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Cerebral hemodynamics and vascular dementia: Identifying opportunities for early intervention

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SUMMARY

Vascular dementia (VaD), unlike Alzheimer's disease, is often preventable and can be slowed down or halted with early intervention. VaD results from impaired cerebral blood flow due to conditions like atherosclerosis or Moyamoya disease, leading to repeated small strokes and, consequently, cognitive decline. VaD can exist separately or co-exist with Alzheimer's disease, with the latter commonly being of a more insidious onset and involving beta amyloid protein depositions in the brain. VaD may be missed due to the focus on treating the stroke symptoms, and sometimes be interpreted as normal age-related cognitive decline. Thus, patients with vascular risk factors, who present with acute or acute-on-chronic neurological deficits that co-exist with features of subtle memory or executive functional changes, should have prompt vascular evaluation using neuroimaging.

INTRODUCTION

World Dementia Day 2025 was observed on 21st September this year with the theme "Ask About Dementia. Ask About Alzheimer's". Although Alzheimer's disease is a well-recognised subtype of dementia worldwide, the prevalence of vascular dementia (VaD) is fairly higher in Asian countries due to a larger population having cardiovascular risk factors.[1] Dementia encompasses a spectrum of progressive neurocognitive disorders characterised by impairments in memory, language, and higher executive functions. Among its various forms, Alzheimer's disease remains the most common, yet its aetiology is largely unknown and effective disease-modifying treatments remain limited. In contrast, VaD, which is also known as multi-infarct dementia, arises from cerebrovascular pathology linked to cardiovascular risk factors, and may present with either abrupt or insidious onset.[2] Importantly, VaD offers a window for intervention, particularly in younger individuals. Timely detection and management of VaD may alter disease progression in this cohort of patients.

VaD results from cumulative neuronal injury secondary to multiple cerebral infarctions, which may occur even without overt motor deficits. Clinicians should therefore maintain vigilance when encountering younger patients reporting progressive memory decline or executive dysfunction. Such presentations should prompt consideration of vascular aetiologies and appropriate diagnostic workup.

While transient ischemic attacks (TIAs) often trigger evaluation for cerebrovascular risk, there is growing evidences which support the findings of more subtle cognitive changes, particularly those involving executive function as an early indicator of cerebral hemodynamic compromise. Progressive alterations in cerebral blood flow (CBF) and cerebral perfusion have been well documented in several cerebrovascular disorders, including advanced large-artery atherosclerotic disease and Moyamoya disease.[3] These conditions are marked by chronic narrowing or occlusion of major intracranial arteries, leading to compensatory dilation of smaller vessels and the development of fragile collateral networks. Ultimately, reduced delivery of oxygen and nutrients to the brain leads to the symptoms of VaD.

To address this issue of chronic cerebral hypoperfusion, an adaptive mechanism of neovascularisation occurs, and although initially adaptive, it is prone to failure. These small-calibre vessels lack the capacity to adequately regulate CBF, rendering the brain vulnerable to episodes of hypoperfusion and subsequent neuronal loss. Impairment of cerebral autoregulation in these settings significantly elevates the risk of recurrent strokes, which can be detected on magnetic resonance imaging (MRI) brain scans. The sequelae of this compromise in CBF are progressive cognitive decline leading to VaD.

Hence, early identification of vascular contributions to cognitive impairment is crucial. Current modern neuroimaging, including both invasive and non-invasive modalities, commonly utilising MRI or nuclear medicine imaging, which can offer a detailed assessment of cerebral morphology, blood perfusion, and haemodynamics, respectively.[2,3,4] When vascular pathology is identified early, clinicians may pursue targeted interventions, ranging from aggressive risk factor modification to antiplatelet therapy or, in selected cases, surgical revascularisation such as extracranial-to-intracranial (EC–IC) bypass procedures.

As the population ages and the burden of dementia rises, it is essential for clinicians to recognise individuals at heightened risk, particularly those who smoke, consume alcohol excessively, or have a strong family history of cardiovascular disease.[5] Subtle cognitive symptoms in such patients warrant careful evaluation to identify potentially reversible or modifiable vascular causes.

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CONCLUSION

Recognition of the clinical signs combined with timely vascular risk assessment and neuroimaging remain the cornerstones of managing vascular dementia. Many modifiable risk factors can be addressed and represent critical opportunities to prevent or delay cognitive decline, reinforcing the importance of a comprehensive diagnostic approach to detect early dementia.

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Determinants of autism spectrum disorder in children: A case-control study in Pontianak, West Kalimantan, Indonesia

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ABSTRACT

Introduction: Children with Autism Spectrum Disorder (ASD) who use the government's service facilities for children with special needs in Pontianak are increasing. This study aims to find out the determinants of ASD in Pontianak.

Material and Methods: This study investigates the determinants of ASD in children in Pontianak, West Kalimantan, using a case-control design. The study included 49 children diagnosed with ASD and 100 age-matched controls, with data collected through maternal questionnaires. The risk factors examined included gender, genetic factors, parental age, maternal health during pregnancy, perinatal risk factors, environmental exposures, and maternal habits. Data analysis using logistic regression.

Results: The results indicate a significantly higher likelihood of ASD in boys. Higher maternal education levels were also associated with increased ASD risk. Family history, particularly having siblings or relatives with ASD, emerged as a significant risk factor. Maternal anxiety during pregnancy doubled the risk of ASD, while frequent fruit consumption during pregnancy and exclusive breastfeeding were identified as protective factors. Exposure to vehicle fumes during pregnancy increased ASD risk. Turning off cell phones during sleep was also protective.

Conclusion: These findings highlight the need to address both genetic and environmental factors in ASD aetiology. Promoting healthy maternal habits and reducing harmful environmental exposures could potentially reduce ASD risk. Future research should focus on larger sample sizes and longitudinal studies to validate these findings and develop targeted interventions.

KEYWORDS:
Autism Spectrum Disorder (ASD); Case-Control Study; Child Health; Environmental Exposures; Maternal Health; Risk Factors

INTRODUCTION

Autism Spectrum Disorder (ASD) affects individuals through social communication difficulties, restricted interests, and repetitive behaviours from early life.[1] ASD encompasses conditions like Autistic disorder, Rett disorder, Asperger syndrome, and pervasive developmental disorder.[1,2] The term "spectrum" reflects the variability in symptoms and severity. ASD symptoms often manifest in the first year, though some children show developmental decline between 18 and 24 months.[3]

The prevalence of ASD in American children has increased significantly. In 2018, the CDC estimated 1 in 59 eight-year-olds had ASD, a rate that doubled over two decades.[4] By 2023, this estimate rose to 1 in 36 children.[5] Globally, 1 in 100 children are estimated to have ASD[6], up from 1 in 160 children in 2015.[7] The precise aetiology of ASD remains to be elucidated, although genetic factors are considered a significant contributor.[8,9] Environmental factors, such as parental age, the fetal environment, perinatal risks, substance exposures, and psychosocial factors, are also considered risks.[10] The exploration of these relationships remains an active area of research.

Understanding the increasing ASD prevalence is crucial to mitigating future risks. ASD significantly impacts life quality, contributing over 58 disability-adjusted life years (DALYs) per 100,000 population globally.[7] This burden affects the quality of life for future generations. In Pontianak, the number of children diagnosed with ASD has increased, with 147 cases being reported between 2015 and 2020. This data was recorded by the Disability Service and Assessment Centre (DSAC) and the Main Clinic of Pontianak Psychiatric Hospital (PPH). On average, 20 new cases of ASD are recorded each year at these two units for children with special needs.[11] The causes of autism in Pontianak remain unstudied. This study aims to identify the relationship between risk factors and autism in Pontianak.

MATERIALS AND METHODS

Study Design

This study employed a case-control design to investigate the determinants of ASD in Pontianak, West Kalimantan. The research involved 49 children diagnosed with ASD and 100 age-matched controls without ASD.

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Participants
Participants comprised children aged 2 to 12 years who resided in Pontianak, with their data obtained from the Disability Services and Assessment Centre and Pontianak Psychiatric Hospital. Inclusion criteria required the participants to be biological children and residents of Pontianak. Exclusion criteria included instances where the patient had relocated, making their new address untraceable, as well as cases where the biological mother had passed away. Fig. 1 shows the data selection flow. Controls were defined as children of the same age as the cases, residing in proximity to them. The subjects of this research were the mothers of the children, who provided informed consent before participating.

Data Collection
Data were collected using a structured questionnaire administered to the mothers. The questionnaire elicited information on the socio-demographic characteristics, including gender (male, female), children's age group (2-<5 years, 5-12 years), birth weight (<2500 grams, ≥2500 grams), gestational age (preterm, term), caesarean section (yes, no), maternal age at pregnancy (<30 years, ≥30 years), paternal age at pregnancy (≤40 years, >40 years), mother's education (primary to middle education ≤12 years, higher education >12 years), father's education (primary to middle education ≤12 years, higher education >12 years), maternal occupation during pregnancy/working outside home (yes, no), and residence during pregnancy (Pontianak, outside Pontianak). We also asked 18 factors associated with ASD, such as whether the child had siblings with ASD (yes, no), relatives with a history of ASD (yes, no), the mother's habit of consuming vegetable and fruit during pregnancy (3 times/week – every day, never-seldom), exposed to smoke from forest and land fires (yes, no), exposed to smoke from forest and land fires when baby <6 months (yes, no). Maternal exposure to vehicle fumes during pregnancy was determined through self-reported data collected via structured interviews. Mothers were asked about their daily activities, including time spent near traffic, commuting habits, and whether they regularly passed or stayed near busy roads. Responses were used to classify daily exposure to vehicle emissions. Exposed to vehicle fume during pregnancy (3 times/week – every day, never-seldom), whether the mother living with smoker, experienced hypertension, hyperemesis, bleeding, and anxiety during pregnancy (yes, no), the baby experience fever – seizure when <2 years old (yes, no), whether the mother provided exclusive breastfeeding (yes, no). Exposure to television and cell phones was assessed through parental interviews. Parents were asked to report the age at which their child was first exposed to these devices. Additionally, they were asked whether this exposure began before or after the child was diagnosed with ASD. This information was used to explore potential temporal relationships between media exposure and ASD development. Mothers were also asked whether they turned off their cell phones when sleeping at night with their children.

Statistical Analysis
Data were analysed using multivariate and bivariate methods. The chi-square test was used to examine the association between each risk factor and ASD. Logistic regression was conducted to identify the most significant risk factors for ASD, providing adjusted odds ratios (ORs) and 95% confidence intervals (CIs). A p-value of <0.05 was considered statistically significant.

Ethical Considerations
The study was approved by the Health Research Ethics Committee (HREC) of Politeknik Kesehatan Kemenkes Pontianak (No. 58/KEPK-PK.PKP/III/2022). Informed consent was obtained from all participants.

Data Management
To ensure confidentiality, the data were anonymised and analysed using appropriate statistical software to verify the reliability and validity of the findings. Adherence to rigorous ethical standards ensured compliance with established guidelines.

RESULTS

Table I represent the sociodemographic characteristics of the respondents. Among the 11 observed variables, four sociodemographic variables had a significant relationship with the incidence of ASD: gender, maternal education, maternal employment outside the home, and maternal residence during pregnancy. Table II shows five related factors that had a significant relationship in the bivariate analysis. These variables were a family history of ASD, maternal fruit consumption habits during pregnancy, exposure to vehicle exhaust during pregnancy, anxiety during pregnancy, and turning off mobile phones while sleeping.

The results indicate a significant difference in gender distribution between cases and controls. Boys were found to have a seven times higher risk of developing ASD compared to girls (OR: 7.04, 95% CI: 2.888–17.179; p<0.05). Even after adjusting for other variables as seen in Table III, boys are eight times as likely to develop ASD (OR: 8.08, 95% CI: 2.93-22.21; p<0.05). Maternal education level emerged as a significant risk factor. Mothers with a higher education level (>12 years) were more likely to have a child with ASD (OR: 2.492, 95% CI: 1.237-5.020; p<0.05). After adjusting for other variables in the multivariate analysis in Table III, mothers with more than 12 years of education had almost a sixfold increased risk of having a child with ASD (OR: 5.96, 95% CI: 2.26-15.70; p<0.05). Furthermore, employed mothers showed an increased risk, although this factor did not remain significant after adjusting for other variables. Living in Pontianak city during pregnancy was a protective factor (OR = 0.216, 95% CI: 0.045-0.860; p<0.05), but this variable was no longer significant after adjusting for other variables.

As demonstrated in Table II, a total of 18 variables were identified as potentially correlating with the incidence of ASD. However, subsequent analysis revealed that only 6 of these variables exhibited a significant relationship. The presence of a family history of ASD in children was found to be a significant predictor of the development of ASD, with an odds ratio of 3.525 (95% confidence interval: 1.177-10.561; p<0.05). This indicates that children with a family history of

Table I: Socio-demographic characteristics

Variable	Categories	Case n = 49	Control n =100	Unadjusted OR (CI 95%)
		n (%)	n (%)	
Gender	Male / Female	42 (86) / 7 (14)	45 (45) / 55 (55)	7.04 (2.888 – 17.179)*
Children's age	2-<5 ys / 5-12 ys	15 (31) / 34 (69)	25 (25) / 75 (75)	1.324 (0.621 - 2.823)
Birth weight	<2500 g / ≥2500 g	6 (12) / 43 (48)	9 (9) / 91 (91)	1.411 (0.472 – 4.216)
Gestational age	Preterm / Term	2 (4) / 47 (96)	6 (6) / 94 (94)	0.668 (0.064 - 3.924)
Caesarean section	Yes / No	14 (29) / 35 (71)	27 (27) / 73 (73)	1.081 (0.505 – 2.315)
Maternal age	<30 ys / ≥30 ys	26 (53) / 23 (47)	57 (57) / 43 (43)	0.853 (0.429 – 1.695)
Paternal age	≤40 ys / >40 ys	21 (43) / 28 (57)	47 (47) / 53 (53)	0.846 (0.425 – 1.684)
Mother's education	>12 ys / ≤12 ys	27 (55) / 22 (45)	33 (33) / 67 (67)	2.492 (1.237 – 5.020)*
Father's education	>12 ys / ≤12 ys	20 (43) / 29 (57)	45 (45) / 55 (55)	0.843 (0.422 – 1.685)
Working outside	Yes / No	19 (39) / 30 (61)	21 (21) / 79 (79)	2.382 (1.126 – 5.041)*
Residence during pregnancy	Pontianak / Outside Pontianak	41 (84) / 8 (16)	96 (96) / 4 (4)	0.216 (0.045 – 0.860)*

CI, confidence interval; OR, odds ratio; *= significant at p<0.05

Table II: Associated factors

Variable	Categories	Case n = 49	Control n =100	Unadjusted OR (CI 95%)
		n (%)	n (%)	
Siblings with ASD	Yes / No	5 (10) / 44 (90)	2 (2) / 98 (98)	5.498 (0.860 – 59.84)
Relative with ASD	Yes / No	9 (18) / 40 (82)	6 (6) / 94 (94)	3.525 (1.177 – 10.561)*
Vegetable consumption	Never-seldom / 3 times a week-everyday	13 (27) / 36 (73)	16 (16) / 84 (84)	1.896 (0.827 – 4.345)
Fruit consumption	Never-seldom / 3 times a week-every day	26 (53) / 23 (47)	74 (74) / 26 (26)	0.397 (0.194 – 0.814)*
Exposed to smoke from forest and land fires	Yes / No	6 (12) / 43 (88)	23 (23) / 77 (77)	0.467 (0.177 – 1.236)
Exposed to smoke from forest and land fires when baby <6 months	Yes / No	4 (8) / 45 (92)	17 (17) / 83 (83)	0.436 (0.101 – 1.449)
Exposed to vehicle fume during pregnancy	3 times a week-everyday / Never-seldom	18 (37) / 31 (63)	21 (21) / 79 (79)	2.184 (1.027 – 4.644)*
Living with smoker	Yes / No	22 (45) / 27 (55)	50 (50) / 50 (50)	0.815 (0.410 – 1.618)
Hypertension	Yes / No	4 (8) / 45 (92)	14 (14) / 86 (86)	0.548 (0.124 – 1.882)
Hyperemesis	Yes / No	22 (45) / 27 (55)	58 (58) / 42 (42)	0.590 (0.296 – 1.175)
Bleeding during pregnancy	Yes / No	4 (8) / 45 (92)	6 (6) / 94 (94)	1.389 (0.274 – 6.198)
Anxiety during pregnancy	Yes / No	19 (39) / 30 (61)	22 (22) / 78 (78)	2.245 (1.067 – 4.727)*
Fever – seizure when baby <2 years old	Yes / No	8 (16) / 41 (84)	8 (8) / 92(92)	2.244 (0.788 – 6.391)
Exclusive breastfeeding	Yes / No	27 (55) / 22 (45)	76 (76) / 24 (24)	0.388 (0.187 – 0.801)*
Exposed to Television	Yes / No	40 (82) / 9 (18)	85 (85) / 15 (15)	0.784 (0.316 – 1.944)
Exposed to cellphone	Yes / No	35 (71) / 14 (29)	83 (83) / 17 (17)	0.512 (0.228 – 1.151)
Turn off the cell phone when sleep	Yes / No	13 (27) / 36 (73)	54 (54) / 46 (46)	0.308 (0.146 – 0.649)*

CI, confidence interval; OR, odds ratio; *= significant at p<0.05

Table III: Multivariate analysis

Variable	Adjusted OR (CI 95%)	Significant
Gender	8.08 (2.93 – 22.21)	*
Mother's education	5.96 (2.26 – 15.70)	*
Fruit consumption	0.25 (0.09 – 0.67)	*
Exclusive breastfeeding	0.32 (0.13 – 0.79)	*
Turn off the cell phone when sleep	0.27 (0.11 – 0.66)	*

OR = Odds Ratio; CI = Confidence Interval; * = signinificant at p<0.05

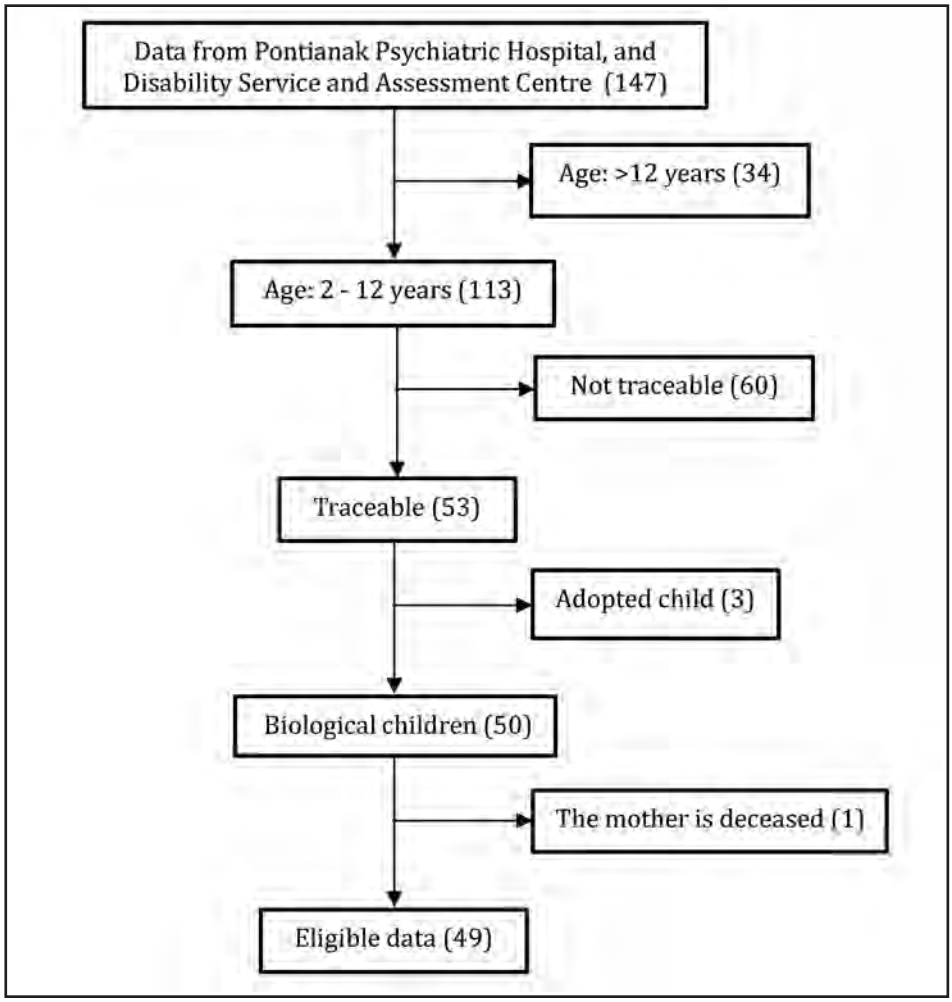

Fig. 1: Data selection flowchart

ASD are 3.5 times more likely to develop the condition themselves. Following adjustment for other variables, the relationship between this variable and the outcome was not found to be significant. The study identified the mother's consumption of fruit during pregnancy as a significant protective factor, with an odds ratio of 0.397 (95% CI: 0.194-0.814; p<0.05). Following adjustments for confounding variables, this dietary habit remained a protective factor for the development of ASD (odds ratio [OR]: 0.25; 95% confidence interval [CI]: 0.09-0.67; p<0.05).

Exposure to vehicle exhaust, occurring three times a week to every day, in pregnant women was identified as a risk factor for ASD (OR: 2.184; 95% CI: 1.027 – 4.644; p<0.05). However, following the adjustment for other variables, this association was no longer observed. Conversely, maternal anxiety during pregnancy has been demonstrated to double the risk of offspring developing ASD. However, following the adjustment for other variables, this anxiety was no longer found to be a causal factor. Exclusive breastfeeding has been identified as a protective factor against the development of ASD (OR: 0.388; 95% CI: 0.187-0.801; p<0.05). Following adjustment for other confounding variables, this variable maintains its protective factor status against the development of ASD (OR: 0.32; 95% CI: 0.13-0.79). Furthermore, the act of mothers turning off their mobile phones while sleeping with their babies has been shown to be a protective factor against the development of ASD (OR: 0.308; 95% CI: 0.146-0.649; p<0.05), and this remains the case after adjusting for other variables (OR: 0.27; 95% CI: 0.11-0.66; p<0.05).

DISCUSSION

One of the most significant findings was the increased risk of ASD in boys. Boys were found to be seven times more likely to develop ASD compared to girls, and this remained significant even after adjusting for other variables. This gender disparity is well-documented in the literature, with numerous studies indicating a higher prevalence of ASD in males.[12,13] The exact reasons for this discrepancy are not entirely understood, but hypotheses include differences in brain development, hormonal influences, and genetic factors.[8] Research suggests that boys might be more susceptible to ASD due to sex-linked genetic factors and differential brain development pathways influenced by sex hormones such as testosterone. Additionally, genetic studies have found that boys are more likely to inherit mutations associated with ASD.[8]

Understanding these mechanisms is crucial for developing gender-specific interventions and supports.

Maternal education level was another significant factor, with mothers having higher education levels (>12 years) being more likely to have children with ASD. This finding is consistent with studies from various regions, including Bangladesh, Bradford, and San Francisco, which also reported higher ASD prevalence in children of highly educated parents.[14–16] One possible explanation is that highly educated parents might be more vigilant and capable of seeking a diagnosis for their children. Moreover, it is hypothesised that highly educated mothers may experience elevated levels of stress and anxiety, which may have a detrimental effect on fetal development. The association between higher maternal education and increased ASD risk may also reflect a heightened awareness and access to diagnostic services among educated parents. It has been hypothesised that such parents may adopt a more proactive stance in seeking evaluations for developmental concerns, thereby resulting in enhanced detection rates.[14] Moreover, the stress associated with high-achieving environments could contribute to neurodevelopmental risks.[10] The initial finding that working mothers were at higher risk of having children with ASD did not remain significant after adjusting for other variables. This suggests that while maternal occupation may contribute to stress and lifestyle factors, it is not a standalone risk factor for ASD. Previous studies have shown mixed results regarding maternal employment and ASD risk, indicating that other underlying factors such as workplace stress and environmental exposures might play a role.[10]

It is acknowledged that the respondents in this study were Pontianak residents; however, it is possible that they did not reside there during their pregnancy. The present study found that being a mother in Pontianak during pregnancy was a protective factor for ASD. This is attributable to the fact that Pontianak is the capital of West Kalimantan Province and possesses superior health facilities in comparison to other regions within West Kalimantan, including antenatal care and the early detection of child developmental disorders. It has been demonstrated that mothers residing in Pontianak have more convenient access to educational resources and antenatal care. The hypothesis that stronger social support in urban environments such as Pontianak can help mothers manage stress during pregnancy is one that merits further investigation, given its potential as a risk factor for ASD.[17] Furthermore, it is hypothesised that mothers residing in Pontianak may possess certain demographic characteristics (e.g., higher education, optimal reproductive age) that indirectly contribute to a reduced risk of ASD.

