and plotted to illustrate temporal trends. Pearson's Correlation Coefficient was used to assess the relationship between years-post specialisation and GPI across all surgical specialties in Malaysia.

RESULTS

Gender Parity Index (GPI) of all surgical specialties in Malaysia on 30th September 2023 (Table I)

In examining gender distribution across Malaysian surgical specialties, a total of 5236 registered surgeons were analysed based on gender. Two surgical specialties, namely Breast and Endocrine Surgery, and Ophthalmology, showed female preponderance. Conversely, Obstetrics and Gynaecology was the sole specialty achieving gender parity, while the remaining surgical specialties demonstrated a dominance of male surgeons. The overrepresentation of female surgeons in Breast and Endocrine Surgery and Ophthalmology varied in intensity. Breast and Endocrine Surgery showed extreme gender disparity (>1.5), with 48 female surgeons compared to 18 male surgeons. Ophthalmology exhibited intermediate disparity with a GPI of 1.27, indicating a more moderate imbalance. In contrast, Obstetrics and Gynaecology achieved gender parity, with a GPI of 1.03, reflecting an almost equal distribution of male and female surgeons.

The thirteen remaining specialties (Cardiothoracic Surgery, Colorectal Surgery, General Surgery, Hepatobiliary Surgery, Neurosurgery, Orthopaedic Surgery, Otorhinolaryngology, Paediatric Surgery, Plastic Surgery, Thoracic Surgery, Upper Gastrointestinal Surgery, Urology, and Vascular Surgery) also recorded gender imbalance, albeit in the opposite direction, with more male surgeons identified. Among these specialties, only Paediatric Surgery and Otorhinolaryngology were in the intermediate category of disparity favouring males.

Vascular Surgery showed the most extreme gender disparity, with just 1 female surgeon compared to 34 male counterparts, resulting in the lowest GPI value (0.03). Cardiothoracic Surgery and Urology shared identical GPIs of 0.04, while Orthopaedic Surgery and Thoracic Surgery both had a GPI of 0.11. The median GPI of all surgical specialties in Malaysia on 30th September 2023 was 0.16 (range 0.03 – 2.64). The mean GPI was 0.48 with standard deviation of 0.17. The estimated GPI had a 98% confidence interval of 0.03 to 0.93.

Gender Parity Index (GPI) according to Number of Years Post-Specialisation for all Surgical Specialties in Malaysia up to September 2023

The number of years post-specialisation for a total of 5217 surgeons was calculated. Excluded from the calculations were 19 surgeons due to missing information on the SR website. These 19 surgeons comprised of 2 general surgeons (GPI: 0.22), 1 neurosurgeon (GPI: 0.15), 3 obstetrics and gynaecology specialists (GPI: 1.03), 3 ophthalmologists (GPI: 1.27), 1 otolaryngologist (GPI: 0.55), 8 orthopaedic surgeons (GPI: 0.11), and 1 urologist (GPI: 0.04). As the years post-specialisation increased, reflecting greater surgeon experience, the GPI values generally declined. GPI values were typically higher when younger surgeons were included in the GPI calculation. There was a very strong and statistically significant negative linear association between years post-specialisation and GPI of all surgical specialties, excluding Thoracic Surgery (Table II).

All graphs do not have data plotted in the first few years after the date of specialist qualification as additional time is required to process each applicant's entry into the National Specialist Registry post exit qualification. This period varies between specialties (Supplementary Figures 1a-1d). Average GPI across decades for each surgical specialty had been calculated (Supplementary Table I) to facilitate the understanding of GPI trend (Figure 1a). Also, each specialty varies in the temporal data available, as some specialties (such as obstetrics & gynaecology and general surgery) have a long history of existence in Malaysia, while other newer specialties (e.g. vascular surgery, thoracic surgery, colorectal surgery) were available only more recently.