A family history of ASD was identified as a significant risk factor, with children having siblings or relatives with ASD being at a higher risk. This finding is consistent with the genetic predisposition theory, which posits that heritable genetic mutations contribute significantly to the risk of developing ASD.[8,9] Studies have shown that siblings of children with ASD are more likely to be diagnosed with the disorder, and familial studies suggest that genetic factors account for a large proportion of ASD cases.[18,19] Genetic studies indicate that specific gene mutations and chromosomal abnormalities increase ASD risk. For example, polymorphisms in genes like Dopa Decarboxylase and Dopamine Receptor-1 have been linked to ASD.[20] Additionally, the presence of interstitial duplications in certain chromosomal regions has been associated with the disorder.[21] These genetic determinants underscore the importance of genetic counseling and early screening for families with a history of ASD.

Conversely, frequent fruit consumption during pregnancy and exclusive breastfeeding were identified as protective factors against ASD. Regular fruit consumption during pregnancy has been linked to better neurodevelopmental outcomes in children.[22] Fruits are rich in essential vitamins, antioxidants, and phytochemicals, which can promote healthy brain development and reduce oxidative stress. Consumption of fruits and vegetables during pregnancy can prevent postpartum depression[23], while postpartum depression was found to be associated with the incidence of autism and mental retardation in children.[24]

Maternal exposure to vehicle exhaust fumes during pregnancy, with exposure levels ranging from three times per week to daily, has been demonstrated to double the likelihood of offspring being diagnosed with ASD. The study also demonstrated that working mothers exhibited a nearly equal risk of having a child with ASD. This phenomenon can be attributed to the increased likelihood of exposure to vehicle exhaust fumes among working mothers. Vehicle exhaust fumes contain various hazardous substances, including the pollutants of concern in this instance are carbon monoxide (CO), nitrogen oxides (NOx), sulfur dioxide (SO_2) and fine particulate matter ($PM_{2.5}$). These substances have the capacity to enter the body of a pregnant woman through inhalation, exerting an effect on placental function, oxygen circulation, and fetal brain development.[11] The potential neurotoxic effects of vehicle emissions are supported by research showing that exposure to high levels of air pollution during pregnancy is associated with increased ASD risk.[10] This finding emphasizes the need for public health measures to reduce pregnant women's exposure to pollutants.

High maternal anxiety during pregnancy was associated with a doubled risk of having a child with ASD. This finding is supported by other research indicating that maternal stress and anxiety can impact fetal brain development and increase the risk of neurodevelopmental disorders.[10] The physiological mechanisms behind this association may involve stress hormones such as cortisol, which can cross the placenta and affect fetal development.

Exclusive breastfeeding was another protective factor, reducing the risk of ASD. Breastfeeding provides essential nutrients and fosters a strong mother-child bond, which is crucial for cognitive and emotional development.[25,26] Breast milk contains bioactive compounds that support brain development and immune function, potentially mitigating the risk of neurodevelopmental disorders. The protective role of exclusive breastfeeding has been documented in several studies. A systematic review and meta-analysis reported that breastfeeding reduces the risk of ASD by 58%, and exclusive

breastfeeding can reduce the risk by 76%.[25] The bonding and interaction during breastfeeding are believed to enhance social and cognitive development, crucial areas impacted in ASD.[27]

Interestingly, the study found that turning off cell phones during sleep was a protective factor against ASD. While the exact mechanism is unclear, it is hypothesised that electromagnetic radiation from cell phones may affect brain development. Studies on animal models have shown behavioral changes due to prolonged exposure to electromagnetic fields.[28] Further research is needed to confirm this finding and understand the underlying mechanisms.

Implications for Public Health

The findings of this study have significant public health implications. Identifying modifiable risk factors for ASD can inform prevention strategies and interventions. For instance, promoting healthy maternal habits such as regular fruit consumption and exclusive breastfeeding can potentially reduce the risk of ASD. Public health campaigns can also raise awareness about the impact of environmental exposures, such as air pollution and electromagnetic radiation, on fetal development. Public health initiatives should focus on educating expectant mothers about the benefits of a nutritious diet and the importance of reducing exposure to environmental toxins. Programs aimed at improving air quality and minimizing pollutant exposure during pregnancy could significantly impact ASD prevalence rates.

Limitations and Future Research

Notwithstanding the insightful information this study offered, a number of limitations must be noted. The results may not be as broadly applicable as they could be because of the tiny sample size. To corroborate these findings, more research with broader sample sizes and a more varied population is required. Furthermore, the study used self-reported data, which is prone to bias in recollections. To improve the accuracy of the findings, objective measurements of exposure and health consequences should be incorporated into future studies.

Longitudinal studies are needed to establish temporal relationships between risk factors and ASD development. Furthermore, while the study identified several significant risk factors, the complex interplay between genetic and environmental factors in ASD aetiology warrants further investigation. Longitudinal research can provide more robust evidence on the causal relationships between risk factors and ASD.

CONCLUSION

This study identified several significant risk factors for ASD in Pontianak, including gender, maternal education, family history, maternal health, and environmental exposures. These findings align with existing literature and highlight the importance of both genetic and environmental factors in the aetiology of ASD. The protective effects of healthy maternal habits, such as regular fruit consumption and exclusive breastfeeding, underscore the potential for preventive strategies. Addressing environmental exposures and promoting healthy maternal behaviors can mitigate the risk of ASD and improve neurodevelopmental outcomes in children. Future research should focus on elucidating the mechanisms underlying these associations and developing targeted interventions to reduce the burden of ASD.

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Author contributions were assigned following the CRediT Taxonomy:

Fathmawati Fathmawati contributed to Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing, and Funding acquisition.

Dini Fitri Damayanti contributed to Methodology, Investigation, and Writing – review & editing.

Fara Chitra contributed to Methodology, Investigation, Data curation, Project administration, Supervision, and Writing – review & editing.

Ayu Rafiony contributed to Methodology and Writing – review & editing.

Ismi Ardhini contributed to Methodology, Investigation, and Writing – review & editing.

All authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

Factors associated with hypertension among the elderly in Kudat, Malaysia

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ABSTRACT

Introduction: Hypertension among the elderly population aged 60 years and above in Malaysia was estimated to be around 69.2%. The high association of hypertension with morbidity and mortality among older communities warranted targeted public health interventions. Hence, this study aimed to determine the prevalence of hypertension and its related factors among the elderly in a rural area in Kudat, Sabah.

Materials and Methods: This cross-sectional study was carried out to determine the prevalence of hypertension, including previously known and newly diagnosed cases, and the associated factors among the elderly aged 60 and older living in the rural part of Sabah. The study was conducted on 700 elderly people living in Kudat using self-administered and interviewer-assisted JAGES questionnaires and physical status measurements from January to March 2023. Multivariate logistic regression analysis was applied to determine the association between sociodemographic and physical factors with hypertension among the elderly.

Results: The prevalence of hypertension among elderly dwelling in Kudat, Sabah was approximately 80.3% (95% CI: 77.35, 83.25), slightly higher than the national prevalence. The findings also indicated that older age group (aOR=3.2; 95% CI: 1.548, 6.489), higher BMI (aOR=1.9; 95% CI: 1.170, 2.997) abnormal waist circumference (aOR=2.5; 95% CI: 1.573, 4.022), and active smoking (aOR=2.4; 95% CI: 1.281, 4.626) were significantly associated with hypertension among the elderly community.

Conclusion Focused and targeted prevention, intervention, and management of hypertension for the elderly, especially those dwelling in rural areas, should be constructed to tackle the issue of high prevalence of hypertension among them, thus reducing morbidity and mortality related to elderly hypertension towards healthy ageing.

KEYWORDS:
elderly, hypertension, factors associated with hypertension, community, rural

INTRODUCTION

The ageing population is a global phenomenon. Advancing life expectancy, improved mortality outcomes, and declining fertility and population growth rates have changed the population's age structure over time.[1] People, especially in developed countries, are living longer and healthier with the amelioration of healthcare delivery worldwide. In 2020, about 727 million people were aged 65 years or over. This share of the world population is expected to increase from 9.3% to 16% in 30 years. This figure already outnumbered children aged less than five years old in 2020.[2]

Many chronic illnesses remain the leading causes of mortality and morbidity among the elderly, therefore instantly impacting their quality of life.[3] Hypertension, while not particularly a degenerative disease, is constantly increasing worldwide. It is a common and significant health issue among the elderly population, affecting around 67% of adults aged 60 and older in the United States [4] and 57% of older adults aged more than 50 years in African regions.[5] Shanghai, China, where a large population of elderly residents resided, also had a high prevalence of hypertension, estimated at around 59.9% among the elderly aged 65 years and older.[6] A similar finding was reflected in Malaysia's National Health and Morbidity Survey 2019. The prevalence of overall high blood pressure increased with age, from 5.7% among those aged 20 to 24 to 81.7% among those aged 75 and older, the highest of any age group in the report.[7] The prevalence was also notably higher in rural areas, at 32.8%, than in urban areas, at 29.2%. Health issues in Malaysian rural regions vary but may not be as well-addressed as in urban areas due to restricted access to healthcare services.[8]

Multiple risk factors for hypertension, including obesity, excessive sodium intake, alcohol consumption, and lack of physical activity, have long been identified and described.[9] Declining handgrip strength has also been consistently linked to an increased risk of hypertension, as evidenced by multiple large-scale studies, including NHANES in the US and KNHANES in South Korea.[10,11] The underlying mechanism may involve age-related muscular degeneration, systemic inflammation, hormonal changes and reduced physical activity, contributing to cardiovascular and metabolic

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vulnerability.[12] Similarly, betel chewing has been identified as a behavioural risk factor for elevated blood pressure.[13] The effect is thought to be mediated through systemic inflammation and stimulation of the renin-angiotensin system, mechanisms comparable to the hypertensive effects of alcohol.

In this study, we focused on determining the association of social, economic, and physical status with hypertension among the elderly. This study is structured to gain knowledge that may tackle the issues, emphasising prevalence and sociodemographic factors (age, sex, ethnic, religion and marital status), socioeconomic factors (education, income, employment), physical status (BMI, waist circumference, handgrip strength), social behaviours (smoking, alcohol, betel chewing), and depression status as modifiable risk factors that can be improved among hypertensive elderly in rural Sabah.

MATERIALS AND METHODS

Research Design and Subjects

This cross-sectional study was conducted in northern Sabah, Kudat, as part of a larger longitudinal survey, "Healthy Ageing in Sabah." The study enrolled participants aged 60 or older who lived in the rural area of Kudat, Sabah. Elderly individuals who were bedridden and cognitively impaired were excluded from the study. Data were collected by trained personnel either by an interviewer-assisted method or self-administered questionnaires.

Instruments Used

The study tool included a self-administered and interviewer-assisted questionnaire, which comprised two main components: social epidemiological questions and general health status, as measured by physical and mental attributes. The social determinants of health and functional status include demographic aspects such as age, sex, ethnicity, income status, employment status, educational level, marital status, lifestyle aspects (tobacco smoking, alcohol drinking and betel chewing) and morbidity (hypertension status).

A validated 15-item Geriatric Depression Scale (GDS-15) in Bahasa Malaysia was used to assess depressive symptoms among the target population. This instrument has been locally validated and demonstrates excellent internal consistency (Cronbach's $\alpha = 0.89$).[14] A score of four or less indicated no depressive symptoms, 5 to 8 for mild, 9 to 11 for moderate, and 12 to 15 for severe depression.

The blood pressure measurement was recorded using an automatic BP machine by Omron (Omron Digital Automatic Blood Pressure Monitor Model HEM-8712). The measurement was set with an appropriately sized cuff bladder (encircling at least 80% of the arm). Two blood pressure readings were taken within a minute of one another, and if there was more than a 10 mmHg difference between the first two, a third reading was taken. The final reading was then determined mathematically by calculating the mean blood pressure reading. Those with abnormal blood pressure were examined again on the next day, and if the systolic or diastolic pressure was 140mm/Hg or higher, and a diastolic pressure of 90mm/Hg or higher was deemed to be hypertensive using Malaysia's Clinical Practice Guidelines on Hypertension 2018. Hypertension in this study was defined to include those with known and unknown hypertension, with or without treatment. A referral letter was given for appointments for proper follow-up if blood pressure was raised.

BMI was then calculated using the measured values of height and weight. Overweight was defined as having BMI of 23.0 kg/m2 or more, while obese as 27.5 kg/m2 or more. Those having BMI of less than 23.0 kg/m2 were considered normal according to Malaysia's Clinical Practice Guidelines on Obesity 2023.

Waist circumference was assessed using a measuring tape, with results of 90 cm or above in males and 80cm or above in females considered abnormal.

Lastly, handgrip strength was employed as a proxy indicator for muscle strength. Measurement was carried out using Takei digital Dynamometer TKK 5001 Grip. A grip strength value of less than 28 kg for males and 18 kg for females was used as a cut-off point for poor strength.

The study also employed the Abbreviated Mental Test (AMT) to screen participants for cognitive function before inclusion. The AMT-10 is a validated and widely used tool to assess cognitive impairment. It consists of ten questions that evaluate orientation, memory, and attention. Participants were required to achieve a score of 7 or higher to ensure sufficient cognitive capacity for understanding and responding accurately to the study instruments.

Ethical Consideration

This study received ethical approval from the Research and Ethics Committee of Universiti Malaysia Sabah (UMS) (Approval Code: JKEtika 2/23 [7]). Informed written consent was obtained from the study participants before filling in the questionnaire, and any inquiries from the participants were answered before signing the consent form. Confidentiality of all the information acquired from the study participants was ensured, and the data was used for the intended purpose only. Any participants who were newly diagnosed with hypertension (blood pressure more than 140/90mmHg) and had the abnormal status of depression (mild, moderate, severe) during the survey were given referral letters for further follow-up with the nearest health clinic.

Statistical Analysis

The data collected were recorded into tables in Microsoft Excel 2019 before being analysed using IBM SPSS Version 28.0. Descriptive statistics were used to describe the sociodemographic, socioeconomic, physical status, social behaviours, and depression characteristics of all the participants. The prevalence of hypertension was calculated with a 95% confidence interval. Simple logistic regression was used in univariable analysis to determine the association between independent variables and the presence of Hypertension. The alpha value was set at 0.05 to reject the null hypothesis and determine statistically significant hypertension factors.[15] For bivariate analysis, multiple regression was applied involving all variables with a p-value

Table I: Characteristics of Participants (n = 700)

Characteristics	Frequency, n	Percentage, %
Age (years old)		
60 – 69	385	55.0
70 – 79	236	33.7
>80	79	11.3
Sex		
Male	333	47.6
Female	367	52.4
Religion		
Islam	139	19.9
Christian	552	78.9
Others	9	1.3
Ethnicity		
Rungus	553	79.0
Others	147	21.0
Marital Status		
Married	522	74.6
Unmarried	178	25.4
Education Level		
Primary and Lower	607	86.7
Secondary and Higher	93	13.3
Employment Status		
Employed	279	39.9
Unemployed	421	60.1
Household Income Level (RM)		
0 – 999	526	75.1
>1000	174	24.9
Body Mass Index (BMI)		
Normal	287	41.0
Overweight	413	59.0
Waist Circumference		
Normal	264	37.7
Abnormal	436	62.3
Handgrip Strength		
Poor	286	40.9
Normal	414	59.1
Smoking Status		
Active Smoker	105	15
Ex-smoker	130	18.6
Never Smoke	465	66.4
Alcohol Status		
Active Drinker	114	16.3
Ex-drinker	274	39.1
Never Drink	312	44.6
Betel Chewing Status		
Active Chewer	240	34.3
Ex-chewer	55	7.9
Never Chew	405	57.9
Depression Status		
No	28	4.0
Mild	480	68.6
Moderate	154	22.0
Severe	38	5.4

of less than 0.25.[16] They were analysed using backward and forward methods in SPSS to get the preliminary model of predictors for hypertension.

RESULTS

700 elderly people in rural villages participated in the study. Table I summarises the participants' sociodemographic, socioeconomic, physical, and behavioural characteristics.

We found that 562 participants (80.3%), approximately four in every five elderly, had hypertension with a 95% CI (77.35, 83.25). Based on the descriptive analysis, the majority of people having hypertension were in 60-69 age group (51.6%), female sex (52.7%), Christian religion (79.0%), Rungus ethnic (79.2%), married (72.8%), having total household income less than RM999 (75.3%), attended primary school or lower education (87.4%), unemployed currently (63.0%), having abnormal waist circumference (67.1%), having overweight BMI (63.2%), standard handgrip power (58.5%), never smoked (65.1%), never drank alcohol (45.4%), never chewed betel products (57.1%) and having mild depression status (67.1%) compared to the other categories in the same variables.

Table II: Simple logistic regression of sociodemographic, socioeconomic, physical status and behavioural factors associated with hypertension among the elderly in Kudat, Sabah (n=700)

Variables	Hypertension, n (%)	Crude OR (95% CI)	p-value
Age (years old)			
60 – 69	290 (51.6)	ref	
70 – 79	204 (36.3)	2.088 (1.347, 3.239)	*0.001
>80	68 (12.1)	2.025 (1.028, 3.988)	*0.041
Sex			
Female	296 (52.7)	ref	
Male	266 (47.3)	0.952 (0.656, 1.382)	0.797
Religion			
Islam	112 (19.9)	ref	
Christian	444 (79.0)	0.991 (0.619, 1.586)	0.970
Others	6 (1.1)	0.482 (0.113, 2.052)	0.323
Ethnicity			
Others	117 (20.8)	ref	0.812
Rungus	445 (79.2)	1.057 (0.672, 1.662)	
Marital Status			
Married	409 (72.8)	ref	
Unmarried	153 (27.2)	1.691 (1.055, 2.709)	*0.029
Total Household Income Level (RM)			
≥1000	139 (24.7)	ref	
0 - 999	423 (75.3)	1.034 (0.674, 1.588)	0.878
Education Level			
Secondary and Higher	71 (12.6)	ref	
Primary and Lower	491 (87.4)	1.312 (0.780, 2.205)	0.306
Employment Status			
Employed	208 (37.0)	ref	
Unemployed	354 (63.0)	1.804 (1.239, 2.625)	*0.002
Handgrip Strength			
Normal	329 (58.5)	ref	
Poor	233 (41.5)	1.136 (0.775, 1.664)	0.513
Waist Circumference			
Normal	185 (32.9)	ref	
Abnormal	377 (67.1)	2.729 (1.865, 3.992)	*<0.001
Body Mass Index (BMI)			
Normal	207 (36.8)	ref	
Overweight	355 (63.2)	2.365 (1.619, 3.455)	*<0.001
Smoking Status			
Never	366 (65.1)	ref	
Ex-smoker	105 (18.7)	1.136 (0.696, 1.853)	0.609
Active	91 (16.2)	1.758 (0.960, 3.219)	*0.067
Alcohol Status			
Never	255 (45.4)	ref	
Ex-drinker	219 (39.0)	0.890 (0.589, 1.344)	0.580
Active	88 (15.7)	0.757 (0.448, 1.277)	0.296
Betel Chewing Status			
Never Chew	321 (57.1)	ref	
Ex-chewer	47 (8.4)	1.537 (0.700, 3.378)	0.284
Active	194 (34.5)	1.104 (0.739, 1.648)	0.630
Depression Status			
No	22 (3.9)	ref	
Mild	377 (67.1)	0.998 (0.394, 2.527)	0.997
Moderate	134 (23.8)	1.827 (0.660, 5.055)	*0.246
Severe	29 (5.2)	0.879 (0.272, 2.838)	0.829

*p < 0.05 considered statistically significant

The associations between various factors and hypertension based on simple logistic regression analysis are presented in Table II.

Regarding physical status, only handgrip strength was found to be an insignificant factor for hypertension, with a p-value of more than 0.05. BMI and waist circumference, on the other hand, were found to have statistical significance in the logistic regression. Those with abnormal waist circumference measurements had an increased odds of 2.7 times (95% CI: 1.865, 3.992; p-value <0.001) of getting hypertension compared to those with standard measurements. Moreover, it was also found that older people with an overweight BMI were more likely to be hypertensive (OR=2.4; 95% CI: 1.619, 3.455; p-value <0.001) compared to the normal BMI category. Social behaviours, including smoking status,

Table III: Factors associated with hypertension among the elderly in Kudat on multivariable logistic regression analysis

Variables	Adjusted OR (aOR) 95% CI	p-value
Age (years old)		
60-69	ref	
70-79	2.685 (1.687, 4.274)	*< 0.001
>80	3.170 (1.548, 6.489)	*0.002
Waist Circumference		
Normal	ref	
Abnormal	2.516 (1.573, 4.022)	*< 0.001
Body Mass Index (BMI)		
Normal	ref	
Overweight	1.873 (1.170, 2.997)	*0.009
Smoking Status		
Never Smoke	ref	
Ex-Smoker	1.229 (0.733, 2.063)	0.434
Active Smoker	2.435 (1.281, 4.626)	*0.007

*p < 0.05 considered statistically significant

alcohol status, betel chewing status and depression status, were found to be statistically not significant at a p-value of more than 0.05 for all four factors.

Table III presents the adjusted odds ratios for significant hypertension-related factors identified through multivariable logistic regression.

In multiple logistic regression, using forward selection, four predictors were included in the model: age, BMI, waist circumference and smoking status. Using backward selection, five predictors were included in the model (age, marital status, BMI, waist circumference and smoking status). However, the p-value for marital status was not a good predictor for the model.17 Variables selected were age, BMI, waist circumference and smoking status. The Nagelkerke R-squared test was 0.136, meaning 13.6% of the hypertension status among the elderly in Kudat could be explained by those factors. Hosmer and Lemeshow tests were run to check for assumptions, resulting in a p-value of 0.335, which was statistically insignificant. The model was deemed fit.

DISCUSSION

In our study, we found that four in every five elderly were hypertensive, with a prevalence of 80.3% among people aged 60 years or older. This figure is comparably higher than the national survey at 69.2% 18 and another study in Selangor, where the prevalence was 53%.[11] The prevalence may be higher for rural communities than urban counterparts. 19 This could be well explained by the limited healthcare facilities available, thus impeding them from getting proper follow-up for their diseases. Awareness and low rate of control among rural dwellers were a concern, too, which would explain the high prevalence of hypertension among them.[20] The vast difference between prevalence in our study compared to national and the state in the Peninsular region indicated that there was a considerable healthcare gap and unmet need for the rural elderly community in Sabah, as they still lack economic stability and social advancement to tackle their health needs, especially the non-communicable diseases.

Risk factors associated with hypertension

Our study significantly concluded that as age increased, they were more likely to have hypertension. The vascular wall's elasticity is lost linearly; thus, thickening of the arterial wall became more prevalent.[21] As a result, the blood pressure was raised inevitably from stiffening, which was the primary consequence of age-related changes in the vasculature of humans. Inevitably, the incidence of cardiovascular disease, mortality, and the rate of decline in renal function were rising tremendously in this population.[22] One study estimated the prevalence of hypertension among the elderly in rural Peninsular Malaysia to be just 54.5%, which was lower than our current finding.[23] A possible explanation for this could be the social and economic environment and development, in addition to the geographical setting, in rural Sabah, which may still be far behind rural Peninsular Malaysia, thus limiting the healthcare awareness and services.[24,25]

Having an abnormal waist circumference increases the likelihood of hypertension. Numerous studies have found a correlation between a larger waist circumference and a higher prevalence of hypertension in Africa [26], China [27], Indonesia[28], and Myanmar[29]. According to a study conducted by the National Health and Nutrition Examination Survey (2004), waist circumference was a more accurate predictor of dyslipidaemia, hypertension, and metabolic syndrome.[30] Waist circumference was a proxy for abdominal obesity, defined as excessive fat deposits in the abdominal region and was independent of the body mass index of the person.[31]

BMI was significantly linked to both hypertension and cardiovascular diseases. Approximately 63% of hypertensive participants in our current study were categorised as overweight. This also included those who were obese. Overweight people were more likely to develop elevated blood pressure by two to three times compared to the average population.[32] These findings are supported by an enormous number of authors and literature worldwide. Urban and rural Africa showed a positive correlation between BMI and raised blood pressure[33], and so was the case among the Chinese population [27] where the risk was 1.7 times higher if overweight and three times higher if obese. In the Indonesian population, those who were overweight had an increased risk

by 1.5 times, but being obese slightly increased the odds by 1.8 times of getting elevated blood pressure compared to people with normal BMI. [28] Those in Myanmar and Nepal also reported a significant association between obesity and hypertension.[29] Hypertension and obesity may be mediated by poor diet and insufficient physical activity.[34]

Smoking was a significant factor in developing hypertension among the elderly community in Kudat, Sabah. Many researchers produced identical reports on the linear effect of smoking on hypertension 35 The effects of nicotine from smoking were quite pronounced in the senior population.[36] Studies showed that nicotine generated adrenaline, noradrenaline, and vasopressin throughout the body and increased the sympathetic nervous system function[37], although the long-term impact was not uniform.