DISCUSSION

Our study examining gender representation across Malaysian surgical specialties reveals a complex landscape. The field of Obstetrics and Gynaecology shows gender parity, while other specialties exhibit varying degrees of gender imbalance, with most favouring males. Breast and Endocrine Surgery, and Ophthalmology stand out with more female surgeons, while thirteen out of sixteen surgical specialties have more male surgeons. These disparities underscore the urgent need for addressing gender imbalances effectively. To our knowledge, this study is the only comprehensive analysis of gender proportions in Asia, utilising a national publicly available governmental registry for up-to-date information on all registered surgeons. This approach ensures inclusivity and provides a precise depiction of GPIs across surgical specialties, enabling informed policy discussions aligned with the World Health Organization (WHO) gender equity principles.[17]

When comparing the number of years post-specialisation of each surgeon with the GPIs of their respective surgical specialties over different time periods, an upward trend was observed as the number of years post-specialisation decreased, indicating the growing inclusion of younger surgeons in GPI calculations. This trend was particularly pronounced in Cardiothoracic Surgery, Colorectal Surgery, General Surgery, Neurosurgery, Orthopaedic Surgery, Otorhinolaryngology, Plastic Surgery, Thoracic Surgery, Upper Gastrointestinal Surgery, Urology and Vascular

Surgery. This finding reflects contextual factors that influence female participation in surgery, including cultural expectations, work–life balance challenges, maternity-related considerations, and perceptions of specialty difficulty. Across all these surgical specialties, GPIs were consistently below 1. Notable exceptions were Breast & Endocrine Surgery and Ophthalmology, in which Breast & Endocrine Surgery had a GPI above 1 for most years, while the Ophthalmology achieved a GPI above 1 when including surgeons with less than 10 years post-specialisation.

For Ophthalmology, Obstetrics and Gynaecology, as well as Paediatric Surgery, there was an early dip in GPI trends. This may be because entrance into the SR was not mandatory at its inception. As such, many senior surgeons, especially those near or post-retirement, did not submit applications for SR registration. We do recognise some limitations in our methodology. Potential omissions of specialists and variations in specialty training pathway structures in Malaysia[18] could impact GPI calculations. For instance, the number of surgeons categorized under General Surgery may have decreased over time, as certain surgical specialties in Malaysia have developed direct entry pathways for specialisation in recent years. Examples of such specialties include Cardiothoracic Surgery, Neurosurgery, Orthopaedic Surgery, Paediatric Surgery, and Plastic Surgery. Conversely, there is a possibility that surgeons initially specialising in General Surgery later pursue further specialisation in another surgical field, thereby contributing to the GPI value of the respective specialty they eventually choose.

Another limitation we detected was that some surgical specialities are more newly recognised, such as Upper Gastrointestinal Surgery, thus affecting the duration of data available when compared to long-established surgical specialities such as Obstetrics and Gynaecology. Moreover, SR registration may exclude older or non-practising surgeons, which could lead to the GPI appearing less male-predominant or even female-predominant. While this limitation introduces a risk of under-representing a small subset of practitioners, the available data still provides a reasonable approximation of parity on which further analysis can be based. Moreover, it is essential to consider the possibility of omissions resulting from specialists who have passed away but whose status may not have been promptly updated in the SR system in the GPI calculation for each surgical specialty. Despite these potential discrepancies, they are believed to have minimal impact on the overall findings, as GPI is calculated fractionally and is relatively stable despite minor changes in surgeon numbers. Nevertheless, it is evident that the number of female surgeons is rising, with evidence of GPI values trending upwards when number of years post-specialisation are lower.[19]

We are progressing; however, more solutions or policies need to be implemented to accelerate progress towards achieving gender parity across all surgical specialties.14,20 Future work should include research that clarifies the underlying drivers of gender disparity especially in Vascular Surgery and tracks the impact of evolving policies as well as workforce trends. Implementation efforts must accelerate, with targeted measures such as strengthened mentorship and sponsorship, improved work–life integration policies, transparent merit-based selection processes, and more inclusive departmental cultures. These strategies are essential to reducing structural barriers and advancing gender equity in the surgical workforce.

CONCLUSION

Surgical specialties in Malaysia, an upper-middle-income country in Southeast Asia, exhibit varying degrees of gender disparity, primarily characterised by the underrepresentation of females across most fields. It is essential to delve deeper into this phenomenon to discern the underlying causes of such gender imbalances within the surgical domain. By understanding these factors, efforts can be directed towards fostering an environment of equity. While progress is evident with more female surgeons joining the ranks, the pace of change remains slow. Future work should clarify the drivers of gender disparity and assess the impact of reforms, while accelerating measures such as stronger mentorship, supportive policies, transparent selection processes, and inclusive cultures to advance gender equity in surgery.