In our study, 27.2% of people with raised blood pressure were unmarried, whether previously divorced or single. The association was found to be statistically significant, as those who were unmarried had a 70% higher risk of getting hypertension compared to the married in univariable analysis. However, in the multivariable model, it was not a significant factor for hypertension. Few studies were also homogenous with ours in that they found the prevalence of raised blood pressure to be significantly associated with being single. 38 It was proposed that, compared to single men, married men have better sleep, less stress, improved moods, and a healthier diet, therefore less chance for CVD risk of hypertension. Divorcees, too, had a similar risk for poor health outcomes. 39

Strengths and Limitations

This study is the first to be carried out among the elderly in rural Sabah to find the factors associated with the prevalence of hypertension. Although few similar studies among older people had been done in Peninsular Malaysia, the results could have differed from those of the Sabahan population. The study tried to find factors which may be specific to the community. The study also included several factors, such as betel nut chewing, depression status and handgrip strength, which were not commonly associated with hypertension previously. In addition, it utilised direct measurement of the participant's physical attributes (BMI, handgrip strength, waist circumference, and blood pressure measurements) with the help of trained volunteers.

There are a few limitations to the study. First, individuals with cognitive impairment were excluded from participation to ensure reliable responses to the questionnaire; this may underestimate the prevalence of known and undiagnosed hypertension among the elderly there. Secondly, using self-reported data through a questionnaire may introduce recall bias, as these elderly may have memory difficulties. They are also subjected to social desirability bias, especially when it is interviewer-assisted. Moreover, due to the selection of a cross-sectional design for this study, no temporality and causality between the independent factors and hypertension could be drawn, limiting the interpretation of the result of the association. Most of the people in the study location are of Rungus ethnicity. They have different cultures, values and dialects. Some of the information or questions in the survey may need to be fully comprehended by them compared to other areas.

Additionally, this study did not examine certain factors that may influence hypertension prevalence, including nutrition, physical activity, comorbidities, stress, and anxiety. Depression was selected as the sole psychological variable due to the wider local validation of depression screening tools compared to stress or anxiety measures, which often require longer instruments and cultural adaptation. This focus helped streamline data collection and minimise respondent burden.

CONCLUSION

In conclusion, this study provided insight into the notably high prevalence of hypertension among the elderly in rural areas of Kudat, Sabah, compared to other previous studies. Several statistically significant factors BMI, waist circumference, smoking status and increasing age were identified highlighting the multifactorial nature of hypertension in later life and highlight the need for integrated risk assessment strategies. Hypertension is becoming a prevailing public health issue globally, whether in developed or developing countries and has been recognised as a risk factor for developing cardiovascular diseases once diagnosed, subsequently contributing to dire health consequences. Given the substantial burden of hypertension and its established link to cardiovascular diseases, these findings reinforce the urgency of implementing a robust screening programme, particularly at the community level. In addition, tailored health education and intervention strategies focusing on modifiable risk factors such as unhealthy weight and smoking are essential to reduce the long-term morbidity and mortality associated with hypertension in this vulnerable population.

Moving forward, public health efforts in rural settings should prioritize accessible and continuous care, enhanced community outreach, and targeted lifestyle interventions to address the growing challenge of hypertension among Malaysia’s ageing population.

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ORIGINAL ARTICLE

Attitude and perception of house officers towards prescribing practice and prescribing competencies in Malaysia: A multi hospital survey

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ABSTRACT

Introduction: Prescribing errors are a significant issue in healthcare systems globally and represent an imminent risk to patient safety. These errors have the potential to result in increased morbidity and mortality. This study seeks to investigate the perceptions of House Officers (HOs) in Malaysia regarding their prescribing skills and competencies, as well as their views on the adequacy of clinical pharmacology and therapeutics training received during their undergraduate medical education.

Materials and Methods: A cross-sectional study was conducted among HOs in 9 hospitals across Malaysia. The study utilized a survey comprising 26 items to assess the HOs' perceptions of their knowledge in clinical pharmacology and therapeutics, as well as their prescribing practices during housemanship training. Data was analysed using descriptive and inferential statistics.

Results: A total of 319 HOs participated in the study, which was conducted between June 2019 and June 2021. The findings revealed that the majority of participants perceived themselves as possessing adequate knowledge to prescribe most commonly used classes of medications. Nevertheless, 45% of respondents reported feeling adequately prepared for prescribing tasks based on their undergraduate medical training. Additionally, 51% expressed confidence in their therapeutic knowledge for prescribing, while approximately 50% reported confidence in preparing and administering medications.

Conclusion: The findings indicate that HOs generally perceive themselves as confident and knowledgeable in prescribing and preparing prescriptions. However, limitations in undergraduate education on prescribing contribute to feelings of inadequate preparedness as they transition into clinical practice. Strengthening educational support in this area is essential to improving prescribing competence, ensuring patient safety, and enhancing overall clinical outcomes.

KEYWORDS:
Prescribing skills, Competency, House officers, Pharmacology and Therapeutics

INTRODUCTION

Prescribing errors are prevalent in healthcare settings globally. Particularly, house officers (HOs),i.e. trainee doctors are a common cause of these oversights.[1–3] Most medication errors are accounted for by prescribing errors (PE) that are preventable.[4–7] Medication plays a vital role in disease management and PE are an imminent threat to patient safety, which can potentially lead to increased morbidity and mortality. A prescription error is defined as 'a failure in the process of prescription writing resulting in a wrong instruction about one or more of the normal features of it'. These include right patient, right drug, right formulation and dose, right route, timing, frequency and duration of administration of drugs.[8] Whilst the occurrence of errors can take place at any stage in the process of medication usage, from prescribing, transcribing, and dispensing to administering the medications to patients, evidence shows that PE are one of the most common type of errors in healthcare settings.[5,9] Among the common PE include dose/strength errors (14.4%), omission errors (11.8%), giving unnecessary drugs (23.5%), and insufficient information (37.9%).10 In support of this, a study on paediatric department showed PE occurred in 13% of prescriptions, with 7.3% of items prescribed incorrectly; most errors were ambiguous prescriptions (61.1%) and unrecommended dose regimens (13.9%), and house officers were significantly more likely to make errors (OR 4.72, p=0.029). Notably, 30.6% of errors were potentially serious, highlighting the impact of prescriber experience on paediatric patient safety.[11] Another cross sectional study involving multicentre paediatric department reported that the overall prescribing error rate was 9.2%, with electronic prescribing showing a higher error rate than manual prescribing (16.9% vs 8.2%, p<0.05). Most errors were linked to human factors such as knowledge gaps and lack of supervision, with 1.7% having serious and 0.1% potentially fatal consequences, highlighting the need for better training and supervision of junior doctors in paediatric

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prescribing.[12] Furthermore, a study conducted at a tertiary hospital identified that of 1,045 medication error reports reviewed, 97.5% classified as near-misses and only 2.5% as actual errors. Most PE occurred during the prescribing stage (97.4%), involved wrong doses (52.3%), and affected geriatric patients (37.1%), though 99.4% caused no harm. Pharmacists detected most errors, and staff factors were the main contributors, highlighting the need for proper guidelines and preventive strategies to enhance patient safety.[13]

A first of its kind comprehensive study in Malaysia evaluating the severity of PE from 2017-2019 revealed a 1.8% (1.36 million) PE of the total 75.5 million prescriptions intervened by pharmacist.[11] Statistics from the Ministry of Health indicate a rise in reported medication errors, increasing from 2,818 cases in 2018 to 3,046 cases in 2019. Among the various types of medication errors, PE accounted for the highest proportion, with 2,878 cases (51%), followed by dispensing errors at 1,512 cases (27%) and administration errors at 1,036 cases (18%).[12] The safety guide reported factors that may lead to prescribing errors by healthcare professionals including the lack of therapeutic training and inadequate knowledge and experience on medication.[13] A review paper had corroborated such findings by reporting that prescription errors are particularly significant in that these errors constituted between 24% and 76% of all medication errors in Malaysia.[14]

Prescribing is not just about the final written prescription. It is a complex task that requires the forming of the right diagnosis followed by an assessment of benefit to harm ratio based on evidence, choosing the right drug therapy by taking into account the alternatives and the right dose regimen, and discussion about the proposed treatment and management plans as well as the benefits and adverse effects of the drugs with the patient.[15] However, several studies have shown unpreparedness for effective and safe prescribing among final year medical students and HOs.[1–4] The lack of knowledge and skills to prescribe drugs have been strongly associated with serious medication errors in a UK hospital.[16] In Malaysia, limited learning opportunities and hands-on practice have been reported, especially in private university as compared to public university.[17] There is an urgent need to review the teaching and assessment of clinical pharmacology and therapeutic to ensure safe and rational prescribing among new doctors.[3]

A key international reference for guiding and assessing safe and rational prescribing is the World Health Organization's Guide to Good Prescribing (1995). This guide outlines a structured six-step approach to the prescribing process: (i) define the patient's problem, (ii) specify the therapeutic objective, (iii) verify the suitability of the P-drug (personal drug), (iv) start the treatment, (v) give information, instructions and warnings, and (vi) monitor (stop) the treatment. These steps emphasize that prescribing is not simply the act of writing a drug order but a comprehensive clinical decision-making process. The framework has been widely adopted in medical curricula globally and serves as a foundation for developing educational content and assessment tools related to prescribing. Incorporating this model into medical education ensures that new doctors are trained to approach prescribing in a systematic, evidence-based, and patient-centered manner.[18]

However, there is limited research on Malaysian house officers' self-perceived prescribing competency. Therefore, this study aimed to determine the attitude and perception of skills and confidence in prescribing among HOs in Malaysia and to evaluate their perceived learning of clinical pharmacology and therapeutics during undergraduate medical education. This study will contribute in improving the medical education in prescribing to produce good and safe doctors.

MATERIALS AND METHODS

Study design

A cross-sectional descriptive study was conducted from June 2019 to June 2021. The HOs were recruited anonymously via hospital clinical research centres (CRC) on voluntary basis . This study was approved by Perdana University Institutional Review Board (PU-IRBBHR01934) and the Malaysian Medical Research Ethics Committee (NMRR 18-1484-42311(IIR)).

Study population

The study population comprised of 319 HOs from various government hospitals in Malaysia. Participation was voluntary and anonymous. A total of 9 out of 25 main MOH training hospitals responded to the study invitation and included in the study. The included hospitals were Hospital Kuala Lumpur, Hospital Tengku Ampuan Rahimah, Klang, Hospital Kajang, Hospital Raja Permaisuri Bainun, Ipoh, Hospital Umum Sarawak, Hospital Queen Elizabeth I and II, Hospital Serdang, Hospital Tengku Ampuan Afzan, Kuantan and Hospital Putrajaya. The Hospital Clinical Research Centre (CRC) distributed the survey to the HOs via their work emails. CRC coordinator while near to the survey completion sent multiple reminders to encourage HOs to complete the survey. On top of hospital CRC, the questionnaire was later shared in the social media platform and alumni groups to increase the response rate.

Study Instrument

The study instrument used in this research was a questionnaire in the form of an online survey. The survey link was shared to HOs via the hospitals' centre for clinical research and using the Qualtrics^{XM}. Demographic data including age, gender, race, type of medical programme and medical school from which they graduated and the training year were collected. The online survey adopted a previously validated questionnaire [19] (Prof Simon Maxwell provided the questionnaire) with minor modifications (demographics) to suit local settings. The revised questionnaire tested for validity and reliability in the previous study based on 106 responses, giving the Cronbach alpha of 0.897 and the Kaiser-Meyer-Olkin of 0.81 indicating good internal consistency of the study instrument.[20]

The survey comprised of 26 questions in total, of which 6 were multiple choice question to assess on teaching and learning in prescribing during undergraduate studies. The remainder 20 questions were 7-point Likert scale questions (strongly disagree – strongly agree) revolving around the assessment of

Table I: Association of gender, race, year of HO training, type of medical school and having formal prescribing training with the median score for 1. Knowledge to prescribe drugs, 2. Prescribing practice and 3. Confidence to prescribe and the Knowledge to prescribe, Prescribing practice and Confidence to prescribe median (IQR), (N = 319).

1. Knowledge to prescribe drugs			
Variables	**Median**	**Interquartile range (IQR)**	**P-value**
Gender			0.003*
Male	52.00	17.50	
Female	48.00	14.00	
Overall	50.00	15.00	
Race			0.006*
Malay	52.00	15.00	
Chinese	49.00	12.75	
Indian	46.00	19.00	
Others	55.00	12.50	
Overall	50.00	15.00	
Year of training			0.000*
Y1	49.00	15.00	
Y2	53.00	14.00	
Overall	50.00	15.00	
Type of Medical School			0.209
Public	50.00	14.00	
Private	50.00	16.00	
No response	48.00	20.00	
Overall	50.00	15.00	
Had formal prescribing training in medical school			0.000*
YES	52.00	14.00	
NO	44.00	15.00	
Overall	50.00	15.00	
2. Prescribing practice			
Variables	Median	IQR	P-value
Gender			0.248
Male	21.00	7.00	
Female	21.00	6.00	
Overall	21.00	6.00	
Race			0.267
Malay	21.00	7.00	
Chinese	21.00	7.00	
Indian	21.00	7.00	
Others	19.00	2.50	
Overall	21.00	6.00	
Year of training			0.004*
Y1	20.00	6.00	
Y2	22.00	7.00	
Overall	21.00	6.00	
Type of Medical School			0.003*
Public	21.50	7.00	
Private	21.00	6.00	
No response	18.00	5.00	
Overall	21.00	6.00	
Had formal prescribing training in medical school			0.000*
YES	22.00	7.00	
NO	18.00	5.00	
Overall	21.00	6.00	
3. Confidence to prescribe			
Variables	Median	IQR	P-value
Gender			0.001*
Male	21.00	6.75	
Female	18.00	6.00	
Overall	19.00	6.00	
Race			0.830
Malay	19.00	6.00	
Chinese	18.00	7.00	
Indian	18.00	8.00	
Others	18.00	10.00	
Overall	19.00	6.00	
Year of training			0.000*
Y1	18.00	6.00	
Y2	21.00	7.00	
Overall	19.00	6.00	

Table II: Median and Interquartile Range (IQR) of Items Assessing Knowledge to Prescribe, Views on Prescribing Practice, and Confidence to Prescribe

Variables	Median	Interquartile range (IQR)	P-value
Type of Medical School			0.045*
Public	19.00	6.00	
Private	19.00	6.00	
No response	16.00	5.00	
Overall	19.00	6.00	
Had formal prescribing training in medical school			0.023*
YES	19.00	7.00	
NO	18.00	6.00	
Overall	19.00	6.00	
Knowledge to prescribe		**Median**	**IQR**
I believe I have sufficient knowledge to prescribe the following drug: Analgesia		5.00	2.00
I believe I have sufficient knowledge to prescribe the following drug: Opiates		4.00	2.00
I believe I have sufficient knowledge to prescribe the following drug: Laxatives		5.00	2.00
I believe I have sufficient knowledge to prescribe the following drug: Antibiotics		5.00	2.00
I believe I have sufficient knowledge to prescribe the following drug: Emetics		5.00	1.00
I believe I have sufficient knowledge to prescribe the following drug: Cytotoxic		2.00	2.00
I believe I have sufficient knowledge to prescribe the following drug: Anti-Hypertensives		5.00	1.00
I feel I have sufficient knowledge to prescribe the following drug: Anti-Diabetes		5.00	1.00
I believe I have sufficient knowledge to prescribe the following drug: Anti-Epileptics		4.00	3.00
I believe I have sufficient knowledge to prescribe the following drug: Anti-coagulants		4.00	2.00
I believe I have sufficient knowledge to prescribe the following drugs: Anti-Histamines		5.00	2.00
Views on Prescribing Practice			
I feel that my medical school training has prepared me for prescribing medications in clinical practice		4.00	2.00
I feel stressed about prescribing medications as a house officer		4.00	3.00
I feel I have sufficient resources to aid my continued learning in prescribing		5.00	2.00
I always allocate time & resources to ensure my prescribing skills are enhanced in hospital setting		5.00	2.00
I only realize the importance of prescribing during house officer training		2.00	2.00
Confidence to prescribe			
I feel confident in prescription writing		5.00	2.00
I feel confident in accessing drug information in the hospital setting		5.00	2.00
I feel confident in therapeutic knowledge for prescribing		5.00	1.00
I feel confident in preparing and administering drugs		5.00	2.00

*Significant association (p<0.05). (Note: 1=Strongly disagree, 2=Disagree, 3=Somewhat disagree, 4=Neither agree nor disagree, 5=Somewhat agree, 6=Agree, 7=Strongly agree)

three main aspects, self-perceived competency to prescribe various classes of drugs, their views on their prescribing practice and confidence in prescribing.

Data analysis

The data collected were analysed using Statistical Package for Social Sciences software (SPSS version 28, IBM Corp., USA). Descriptive statistics (frequency in percentage) were applied for data analysis. Likert scale responses were reported as percentages. The median total score for 1. Knowledge to prescribe drugs, 2. Prescribing practice and 3. Confidence to prescribe were analysed for differences among gender, year of training, type of medical school and whether received a formal prescribing training in medical school to identify factors that predict high confidence in prescribing with independent variables using non-parametric independent samples test (Mann-Whitney U test for 2 samples or Kruskal Wallis test for 3 or more samples accordingly).

RESULTS

A total of 319 responses were collected between June 2019 and June 2021 from HOs working in various government hospitals in Malaysia. The overall response rate for this study was 6% (based on responses from Hospital Raja Permaisuri Bainun, Ipoh: 21 out of 345 HOs responded).

Sixty-one percentage (195/319) of the HOs were currently in their first year of house officer training while 36% (115/319) of them were in their second year and 3% (9/319) were classified as others. The majority of the HOs (98%; 314/3)19) were aged between 21 to 30 years old and only 2% (5/319) of them were aged between 31 to 40 years old. There were 112 male participants and 207 female HOs. There were 151 Malays, 100 Chinese, 51 Indian participants and 17 HOs of other races. Majority of the HOs were from the undergraduate programme while 9% (27/319) of them were from the graduate entry programme.

Learning of clinical pharmacology & therapeutics during medical school

When enquired about the number of times the HOs had practised writing up a full drug prescription during undergraduate training, 46% (146/319) of them identified the number of times as less than 5 times, 21% (66/319) of them as 5-10 times and 33% (105/319) of them as more than

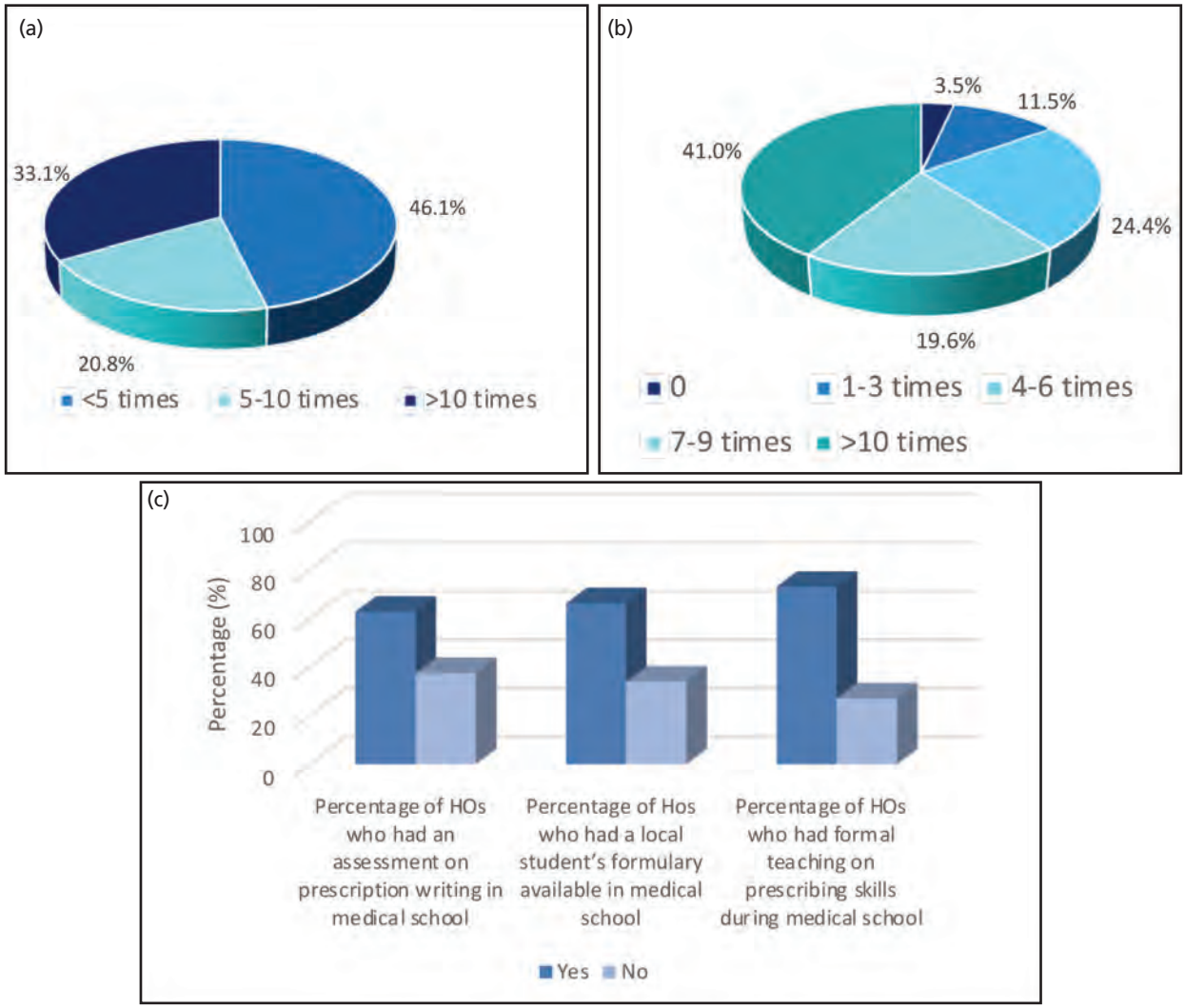

Fig. 1: (a). Number of times HOs had practiced writing up a full drug prescription during undergraduate training. (b) Average number of prescriptions written in a day in hospital practice. (c) : The percentage of HOs [i] who had been assessed on their level of competency in prescription writing during their study at a medical school, [ii] who had a local student's formulary available and [iii] who had received formal training on prescribing skills during their study at a medical school.

10 times (Figure 1a). About 63% (200/319) of the HOs confirmed that they were assessed on writing prescriptions either in the format of written or OSCE in year 4 or 5 of medical school and 66% (210/319) of them said they had a local student formulary (list of common drugs and adverse effects) available to them in medical school. Overall, a majority of 73% (232/319) responded that they had formal teaching in prescribing skills during medical school training (Figure 1c).

Prescribing practice during internship

When asked about the average number of prescription writing in a single day in hospital practice, majority of them (41%; 130/319) stated the number of times as more than 10 times, 20% (63/319) of them stated they prescribe 7-9 times, 24% (76/319) of them identified the number of times as 4-6 times and 15% (47/319) of them less than 1-3 times (Figure 1b).

Self-perceived having sufficient knowledge to prescribe

The majority of the HOs confidently said they have sufficient knowledge to prescribe the drugs such as analgesia (71%; 226/319), laxatives (72%; 229/319), antibiotics (62%; 197/319), anti-emetics (78%; 248/319), anti-hypertensives (79%; 252/319), anti-diabetics (77%; 245/319) and anti-histamines (64%; 204/319). Less than half of the HOs thought to have sufficient knowledge to prescribe some classes of drugs such as anticoagulants (48%; 153/319), opiates (46%; 146/319), epileptics (35%; 111/319) and cytotoxic drugs (13%;41/319) Figure 2). HOs reported high confidence in prescribing analgesics and anti-hypertensives but low confidence in cytotoxic drugs, reflecting limited exposure to oncology settings.