DECLARATIONS

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AUTHORS' CONTRIBUTIONS

Jing Xuan Teh and Shireen Anne Nah had full access to all of the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. Study concept and design [Jing Xuan Teh] and [Shireen Anne Nah]; Acquisition of the data [Jing Xuan Teh]; Analysis and interpretation of the data [Jing Xuan Teh] and [Shireen Anne Nah]; Drafting of the manuscript [Jing Xuan Teh] and [Shireen Anne Nah]; Critical revision of the manuscript for important intellectual content [Shireen Anne Nah]

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Diagnostic performance of computed tomography colonography following incomplete colonoscopy and its associated factors: A single-centre retrospective study

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ABSTRACT

Introduction: Incomplete colonoscopy presents an important clinical challenge, as segments of the colon that are not visualised may contain significant pathology. Computed tomography colonography (CTC) provides a minimally invasive alternative for comprehensive luminal evaluation, but local evidence regarding its diagnostic yield remains limited. This study aimed to evaluate the diagnostic yield of CTC following incomplete colonoscopy and to determine its associated factors with demography.

Materials and Methods: A retrospective cohort study was conducted among 93 adult patients who underwent CTC after incomplete colonoscopy between 2018 and 2023 at Hospital Tengku Ampuan Afzan, Kuantan. Patient demographics, prior surgical history, CTC findings and lesion characteristics were analysed using descriptive statistics, Chi-square and Fisher's exact tests.

Results: CTC demonstrated a diagnostic yield of 21.5%. In this cohort, females accounted a 58.1% of the population. Polyps were the most frequent pathology, followed by diverticulosis, segmental wall thickening, and a single case of colorectal mass. Statistical analysis showed no significant association between abnormal findings and demographic factors such as age, gender, ethnicity, previous abdominal surgery, clinical indications, or most proximal colonoscopic intubation (p >0.05). Although statistical significance was not significant, abnormalities were more often detected in older patients and when colonoscopic intubation was confined to the rectosigmoid colon.

Conclusion: CTC detected clinically important finding in more than one-fifth of patients, reconfirming its role as a valuable adjunct when colonoscopy is incomplete. These results showed polyps and diverticulosis as the main abnormalities with no clear predictors from patient factors. Larger prospective studies are needed to refine patient selection and optimise imaging quality in local setting.

KEYWORDS:
Computed Tomographic Colonography; Colonoscopy; Diverticulosis; Polyps

INTRODUCTION

Colorectal cancer remains a significant global health concern, ranking as the third most common malignancy and a leading cause of cancer-related mortality.[1] In Malaysia, it falls into the number two cause of cancer mortality.[2] Early detection and intervention through screening programs, particularly colonoscopy, have been instrumental in reducing incidence and improving patient outcomes.[3] However, colonoscopy, despite being the gold standard for colorectal cancer detection, is an invasive procedure associated with risks such as bowel perforation and bleeding, and it may not always achieve complete colonic visualization.[4] In cases of incomplete colonoscopy, where the caecum is not reached, a significant portion of the colon may remain unexamined, potentially missing critical lesions with a reported failure rates range from 4% to 25%.[5,6] Moreover, data from earlier research have demonstrated that a significant adenoma missing rates differences by size (36%, adenomas 1–5 mm; 27%, adenomas 6–9 mm; 12%, adenomas ≥ 10 mm), histology (non-advanced: 42%, advanced: 21%) and morphology (flat: 50%, polypoid: 27%).7 Factors such as patient discomfort, sharp angulation, strictures, looping, adhesions, diverticulosis, redundant colon, poor bowel preparation and anatomical variations can prevent full insertion of the colonoscope.[5]

This scenario necessitates alternative imaging modalities to ensure complete colonic evaluation and mitigate the risk of delayed diagnosis.[8] Computed tomography colonography (CTC) has emerged as a robust, less invasive alternative for visualizing the entire colon, particularly after an incomplete optical colonoscopy.[9] CTC offers a comprehensive luminal assessment, identifying polyps and masses that might otherwise be overlooked, thereby contributing to earlier diagnosis and improved patient management.[10] Moreover, the non-invasive nature and relative safety of CTC, coupled with its high diagnostic accuracy for significant colonic neoplasia, make it an increasingly attractive option for colorectal cancer screening and surveillance, especially for patients who are unable or unwilling to undergo conventional colonoscopy.[11,12] Furthermore, CTC can assess extraluminal structures, providing additional diagnostic information that is not available with colonoscopy, which is crucial for colorectal cancer staging.[13,14] This capability allows for the identification of metastatic disease and provides a more complete picture of disease burden, informing critical treatment decisions.[15]