Views on HO's own prescribing practice

When asked if medical school training has prepared HOs for prescribing medications in clinical practice, 45% (143/319) of them showed agreement meanwhile 32% (102/319) of the respondents said they were stressed about prescribing

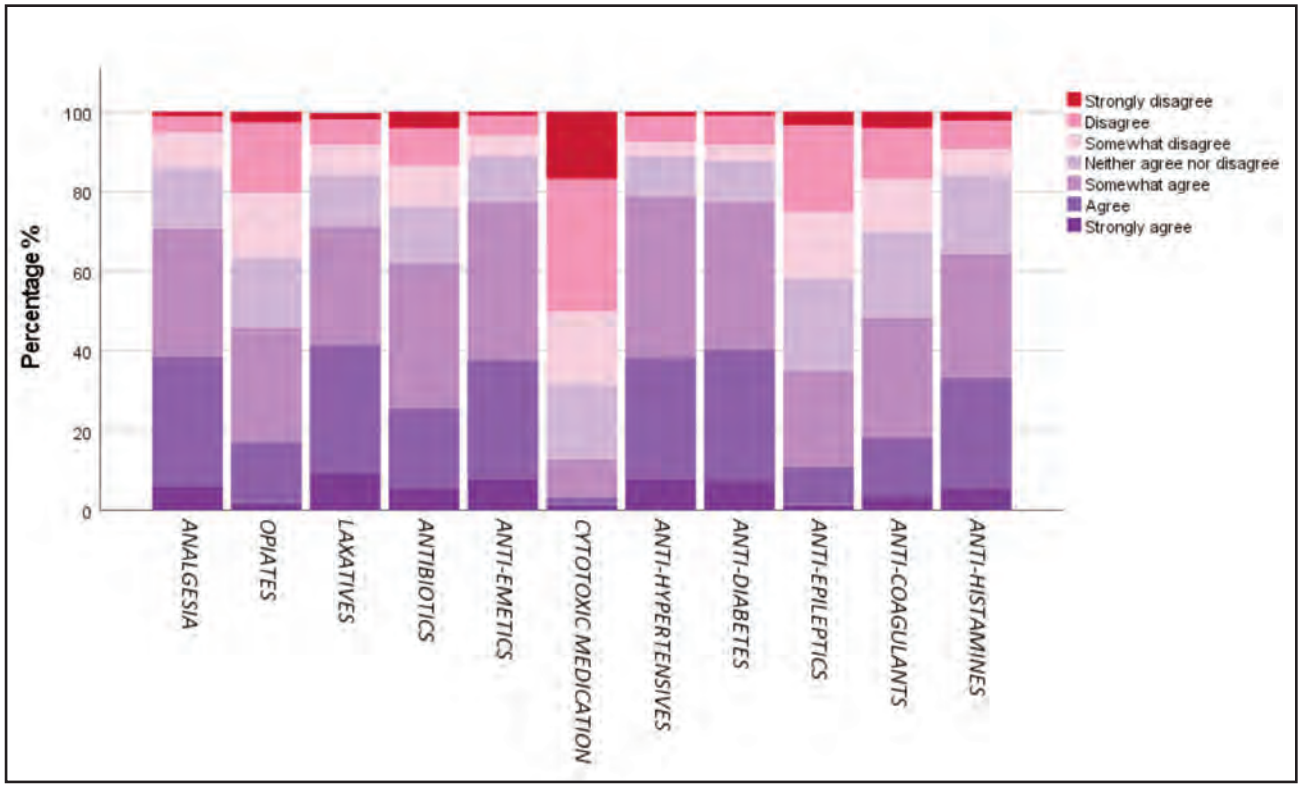

Fig. 2: Self-perceived level of knowledge of HO in prescribing various classes of commonly used drugs

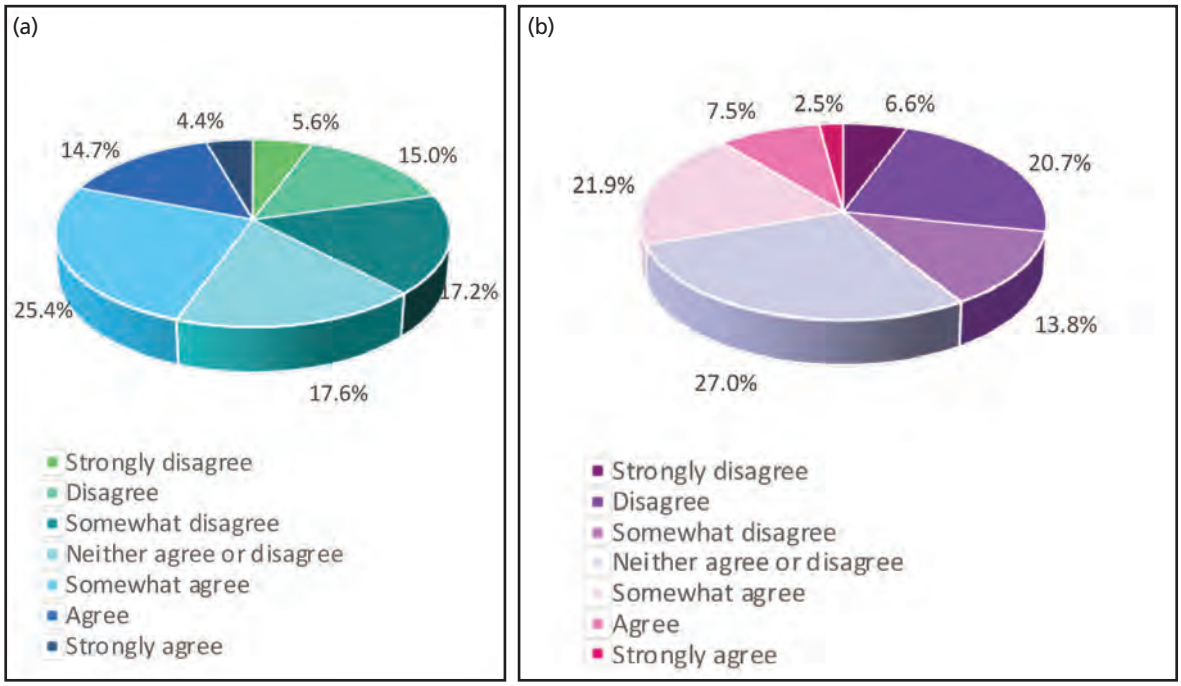

Fig. 3: Views of HOs on (a) medical school training preparing them for prescribing medications in clinical practice and (b) about being stressed when prescribing medication

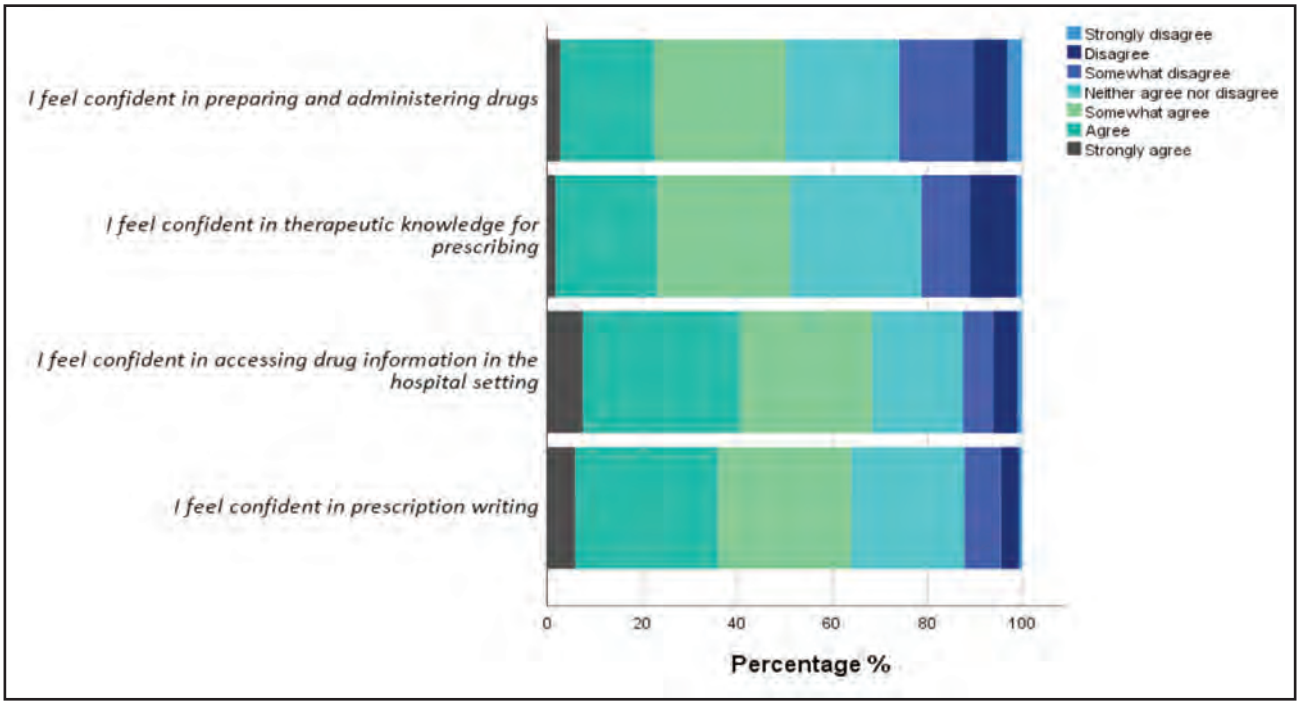

Fig. 4: Level of confidence of HOs regarding their prescribing skill

medications as a house officer. Overall, 64% (204/319) of the HOs identified themselves as having sufficient resources to aid their continued learning in prescribing. Pertaining to the improvement of prescribing skills, 57% (181/319) of them said that they had always have the opportunity to allocate the time and resources necessary for enhancing that their prescribing skills in the hospital setting. In addition, this survey found that about 68% (216/319) of the HOs felt that they had only realised the importance of prescribing during internship (Figure 3).

Self-perceived confidence to prescribe

A total of 64% (204/319) of the HOs stated that they feel confident in prescription writing. Regarding the level of confidence in accessing drug information in the hospital setting, 68% (216/319) responded positively to having confidence whereas 51% (162/319) of the study HOs expressed confidence in their therapeutic knowledge for prescribing. Besides, when enquired about confidence in preparing and administering drugs, half of the HOs (50%; 159/319) believed to having confidence (Figure 4).

Association of 1.Knowledge to prescribe drugs 2. Prescribing practise 3. Confidence to prescribe with gender, race, type of medical school, year of training and whether received a formal prescribing teaching in medical school.

The median total score for 1.Knowledge to prescribe drugs 2. Prescribing practise 3. Confidence to prescribe were analysed for association with gender, race, type of medical school, year of training and whether received formal teaching in prescribing skills during the medical school training (Table I). For Knowledge to prescribe drugs, significant association is with gender, race, year of training and for formal teaching in prescribing skills. Year 1 HOs showed a lower median (49.00) compared to Y2 HOs (53.00). For those who had formal teaching in prescribing in medical school showed a higher median (52.00) compared with those who did not receive a formal teaching in prescribing in medical school (44.00). For HOs views on their Prescribing practice, significant association with year of training, type of medical school and for formal teaching in prescribing skills. Y1 (20.00) HOs median was lower than Y2 (22.00) HOs.

For HOs Confidence to prescribing, significant association was with gender, year of training, type of medical school and for formal teaching in prescribing skills. The Y2 HOs had higher confidence to prescribe (21.00) when compared with Y1 HOs (18.00). Those who had received formal training in the prescribing of drug treatment at their medical schools were reported to have a higher level of confidence in prescribing (19.00) than those who did not (18.00).

Confidence in specific prescribing competency

For Confidence to prescribe items: 1. I feel confident in prescription writing, 2. I feel confident in accessing drug information in the hospital setting. 3. I feel confident in therapeutic knowledge for prescribing. 4. I feel confident in preparing and administering drugs, the median is 5.00 for all 4 items indicating that half of HOS somewhat agreed to the questions (Table I).

DISCUSSION

This study investigated the perceptions of House Officers (HOs) in Malaysia regarding their prescribing skills and competencies, as well as their views on the adequacy of

clinical pharmacology and therapeutics training received during their undergraduate medical education. HOs are required to demonstrate the attributes and competencies of a thoughtful, safe, and effective prescriber upon commencing their clinical practice. In the present study, a proportion of HOs reported a lack of confidence in their prescribing skills. That is unsurprising given that the majority perceived their undergraduate training in prescribing to be inadequate with minimal practice of prescription writing. Notably, this study revealed that most HOs (66%; 212/319) had practised completing drug prescriptions fewer than ten times during their undergraduate medical education, and some (27%; 86/319) reported not receiving any formal instruction on prescribing practices. The inadequate training reported may stem from a lack of practical exposure, insufficient teaching methods, or limited focus on clinical pharmacology in medical school curriculums. Supporting this study, one study highlighted the absence of formal teaching and feedback on prescription writing resulted in low competency among final-year medical students.[21] In contrast, another study found no significant difference in self-perceived prescribing competency between students with and without prescribing safety assessment (PSA) training, suggesting that the curriculum emphasizing pharmacological knowledge, early exposure, and practical experience may sufficiently prepare students for safe prescribing.[20] These findings underscore the critical importance of structured and practical prescribing training in medical school, as inadequate teaching and limited feedback can lead to poor competency, while comprehensive curricula that integrate early pharmacological education, real-world exposure, and simulation exercises have been shown to effectively enhance prescribing confidence and readiness among future doctors.

The inadequate training provided to medical students during their undergraduate medical curriculum could logically account for the lack of confidence in prescription writing for approximately 36% of HOs in this study. This shows that knowledge is a crucial factor in an accurate determination of prescribing competency among the HOs. Although many medical schools have incorporated the teaching of clinical pharmacology and therapeutics as part of the curriculum for all medical students, this study had reported that many HOs in Malaysia did not demonstrate adequate confidence in having sufficient knowledge in this area. Despite having equipped with theoretical knowledge, many newly qualified doctors still feel unprepared for practical prescribing tasks. A thematic analysis revealed that intern doctors often lack practical knowledge of prescribing, including dosage, formulations, frequency, and duration of treatment. They reported difficulties in applying knowledge from medical school to clinical practice, highlighting the need for experiential learning opportunities during their training.[22] The current study found many House Officers in Malaysia lack confidence in prescribing due to limited practical training during undergraduate education. This supports the above thematic analysis showing interns struggle with practical prescribing knowledge and applying theory to practice. Our survey expands on that analysis by quantifying how inadequate training and minimal prescription writing experience reduce confidence, emphasizing the need for early, practical pharmacology education with real-world exposure.

This study identified a gap between the skills demanded of the HOs to prescribe competently and the quantity of available learning opportunities especially hospital based prescribing training during their medical school. It might be helpful to scrutinize more closely on the total number of times the drug Kardex (medication record) which had been written by these medical students during their medical school training because it would be helpful in increasing their familiarity with prescribing practice. Not only is it a skill that the HOs will be required to demonstrate on many occasions during their work, it is also vital in avoiding the possibility of prescribing errors and the resulting adverse drug reactions from occurring, in order to maximise the effectiveness of drug therapy.[23] In addition, having sufficient information such as reference to drug formulary is important to aid with prescribing information and prevent adverse drug reactions.[24] Overall, enhancing practical training and ensuring access to prescribing resources during medical education are critical steps to better prepare HOs for safe and effective medication management.

However, the knowledge gained from having experienced many rotations during housemanship may be the reason why some other HOs believed to be competent in prescribing most classes of drugs. Their competency and knowledge about prescribing certain classes of drugs would most likely reflect the patients whom they had already attended to as well as their prescribing workload during their rotations and the supervision and guidance given by senior doctors during their attachments rather than their own theoretical knowledge alone.[2,19] Research has shown that the more numbers of clinical rotations done, the more confident the HOs were to prescribe unsupervised.[2] Of all drug classes, HOs perceived to be least competent in prescribing cytotoxic drugs. This could be because cytotoxic drugs are mostly prescribed by oncologists and the lack of exposure to that particular specialty during their housemanship. The increased clinical experience gained through multiple rotations during housemanship appears to enhance some HOs' prescribing competency, which is largely influenced by their direct patient exposure, prescribing responsibilities, and senior supervision rather than theoretical knowledge alone. Confidence in prescribing generally grows with more rotations, though limited exposure to specialties like oncology explains why HOs feel least competent prescribing specialized drugs such as cytotoxics.

Prescribing is an amalgamation of knowledge, skill and behaviour, as all of these aspects need to be contextualised with real-life patients and the real-life scenario. The Objective Structured Clinical Examination (OSCE) and structured clinical examination is widely practised across most medical schools in Malaysia for the purpose of adopting the competence paradigm for medical practice by appraising the performance of a medical doctor in terms of his/her prescribing competency. This study has shown that some HOs were not tested on their prescribing skill back in their medical school, which explains why some of them did not feel confident in prescription writing. Therefore, OSCE could serve as an effective assessment tool that can be integrated into the medical curriculum to test the students' ability in translating their learning of pharmacology and therapeutics into

practical skills.[25-26] The integration of OSCEs into the medical curriculum can play a pivotal role in enhancing both the ability and confidence of medical graduates in rational prescribing. By incorporating practical stations that simulate real-life prescribing scenarios, OSCEs allow students to apply their pharmacological knowledge and therapeutic reasoning in a controlled environment. This not only tests their ability to select appropriate drugs, dosages, and routes of administration but also reinforces safe and evidence-based prescribing practices. Additionally, OSCEs provide immediate feedback, enabling students to identify and correct errors early in their training. Such experiential learning helps graduates develop critical thinking and decision-making skills necessary for prescribing under pressure, ultimately fostering greater confidence and competence as they transition into clinical practice.[27] Furthermore, a recent systematic review demonstrated that additional prescription writing education using diverse methods such as case-based, patient-based, tutorial-based, didactic, and mixed approaches, followed by OSPE or OSCE assessments was more effective at developing prescribing skills than the absence of such targeted training.[28-29]

There are a few limitations in this study that need to be considered. Firstly, the response rate for this study is poor, therefore this study findings are based on individuals' perception on their level of competency rather than evident demonstration of prescribing competence and knowledge. Secondly, it was acknowledged that an inherent source of bias in this study arises from the fact that self-perceived competency expressed by each respondent may not reflect his/her depth of knowledge, ability as well as confidence to excel at prescription writing. Thirdly, the hospital environment may have been exacerbated and caused additional stress among the HOs due to the COVID-19. It may have caused varied clinical training and experience of the HOs, which may influence their level of confidence in prescribing.

Future research could explore the underlying factors influencing HOs prescribing practices through qualitative studies, such as interviews or focus groups, to better understand barriers to skill development. Analytical studies examining associations between demographic variables (e.g., type of medical school or prior clinical exposure) and prescribing competence may help identify key predictors, while interventional studies could evaluate targeted training programs to enhance HOs' prescribing confidence and proficiency in the hospital setting.

CONCLUSION

This study highlights areas for improvement in prescribing preparedness among House Officers, rooted primarily in gaps in undergraduate pharmacology and therapeutics education. The superior knowledge, confidence, and prescribing attitudes observed in those receiving formal training underscore the imperative to strengthen medical curricula and implement standardized competency assessments. While self-perceived measures may introduce bias, the findings nonetheless call for urgent educational reforms, including increased practical exposure and targeted training interventions. By addressing these critical areas, medical education can better prepare future clinicians to prescribe safely and effectively, ultimately enhancing patient safety and healthcare quality on a broader scale.

DECLARATION OF INTEREST

The authors report no conflicts of interest.

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ORIGINAL ARTICLE

Knees on fire: Investigating the impact of knee discomfort on cardiovascular fitness among Malaysian firefighters

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ABSTRACT

Introduction: Firefighters require optimal cardiovascular fitness (CVF) to effectively perform fire suppression activities and other essential tasks. However, knee discomfort can reduce their engagement in leisure-time physical activity (LTPA), subsequently affecting their CVF during individual field-based testing. This study aimed to determine the impact of knee discomfort on CVF and to assess the necessity of adjusting field-based CVF test scores for firefighters experiencing such physical limitations.

Materials and methods: This study used secondary data from 5,680 firefighters, collected between September and October 2023. A final 3,885 datasets that met the eligibility criteria were included for analysis. Knee discomfort was assessed using the Cornell Musculoskeletal Discomfort Questionnaire, with scores derived from the Rasch Measurement Model based on three items: frequency, severity, and work interference due to knee discomfort.

CVF was estimated using self-reported field-based CVF tests, including the time taken to run 2.4 km, the beep test (level and shuttle), and the 6-minute walking test. VO_2 max estimation was calculated as a proxy for CVF. Multiple linear regression was used to analyse the impact of knee discomfort on CVF, controlling for age, male gender, sleep duration, intensity of weekly LTPA, and perceived work demands. Cohen's effect size ($f2$) was observed, with values of 0.02, 0.15, and 0.35 indicating small, medium, and large effect sizes, respectively.

Results: The prevalence of knee discomfort among operational firefighters was 51.3%. Of these, 43.9% described the discomfort as mild, while 77.9% reported that it did not interfere or only slightly interfered with their work. LTPA ($\beta = 0.70$; 95%CI: 0.55, 0.85; $p < 0.001$) and knee discomfort scores ($\beta = -0.04$; 95%CI: -0.05, -0.03; $p < 0.001$) were associated with CVF among the participants, after controlling for age and gender. However, the impact of knee discomfort on CVF was negligible ($f2 = 0.012$).

Conclusion: Knee discomfort showed a statistically precise yet negligible effect on CVF, indicating that adjustment of field-based CVF test scores is unnecessary. However, for firefighters experiencing severe knee discomfort, a more lenient test, such as the 6-minute walking test, should be considered rather than exempting them from assessment.

KEYWORDS:
Firefighters, knee discomfort, cardiovascular fitness, physical activity, prevalence

INTRODUCTION

Firefighters face numerous health risks due to the physically demanding nature of their work, high metabolic demand, and substantial physical exertion required for their essential tasks. Maintaining optimal cardiovascular fitness (CVF) is crucial, with a recommended VO_2 max of 42 ml/kg/min (12 metabolic equivalents [METs]). Firefighters with a VO_2 max at or below 28 ml/kg/min (8 METs) are restricted from performing many critical tasks.[1] Compliance with this optimal standard is vital, as the use of self-contained breathing apparatus (SCBA) during firefighting operations places significant physiological demands on the body. SCBA use has been shown to reduce peak power generation and oxyhaemoglobin saturation, lowering VO_2 max by 14.9% and maximal exercise performance by 4.8% due to the additional weight of the SCBA pack.[2]

Firefighters' occupational demands require repetitive pulling, pushing, lifting, carrying, and dragging while wearing 20 kg of protective gear and SCBA.[3] These demands can trigger a cascade of musculoskeletal injuries, with the knee joint being the most commonly affected.[4] Other joints, including the head, neck, shoulders, elbows, arms, hands, back, thighs, and feet, are also impacted,[5] further compromising the holistic function of weight-bearing knee joints. A systematic review of tactical athletes found that firefighters face an increased risk of developing osteoarthritis in their knees and hips, with symptoms worsening during the third and fourth decades of life.[6]

Knee disorders present a dual challenge. On the one hand, firefighters may lose interest in unsupervised leisure-time physical activities (LTPAs) due to discomfort. On the other hand, engaging in such activities without proper supervision increases the risk of injury to the ankles, knees, and legs,[7]

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often resulting from poor exercise technique, insufficient training experience, lack of warm-up, or fatigue.[8] A decline in physical activity can lead to measurable reductions in CVF and conditioning in less than a week.

The fear of being deemed unfit for operational deployment due to knee injuries often leads firefighters to adopt a "safe play" practice rather than engaging in active training.[9] Many firefighters refrain from unsupervised exercise, unaware of the principle that "mobility is medicine." Their primary concern is avoiding medical interventions that could compromise functioning and lead to lost workdays. However, despite these apprehensions, firefighters remain motivated to undertake field-based CVF tests to maintain their operational status within their teams. In light of these challenges, the present study aimed to determine the impact of knee discomfort on CVF and to assess the necessity of adjusting field-based CVF test scores for firefighters experiencing such physical limitations (Figure 1).

MATERIALS AND METHODS

Study design and sampling

This study utilised national secondary data from 5,680 firefighters collected cross-sectionally via an online platform between September 8 and October 27, 2023. A final 3,885 datasets that met the eligibility criteria were included in the analysis. To meet the inclusion criteria, firefighters i) had to be active and permanently appointed firefighters, ii) be currently placed in a Fire and Rescue Operation Unit, iii) have a job title grade KB 19/KUP 22 or KB 22/24/26, iv) have at least 2 years of work experience, v) provide consent to participate in the study, and vi) provide their results from a field-based CVF test involving a 2.4 km run, beep test (level and shuttle) or 6-minute walking test. Firefighters were excluded if they i) were voluntary or auxiliary firefighters, ii) were on medical leave for more than 3 months, iii) had returned from another country within the last 7 days, iv) were on study leave or training for the past 3 months, v) regularly took analgesics prescribed by an orthopaedic specialist or rehabilitative doctor, vi) were receiving regular medical follow-up for a musculoskeletal disorder, vii) were pregnant, and viii) had experienced an accident or injury outside of working hours within the past 3 months.

The final sample comprised 3,885 responses, exceeding the minimum requirement calculated using G*Power and the F-test family for multiple linear regressions.10 A fixed model assuming R^2 deviation from zero was used, with an α error probability of 0.05, statistical power of 0.80, a small effect size ($f^2 = 0.02$), and seven predictors.11 Based on these parameters, the minimum required sample size was 725. Accounting for a 20% anticipated non-response rate, the target sample size was 906. Post-hoc analysis indicated that the study achieved a statistical power of 99.99% based on an observed effect size of $f^2 = 0.012$ and an α error probability of 0.05. Purposive sampling was employed, whereby respondents were selected from the primary dataset according to predefined inclusion and exclusion criteria to ensure eligibility.

Data collection

Before data collection, participants were provided with a link to an information sheet detailing the study's purpose and scope. They were informed that participation was voluntary and that confidentiality would be maintained through the use of anonymous identification numbers. Informed consent was obtained from all participants. Ethical approval for the study was granted by the Research Ethics Committee of Universiti Kebangsaan Malaysia (Code: JEP-2023-164).