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While the diagnostic accuracy of CTC is well-supported internationally, its clinical performance remains highly context-dependent.16 Hospital Tengku Ampuan Afzan, as a public tertiary centre serving a diverse population in Malaysia's East Coast region, operates within healthcare delivery systems, infrastructure, and patient profiles that may differ significantly from those in global studies. Despite the growing relevance of CTC following incomplete colonoscopy, local data—especially within Malaysian government hospitals—remain scarce. Given the prevalence of colorectal cancer and the challenges associated with incomplete colonoscopy, understanding the local diagnostic utility of CTC is paramount for optimizing patient care and resource allocation within the Malaysian healthcare system. This study was conducted to address the limited local data on CTC by assessing its diagnostic performance and identifying factors associated with abnormal or inadequate outcomes.

MATERIALS AND METHODS

This retrospective cohort study was conducted at Hospital Tengku Ampuan Afzan, Kuantan, and included all adult patients who underwent CTC following an incomplete colonoscopy between January 2018 and December 2023. Inclusion criteria encompassed patients aged 18 years or older with documented incomplete colonoscopy, while patients with contraindications to CTC, prior history of colorectal surgery or diagnosed colorectal cancer, those with poor-quality CTC images rendering interpretation unreliable, and patients who were either lost to follow-up or failed to complete the recommended diagnostic or therapeutic procedures following CTC were excluded from the analysis. Patients with incomplete medical records were excluded to maintain data integrity. The study protocol received ethical approval from the Medical Research and Ethics Committee, Ministry of Health Malaysia (NMRR-25-03001-VA9), ensuring adherence to ethical guidelines for retrospective data analysis.

The dataset, obtained from institutional records unit was reviewed and analysed in accordance with ethical standards and anonymised study procedures. Consent was not required due to the retrospective nature of the study and the use of deidentified patient data. Clinical variables collected included age, gender, ethnicity, history of previous abdominal surgery and CTC findings as well as lesion characteristics including radiological reports and endoscopy notes. Each CTC examination was performed according to standardized protocols, involving bowel preparation with polyethylene glycol and subsequent insufflation of carbon dioxide. Reconstructions including 2D axial, coronal, and sagittal images, along with 3D volumetric renderings, were generated and interpreted by experienced radiologist. Imaging results were categorised as normal, inadequate or abnormal. Abnormal findings were further subclassified into polyps, diverticulosis, segmental wall thickening or colorectal masses. The primary outcome measure was the diagnostic yield of CTC, defined as the proportion of abnormal imaging reports among all CTC studies performed. Secondary outcomes included lesion distribution and potential associations between abnormal findings and patient-related factors.

Statistical analysis was performed using SPSS version 30. Descriptive statistics were used to summarise patient characteristics and imaging findings. Categorical variables were compared using Chi-square or Fisher's exact test as appropriate, with a p-value <0.05 considered statistically significant.

RESULTS

The data summary of the population studied is summarized in Table I. A total of 93 patients underwent CTC following incomplete colonoscopy during the study period. The commonest age group that underwent CTC was from age of 60-69 years old (28.0%) followed by age group 70 and above (25.8%). The mean age of approximately 60.4 years (±11.9). Females represented a slight majority, accounting for 58.1% of the population. In terms of ethnic distribution, the majority were Malay (50.5%), followed by Chinese (39.8%) and Indian (8.6%), which aligns with regional demographics in Pahang. Notably, 9.7% of patients had a history of previous abdominal surgery, while 88.2% reported no such history. These demographic features provide context for interpreting diagnostic trends and may influence factors such as bowel preparation quality and colonic angulation, which are relevant in assessing the utility of CTC following incomplete colonoscopy.

Most scans were either normal (38.7%) or inadequate (39.8%), while 21.5% demonstrated abnormal findings, corresponding to a diagnostic yield of just over one-fifth. Among those with abnormal findings, polyps were the most identified lesions, accounting for 45% of cases. Diverticulosis was identified in 40% of abnormal scans, while segmental wall thickening was detected in 10%. Only one patient (5%) had a colorectal mass suggestive of malignancy. The following figures show various positive findings (Figure 1) and inadequate CTC (Figure 2) during CTC.

Based on the analysis of the CTC data from Hospital Tengku Ampuan Afzan, no statistically significant associations were found between patient demographics and abnormal CTC findings (Table II) namely polyps, diverticulosis, segmental wall thickening, or colonic mass. Although abnormalities were more frequently seen among older patients (notably in the 50–69 age group), this trend did not reach statistical significance ($p=0.741$). Similarly, the distribution of abnormalities did not differ significantly by gender ($p=0.242$) or ethnicity ($p=0.349$), though Chinese patients accounted for a proportionally higher number of diverticular findings. Prior abdominal surgery and clinical indications for CTC also showed no meaningful association with abnormal outcomes ($p=0.553$ and $p=0.810$, respectively). Interestingly, although not statistically significant, most abnormal findings were seen in patients whose colonoscopy reached only the rectosigmoid region, suggesting that limited initial scope access may slightly increase diagnostic yield from CTC ($p=0.077$).

The subsequent management of patients with abnormal CTC findings (Figure 3) demonstrated a range of clinical pathways and outcomes. The single case of colonic mass was further evaluated with colonoscopy, confirmed as descending colon adenocarcinoma, and treated with subtotal colectomy.

Table I: Patients' demographics

Variables	N (%)
Age	
18 – 29 years old	7 (7.5)
30 – 39 years old	4 (4.3)
40 – 49 years old	12 (12.9)
50 – 59 years old	19 (20.4)
60 – 69 years old	26 (28.0)
70 and above	24 (25.8)
Gender	
Male	39 (41.9)
Female	54 (58.1)
Ethnicity	
Malay	47 (50.5)
Chinese	37 (39.8)
Indian	8 (8.6)
Previous abdominal surgery	
Yes	9 (9.7)
No	82 (88.2)
Indication for CTC	
Change in bowel habit	21 (22.6)
Per rectal bleeding	20 (21.5)
Positive faecal occult blood test	15 (16.1)
Abdominal pain	14 (15.1)
Constipation	12 (12.9)
Others	11 (11.8)
Most proximal intubation	
Rectosigmoid	46 (49.5)
Descending colon	9 (9.7)
Transverse colon	3 (3.2)
Ascending colon	1 (1.1)
Hepatic flexure	12 (12.9)
Splenic flexure	22 (23.7)
CTC findings	
Inadequate	37 (39.8)
Normal study	36 (38.7)
Abnormal	20 (21.5)
Abnormal CTC Findings	
Colonic polyps	9 (9.7)
Diverticulosis	8 (8.6)
Segmental wall thickening	2 (2.2)
Colonic mass	1 (1.1)

Among patients with polyps (n=9), five underwent follow-up colonoscopy, which revealed benign findings in three cases, diverticulosis in one, and normal findings in one, while the remaining four were managed with clinical surveillance. Both cases of segmental wall thickening (n=2) proceeded to colonoscopy, showing normal findings in one and diverticulosis in the other. All patients with diverticulosis (n=8) were managed conservatively with symptom monitoring and follow-up. These findings reflect the variability in downstream management and confirmatory outcomes following abnormalities detected on CTC.

DISCUSSION

This study demonstrates that CTC provided clinically useful diagnostic information in 21.5% of patients who had incomplete colonoscopy, aligning with international literature where reported yields up to 22.9%.[17] For instance, a review of CTC applications reported neoplasia in 19% of patients, with polyps greater than 1 cm in 7.7% and smaller polyps in 5.7%.[18] This yield is further supported by findings from a clinical screening program which noted a 14.3% overall positive rate at CTC, with 85.0% negative and 0.7% non-diagnostic rates.[19] These findings are consistent with prior research indicating that CTC is effective in detecting colorectal polyps, with diagnostic yields comparable to those previously reported in the literature.[20] Most abnormalities detected were colonic polyps and diverticulosis, reinforcing prior evidence that CTC performs reliably in identifying such structural lesions, particularly in the segments of the colon not reached during endoscopy. For example, meta-analyses evaluating CTC and second-generation capsule colonoscopy on incomplete colonoscopies reported diagnostic yields of 13% for polyps greater than 5 mm and 4% for those exceeding 9 mm, specifically for CTC.1 Moreover, research indicates that CTC can detect polyps with high sensitivity and specificity, making it a valuable tool for surveillance in patients with incomplete colonoscopies.[17]

Over half of the patients in this cohort were aged 60 and above, and a higher proportion were female - the demographics commonly seen in colorectal cancer screening populations.[21] This age group is more likely to experience incomplete colonoscopy, often due to anatomical challenges such as tortuous or elongated colon segments and the presence of diverticular disease, particularly affecting the

Table II: Associations between demography and abnormal findings.