Data were collected using an online self-administered questionnaire comprising seven sections: demographic information, work demands, task characteristics, LTPA, CVF, sleep duration, and the Cornell Musculoskeletal Discomfort Questionnaire focused on the knee region. All sections underwent cognitive debriefing to ensure clarity and alignment with the colloquial language used by the firefighters. The demographic section included items focused on variables such as age, gender, marital status, and years of service in the Fire and Rescue Department of Malaysia

Measures

Work Demand

An adapted version of Van Veldhoven and Meijman's eight-item questionnaire[12] was used to assess the psychological work demands of firefighters, based on previous research.[13] Responses were rated on a five-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree). The original questionnaire reported a Cronbach's α coefficient of 0.80,[14] while the Cronbach's α value for the current study was 0.85, indicating good internal consistency. The items were modified from questions into statements, such as "I have to work fast," "I have to work under time pressure," and "I work in comfort".

Task characteristics

The task characteristics questionnaire was adapted from a previous study,[13] with the number of items was expanded to 14 to avoid double-barrelled questions and to incorporate feedback obtained through cognitive debriefing. Items were rated on a five-point Likert scale, ranging from 1 (low severity) to 5 (critical). The original questionnaire reported Cronbach's α coefficients ranging from 0.72 to 0.92.[15] In the present study, after removing one item related to workload imbalance to enhance statistical validity, Cronbach's α was 0.90, indicating excellent internal consistency. Typical items included "degree of uncertainty," "exposure to human loss," and "traumatic incidents".

LTPA

LTPA evaluation was based on self-reports for 12 types of activities commonly performed by firefighters during the week. These included jogging for more than 15 minutes, cycling for more than 15 minutes, using gym equipment, and engaging in sports like badminton, table tennis, tennis, volleyball, and football. LTPA was quantified using the metabolic equivalent of task (MET) based on the 2024 Compendium of Physical Activities.[16] For example, leisure cycling at 15 km/h corresponds to 5.8 METs, while jogging at a pace of 7.5 min/km corresponds to 8.5 METs. The MET value for gym-based physical activities was multiplied by the reported intensity category: Category 1: < 8 repetitions x 3

sets; Category 2: 8 repetitions x 3 sets; Category 3: 9–20 repetitions x 3 sets, and Category 4: > 20 repetitions x 3 sets. Similarly, the MET value of each sports activity was multiplied by the reported duration category: Category 1: < 75 minutes/week; Category 2: 75–150 minutes/week; and Category 3: > 150 minutes/week. The total METs were summed and averaged by the number of activities per week.[17]

CVF
CVF, proxied by VO_2 max, was estimated using self-reported field-based CVF tests, such as the time taken to run 2.4 km, the beep test (level and shuttle), and the 6-minute walking test.

For the 2.4 km run test, the VO_2 max was calculated using the following equation from previous research,18 which is available online:[19]

VO_2 max, in mL/kg/min = (483 / time) + 3.5.

In this, "time" is the time taken to finish the 2.4 km run in minutes.

For respondents who completed the beep test, an online calculator was used to estimate VO_2 max values based on their age, gender, test level, and the number of shuttles completed.[20] For those who completed the 6-minute walking test, the distance walked (in metres) was used to calculate walking speed (in metres per minute).[21] This value was then used in the following equation to estimate VO_2 max:

VO_2 max = 3.5 ml/kg/min + (speed in m/min × 0.1)

When more than one self-reported field-based CVF test was available, the 2.4 km run time was prioritised due to its higher reliability, as firefighters are more accustomed to this test compared to the recently introduced beep test or six-minute walk test, which may be harder to recall accurately and have limited familiarity.

Age and gender were controlled for in the analysis due to their established influence on CVF.

Sleep duration
Sleep duration was assessed using a single-item measure with three response categories: less than 5 hours, more than 5 but less than 7 hours, and more than 7 hours. For analytical purposes, the responses were subsequently recategorized dichotomously as less than 5 hours and 5 hours or more to enhance statistical power.

Knee discomfort
Knee discomfort was assessed using the Malay-translated version of the Cornell Musculoskeletal Discomfort Questionnaire.[22] Total scores were derived using the Rasch Measurement Model based on three polychotomous response items: frequency of discomfort, intensity of discomfort, and the extent to which discomfort interfered with work. The Cronbach alpha was 0.93. The Rasch Measurement Model was used to convert ordinal scores into interval-level data, following verification of unidimensionality assumptions, thereby enhancing both the validity and interpretability of the results.

Statistical analysis
Ordinal scores were transformed into interval-level data using the Rasch Measurement Model, replicating the procedure described in previous research.[23] The conversion was applied as follows:

USCALE = (wanted range) / (current range)
UMEAN = (wanted low) – (current low x USCALE)

Descriptive statistics were calculated using IBM SPSS version 29. Firefighters' characteristics, including demographic and other variables, were presented as frequencies and percentages, as well as means with standard deviations (SDs). Multiple linear regression was used to analyse the impact of knee discomfort and intensity of LTPA per week on CVF, controlling for age, male gender, sleep duration, perceived work demands, and task characteristics. Cohen's effect size (f^2) for multiple linear regression was observed, with values of 0.02, 0.15, and 0.35 indicating small, medium, and large effect sizes, respectively. The effect size, f^2 was calculated using the following formula:[24]

$f^2 = R^2\text{included} - R^2\text{excluded} / 1 - R^2\text{included}$

Where:

R^2included = R^2 when the total knee score is included in the model.
R^2excluded = R^2 when the total knee score is excluded in the model.

RESULTS

Most of the participants were male (96.7%), aged between 30 – 34 years old (20.3%) had job grade KB19/KUP22 (85.9%), and slept for more than 5 hours each night (74.7%). Over one week, 3,734 firefighters (96.1%) engaged in exercise or sport during their leisure time, with 77.8% reporting moderate levels of LTPA intensity.

Approximately 51.3% of participants reported experiencing knee discomfort, with the highest prevalence (20%) observed among those aged between 40 – 45. Among those with knee discomfort, 43.9% described the discomfort as mild and 77.9% indicated that it did not interfere or only slightly interfered with their work. Those with knee discomfort had statistically significantly lower LTPA values (M = 5.18, SD = 1.38 METs) compared to those without knee discomfort (M = 5.32, SD = 1.27 METs; $t(3883) = 3.26$, $p < 0.001$, Cohen's d = 0.11), indicating a negligible effect size.

Overall, 26% of participants had a VO2 max estimation of 42ml/kg/min or more, meeting the National Fire Protection Association requirement (Table I). Those with a VO2 of 42ml/kg/min or more had statistically significantly higher LTPA values (M = 5.56, SD = 0.99 METs) compared to those with a VO2 max less than 42ml/kg/min (M= 5.14, SD = 1.41 METs; $t(3883) = 8.72$, $p < 0.001$, Cohen's d = 0.32), indicating a small effect size. Table II shows the multiple linear regression of knee discomfort on CVF, adjusted for LTPA, age,

Table I: Descriptive Analysis

Profile	n	%	Mean (SD)	95% CI for Mean
Age			39.00 (8.85)	38.72, 39.28
20-24 years	85	2.2		
25-29 years	565	14.5		
30-34 years	790	20.3		
35-39 years	577	14.8		
40-44 years	730	18.8		
45-49 years	544	14.0		
50-54 years	465	12.0		
55 years and above	129	3.4		
Gender				
Male	3755	96.7		
Female	130	3.3		
Position grade				
KB19 /KUP 22	3336	85.9		
KB22/24/26	549	14.1		
Sleep duration				
5 hours and less	983	25.3		
More than 5 hours	2902	74.7		
Work demand			26.84 (4.18)	26.71, 26.97
Task characteristics			35.60 (5.87)	35.42, 35.79
Total leisure-time physical activity, MET/week			48.60 (19.08)	48.00, 49.20
Leisure time physical activity intensity:				
Sedentary (0 - 2.9)	160	4.1		
Moderate (3 - 5.9)	3023	77.8		
High (6 and above)	702	18.1		
Knee discomfort				
Yes	1994	51.3		
No	1891	48.7		
Frequency of knee discomfort, n=1994				
Never	52	2.6		
1-2 times/week	713	35.8		
3-4 times/week	489	24.5		
Once everyday	395	19.8		
Several times every day	345	17.3		
Level of knee discomfort, n=1994				
None	47	2.4		
Slight	872	43.7		
Moderate	646	32.4		
High	429	21.5		
Knee discomfort with work interference, n=1994				
Not at all	675	33.9		
Slightly	949	47.6		
Substantial	370	18.5		
Knee discomfort score, n=1994	33.45 (10.09)	33.00, 33.89		
Cardiovascular fitness, n=3885	37.26 (7.63)	37.02, 37.50		
Less than 42, ml/kg/min	2875	74.0		
42 and above, ml/kg/min	1010	26.0		

Note: MET =metabolic equivalent of task

and gender. Despite the large sample size (n = 3,885) and narrow confidence intervals, the effect was negligible (f^2 = 0.012), indicating no need to adjust field-based CVF test scores for knee discomfort.

DISCUSSION

This study aimed to evaluate the impact of knee discomfort on CVF among firefighters and to assess whether score adjustments are warranted for those experiencing such physical challenges. Two factors, knee discomfort and LTPA, were found to be associated with CVF among the participants after controlling for age and gender.

Knee discomfort was found to be prevalent among the participating firefighters, consistent with observations from Western populations.[5] While age is a known contributor, occupational exposures also play an important role. Prolonged dynamic and static loading during firefighting duties likely increases patellofemoral biomechanical stress. Retrospective analyses have further identified distinctive trochlear lesions in firefighters undergoing arthroscopy for seemingly unrelated meniscal or ligamentous injuries.[25] This finding challenges the traditional view that anterior cruciate ligament, medial collateral ligament, and meniscal tears are the predominant pathologies resulting from athletic loads.[26] Instead, it suggests that firefighting tasks may give rise to a broader spectrum of knee pathologies. For example, SCBA

Table II: Factors influencing cardiovascular fitness among firefighters (n=3885)

Variables	Simple Linear Regression				Multiple Linear Regression				
	95% CI for β				95% CI β				
	β	Lower Limit	Upper Limit	p-value	β	Lower Limit	Upper Limit	t-test	p-value
Age	-0.44	-0.46	-0.42	<0.001	-0.43	-0.45	-0.41	36.81	<0.001
Male gender	4.46	3.14	5.79	<0.001	5.82	4.70	6.94	10.20	<0.001
Leisure-time physical activity	1.01	0.83	1.19	<0.001	0.70	0.55	0.85	9.06	<0.001
Knee discomfort	-0.07	-0.08	-0.06	<0.001	-0.04	-0.05	-0.03	6.53	<0.001
Sleep <5 hours	-0.32	-0.87	0.23	0.253					
Work demand	0.06	0.01	0.12	0.029					
Work characteristics	-0.02	-0.06	0.03	0.477					

Note: CI = Confidence Interval, Forward method (R2 = 0.306); the model reasonably fits well; model assumptions are met; no multicollinearity problem, the effect of knee discomfort on cardiovascular capacity is negligible i.e. $f2$= 0.012

carriage during firefighting activities alters firefighters' body kinematics, such as reducing step length, increasing hip and knee flexion ranges of motion, and increasing the centre of mass deviation, which results in the highest load of internal force being placed on the knee.[4,27]

Although ageing is a well-established factor contributing to CVF decline,[28] the present study shows that the additional effect of knee discomfort on CVF is minimal. Several explanations may account for this negligible effect. Firefighters' passion for their profession, their strong sense of camaraderie with shift partners, and their altruistic commitment to supporting fellow emergency responders [29] may result in them overlooking or tolerating physical challenges, including knee discomfort. Furthermore, psychological resilience, developed through repeated exposure to risk and sacrifice, may diminish the perceived significance of knee pain.[30] Importantly, firefighters are also highly aware that maintaining fitness is essential for both personal safety and operational effectiveness, an expectation reinforced by organizational standards and public trust. Consequently, many of them engage in regular exercise and sports during leisure time, which may buffer any potential negative effects of knee discomfort on CVF. Taken together, these occupational, psychological, and behavioural factors help explain why knee discomfort, while common, exerts little measurable influence on cardiovascular fitness in this population.

The benefits of regular physical activity in mitigating age-related physiological decline have been well-established in the last three decades. Exercise can attenuate age-related decline in VO_2 max, lower mean blood pressure and systemic vascular resistance, preserve lean body mass while reducing fat deposits, increase high-density lipoprotein levels, decrease triglyceride levels, enhance bone mineral content, improve basal metabolic rate, boost muscle strength, and support cognitive functioning.[31] Recent findings suggest that ageing is also associated with significant telomere shortening, leading to gradual cellular deterioration. However, regular physical activity appears to preserve telomere length. Adults who engage in high levels of physical activity have been estimated to have a "reversed biological clock," appearing biologically 9 and 7.1 years younger than those with sedentary and moderately active lifestyles, respectively.[32]

The current study demonstrated that firefighters continue to engage in moderate physical activities during their leisure time, despite experiencing knee discomfort. Individuals who participate in at least a moderate level of physical activity (600–3000 MET-min/week) may attain VO_2 max values of 44.0 ml/kg/min or higher.[33] Such improvements are largely attributed to lower arterial stiffness, which results in enhanced cardiovascular health. Regular physical activity promotes cardiovascular adaptations by improving oxygen delivery, inducing vasodilation and angiogenesis within the vasculature, and stimulating mitochondrial biogenesis in peripheral tissues, such as adipocytes, skeletal muscle myotubes, and cardiomyocytes.[34] Additionally, it exerts anti-inflammatory effects,[35] further enhancing overall cardiovascular function and efficiency.

Improving cardiovascular function enhances the heart's ability to pump blood to the lungs and throughout the body. As a result, blood flow to the skeletal muscles can increase by 20- to 50-fold during peak muscle perfusion,[36] leading to a 17- to 24-fold increase in VO_2 max compared to resting values.[37] The demands of physical activity, which drive muscular adaptations, induce changes in both muscle fibre composition and function. Regular physical activity improves the ability of muscles to extract oxygen from the blood, thereby reducing the burden on the heart to supply additional blood to meet muscular demands. Additionally, capillaries, which are the smallest blood vessels, undergo dilation, enhancing their capacity to deliver oxygen to the tissues and effectively remove waste products.[38]

Engaging in an adequate amount of physical activity is a powerful, non-pharmacological strategy for improving CVF. It functions similarly to a beta-blocker by lowering resting heart rate and reducing blood pressure.[39] Physical activity has been recognised as an effective stress reliever, reducing levels of stress hormones such as cortisol and adrenaline while promoting the release of "happy chemicals" like endorphins.[40] This response reduces the cardiovascular strain caused by stress hormones. Furthermore, regular physical activity can reduce atherogenic markers by improving endothelial function, decreasing inflammation, and favourably modifying lipid profiles, including increasing levels of high-density lipoprotein and optimising triglyceride concentrations.

Strengths and Limitations

This study represents the first national investigation in Malaysia to determine the association between knee discomfort and CVF among firefighters. Despite the inherent limitations of cross-sectional designs, this approach was deemed the most suitable for assessing the study variables. All research instruments demonstrated robust validity and were appropriately matched to their respective domains. Data collection via an online survey using Google Forms enabled rapid, large-scale participation, which was supported by the regimented organisational structure of the firefighting workforce. Although self-reported data may be subject to recall or social desirability bias, the consistency of VO_2 max estimates with previous internal published firefighter data supports the plausibility of our findings. This method was selected for its feasibility in a large operational workforce and was applied consistently across participants.

The use of purposive sampling, while appropriate for targeting the study population, inherently limits external validity and restricts the generalisability of the findings beyond the specific occupational group examined. However, this approach was necessary to capture the unique characteristics of firefighters, thereby ensuring the relevance and applicability of the results to this high-risk occupational setting. Sampling error was minimised by the use of a substantial sample size and adequate responder variability, strengthening the study's external validity. However, the cross-sectional nature of the study limits the ability to infer causality. Future research employing two-wave or multi-wave longitudinal panel designs is recommended to clarify temporal relationships and more definitively establish the mediating role of LTPA.

A key limitation is the exclusion of work-related physical activity, which is critical for accurately assessing occupational fitness demands. However, this was partially mitigated by focusing on leisure-time physical activity, a domain more amenable to standardised measurement. The sample was relatively homogeneous, focusing exclusively on operational firefighters rather than the entire firefighter hierarchy, yet this enhances the internal validity by reducing variability in occupational exposure. Lastly, the use of self-administered questionnaires and retrospective recall of LTPA may have introduced recall bias, although the use of validated instruments and clear instructions was intended to minimise this risk.

CONCLUSION

LTPA and knee discomfort scores were found to be associated with CVF among the participant firefighters, after controlling for age and gender. Even with a large sample size ensuring precise results, knee discomfort showed only a very small impact on cardiovascular fitness, indicating that field-based CVF test scores do not need adjustment for this factor. However, for firefighters reporting severe knee discomfort, the implementation of more accessible assessments, such as the 6-minute walking test, is recommended.

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Patient-reported outcome measures and patient satisfaction after total knee replacement for osteoarthritis in Egyptian patients: An observational Study

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ABSTRACT

Introduction: Together with the clinical and radiological evaluation, patient-reported outcome measures (PROMs) provide a valuable tool to measure the success of TKA. This prospective study looked at the clinical outcome and patients' satisfaction following TKA using different PROM and scores at one-year post-operative.

Materials and Methods: A prospective cohort study was performed at an elective arthroplasty unit in Menoufia University Hospitals, Egypt, on 132 patients who received primary TKA from 1 May 2021 to 1 May 2022 with a minimum one-year follow-up. All Patients received fixed bearing posterior stabilized knee TKA because knee arthritis, either primary or secondary to autoimmune disorder were included. Demographic data were collected: age, sex, weight, height, body mass index (kg/m2), comorbidities, socioeconomic status, and occupation. Three scores were used for prospective evaluation. Oxford Knee Score (OKS), Western Ontario and McMaster Universities Osteoarthritis Index score (WOMAC), and VAS (Visual Analogue Scale). During the follow-up visits, the participants were then asked to conduct their PROM (6 months and one year), and radiological and functional outcomes were recorded.

Results : 132 patients with mean age 58.5±8.1 (range 35 to 80), a higher proportion of the patient's population were females 105 (79.5%), the body mass index was 28.8±1.37.

Comparing the results received on 6 months and 12-month follow-up visits to that recorded preoperative. significant improvement of OKS, WOMAC score, and VAS, this was seen when comparing the measures at 6 months postoperative to the preoperative,12 months postoperative to the preoperative, and 6 months postoperative to 12 months postoperatively, with significant improvement between each of the pairs (P= <0.001).

Correlation between both OKS and WOMAC score at 12 months postoperative and age, and BMI.

At the 12-month follow-up visit, patients who gave responses on a 4-point Likert scale, with overall patient satisfaction was 72.7% (96 patients); with a dissatisfaction rate of 27.3% (36 patients).

Conclusion: Despite being highly successful in relieving pain, TKA does not meet the expectations of all patients, especially those with demanding levels of knee activities. PROMs that measure functional outcomes should consider patients of different cultures and lifestyles.

INTRODUCTION

Total knee arthroplasty (TKA) has been one of the most successful surgical procedures over the last 50 years that reduce pain and improve the patient's quality of life. There have been reports of varying patient satisfaction levels, ranging from 80% to 90%. However, this level of satisfaction may drop to only 65% when specific types of activities performed with the knee in mid-flexion were evaluated.[1-4] Hence, implant design, limb alignment, and surgical techniques are in continuous development.

Patient-reported outcome measures (PROMs) offer a useful tool to assess the effectiveness of TKA in addition to the clinical and radiological evaluation.[5] Oxford Knee Score (OKS)[6], WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index)[7], and Knee Injury and Osteoarthritis Outcome Score for joint replacement (KOOS, JR)[8] are now widely used for predicting the outcome after TKA with preoperative pain and functional status, as measured by PROMs, and are used to predict pain and functional ability after TKA.

Interestingly, though patients with higher levels of preoperative pain and disability show the greatest improvements in PROM scores, they do not achieve as good postoperative scores comparable to patients with less preoperative pain and better baseline functions.[9,10]

Indeed, a variety of factors, even those unrelated to the surgery itself, influence patient satisfaction, making it a multifaceted problem. (type of surgery, type of anesthesia, operative time, complications, implant type, component alignment, soft tissue balance, and deformity correction), postoperative factors (postoperative care, improved range of motion, pain improvement, hospital experience, etc.) as well as patients' non-modifiable parameters.[11,12]

PROM is a valuable tool for the assessment of patients' satisfaction in relation to their daily activities. It is important

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to note that these activities vary in different societies and cultures. So, what may be suitable for a patient in a Western culture might not necessarily be satisfactory for the Asian and Middle Eastern populations. Female sex and related co-morbidities were the main preoperative variables that had a negative impact on patient satisfaction.[1,13]

PROMS reporting in the North African population was deficient[13,14] with a big differences between such population and Western patients regarding activity of daily living and their culture.

This prospective study looked at the clinical outcome and patient satisfaction following TKA in a North African society using different PROM and scores at one year post-operative.

MATERIALS AND METHODS

Study design

This is a prospective cohort study performed at an elective arthroplasty unit in Menoufia University Hospitals-EGYPT on 132 patients who received primary TKA from 1 May 2021 to 1 May 2022 with a minimum one-year follow-up. Written informed consent was obtained from each patient, and the Menoufia University Research Ethics Committee granted ethical approval. All methods were performed in accordance with the relevant guidelines and regulations.

All Patients received fixed bearing posterior stabilized knee TKA (PS Nex Gen Zimmer-Biomet) due to knee arthritis either primary or secondary to autoimmune disorder were included. All patients received cemented implants without patellar resurfacing aiming for neutral mechanical alignment. Having a stem to the tibial tray was not an exclusion criterion while using a constrained implant, metal augments, bone graft, or revision surgery were excluded. Patients with cognitive disorders, who missed follow-up or did not respond to their questionnaire were excluded from the study. 165 patients were operated on during the study inclusion period. Twenty-six patients were lost to follow-up, most of whom were from distant districts. Seven patients completed the follow-up period but did not respond to the PROMs questionnaire. A total of 132 patients were included in the final analysis.

Data collection

The following demographic data were collected: Age, sex, weight, height, body mass index (kg/m2), comorbidities, socioeconomic status, and occupation.

All patients received standard preoperative evaluation including medical assessment and informed consent (giving full details about the procedure and, a video demonstration that was prepared for the patients published on social media). Standard radiological evaluation of standing weight-bearing anteroposterior (AP), Lateral, and Patellofemoral (skyline) radiographs in addition to long leg standing radiographs from pelvis to ankle to assess limb alignment and degree of deformity.

Three scores were used for prospective evaluation. The Oxford Knee Score (OKS), The Western Ontario and McMaster Universities Osteoarthritis Index score (WOMAC), and the VAS (Visual Analogue Scale). During the follow-up visits, the participants were then asked to conduct their PROM (6 months and one year), and radiological and functional outcomes were recorded.

At 12-month patients were asked to report their overall satisfaction with their operation on a 4-point Likert scale with response categories consisting of very satisfied, somewhat satisfied, somewhat dissatisfied, and very dissatisfied.[15] Patients were specifically asked if they would recommend total knee replacement for one of their relatives if needed.

Surgical technique

All procedures were performed at a university hospital that provides free health services under the care of arthroplasty surgeons. The surgical interventions were performed by supervised trainees, consultants, and senior consultants.

Spinal anesthesia was used in all cases. Surgical interventions were performed with the use of pneumatic tourniquets through the medial parapatellar approach. Double skin preparation and draping using alcohol-based Povidine iodine 10% was applied.

Posterior stabilized Nex-Gen (Zimmer Biomet ®) implants were used in all patients aiming for neutral mechanical alignment. Pain control protocol using periarticular cocktail injection, NSAIDs was used. The postoperative protocol included early mobilization, chemical prophylaxis for venous thromboembolism (VTE) and antibiotic prophylaxis for 48 hours post-operative. After discharge, patients were scheduled for outpatient follow-up visits at 6 and 12 weeks, followed by assessments at 6 months and 1 year postoperatively.

Statistical analysis

IBM SPSS version 26 was used to gather, tabulate, and statistically analyze the data. Quantitative data were expressed as mean ($\bar{x}$) and standard deviation (SD), whilst qualitative data were expressed as number (No.) and percentage (%). Quantitative variables between two groups of regularly distributed data are compared using the Student's t-test (t), a test of significance; quantitative variables between two groups of non-normally distributed data are compared using the Mann-Whitney's test (U). The Wilcoxon test was used to compare different readings of non-normally distributed data in the same group. The Friedman test was used for the comparison of quantitative variables between more than two consecutive measures in the same group of not-normally distributed data with the LSD test as a post hoc test. Chi-square test ($\chi 2$) was used to study the association between qualitative variables. Pearson correlation was used to show the correlation between two continuous normally distributed variables. Significant variables in bivariate analysis were entered into the regression model. We adjusted for age, sex, BMI, and preoperative and postoperative VAS pain scores by adding these variables to the model. Statistical significance was set at a $p\text{-value} < 0.05$.