Variables	CT Findings			p-value
	Inadequate	Normal	Abnormal	
Age				0.768[a]
18 – 29 years old	2	4	1	
30 – 39 years old	0	3	1	
40 – 49 years old	5	5	2	
50 – 59 years old	6	7	6	
60 – 69 years old	12	9	5	
70 and above	12	8	4	
Gender				0.893[b]
Male	16	14	9	
Female	21	22	11	
Ethnicity				0.259[a]
Malay	22	18	7	
Chinese	13	15	9	
Indian	2	2	4	
Previous abdominal surgery				0.591[a]
Yes	3	3	3	
No	34	33	15	
Indication for CTC				0.624[a]
Change in bowel habit	7	9	5	
Per rectal bleeding	7	10	3	
Positive faecal occult blood test	8	6	1	
Abdominal pain	6	3	5	
Constipation	3	5	4	
Others	5	3	2	
Most proximal intubation				0.214[a]
Rectosigmoid	22	12	12	
Descending colon	2	5	2	
Transverse colon	2	1	0	
Ascending colon	0	0	1	
Hepatic flexure	5	5	2	
Splenic flexure	6	13	3	

a Fisher's exact test
b Pearson's chi-square test

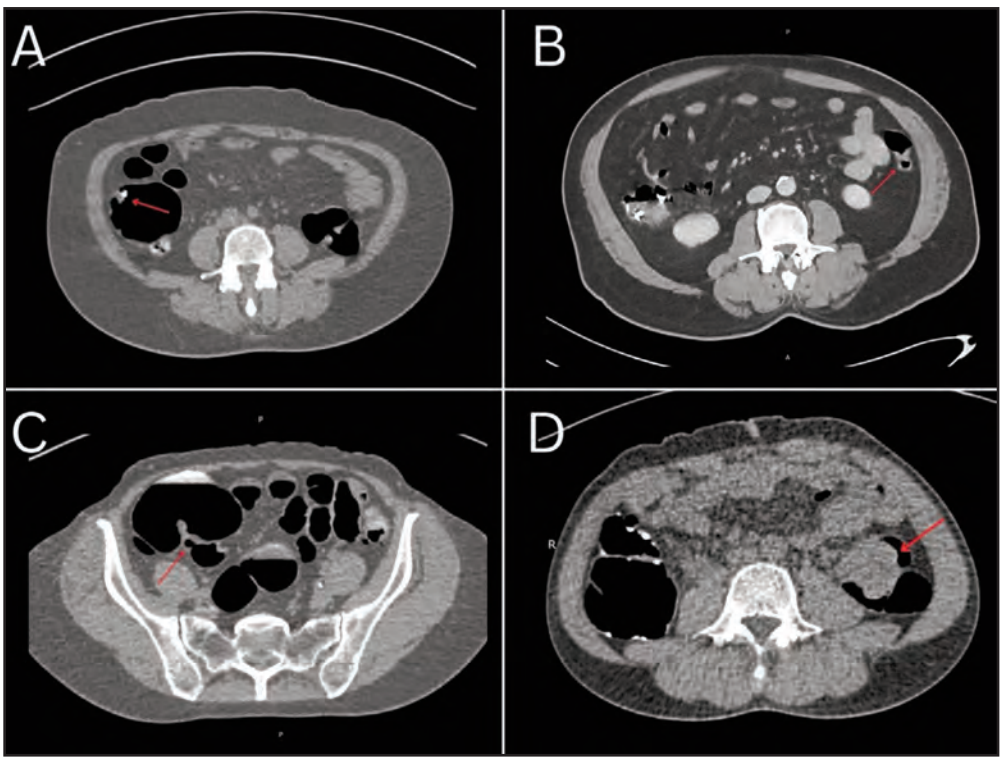

Fig. 1: (A) A case with colonic polyp (red arrow). (B) A case with descending colon thickening (red arrow). (C) A case with colonic diverticulum (red arrow). (D) A case with descending colon mass (red arrow).

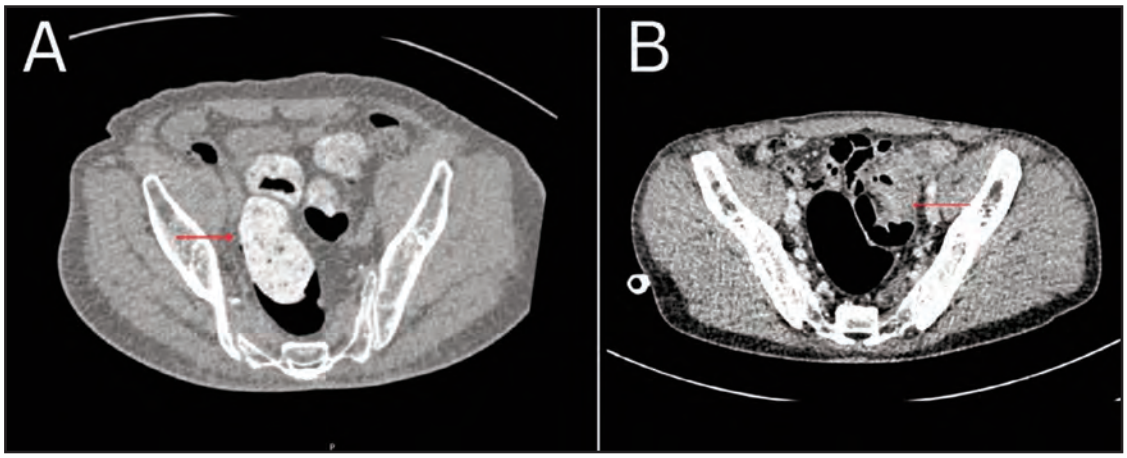

Fig. 2: (A) A case with residual solid stool (red arrow) in the rectosigmoid colon due to poor bowel preparation. (B) A case with segmental under-distension mimicking wall thickening (red arrow)

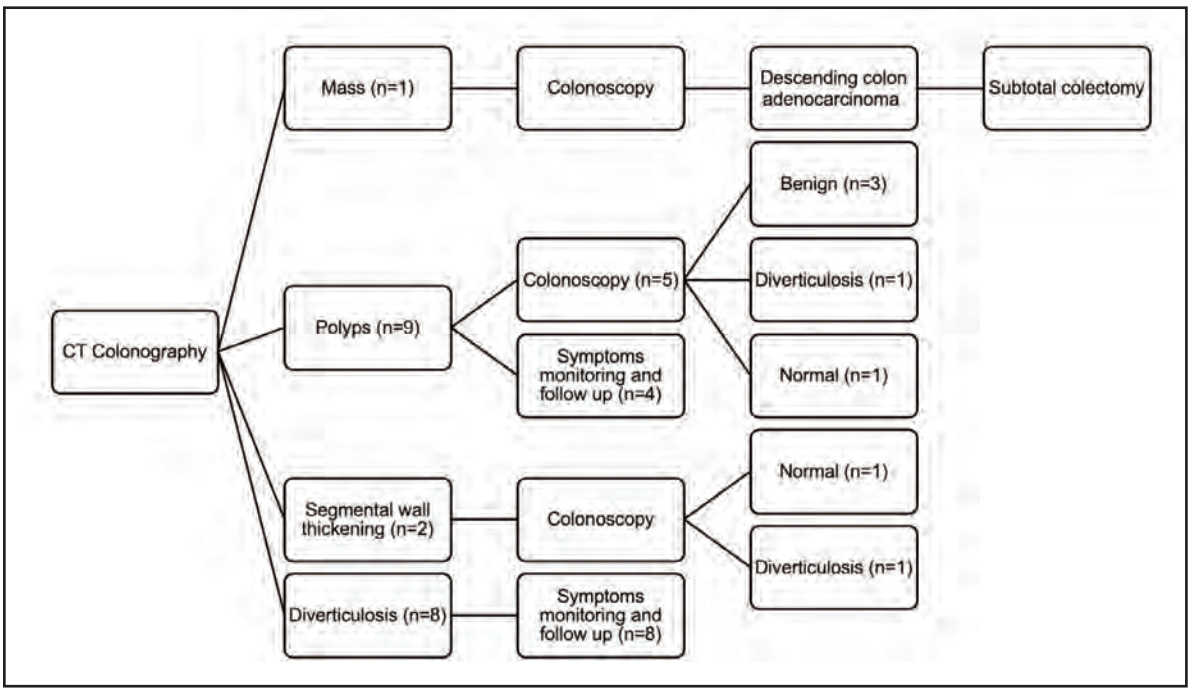

Fig. 3: Clinical pathways and outcomes of abnormal findings detected on CTC

proximal colon, which can remain unexamined during standard procedures.[10,22] The predominance of female patients also reflects established findings that women tend to have higher rates of incomplete colonoscopy, influenced by narrower pelvic anatomy or surgical adhesions from prior abdominal operations.[23] While previous abdominal surgery may contribute to procedural difficulty, our analysis did not show a statistically significant association between such history and abnormal CTC findings in this group. Nonetheless, these demographic patterns support the continued role of CTC as a practical adjunct, particularly in older or female patients, where complete endoscopic evaluation is frequently limited.[21]