RESULTS

132 patients were included in this study with mean age 58.5±8.1(range 35 to 80), a higher proportion of the patient's population were females 105(79.5%) while males were 27 (20.5%). body mass index was 28.8±1.37(range 26-34). The surgical intervention was conducted by trainees in 66 patients, consultants in 40 patients, and senior consultants in 26 patients. A tourniquet was applied in all cases with a mean tourniquet time of 70 +/- 12 (average +/- SD). (Table I) During the 6-month and 12-month visits, a significant improvement in OKS, WOMAC score, and VAS showed significant improvement compared to the preoperative measures, the best records were reached at 12-month follow-up visits. (Table II)

Comparing the results obtained at 6-month and 12-month follow-up visits to that recorded preoperative. significant improvement of OKS, WOMAC score, and VAS, this was seen when comparing the measures at 6 months postoperative to the preoperative,[12] months postoperative to the preoperative, and 6 months postoperative to 12 months postoperative, with significant improvement between each of the pairs (p=<0.001). (Table III)

Significant Correlation between WOMAC score at 12 months postoperative and comorbidities such as DM and combined DM and HTN, while no association with gender and other comorbidities such as HTN and RA. Significant Association between OKS score at 12 months postoperative and comorbidities, while no association with gender. (Table IV, V) low BMI, controlled blood pressure, and low VAS at 6 and 12 months postoperative were significant predictors of higher Oxford knee score. High VAS for pain at 6 and 12 months postoperative were significant predictors of higher WOMAC scores.

Correlation between both OKS and WOMAC score at 12 months postoperative and age, and BMI.

At the 12-month follow-up visit, patients who gave a response on a 4-point Likert scale as very satisfied, or somewhat satisfied, were considered satisfied with overall patient satisfaction of 72.7% (96 patients); while patients who gave responses as somewhat dissatisfied or very dissatisfied were considered as dissatisfied with dissatisfaction rate 27.3% (36 patients).

Radiological evaluation of the operated knees showed satisfactory postoperative alignment within 3 degrees from the neutral mechanical axis with no outliers.

DISCUSSION

This study on Egyptian patients who received TKA for OA revealed an overall dissatisfaction rate of (27.3%). The detailed analysis of the data confirmed a significant improvement in their knee scores OKS from 8.09±3.23 to 31.6±5.86 (-9.979, P value <0.001) and WOMAC score from 80.11±6.05 to 32.98±12.2 (-9.973 p-value <0.001) (preoperative to postoperative at 12 months, respectively). However, 27.3% of the patients were dissatisfied to some extent.

Dissatisfaction is multifactorial.[12,16–19] Patient satisfaction is one of the most important outcome measurements after TKA.[1,20] Patient selection, preoperative preparation, surgical procedure, and postoperative rehabilitation protocols are key factors for successful knee arthroplasty and hence patient satisfaction. Pain relief and correcting deformity do not always guarantee patients' satisfaction.

A negative correlation has been drawn between the postoperative OKS and old age or high BMI. Hasegawa et al. analyzed 109 patients (130 osteoarthritic knees) who underwent primary TKA with navigation and reported that patient satisfaction after TKA correlated negatively with old age 20. However, Lange et al. found a higher satisfaction rate with TKA in older patients (91%) compared to the younger (86%).[21]

Matsuda et al. reported that older age and postoperative varus alignment were negatively correlated with patient satisfaction. Postoperative stiffness or limited ROM was also suggested as an important factor in postoperative patient dissatisfaction.[22]

Most of the patients experienced pain relief, better mobility, good alignment, and improved activities of daily living. At one-year postoperative follow-up, 27.3% of patients were not satisfied after their TKA, The Lower satisfaction rate compared to what was reported in the literature may be attributed to cultural issues as many of the daily activities in the eastern societies (squatting, kneeling, social life, religious activities and sitting on the ground) needs wide ROM and axial loading in flexion. Hence, patients can achieve significant improvement in the WOMAC score yet can still be dissatisfied with the overall outcome. This observation raises the point that scores that measured functional demand in Western culture may not be suitable to measure outcomes in Asian or Middle Eastern cultures.

The large variation in satisfaction rates (65–90%) could be a result of variations in the cultural setting and the way PROMs are implemented. Although PROMs have been translated and validated in Egypt, a recent assessment found limitations in measurement error reporting and response that could compromise dependability.[23] Saudi Arabia, on the other hand, has incorporated PROMs into its Vision 2030 plan in order to support patient-centered, standardized treatment.[24] Despite the scattered implementation of PROMs in various Asian nations, these efforts demonstrate regional development. Therefore, the results for Egyptian patients probably show both methodological shortcomings and regional strengths, highlighting the necessity of harmonizing PROMs in non-Western contexts.[25,26]

Scott et al. in their study have focused on the inability of TKA to meet patient high knee flexion activities such as kneeling and squatting, considering both the least fulfilled patient expectations together with the ability to return to paid work and sexual activity.[15,16] Also, some patients experienced a variable degree of pain at 12 months follow-up (3.39±1.27). Unfulfilled pain relief was the most crucial factor for patients who did not report being satisfied with their surgery at six weeks and one year.[17,18] Postoperative pain improves over time, and satisfaction also improves.[4,17,18]

Table I: Demographic data

Variable		Studied cases No.=132
Age (years):	Mean ±SD	58.5±8.1
	Range	35-80
Gender		
No. (%)	Female	105 (79.5%)
	Male	27 (20.5%)
BMI	(Mean ± SD)	28.79±1.37
	Range	26-34
Socioeconomic status	Low	17 (12.9)
	Middle	115 (87.1)
Surgeon	Less than 5 years post doctorate	66(50)
	5 years to 10 years	40(30.3)
	More than 10 years	26(19.7)
Diagnosis	OA	122(92.4%)
	RA	10(7.6%)
Comorbidities	DM	13(9.8)
	HTN	17(12.9)
	DM&HTN	11(8.3)
	COPD	2(1.5)

Table II: Repeated measures of preoperative, 6- and 12-months postoperative scores of WOMAC score, OKS, VAS

Variable		Preoperative	6 months postoperative	12 months postoperative	Test of sign#	p-value
WOMAC score	Mean ± SD.	80.11±6.05	47.9±10.44	32.98±12.2	262.015	<0.001**
	Range	70-92	30 – 72	15 – 62		
	Median (IQR)	79(75.3 -86)	47(40 – 54)	30(23 – 42)		
OKS	Mean ± SD.	8.09±3.23	24±5.11	31.6±5.86	262.015	<0.001**
	Range	2 – 17	12- 33	17 – 40		
	Median (IQR)	9(5 – 11)	24(21 – 28)	33(27 – 36)		
VAS	Mean ± SD.	8.36±0.7	5±1.13	3.39±1.27	259.107	<0.001**
	Range	7-10	3-8	2-7		
	Median (IQR)	5(8 – 9)	5(4-6)	3(2-4)		

#=Friedman Test
IQR=Interquartile range
**P value statistically highly significant

Table III: Paired differences in OKS and WOMAC score between preoperative, 6 months postoperative and 12 months postoperative

Variable		6 months postoperative-preoperative	12 months postoperative-preoperative	6 months postoperative-12 months postoperative
WOMAC score	Z	-9.972	-9.973	-9.912
	P value	<0.001**	<0.001**	<0.001**
OKS	Z	-9.976	-9.979	-9.909
	P value	<0.001**	<0.001**	<0.001**
VAS	Z	-10.052	-10.078	-9.924
	P value	<0.001**	<0.001**	<0.001**

**P value statistically highly significant

Table IV: Association between WOMAC score at 12 months postoperative and sex, and comorbidities

Variable		WOMAC score 12 m postoperative Median (IQR)	Test of sign. @	p-value
Gender	Female	30(18 - 43)	0.068	0.946
	Male	30(18 – 41)		
DM	Yes	42(27 -55)	2.297	0.017*
	NO	30(23 – 38)		
HTN	Yes	33(30 – 45)	1.717	0.086
	NO	30(23 – 42)		
Both DM&HTN	Yes	44(35 -57)	2.732	0.006*
	NO	30(23 – 38.5)		
RA	Yes	42(28.5 – 56)	1.933	0.053
	NO	30(23 – 40.25)		

@=Mann-Whitney Test
IQR=Interquartile range
*P value statistically significant

Table V: Association between OKS at 12 months postoperative and sex, and comorbidities

Variable		OKS—12 m postoperative Mean ± SD.	Test of sign. ^	p-value
Gender	Female	31.63±5.9	0.036	0.971
	Male	31.59±5.7		
DM	Yes	27±7	3.092	0.002*
	NO	32.12±5.52		
HTN	Yes	29.94±4.7	1.273	0.025*
	NO	31.87±5.99		
Both DM&HTN	Yes	27±6.27	2.803	0.006*
	NO	32.05±5.6		
RA	Yes	27.3±7.33	2.473	0.015*
	NO	31.98±5.6		

^= Student t Test IQR=Interquartile range
*P value statistically significant

For many patients, pain relief and improved mobility are sufficient for satisfaction 27. However, Deakin et al suggest that a preoperative focus on the pain relief and mobility advantages of TKA is most likely to give an accurate idea of what expectations may be fulfilled by surgery.

Preoperative counseling of the patients includes activities that they may not be able to engage in such as squatting and kneeling. the author thought that Dissatisfaction did not seem to be only a result of unrealistic expectations such as squatting and kneeling.[4] Dissatisfaction may be related to other symptoms unrelated to the replaced knee.[19]

Deakin et al show that TKA did not fulfill patients' expectations of kneeling, squatting, ability to return to paid work, and sexual activity, and these expectations should be better managed in the preoperative education process4.

Practical advice is crucial for treating patients with high flexion needs, which are typical in many non-Western contexts, in addition to the requirement for culturally appropriate PROMs. Using visual aids and examples that are culturally appropriate, preoperative counseling should evaluate lifestyle and functional expectations. It takes customized surgical planning, the right implant choice, and the optimization of modifiable risk factors including obesity and restricted preoperative movement to achieve deep flexion after surgery. By using these tactics, patient satisfaction can be raised and expectations can be more realistically met.

The high correlation with pain and function and satisfaction emphasizes the need to relate these as appropriate preoperative expectations.[16]

In this study, the presence of preoperative comorbidities like Diabetes, HTN, and RA negatively affected the postoperative PROMs (OKS, WOMAC) results.

Clement et al compared the PROMs preoperatively to those at 2 years post-surgery, the overall satisfaction was influenced by DM, depression, and back pain.[28]

A retrospective cohort of 2521 patients undergoing primary unilateral TKA was identified from an established regional arthroplasty database. Walker et al encountered those patients with lung disease, DM, gastric ulcer, kidney disease, liver disease, depression, and back pain, and those with poorer preoperative functional scores (WOMAC and SF12) to have significantly lower levels of satisfaction.[7]

Simon et al concluded that Finding the factors that affect survey completion can assist remove selection biases in PROMs, which are being utilized more and more as a quality measurement.[25]

Felix et al analyzed a prospective cohort study, 61% of the patients reported satisfactory outcomes; patients were satisfied with the results if postoperative WOMAC was ≥82.49. Patients with high absolute preoperative PROM scores were more likely to remain dissatisfied.[29] According to Jain et al (prospective multicenter study), greater patient expectations anticipate greater PROMs, but not satisfaction, in TKA patients.[16]

First, the study was limited by a small sample size and a relatively short follow-up period. Additionally, the narrow inclusion criteria and broad exclusion of patient samples may limit generalizability. Participation in the PROMs was also potentially influenced by external factors such as literacy, language barriers, and the fact that some patients had traveled from distant regions for their surgery 30. On the other hand, the study's strengths include its prospective design, the use of three different assessment scores, and a study population representative of an Eastern cultural background. One year follow-up is the standard point of best functional outcome and a common point of outcome reporting, so in terms of satisfaction, one year is an appropriate point 31.we believe that longer follow up period and a bigger sample size will makes the interpretation of data more confident , we will try to avoid these confounding issues in the future studies , considering multi centric studies with long term follow up period. Also, a more qualitative based PROMs will be considered in future research for better understanding and interpretation of the outcome.

CONCLUSION

Despite being highly successful in relieving pain, TKA does not meet the expectations of all patients, especially those

with demanding levels of knee activities. PROMs that measure functional outcomes should consider patients of different cultures and lifestyles. The older group of patients, those with high BMI and different comorbidities, should be counseled carefully in regard to the postoperative outcome. Recent philosophies in phenotypic knee joint inclination as well as development in prosthetic designs could improve patients' satisfaction but this remains to be seen.

Ethics approval

The study was conducted after the approval of the institutional review board of Menoufia university-faculty of medicine

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A survey study of vaccine hesitancy among children to COVID-19 vaccination and the roles of parental and social media influence

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ABSTRACT

Introduction: The COVID-19 pandemic brought unprecedented shifts in public health measures, including accelerated mass vaccination programmes. Although most children with COVID-19 are asymptomatic or have mild disease, they may act as reservoirs for SARS-CoV-2 transmission. Furthermore, multisystem inflammatory syndrome in children (MIS-C) can cause serious complications. COVID-19 vaccines became available in 2022 for Malaysian children aged 5–18, sparking public discussions on safety and necessity, which may have contributed to modest uptake in younger children. As most vaccine hesitancy studies focus on adults, our study aimed to assess hesitancy among children aged 10–17 and explore parental and social media influences on minors' assent to vaccination.

Materials and Methods: This study was conducted in the outpatient clinic of a tertiary and academic children's specialist hospital. A total of 200 parent-child pairs participated in a survey using an adapted and translated questionnaire in the Malay language, comprising 35-items divided into three sections with the attendance of a trained interviewer. Vaccine hesitancy was assessed using a 5-point Likert scale adapted from the Oxford COVID-19 Vaccine Hesitancy Scale.

Results: The parent-participants were predominantly mothers (81%) and child-participants were equally distributed between primary and secondary schoolers. Vaccine hesitancy rates were 50% and 46% among parents and children, respectively. The overall vaccine hesitancy score was graded as moderate (mean score, 2.44; SD 0.43) among the children. Parents who were unemployed or homemakers were significantly associated with vaccine hesitancy in the child when compared with those on fulltime jobs (69.4% versus 30.6%, p=0.010). Parental history of COVID-19 was significantly associated with vaccine hesitancy (p=0.025), whereas parental hesitancy to vaccinate their child was associated with increased child vaccine hesitancy (p=0.004). Primary school than secondary school children were more likely to be vaccine hesitant (56% versus 36%, p=0.005). Vaccine hesitancy was negatively associated with the child's full-vaccination status (p=0.021). More than half of the children surveyed spent at least 6 hours daily on their smart devices, with one-third spending at least three hours on social media. However, their preferred choice of media platforms to seek Covid-19 information, was television (20.5%), followed by social media (17%) and printed media (11.5%). Of note, children in the non-vaccine hesitant group preferred COVID-19 information accessed from television and printed media (t=2.755, p=0.006 and t=2.539, p=0.011, respectively).

Conclusion: This study demonstrates that vaccine hesitancy in children negatively impacted the uptake of COVID-19 vaccine. Parental hesitancy significantly influences the child's hesitancy to vaccination. Health promotion programmes on vaccination may need to be intensified to the more at-risk for vaccine hesitancy among parents who are unemployed or homemakers and primary school children. Addressing vaccine hesitancy incorporating the child's agency in this respect for assent to vaccination may be a positive strategy in enhancing its uptake. While social media is undeniably an important channel, traditional media such as television remains an established and trusted option for dissemination of health policies and recommendations.

KEYWORDS:
Assent, COVID-19, Vaccination, Vaccine hesitancy, Parental consent, SARS-CoV-2, Social media

INTRODUCTION

COVID-19 first emerged in Wuhan, China in December 2019 and rapidly became a global pandemic within months of its emergence. In Malaysia, the Ministry of Health's Crisis Preparedness and Response Centre reported that 15.3% of total COVID-19 cases occurred in children.[1] By August 30, 2021, 310,074 children had contracted COVID-19, resulting in 41 deaths. Although children infected with COVID-19 are often asymptomatic and have a lower risk of death, they may suffer from morbidities such as, fear of isolation, depression, social stigma, and long-term cognitive and health issues.[2,3] Additionally, multi system inflammatory syndrome in children (MIS-C), is a serious and potentially life-threatening complication of the virus.[3] As an immediate control strategy, vaccines against Covid-19 underwent accelerated development, clinical trials and regulatory approval with

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eventual implementation of mass vaccination programmes globally. First indicated for adults aged 18 and above, the COVID-19 vaccine was subsequently approved for use in teenagers aged 12 years and older, followed by children aged 5-11 years by late 2021. The College of Paediatrics, Academy of Medicine of Malaysia also endorsed and published a position statement to recommend vaccination against COVID-19 for children, 5 years old and above, in 2022.[4] Administration of the vaccine to children in Malaysia via the National COVID-19 Immunisation Programme for Children (PICKids) initiative commenced in September, 2021 for teenagers aged 12 years and older, and in February, 2022 for children aged 5 to 11 years.[5] By January 2024, the majority (90.8%) of teenagers have received 2 doses of the vaccine, compared to less than half (43.3%) of children aged 5-11 years who have received 2 doses of the vaccine.[1] The lower uptake in younger children may be the result of hesitancy from parental concerns with regards to vaccine safety profile and side effects balanced against the benefits for children who were deemed to experience much milder forms of COVID-19. Many adults have also expressed hesitancy toward COVID-19 vaccination, particularly concerning the use of newer mRNA technology.[6]

"Vaccine hesitancy" as proposed by the Strategic Advisory Group of Experts on Immunization (SAGE), defines it as, delay in the acceptance or refusal of vaccination despite the availability of vaccination services.[7] Despite significant efforts in developing and implementing Covid-19 public health policies, vaccine hesitancy towards approved COVID-19 vaccines continue to be a major barrier, especially for children.[8] Inaccurate and conflicting information available to the public, especially on social media, parental mistrust could be factors that may impede the success of future paediatric vaccination programmes.[9] Studying the COVID-19 vaccination program uptake in children may provide an understanding of the multiple factors contributing to vaccine hesitancy. Addressing these factors appropriately may assist in strategizing effective vaccination programmes in the future.

It has been suggested that the trust in COVID-19 vaccination can be built through timely and clearly disseminated messages on social platforms advocating the safety and efficacy of the vaccines.[10] In this regard, social media reportedly contributes to at least 35% of the decision to get vaccinated.[11] The risk-benefit evaluation on COVID-19 vaccines such as perceived risks, side effects, anti-vaccination reports from information shared through various sources including social media to the public are associated with an individual's vaccine hesitancy.[12,13] Vaccine hesitancy may also be highly influenced by behavioural and attitudinal factors.[14] A systematic review reported that Malaysia has one of the highest acceptance rates, globally, of COVID-19 vaccination among adults (94.3%).[10] For minors, studies have primarily focused on parental consent or hesitancy to vaccinate their children. The hesitancy rates ranged from 12.6% to 33%.[11,15] However, studies looking at vaccine hesitancy and the children assent to vaccination in the context of parental opinions are lacking. We conducted this survey in the hope to gather valuable insights into how children independently perceive vaccines in the era of COVID-19, evaluate children's agency in appropriate decision making and the extent in accessing social media for informed choices.

MATERIALS AND METHODS

Study design, sampling and conduct

This was a descriptive cross-sectional survey-based study conducted at the outpatient clinic of the Universiti Kebangsaan Malaysia (UKM) Specialist Children's Hospital, Kuala Lumpur. The sample size was calculated using the formula proposed by Daniel.[16] The formula, , accounts for the desired confidence level (Z), estimated population proportion (P), and margin of error (d). For this study, a 95% confidence level was applied, along with an estimated vaccination hesitancy prevalence of 50% to maximize variability, and a 7% margin of error. This resulted in a final sample size of 200 participants. Each study participant comprised a child paired with one parent, who provided consent and served as the primary decision-maker. Children who were 10 to 17 years old were recruited. Parents and children must be able to converse, respond, and read in the Malay language.

This study was approved by the Research Ethics Committee of UKM (RECUKM) (Reference: JEP-2021-824). Potential participants were approached in the outpatient clinic and with the parental informed written consent obtained, each participant pair was given a QR code linking to a Google Form based questionnaire to be completed. The survey was completed in the presence of a trained investigator who was available to assist in clarifying any uncertainties. Overall, each participant pair took 10 – 15 minutes to complete the survey.

Development and validation of the study instrument

The study data was collected using a newly developed and validated questionnaire, adapted from the SOMEHAVE study, a survey aimed to assess the influence of social media on COVID-19 vaccine hesitancy among parents in Singapore and Malaysia for their children.[17] This survey questionnaire, originally in English, was translated into the Malay language by a native Malay-speaking study supervisor and medical officers to ensure clarity, cultural and linguistic relevance for the majority who are Malay children in this targeted study population. Additionally, a special section specific for children was adapted and translated using the Oxford COVID-19 Vaccine Hesitancy Scale.[18] This Malay-language based questionnaire is referred to in this study as the "Modified Oxford COVID-19 Vaccine Hesitancy Scale", which is unpublished but copyrighted.[19]

Following the translation, a cognitive debriefing was conducted with six parents and their children to identify potential misunderstandings or ambiguities in the translated questionnaire. Feedback on wording, comprehension, cultural nuances, sentence structure, word choice, and grammar were gathered, and the questionnaire was revised accordingly. After this refinement, the revised questionnaire underwent pilot testing with a larger sample of 20 patients to assess its practical application. To ensure the reliability of the questionnaire, internal consistency was evaluated using Cronbach's alpha. The overall reliability coefficient was 0.52,

indicating a moderate level of internal consistency. Specifically, Section A had a Cronbach's alpha of 0.56, Section B scored 0.60, and Section C scored 0.75. The lower score in Section A was attributed to the different response options for demographic-related questions.

Further adjustments were made to enhance sentence structure, word choice, and overall grammatical accuracy, before the final version of the questionnaire was produced (Supplement 1). This questionnaire comprises of 35 questions that are divided into three sections.

Section A: Parental demographics, COVID-19 history, vaccination history, and hesitancy towards vaccinating their children.

Section B: Child demographics, COVID-19 history, vaccination history, smart device and social media use, sources of COVID-19-related information accessed, and knowledge gained.

Section C: The Modified Oxford Covid-19 Vaccine Hesitancy Scale.[19]

Section A and Sections B and C were to be completed by the parent and the child, respectively.

The independent variables in this study include the socio-demographic data of the parent and child pair, COVID-19 vaccination and infection history, and the use of smart devices, social media, and traditional media. Items were assessed using multiple-choice or yes/no response options. The frequency and preferred sources accessed to obtain COVID-19 information reported by children, and parental attitudes towards vaccination were captured. These items were measured using a 5-point Likert scale, where higher scores reflected greater frequency, preference, and more positive attitudes.

The dependent variable pertained to COVID-19 vaccination hesitancy in the child, which was assessed using the Modified Oxford COVID-19 Vaccine Hesitancy Scale.[19] This is a 7-item adapted questionnaire, whereby a survey participant could score from a minimum of 7 to a maximum of 35 points with a higher score indicating greater hesitancy. A mean score was then calculated from the cumulative scores obtained from the seven items, and the mean scores were categorized into one of the three grades of vaccine hesitancy: low (1–2.33), moderate (2.34–3.66), or high (3.67–5.00). The moderate and high grades are considered as vaccine hesitant in this study.

Statistical analysis

Data analysis was performed using IBM SPSS version 26. Continuous data were presented as mean and standard deviation. Due to small number of participants with high scores, both moderate and high scores were combined to form one group of vaccine hesitant, to be balanced for comparison against the low scores, non-hesitant group. Chi-square analysis was performed to assess the differences between these two groups against the independent variables. Linear logistic regression and Pearson correlation analysis were used to assess the strength and direction of the association between independent variables and vaccine hesitancy.

RESULTS

The parents who participated in this survey were predominantly mothers (81%). Almost half (42%) had a minimum education at the college/matriculation/pre-university/diploma level, and are from the middle-income category (41.5%). Approximately 50% of the parents worked in the health, education and science fields. A small proportion (5%) had overseas education or work experience. The children participants showed slightly more males (56.5%) than females (43.5%), but equally distributed between primary and secondary schools (Table I).

Figure 1 shows the distribution of mean vaccine hesitancy scores among the children. The overall mean score for the group was 2.44 (SD 0.43), indicating moderate hesitancy. However, this score is likely skewed by one child participant with an overall score of 3.86. The participant was a 13-year old male participant who was unvaccinated because of the fear of side effects, and has had a history of asymptomatic Covid-19 infection. Of note, his mother, who also participated in the survey showed similar characteristics and she was hesitant to vaccinate this child.

Several parental and child factors were associated with vaccine hesitancy in children. Children of unemployed parents were significantly associated with vaccine hesitancy. Conversely, children of parents who had overseas education/work experience were significantly associated with non-vaccine hesitant. Primary school than secondary school children were more likely to be vaccine hesitant (Table IIa).

Our study population showed high rates of 96.5% in adults and 93.5% in children who received complete COVID-19 vaccination. The small proportion of unvaccinated adults cited “medical reasons” (57.1%) and “the lack of interest” (28.6%) as the two most common justification. The reasons for non-vaccination in children were mainly because of the fear of side effects (30.7%), a pre-existing medical condition (23.21%) and non-consenting parents (23.1%). Despite a high uptake in vaccination, more than one-third (35.5%) of the parent participants had breakthrough COVID-19 infections with two- third reported being symptomatic. Slightly fewer children (29.5%) contracted COVID-19 infections and approximately half (42.4%) were asymptomatic. (Table IIa).

There were significantly more children who were vaccine hesitant among those who were unvaccinated against COVID-19. Notably, parental hesitancy to vaccinate their child was significantly associated with increased vaccine hesitancy in children. Half of the parents surveyed in this study reportedly were hesitant to vaccinate their children at some stage. Child and parental history of COVID-19 infection and parental vaccination status did not have a statistically significant association with vaccine hesitancy in children (Table IIa).

Looking at each of the 7 items in the Oxford COVID-19 Vaccine Hesitancy Scale, all but one showed average scores of low-grade hesitancies in a population of almost exclusively and fully vaccinated children (187/200) (Table IIb). There were only 10 children (5%) who were not vaccinated. Of all the seven items in the hesitancy scale, six items were

Table I: Demographic data of 200 pairs of child-parent study participants

Variables	
Parent (n=200)	
Gender	N (%)
Male (father)	38(19.0)
Female (mother)	162(81.0)
Education level	
Primary school	9(4.5)
secondary school	63(31.5)
college/ matriculation/A-level/diploma	84(42.0)
Degree	32(16.0)
Master and above	12(6.0)
Occupation	
Health	18(9.0)
Finance	22(11.0)
Service	32(16.0)
Education	25(12.5)
Self-employed	18(9.0)
Unemployed/ housewife/ retired	36(18.0)
Others (Manufacturing, energy, science, IT, transport)	49 (29.5)
Been working or studying overseas	
No	189(94.5)
Yes	11(5.5)
Monthly household income (RM)	
B40	73(36.5)
M40	83(41.5)
T20	44(22.0)
Marital Status	
Married	188(94.0)
Divorced/ widowed	12(6.0)
Child (n=200)	
Gender	
Male	113(56.5)
Female	87(43.5)
Age (years)	
Primary school (10 -12 years old)	100 (50.0)
Secondary school (13 – 17 years old)	100 (50.0)

statistically significant and positively correlated with a non-vaccinated status. Only the likelihood to refuse COVID-19 vaccination showed a non-significant correlation (Table IIb).

Almost all (93%) children own a smart device. More than half (57.5%) of the children spent at least 6 hours per day on their smart devices, with one-third spending at least three hours on social media. In comparison, only one-third of child participants spent at least 6 hours per day watching television. (Table III). With regards to news about COVID-19 encountered when the child had access on social media platforms, majority reported when they were on YouTube (40.5%), followed by TikTok (39.5%), Facebook (26.5%) and Instagram (21%). Specifically, the children maintained that their preferred choice of media platforms if they were to seek Covid-19 information, were television (20.5%) followed by social media (17%) and lastly printed media (11.5%). There was however, no association between vaccine hesitancy and the different social media platforms accessed. Interestingly, children in the non-vaccine hesitant group preferred printed media and television to access COVID-19 information; t=2.539, p=0.011 and t=2.755, p=0.006 respectively.

In exploring the independent factors for vaccine hesitancy, multivariate analysis showed parental COVID-19 infection was directly associated with vaccine hesitancy among children (Table IV). Of note, parental hesitancy to vaccinate their child was inversely associated with the child's vaccine hesitancy. Partners (80%, fathers) of the parent participants who did not consent to vaccinate their child were directly associated with vaccine hesitancy in the children (Table IV). As for child factors, those who were vaccinated were inversely associated with vaccine hesitancy. Frequently obtaining COVID-19 information on television was also inversely associated with vaccine hesitancy (Table IV).

DISCUSSION

Vaccine hesitancy is a recognised factor that impedes success in the uptake of vaccine preventable diseases. During an epidemic, this could have a significant impact on the control of the spread of diseases and the burden to healthcare services in managing related increases in morbidity and mortality. This study reports results of a survey exploring vaccine hesitancy among children, specifically, and how it relates to their assent to COVID-19 vaccination. In conducting the survey, a valid and reliable instrument to assess COVID-19 vaccine hesitancy among children in the Malaysian context was first developed. It is hoped that this reliable questionnaire can be used for future studies related to childhood vaccination programmes in this country.

Table IIa: Parent-child demographic factors, parental COVID-19 vaccination status, infection history, parental hesitancy to vaccinate, and vaccine hesitancy among Malaysian children aged 10 -17 years

Variables	Vaccine Hesitancy			
	N (%) n = 108 (54.0%)	Non-hesitant n = 92 (46.0%)	Hesitant (p-value)	χ^2
Parent participant				
Father	38(19.0)	20(53.6)	18(47.4)	0.035 (0.851)
Mother	162(81.0)	88(54.3)	74(45.7)	
Education level				
Primary school	9(4.5)	4(44.4)	5(55.6)	4.429 (0.351)
Secondary school	63(31.5)	28(44.4)	35(55.6)	
College/ matriculation/A-level/diploma	84(42.0)	49(58.3)	35(41.7)	
Degree	32(16.0)	19(58.3)	13(40.6)	
Masters and above	12(6.0)	8(66.7)	4(33.3)	
Occupation				
Health	18(9.0)	15(83.3)	3(16.7)	23.303 (0.010)*
Finance	22(11.0)	10(45.5)	12(54.5)	
Service	32(16.0)	20(62.5)	12(37.5)	
Education	25(12.5)	13(52.0)	12(48.0)	
Self-employed	18(9.0)	10(55.6)	8(44.4)	
Unemployed/ housewife/ retired		36(18.0)	11(30.6)	25(69.4)
Others (Manufacturing, energy, science, IT, transport)	49(29.5)	29 (59.0)	20 (41.0)	
Had overseas work or study experience				
No	189(94.5)	98(51.9)	91(48.1)	6.384 (0.012)*
Yes	11(5.5)	10(90.9)	1(9.1)	
Household income categories				
B40	73(36.5)	36(49.3)	37(50.7)	3.318 (0.190)
M40	83(41.5)	43(51.8)	40(48.2)	
T20	44(22.0)	29(65.9)	15(34.1)	
Marital Status				
Married	188(94.0)	102(54.3)	86(45.7)	0.082 (0.774)
Divorced/ widowed	12(6.0)	6(50.0)	6(50.0)	
Child participant				
Gender				
Male	113(56.5)	66(58.4)	47(41.6)	2.031 (0.154)
Female	87(43.5)	42(48.3)	45(51.7)	
School level				
Primary school	100 (50.0)	44(44.0)	56(56.0)	8.052 (0.005)*
Secondary school	100 (50.0)	64(64.0)	36(36.0)	
Vaccination status and Covid-19 infection history				
Parent				
Not vaccinated	7(3.5)	3(42.9)	4(57.1)	0.3626 (0.547)
Fully vaccinated	193(96.5)	105(54.4)	88(45.6)	
Parental COVID-19 infection				
No	129(64.5)	70(54.3)	59(45.7)	0.010 (0.920)
Yes	71(35.5)	38(53.5)	33(46.5)	
Child				
Not vaccinated	13(6.5)	3(23.0)	10(76.9)	5.352 (0.020)*
Fully vaccinated	187(93.5)	105(56.1)	82(43.9)	
Child Covid-19 infection				
No	141(70.5)	76(53.9)	65(46.1)	0.002 (0.965)
Yes	59(29.5)	32(54.2)	27(45.8)	
Parental hesitance to vaccinate child(ren) for COVID-19				
Not hesitant	100 (50.0)	71 (71.0)	29 (29.0)	23.28 (<0.001)*
Slightly hesitant	86 (43.0)	32 (37.2)s	54 (62.8)	
Very hesitant	14 (7.0)	5 (35.7)	9 (64.3)	
Give consent for child(ren) to be vaccinated				
No	18 (9.0)	6 (33.3)	12 (66.7)	3.401 (0.065)
Yes	182 (91.0)	102 (56.0)	80 (44.0)	
Partner give consent for child(ren) to be vaccinated				
No	22 (11.0)	8 (36.4)	14 (63.6)	3.095 (0.079)
Yes	178 (89.0)	100 (56.2)	78 (43.8)	

Table IIb: Modified Oxford Covid-19 Vaccine Hesitancy Scores for each item and their correlations with children's non-vaccinated status

Modified Oxford Covid-19 Vaccine Hesitancy Scale[19]	Mean (SD)	Pearson correlation
Total score	2.44 (0.43)	1
Hesitant about taking the COVID-19 vaccine, even though it has been approved for use in Malaysia	2.22 (1.01)	0.476
Unsure or unwilling to get the COVID-19 vaccination	2.16 (0.83)	0.755
Consider taking the COVID-19 vaccine to be of low importance	2.19 (0.83)	0.744
No encouragement or positive opinions if friends are considering getting the COVID-19 vaccine	2.28 (0.80)	0.766
Uncertain about following my parents' decision regarding COVID-19 vaccination	2.21 (1.03)	0.685
Likely to refuse the COVID-19 vaccination	3.44 (0.99)	0.075
Hesitant or unlikely to request the COVID-19 vaccination	2.25 (0.93)	0.728

Table III: Daily usage of various media sources by children

Variables	Vaccine Hesitancy			
	N (%)	Non-hesitant n = 108 (54.0%)	Hesitant n = 92 (46.0%)	χ^2 statistics (p-value)
Usage of smart device				
Parent				
No	3(1.5)	0	3(100.0)	3.575 (0.059)
Yes	197 (98.5)	108 (54.8)	89 (45.2)	
Child				
Usage of smart device				
No	14 (7.0)	10(71.4)	4(28.6)	1.841 (0.175)
Yes	186 (93.0)	98(52.7)	88(47.3)	
Hours of smart device use (per day)				
< 6	85 (42.5)	44 (51.8)	41 (48.2)	0.301 (0.860)
6 - 12	95 (47.5)	53 (55.8)	42 (44.2)	
> 12	20 (10.0)	11 (55.0)	9 (45.0)	
Duration spent by children on social media when with a smart device				
Low (less than half the time)	127 (63.5)	67 (52.8)	60 (47.2)	0.217 (0.641)
High (more than half the time)	73 (36.5)	41 (56.2)	32(43.8)	
Hours spent watching television (per day)				
< 6	135 (67.5)	75 (55.6)	60 (44.4)	0.931 (0.700)
6 - 12	57 (28.5)	28 (49.1)	29 (50.9)	
> 12	8 (4.0)	5 (62.5)	3 (37.5)	

Table IV: Univariate and Multivariate Linear regression of determinants associated with vaccine hesitancy among Malaysian school children aged 10-17 years

Variables	Simple Linear Regression analysis			Multiple Linear Regression analysis		
	Crude β	95% CI	p-value	Adjusted β	95% CI	p-value
Parents						
Occupation	0.175	0.004,0.036	0.013*	0.078	-0.006, 0.024	0.248
Household income	-0.181	-0.184,				
-0.025	0.010*	-0.078	-0.022, 0.008	0.256		
COVID-19 infection	0.159	0.018,0.269	0.025*	0.148	0.017, 0.252	0.025*
Smart device usage	-0.160	-1.066, -0.078	0.023*	-0.114	-0.891, 0.080	0.101
Hesitant to vaccinate child(ren) for COVID-19	-0.326	-0.320, -0.135	<0.001*	-0.211	-0.249, -0.046	0.004*
Give consent for child(ren) to be vaccinated	-0.270	-0.615, -0.205	<0.001*	-0.153	-0.472, 0.009	0.059
Partner gives consent for child(ren) to be vaccinated	-0.151	-0.402, -0.018	0.032*	0.175	0.015, 0.472	0.037*
Children						
Age (years)	-0.153	-0.253, -0.013	0.030*	-0.074	-0.175. 0.047	0.256
Vaccination status	-0.259	-0.381, -0.120	<0.001*	-0.176	-0.303, -0.037	0.013*
COVID-19 information Intensity: newspaper and printed materials	-0.196	-0.158, -0.028	0.005*	-0.066	-0.098. 0.035	0.357
COVID-19 information Intensity: television	-0.245	-0.154, -0.044	<0.001*	-0.173	-0.129. -0.011	0.020*

Our study found almost half of the child participants between ages of 10 and 17 years were vaccine hesitant. This is 5-10 times higher compared to the vaccine hesitancy rates reported among Malaysian parents by Lee et al. (11.6%) and Wong et al. (5.7%).[3,20] A comparison study between Malaysian and Singaporean parents showed similar rates of 16.4% and 5.8%, respectively.[17] It is speculated that hesitancy rates may be low depending on the perception and trust in governmental channelled publicity and mandatory vaccination policies enforced. Nevertheless, vaccine hesitancy was high in certain populations, such as in Hong Kong, with the highest rates in Asia at 60%.[10] It is conceivable that children who may be lacking in understanding and exposure to such policies, mandates and recommendations, could result in the higher vaccine hesitancy rate.

Our study also found that a history of parental COVID-19 infection increases vaccine hesitancy among children. Doubts over the efficacy of the vaccine itself, especially in situations of breakthrough infections may contribute to developing vaccine hesitancy. Witnessing the disease manifestation in their parents despite having been vaccinated, potentially compromise further their conviction of the benefit and need for vaccination. Previous research supports this finding too, whereby parents with a history of COVID-19 infection are more likely to be hesitant about vaccination, and this hesitation may also influence similar perception in their children. Others reported that a history of COVID-19 infection may lead to greater vaccine hesitancy as parents began to develop an inclination towards the sufficiency of natural immunity.[21-23]

Interestingly, our study found that parental hesitancy to vaccinate their child was inversely associated with vaccine hesitancy in the child. Parental vaccine acceptance may thus be the opposite in the child. Parental consent for a child to be vaccinated is best met with the assent from the child. Engaging children in the discussion of an intervention could tailor better to meet their own expectations and this may result in more effective outcomes in the long run. It also fosters a sense of agency in their own health decision making. Children are able to process information from trusted sources, personal experiences, household influences, and peer interactions, which allows them to develop consistent views on vaccine acceptance or hesitancy.[24-26] Importantly, children can influence the decisions of those around them, including their parents, making their involvement crucial in discussions. To that effect, children might become even more informed and less hesitant despite their parents' opposing views.[24,25] It is imperative to cultivate and promote a positive perspective in a child towards assenting to a medical procedure or health intervention. It is suggested that children aged at least 9 years should be involved in this process.[27] Our survey of 200 children of 10 years old and above showed it was possible and reliable to engage children for their opinions and assent to vaccination. Moreover, our study showed that children who were vaccinated were those who were non-hesitant. Our research provides unique insights into vaccine hesitancy from the perspective of children themselves, demonstrating that they are capable of forming informed, reliable opinions about vaccines. Their input could offer valuable insights for designing effective communication strategies and policies in preventive health education targeting to specific age groups while promoting and respecting children's agency in decision making. Positive prior vaccination experiences in parents—mild side effects in a supportive vaccination environment—can shape children's attitudes towards future vaccines and strengthen their trust in the healthcare system.[28]

Our study also revealed an interesting observation of children who preferred obtaining COVID-19 information from television and printed media was inversely associated with vaccine hesitancy. Whether this reflects on the maturity of the child in discerning that official news portals are trusted sources of verified information on vaccination will need to be confirmed in future studies. Conversely, children may be exposed to misinformation on social media, which has been shown to negatively influence vaccine attitudes.[13,29] Instead publicly-run, government regulated television stations has been reported as a source that provides consistent and credible information, which can counteract vaccine hesitancy effectively.[30,31] Even so, almost all the child participants in this survey who actually owned a smart device and the overwhelmingly more time spent preferentially on social media, should justify the need to leverage on this platform as a way to reach out to children on health promotion programmes such as vaccination.

This study has several limitations of which, the cross-sectional design limits our ability to establish any causal relationships and the temporal relationship between vaccination uptake, COVID-19 infections and vaccine hesitancy. Additionally, the purposive cluster sampling of study participants in a single-centre at a tertiary-level and academic specialist children's hospital may introduce selection bias, and restrict the generalizability of the results to the broader Malaysian population. A larger, more diverse sample size including normal healthy school children, for example, may be necessary to address factors associated with vaccine hesitancy among children. A comparative prospective study of vaccine hesitancy, assent to vaccination, parental consent and the actual vaccination uptake would be an important area for research in the future. A mixed-method study design incorporating qualitative research questions could identify additional factors that may lead to vaccine hesitancy.

CONCLUSION

In surveying children's assent to COVID-19 vaccination, we identified three significant factors that were associated with increased vaccine hesitancy: parental COVID-19 infection; parental hesitancy to vaccinate their child; parental partners, mainly fathers who did not consent to vaccination, and two factors were negatively associated with vaccine hesitancy: vaccinated status of the child and, preferred COVID-19 information from television source. These findings may be applicable for health policymakers to consider and in particular to incorporate assent from minor when developing health promotion programmes to bolster vaccination acceptance.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest in the conduct and completion of this study.

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ORIGINAL ARTICLE

Prevalence and associated factors of meibomian gland dysfunction and dry eye disease among subjects presenting for transepithelial photorefractive keratectomy

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ABSTRACT

Introduction: Transepithelial Photorefractive Keratectomy (Trans-PRK) is a modern refractive surgery that improves comfort and recovery but may predispose to meibomian gland dysfunction (MGD) and dry eye disease (DED), causing postoperative discomfort. Preoperative assessment of meibomian glands among Trans-PRK candidates remain limited. This study aimed to determine the prevalence of MGD and DED, identify associated factors, and assess the correlation of meibomian gland loss (MGL) among subjects undergoing Trans-PRK at Hospital Pakar Universiti Sains Malaysia.

Materials and Methods: A descriptive cross-sectional study was conducted from January 2024 to January 2025 among 110 subjects aged 20–45 years undergoing preoperative Trans-PRK evaluation. Demographic, occupational, and lifestyle data were collected, while ocular surface parameters were assessed through clinical examination, meibography, and standardized questionnaires. MGD and DED were diagnosed based on established criteria. Statistical analyses were performed using SPSS version 29.0.

Results: The prevalence of MGD and DED was 17.3% and 19.1%, respectively, with a mean age of 32.76 ± 7.65 years. Screen exposure exceeding four hours daily was significantly associated with MGD (OR = 9.05, 95% CI: 2.14–38.28, p = 0.003) and DED (OR = 8.12, 95% CI: 2.16–30.54, p < 0.001). Increasing age increased the odds of MGD (OR = 3.65, 95% CI: 1.15–11.51, p = 0.027), while male gender was a significant risk factor for both. MGL correlated moderately with OSDI (r = 0.58) and meibum quality (r = 0.46), and weakly with meibum expressibility (r = 0.35) and corneal fluorescein staining (r = 0.36). Common gland changes were dropout (29.1%), tortuosity (25.5%), and shortening (20.9%).

Conclusion: MGD and DED were observed in 17.3% and 19.1% of Trans-PRK candidates. Age, male gender, and screen exposure were associated with MGD, while male gender and screen exposure were associated with DED. MGL correlated with key ocular surface indices, highlighting the importance of comprehensive preoperative ocular surface assessment.

KEYWORDS:
Meibomian gland dysfunction, transepithelial photorefractive keratectomy, dry eye diseases, meibomian glands, tear film, ocular surface

INTRODUCTION

Laser corneal refractive surgery, particularly Transepithelial Photorefractive Keratectomy (Trans-PRK), has gained popularity for its safety and efficacy in correcting refractive errors.[1] Unlike conventional PRK, Trans-PRK ablates both the corneal epithelium and stroma in a single step using an excimer laser, potentially reducing discomfort and promoting faster recovery.[2,3] Despite its advantages, Trans-PRK may induce ocular surface changes that disrupt corneal innervation and meibomian gland function. These changes can lead to meibomian gland dysfunction (MGD) and dry eye disease (DED), both of which impact postoperative comfort and visual outcomes.[4–10]

Several studies have emphasized the significance of preoperative ocular surface health, particularly the condition of the meibomian glands, in predicting postoperative dry eye symptoms, dry eye severity and tear film stability. Recognizing and addressing these pre-existing conditions is essential for optimizing surgical outcomes and minimizing postoperative complications.[1,4,5,11]

Prevalence of MGD and DED in subjects undergoing Trans-PRK remain scarce although Trans-PRK is increasingly used. This study aims to determine the prevalence of MGD and DED among Trans-PRK candidates, identify associated risk factors and examine the correlation between MGL and ocular surface parameters. The findings may support the development of targeted preoperative screening strategies to optimize refractive surgery outcomes.

MATERIALS AND METHODS

Study design and study population

A descriptive cross-sectional study was conducted at the Laser Refractive Service, Hospital Pakar Universiti Sains Malaysia (HPUSM), from January 2024 to January 2025. This study was approved by the Human Research Ethics Committee of

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Universiti Sains Malaysia (JEPeM Code: USM/JEPeM/KK/23080628) and was carried out in accordance with the principles of the Declaration of Helsinki.

Participants were screened based on specific inclusion and exclusion criteria. A total of 110 participants presenting for Trans-PRK, aged 20 to 45 years were recruited. Exclusion criteria included those who were contraindicated for Trans-PRK and those with systemic diseases (e.g., diabetes), ocular surface disorders, recent contact lens use (within three months) or prior ocular surgery.

Sample size calculation

The sample size was determined according to each study objective. Calculations were performed using the single mean formula (Ariffin sample size calculator) and G*Power version 3.1.9.4 for linear multiple regression (fixed model, R^2 deviation from zero) and correlation analyses.[12] The largest estimated sample size, derived from the meibomian gland meiboscale using the single mean formula, was 108 participants, which was adopted to ensure adequate statistical power across all objectives.

Demographic data, systemic and ocular history

Sociodemographic data (age, gender, occupation, screen time, smoking status, contact lens use) and refractive measurements were recorded. Manifest spherical equivalent (SE) and astigmatism were categorised by standard refractive error classifications.

Ocular examination

Participants who provided informed consent underwent thorough examinations at the Laser Refractive Service. Subjects then completed the Ocular Surface Disease Index (OSDI) questionnaire.[4] The examination sequence commenced with assessment of visual acuity, non-invasive and non-contact meibography, followed by a slit-lamp examination.

Meibography was conducted using infrared Schwind Sirius® Scheimpflug-Placido Topography System (manufactured by CSO Srl, Italy). Meibomian gland loss and morphology were evaluated. The right upper eyelid was utilised to assess gland structure, degree of gland loss, and severity, as the upper eyelid contains more meibomian glands structural features and exhibits more prominent dropout areas.[13] To ensure accuracy, the principal investigator manually delineated the upper eyelid boundaries for analysis while minimizing the impact of glare and repeating this process three times. Meibomian gland loss (MGL) was calculated as the proportion of gland loss relative to the total upper tarsal area and classified into five grades: Grade 0 for no MGL, grade 1 for equal or less than 25% loss, grade 2 for 26 to 50% loss, Grade 3 for 51 to 75% loss, and Grade 4 for more than 75% loss.[1] Meibomian gland morphology was assessed and categorised based on characteristic features, including ghost areas, dropout, shortened, thickened, thinned, tortuous, hooked, and overlapping patterns.[13]

Subsequently, non-invasive tear break-up time (NIBUT) was measured. It measures the time for the first dry spot to appear on the corneal surface after a blink. The three readings of the first and the average NIBUT were documented, with a cut-off value of less than or equal to 10 seconds indicating tear film instability and DED.[14]

On slit lamp examination, first the lid margin was examined for abnormalities such as irregularities, vascular engorgement, plugged meibomian gland orifices, and anterior or posterior displacement of the mucocutaneous junction, with findings scored as either present (1) or absent (0).[15] Meibomian gland expression was assessed by applying digital compression over five visible meibomian gland orifices of the upper or lower lids. Meibomian gland expression was evaluated and categorized into the following grades: Grade 0 if all glands were expressible, Grade 1 if 3 to 4 glands were expressible, Grade 2 if only 1 to 2 glands were expressible, and Grade 3 if no glands were expressible. Meibum quality was graded as follows: Grade 0 for clear fluid, Grade 1 for cloudy or particulate fluid, and Grade 2 for opaque, toothpaste-like secretions.[16] Tear break-up time (TBUT) was measured using fluorescein strips, and dry spots appearing in under 10 seconds were considered abnormal.[14] Corneal fluorescein staining was graded using the Oxford grading scale. Grade 0 indicates no or minimal staining. Grade I shows slight staining, more than Grade 0. Grade II shows moderate staining, greater than Grade I. Grade III indicates dense staining, more than Grade II. Grade IV shows confluent staining, more severe than Grade III. Grade V represents very severe staining, greater than Grade IV.[17] Schirmer I testing without anaesthesia was performed to assess basal and reflex tearing, with values below 10 mm at five minutes considered abnormal.[14] To minimize errors, all ocular examinations were conducted by the primary principal investigator.

MGD was diagnosed in participants who met all the following criteria, as adapted from the 2011 International Workshop on MGD[5,18]:

- Ocular Surface Disease Index (OSDI) score >12,
- Presence of at least one lid margin abnormality, and
- Meibum expressibility or meibum quality grading ≥1.

DED was defined based on the TFOS DEWS II criteria[5,14], requiring:

- OSDI score >12, and
- The following objective signs:
- Corneal fluorescein staining score ≥1,
- Tear Break-Up Time (TBUT) or Non-Invasive TBUT (first or average) < 10 seconds, or
- Schirmer I test result <10 mm in five minutes.