The study cohort was largely made up of Malay patients, followed by those of Chinese and Indian ethnicity, a distribution that mirrors the population makeup of Pahang. While representative of the local demographic landscape, this composition contrasts with national data showing higher rates of colorectal cancer among Chinese and Indian populations in Malaysia.[19,24] This discrepancy is important, as the background risk of colorectal pathology may vary across ethnic groups and, in turn, influence the diagnostic yield of CT colonography. Recognising these differences is crucial when interpreting imaging outcomes in heterogeneous populations. Therefore, future efforts to improve colorectal cancer screening strategies should integrate ethnic-specific epidemiological insights to enhance diagnostic precision and ensure equitable care delivery.[25,26]

Despite widespread awareness of the technical causes behind inadequate CTC – such as poor bowel preparation, ineffective

faecal tagging, and insufficient colonic distention—these issues remain persistent, even in institutions with established imaging protocols. Their recurrence points not only to technical oversights but to a broader need for consistent execution and better system integration. Tackling these challenges calls for more than reiterating standard instructions. Instead, centres should consider implementing structured audit-and-feedback systems to identify recurring inadequacies, assigning dedicated staff to monitor prep compliance, and adopting risk-stratified bowel prep regimens. Radiographer credentialing and continuous technical training may also help raise the baseline quality of image acquisition. Enhancing patient education, particularly with visual aids or mobile reminders, can improve compliance, while newer solutions such as AI-supported post-processing may help mitigate the effects of residual stool or poor distension on image interpretation.[17] Together, these targeted and patient-centred strategies offer a more accountable and responsive approach to improving CTC quality at the institutional level.

Incomplete colonoscopy continues to present a significant clinical challenge, particularly when anatomical factors such as marked diverticulosis or a tortuous colon impede the passage of the endoscope.[14–16] These anatomical barriers frequently necessitate alternative imaging solutions like CTC to ensure full colonic evaluation beyond the reach of conventional endoscopy. In this study, nearly 40% of CTCs were found to be technically inadequate, a rate substantially higher than the commonly cited 5–10% in the literature.[17] This disparity points to critical gaps in current practices, especially in bowel preparation quality, faecal tagging adequacy, and technical consistency during scanning. It underscores the need to refine preparation protocols and improve imaging workflows for better diagnostic yield.[8] Additionally, suboptimal sedation and inadequate cleansing, especially in centres lacking anaesthetic support, remain key contributors to incomplete procedures.[18,19] Patients who experience discomfort or sedation failure are rarely re-counselled or offered a better-prepared repeat colonoscopy, leading to procedural inefficiencies. In such cases, CTC stands out as a viable, sedation-free, and patient-friendly alternative that provides comprehensive colonic assessment while easing the burden on already strained endoscopy units.[9]

The strengths of this study include its real-world clinical dataset collected over several years and its relevance to Malaysian healthcare practice. Another key strength of this study is that it shows what happens after CT colonography findings in real clinical practice, not just what is detected. It outlines how patients were managed, including repeat colonoscopy, surgery, or simple follow-up. This is especially useful in cases of incomplete colonoscopy, where decisions are often uncertain. However, limitations include the retrospective design, single-centre setting and modest sample size, which may limit generalisability. Additionally, the high proportion of inadequate CTC scans may have underestimated the true diagnostic yield. Future prospective studies with larger, multicenter cohorts are warranted to validate these findings and to evaluate strategies to improve the technical adequacy of CTC, particularly across diverse patient populations.

CONCLUSION

CTC remains a valuable imaging modality for evaluating the colon following incomplete colonoscopy and contributed to the detection of clinically relevant abnormalities in more than 20% of patients in this study. The predominance of polyps and diverticulosis among abnormal findings underscores the importance of complete colonic evaluation in preventing missed pathology. Although demographic and clinical variables did not predict abnormal CTC outcomes, these findings support the broad application of CTC in such clinical scenarios. Future multicentre prospective studies are warranted to refine patient selection, improve imaging techniques and enhance overall diagnostic performance in Malaysian clinical practice.

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