Statistical analysis

All data were analysed using IBM SPSS Statistics version 29.0 (IBM Corp., Armonk, NY, USA). Simple and multiple logistic regression analyses were performed to identify factors associated with MGD and DED.

Pearson correlation analysis was used to examine the relationship between the percentage of MGL and clinical parameters including OSDI score, meibum expressibility score, meibum quality score, lid margin scores, TBUT, first and average NIBUT, Oxford corneal fluorescein staining score and Schirmer I test values. A p-value < 0.05 was

Table I: Demographic and clinical characteristics for subjects presenting for Trans-PRK

Variable	n (%)
Age (years), mean ± SD	32.76 (7.65)
< 35	62 (56.4)
≥ 35	48 (43.6)
Gender	
Male	46 (41.8)
Female	64 (58.2)
Race,	
Malay	104 (94.5)
Chinese	6 (5.5)
Working environment	
Indoor	76 (69.1)
Outdoor	34 (30.9)
Screen time	
< 4 hours	49 (44.5)
≥ 4 hours	61 (55.5)
Smoking	
No	98 (89.1)
Yes	12 (10.9)
Contact lens	
No	52 (47.3)
Yes	58 (52.7)
Degree myopia (dioptres), Mean ± SD	-3.98 ± 0.15
Low (<-3.0)	30 (27.3)
Moderate (-3.0 to -6.0)	69 (62.7)
High (>-6.0)	11 (10.0)
Degree of astigmatism (dioptres), Mean ± SD	-0.83 ± 0.06
Mild (<1.5)	97 (87.4)
Moderate (1.5 to 2.5)	10 (9.0)
Severe (>2.5)	3 (2.7)
UCDVA (LogMAR)	
Normal (0.00 to 0.30)	1 (0.9)
Mild (0.50)	7 (6.4)
Moderate (0.60 to 1.00)	65 (59.1)
Severe (1.10 to 1.30)	37 (33.6)
Blind (Worse than 1.30)	-
BCDVA (LogMAR)	
Normal (0.00 to 0.30)	72 (65.5)
Mild (0.50)	13 (11.8)
Moderate (0.60 to 1.00)	20 (18.2)
Severe (1.10 to 1.30)	5 (4.5)
Blind (Worse than 1.30)	-
Manifest spherical equivalent in dioptres, mean ± SD	-4.37 ± 0.17

Abbreviations: SD: standard deviation, UCDVA: uncorrected distant visual acuity, BCDVA: best corrected distant visual acuity

considered statistically significant. The strength of correlation was interpreted using r-values according to the classification by Schober et al.[19]

RESULTS

Demographic characteristics

A total of 110 subjects who presented for Trans-PRK were included in the study. The mean age ⌖ standard deviation (SD) was 32.76 years ± 7.65, with a majority being female (58.2%, 64 subjects) and of Malay ethnicity (94.5%, 104 subjects). Majority worked in indoor environments (69.1%, 76 subjects) and 55.5% (61 subjects) reported screen time of more than four hours per day.

Clinical characteristics

Contact lens wear was reported in 52.7% (58 subjects), while smoking was noted in 12 participants (10.9%). Most subjects having moderate myopia (62.7%, 69 subjects). Astigmatism was generally mild, with 97 of subjects (87.4%) fell within the mild astigmatism category. Regarding visual acuity, most subjects had moderate uncorrected distance visual acuity (UCDVA) (59.1%, 65 subjects) and about 72 subjects (65.5%) fell within normal category of best corrected distance visual acuity (BCDVA). (Table I)

Meibomian gland characteristics

Table II describes the characteristics of meibomian gland parameters among subjects. OSDI had a mean score of 9.51 ± 4.33, with the majority of subjects falling within the normal range (80.9%), which suggest most subjects were asymptomatic. In terms of meibomian gland, it revealed that most participants had good meibum expressibility and quality score, indicating good meibomian gland function, which seen in 57 (51.8%) and 63 participants (57.3%) respectively. Abnormal lid margin findings were observed in 77 participants (70%), with the most common signs being meibomian gland capping (71.4%), suggesting some degree

Table II: Meibomian gland parameters and prevalence among subjects presenting for Trans-PRK

VariablesMeibomian gland parameters	n (%)
OSDI, Mean ± SD	9.51 (4.33)
Normal: 0 to 12	89 (80.9)
Mild: 13 to 22	19 (17.3)
Moderate: 23 to 32	2 (1.8)
Severe: 33 and above	-
Lid margin score, Mean ± SD	0.70 (0.46)
Score 0: Normal	33 (30.0)
Score 1: Abnormal	77 (70.0)
• Telangiectatic vessel	10 (13.0)
• Meibomian capping	55 (71.4)
• Vascular engorgement	5 (6.5)
• Mucocutaneous junction	7 (9.1)
Meibum expressibility score, Mean ± SD	0.53 (0.59)
Grade 0: All glands	57 (51.8)
Grade 1: 3 to 4 glands	48 (43.6)
Grade 2: 1 to 2 glands	5 (4.5)
Grade 3: No glands	0
Meibum quality score, Mean ± SD	0.45 (0.54)
Grade 0: Clear fluid	63 (57.3)
Grade 1: Cloudy or particulate	45 (40.9)
Grade 2: Opaque	2 (1.8)
Area of MGL (%), Mean ± SD	20.84 (13.27)
Grade 0	0
Grade 1 (<25)	78 (70.9)
Grade 2 (26 to 50)	30 (27.3)
Grade 3 (51 to 75)	2 (1.8)
Grade 4 (>75)	0
Meibomian gland morphology	
Ghost area	8 (7.3)
Dropped out	32 (29.1)
Shortened	23 (20.9)
Thickened	0
Thinned	15 (13.6)
Tortuous	28 (25.5)
Hooked	3 (2.7)
Overlapping	1 (0.9)
MGD	
No	91 (82.7)
Yes	19 (17.3)

Abbreviation: OSDI: Ocular Surface Disease Index, SD: standard deviation, MGL: meibomian gland loss
MGD: meibomian gland dysfunction
MGD criteria: OSDI > 12, presence of at least one lid margin abnormality, and meibum expressibility or meibum quality grading ≥1.

of obstruction of the gland orifices. Meibography examination showed the mean percentage of MGL was 20.84% ± 13.27, with the majority (70.9%, 78 subjects) classified as grade 1 loss (<25%). Morphological abnormalities such as gland dropout (29.1%), tortuosity (25.5%), and shortened glands (20.9%) were commonly observed. Overall, 17.3% of the participants (19 participants) met the diagnostic criteria for MGD.

Tear film parameters

Table III summarizes dry eye parameters among subjects. OSDI was predominantly in the normal range (80.9%, 89 subjects), suggesting most of the subjects do not any dry eye symptoms. The mean tear break-up time (TBUT) was 8.85 ± 2.81 seconds, with more than half of the subjects (51.8%, 57 subjects) having TBUT less than 10 seconds, implying tear film instability. The mean first NIBUT were 9.97 ± 5.68 seconds with majority (57.3%, 63 participants) score less than 10 seconds. However, for average NIBUT, 77 participants (70%) scored more than 10 seconds, indicating normal value. The mean corneal fluorescein staining was 1.55 ± 0.60, with most eyes graded as Grade 1 (49.1%, 54 participants) or 2 (46.4%, 51 participants). Schirmer I test without anaesthesia showed a mean value of 16.1 ± 4.69 mm, with 88.2% (97 subjects) having normal reflex tear secretion. 21 of the subjects (19.1%) met the diagnostic criteria for DED.

Associated factors for MGD and DED

Table IV and V showed the associated factors of MGD and DED among participants presenting for Trans-PRK. Multivariate logistic regression revealed that older age (OR 3.65, 95% CI 1.15–11.51, p = 0.027) and screen time of more than four hours daily (OR 9.05, 95% CI 2.14–38.28, p = 0.003) were significantly associated with the presence of MGD. Furthermore, table IV demonstrates that, using males as the reference group, female gender was significantly associated with 81% reduced odds of developing MGD compared to males (OR = 0.19, 95% CI: 0.055–0.68, p = 0.011).

In relation to DED, individuals with screen time exceeding four hours per day demonstrated significantly higher odds of developing DED, with an eightfold increase in risk (OR=8.12,

Table III: Dry eye parameters and prevalence among subjects presenting for Trans-PRK

VariablesDry eye parameters	n (%)
OSDI, Mean ± SD	9.51 (4.33)
Normal: Score 0 to 12	89 (80.9)
Mild: 13 to 22	19 (17.3)
Moderate: 23 to 32	2 (1.8)
Severe: 33 and above	-
TBUT (sec), Mean ± SD	8.85 (2.81)
< 10 seconds	57 (51.8)
≥ 10 seconds	53.0 (48.2)
Corneal fluorescein staining, Mean ± SD	1.55 (0.60)
Grade 1	54 (49.1)
Grade 2	51 (46.4)
Grade 3	5 (4.5)
Grade 4	0
Grade 5	0
NIBUT first (sec), Mean ± SD	9.97 (5.68)
< 10 seconds	63 (57.3)
≥ 10 seconds	47 (42.7)
NIBUT average (sec), Mean ± SD	11.9 (3.72)
< 10 seconds	33 (30.0)
≥ 10 seconds	77 (70.0)
Schirmer I, Mean ± SD	16.1 (4.69)
< 10mm	13 (11.8)
≥ 10mm	97 (88.2)
DED	
No	89 (80.9)
Yes	21 (19.1)

Abbreviation: OSDI: Ocular Surface Disease Index, SD: standard deviation, TBUT: tear break up time , NIBUT: non-invasive break up time, DED: dry eye disease
DED criteria: OSDI score >12, and the following objective signs: corneal fluorescein staining score ≥1, TBUT or NIBUT (first or average) < 10 seconds or schirmer I test result <10 mm in five minutes

95% CI: 2.16–30.54, p=0.002). Additionally, female gender appeared to be a protective factor, with females exhibiting 74% lower odds of developing DED compared to their male counterparts (OR=0.26, 95% CI: 0.08–0.80, p=0.019). Age was not found to be a statistically significant factor associated with the development of DED. Other variables such as myopia, working environment (indoor or outdoor), contact lens wear and smoking status did not show significant associations with either MGD or DED.

Correlation analysis between meibomian gland parameters and tear film parameters

Correlation analysis showed a moderate positive correlation between meibomian gland loss and OSDI scores (r=0.58, p<0.001) and meibum quality scores (r=0.46, p<0.001). Whereas weak correlation was seen in oxford cornea fluorescent staining (r=0.36, p<0.001) and meibum expressibility (r=0.35, p<0.001). However, there was no significant correlations (p value of >0.05) were observed with TBUT, first and average NIBUT, Schirmer I test, and lid margin scores.

DISCUSSION

In this study, we investigated the prevalence of MGD and DED among subjects presenting for Trans-PRK. There have been limited reviews of the prevalence of MGD and DED in Malaysia, especially among subjects presenting for refractive surgery. To our knowledge, there is no published data looking into the prevalence of MGD and DED among subjects presenting for Trans-PRK. The findings of this study allow for better preoperative risk stratification, more targeted patient counselling and the integration of MGD and DED management into the refractive surgery workflow. This proactive approach may enhance postoperative outcomes and patient satisfaction, while also reducing long-term complication rates.

The demographic characteristics of our cohort are largely consistent with international studies involving refractive surgery candidates. Our study population, with a mean age of 32.76 ± 7.65 years, reflects the typical age group seeking refractive correction, comparable to the slightly younger cohorts reported by Li et al. and Gong et al. in China and similar to Brooks and Gupta's US-based study.[1,4,20] Female predominance in our sample aligns with findings from Brooks and Gupta and may reflect greater aesthetic motivation or health-seeking behaviour among women.[1] Our sample comprising majority of Malay ethnicity, reflective of the general population demographics accessing refractive surgery services in our geographic location.[21,22] Contact lens use was reported by over half of our participants, consistent with international data, and is a relevant factor as prior contact lens wear has been associated with lid margin changes and meibomian gland dropout.[23] Most participants worked indoors and had prolonged screen exposure, which may exacerbate evaporative dry eye, a risk factor less frequently documented in the reviewed studies but highly relevant in modern clinical settings.[10,24] The majority also had moderate degrees of myopia and mild astigmatism, further

Table IV: Associated factors of MGD among subjects presenting for Trans-PRK

Variable	MGD		Simple Logistic Regression		Multiple Logistic Regression	
	No n (%)	Yes n (%)	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age (years)						
< 35	56 (90.3)	6 (9.7)	3.47	0.021*	3.65	0.027*
≥ 35	35 (72.9)	13 (27.1)	(1.21, 9.96)		(1.15, 11.51)	
Gender						
Male	35 (76.1)	11 (23.9)	0.46	0.124	0.19	0.011*
Female	56 (87.5)	8 (12.5)	(0.17, 1.24)		(0.055, 0.68)	
Myopia						
Grade 0	26 (86.7)	4 (13.3)	1.50	0.505		
Grade 1-2	65 (81.3)	15 (18.7)	(0.46, 4.95)			
Indoor						
No	31 (91.2)	3 (8.8)	2.76	0.129		
Yes	60 (78.9)	16 (21.1)	(0.75, 10.18)			
Outdoor						
No	60 (78.9)	16 (21.1)	3.67	0.129		
Yes	31 (91.2)	3 (8.8)	(0.1, 1.34)			
Screen time						
No	45 (91.8)	4 (8.2)	3.67	0.030*	9.05	0.003*
Yes	46 (75.4)	15 (24.6)	(1.13, 11.90)		(2.14, 38.28)	
Contact Lens						
No	41 (78.8)	11 (21.2)	0.60	0.311		
Yes	50 (86.2)	8 (13.8)	(0.22, 1.62)			
Smoking						
No	81 (82.7)	17 (17.3)	0.95	0.953		
Yes	10 (83.3)	2 (16.7)	(0.19, 4.74)			

Abbreviations: OR: odds ratio, CI: confidence interval
p-value <0.05 is significant for simple logistic regression and multiple logistic regression
*Statistically significant value
Forward LR method was applied for variable selection. No multicollinearity and no interaction detected. Hosmer Lemeshow test, p-value=0.119, Classification table 81.8% correctly classified

Table V: Associated factors of DED among subjects presenting for Trans-PRK

Variable	DED		Simple Logistic Regression		Multiple Logistic Regression	
	No n (%)	Yes n (%)	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age (years)						
< 35	54 (87.1)	8 (12.9)	2.51	0.065		
≥ 35	35 (72.9)	13 (27.1)	(0.94, 6.67)			
Gender						
Male	35 (76.1)	11 (23.9)	0.59	0.278	0.26	0.019*
Female	54 (84.4)	10 (15.6)	(0.23, 1.53)		(0.08, 0.80)	
Myopia						
Grade 0	25 (83.3)	5 (16.7)	1.25	0.692		
Grade 1-2	64 (80.0)	16 (20.0)	(0.41, 3.78)			
Indoor						
No	31 (91.2)	3 (8.8)	3.21	0.078		
Yes	58 (76.3)	18 (23.7)	(0.88, 11.74)			
Outdoor						
No	58 (76.3)	18 (23.7)	0.312	0.078		
Yes	31 (91.2)	3 (8.8)	(0.09, 1.14)			
Screen time						
No	45 (91.8)	4 (8.2)	4.35	0.013*	8.12	0.002*
Yes	44 (72.1)	17 (27.9)	(1.36, 13.95)		(2.16, 30.54)	
Contact Lens						
No	41 (78.8)	11 (21.2)	0.78	0.603		
Yes	48 (82.8)	10 (17.2)	(0.3, 2.01)			
Smoking						
No	79 (80.6)	19 (19.4)	0.83	0.821		
Yes	10 (83.3)	2 (16.7)	(0.17, 4.11)			

Abbreviations: OR: odds ratio, CI: confidence interval
p-value <0.05 is significant for simple logistic regression and multiple logistic regression.
*Statistically significant value
Forward LR method was applied for variable selection. No multicollinearity and no interaction detected.
Hosmer Lemeshow test, p-value=0.671, Classification table 80.0% correctly classified

supporting their suitability for Trans-PRK. Understanding these demographic trends is essential in tailoring refractive services, identifying at-risk groups for preoperative dry eye screening and enhancing patient education and postoperative care planning.

In our study, the prevalence of MGD and DED among Trans-PRK candidates was 17.3% and 19.1%, respectively. These rates are consistent with those reported in prior studies on refractive surgery populations, albeit with some variability due to differences in geographic, ethnic, and methodological factors. For instance, Li et al. reported a broad range of DED prevalence (14.7% to 63.4%) among refractive surgery candidates in China, while Maychuk observed DED rates between 15.6% and 55% among LASIK candidates in Russian.[20,25] Brooks and Gupta found a notably high prevalence of meibomian gland atrophy (72.5%) among U.S. candidates, highlighting the under-recognised presence of MGD even in asymptomatic individuals.[1] Gong et al. similarly demonstrated that preoperative meibomian gland loss was associated with worse postoperative dry eye symptoms, emphasizing the importance of baseline gland assessment.[4]

The relatively lower prevalence observed in our cohort can be attributed to a multitude of factors, including differences in diagnostic criteria, variations in testing methodologies for DED assessment and differences in the demographic and environmental characteristics of the studied populations.[20] Aljarousha et al. also described this, explaining that the prevalence varies by location and depends on the type of clinical examination, the method of diagnosis, and the population studied.[26]

We also studied the morphological changes in meibomian gland of our patients. Our study reported the most common meibomian gland morphology observed was dropped out glands, followed by tortuous glands. Brooks and Gupta demonstrated higher degree of meibomian gland tortuosity in his study, using a different grading system.[1] The difference in the reported prevalence of meibomian gland morphology and MGD may reflect the discrepancy between structural changes and clinical function. While meibography can reveal gland atrophy or morphological abnormalities such as gland dropout, tortuosity, and shortening, these changes do not always correlate with symptomatic or functional MGD.[16,27] MGD diagnosis relies on clinical signs and symptoms like altered meibum quality and expressibility, lid margin abnormalities and tear film instability. Likewise, Daniel et al. suggested that further research is needed to establish the correlation between ocular imaging of the meibomian glands and clinical findings in DED.[13]

In this study, increasing age is associated with fourfold higher odds of developing MGD after adjusting potential confounding factors in multivariate logistic regression associated with MGD. Brooks and Gupta reported similar findings as their study focused on the relationship between meibomian gland atrophy and age.[1] With increasing age, it is postulated that there will be a decline in meibocyte differentiation and cell cycling, which can lead to meibomian gland atrophy over time.[23] Another hypothesis would be hyperkeratinization, stasis and increased pressure with gland dilatation, resulting in chronic MGD. This subsequently leads to atrophy of the meibomian glands.[1] Hormonal imbalances resulting from androgen deficiency may represent another underlying mechanism for age-related meibomian gland dysfunction.[28,29]

Our study population consisted primarily of female participants. After adjusting for screen time and age, males were found to be approximately four and five times more likely to develop MGD and DED, respectively. Traditionally, females have been more commonly associated with the development of MGD, although some studies have concluded that there is no gender predisposition to MGD.[23,24] Our findings, however, align with other studies that support a higher likelihood of males developing MGD and DED. Androgen deficiency is believed to be a key factor in the onset of MGD in males.[29–31]

Our data showed that screen time of more than four hours was associated with nine times and eight times higher odds to get MGD and DED. These findings are consistent with the existing literatures. Prolonged periods of screen exposure may lead to reduced blinking rates, resulting in tear film instability and subsequent desiccation of the ocular surface, potentially contributing or exacerbating of meibomian gland dysfunction.[10,21] Muniraju et al. have reported that prolonged screen time reduces the blink rate to approximately five to six times per minute due to continuous staring at the screen.[32] Moreover, the emission of blue light from visual display terminals, including computer and mobile screens, may further destabilize the tear film.[21]

Although no significant associations were found between myopia, environmental exposure, contact lens wear, or smoking with MGD and DED, these factors may still have exerted confounding effects on the observed associations. Contact lens wear can induce chronic structural and functional alterations in the meibomian glands, while environmental factors such as high temperature and low humidity which is common in the fluctuating hot and humid climate of East Coast Malaysia, may further destabilize the tear film and contribute to residual confounding.[10,23] While myopia is not directly associated with MGD, it is frequently linked to prolonged near work and screen use, which can reduce blink rate and lead to gland stasis and ocular surface instability.[33] Prolonged screen exposure which is often cumulative with increasing age, may exacerbate ocular surface stress and evaporative dry eye, potentially compounding these effects.[23,34]

The study also found that the meibum expressibility score and meibum quality score correlated with the degree of meibomian gland loss. These are clinical assessments of meibomian gland function.[1,16] This was also seen by MacHalińska et al, where severity of MGD correlates with meibum quality and quantity scores.[23] Besides that, Arita et al proposed that meibomian score as one of the reliable markers to differentiate obstructive MGD from healthy subjects.[35] The observed relationships align with the understanding of MGD, where stagnation of meibum is typically associated with alterations in both the quality and ease of meibum secretion.

Besides that, our study showed higher scores of corneal fluorescein staining correlates with meibomian gland loss, as seen in other studies.[16,18] Corneal staining is an indicator of corneal epithelial damage, which is often associated with tear film instability and meibomian gland dysfunction.[18] It is proposed that the release of inflammatory mediators such as breakdown products of meibomian lipids into the tear film results in ocular surface damage.[16]

We observed that OSDI scores, which reflects the subjective experience of ocular discomfort, were significantly elevated in participants exhibiting greater meibomian gland loss. This was also observed by MacHalińska et al who reported that OSDI can independently predict an abnormal meiboscore, emphasizing the importance of patient-reported outcomes in the assessment of meibomian gland dysfunction.[23,36] Interestingly, the majority of subjects in our study demonstrated clinical signs yet remained asymptomatic. The use of an OSDI cutoff of more than 12 may have influenced the estimated prevalence, as individuals with clinical ocular surface changes could remain asymptomatic despite low OSDI scores. This aligns with Craig et al., who reported that reduced corneal sensitivity from longstanding dry eye may mask discomfort despite evident clinical signs.[37]

Conventional measures of tear film function, including tear breakup time (TBUT), non-invasive tear breakup time (NIBUT), and Schirmer I testing, did not exhibit statistically significant correlations with the degree of meibomian gland loss. This was also highlighted in other studies.[23,35] It is probably due to TBUT having a relatively low power to differentiate MGD from healthy subjects, as described by Arita et al.[35] Besides that, Schirmer test is a measurement for aqueous component in the tear film, which is usually not seen in MGD.[38] This suggests that standard tear film assessment techniques may be insufficient for evaluating meibomian gland dysfunction-related pathology.

These findings have important implications for both clinical practice and future research. The results of this study can inform the development of a local institutional protocol that integrates meibography and comprehensive dry-eye screening into preoperative assessments to optimise patient selection and postoperative outcomes in refractive surgery. Future prospective or longitudinal studies should evaluate whether targeted preoperative management of MGD or DED can reduce postoperative complications and enhance ocular-surface recovery.

The limitations of this study include its cross-sectional design, which precludes establishing causal relationships between the identified risk factors and the development of MGD or DED. Furthermore, the findings may have limited generalisability beyond the East Coast region of Malaysia, where the population is predominantly Malay and the climate is hot and humid with seasonal monsoon influence. These environmental and demographic characteristics differ from other Malaysian regions. Hence, future longitudinal and multicentre studies across Malaysia are recommended to enhance external validity.

The grading scales used to assess meibomian gland morphology and function were subjective, which could have introduced intra-observer variability and biased the results. In the future, the integration of automated image analysis tools or AI-assisted software may enhance the consistency and reliability of assessments. Another limitation would be the reliance on recall-based estimations to assess working environment and screen time. To minimize recall bias in future research, standardized and validated questionnaires should be used to assess working environment and screen time.

CONCLUSION

This study found that the prevalence of MGD and DED among individuals undergoing Trans-PRK was 17.3% and 19.1%, respectively. MGD was significantly associated with age, gender, and screen time, while DED showed significant associations with gender and screen time, identifying these as potential risk factors in this population. The degree of MGL demonstrated weak to moderate positive correlations with OSDI scores, meibum quality, corneal fluorescein staining, and meibum expressibility. These findings offer important insights into the prevalence and associated factors of MGD and DED in refractive surgery candidates in East Coast Malaysia and highlight the importance of comprehensive preoperative ocular surface assessment.

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Exosomes derived from human umbilical cord mesenchymal stem cells attenuate kidney inflammation in a 5/6 subtotal nephrectomy rat model

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ABSTRACT

Introduction: Chronic kidney disease (CKD) is a non-communicable disease that contributes to the rise of global mortality rate. The condition is marked by reduced kidney function persisting for three months or longer. The main cause of CKD is kidney fibrosis, resulting from chronic inflammation. Current CKD therapies, such as hemodialysis and kidney transplants, are limited in effectiveness. Stem cell-derived therapy, particularly mesenchymal stem cells (MSC), provide great potential for reducing inflammation and fibrosis. Notably, exosomes secreted by MSC offer a safer and more effective alternative by carrying bioactive molecules that can repair kidney function through modulating inflammatory processes.

Materials and Methods: Twenty-five male 3-month-old Wistar rat were divided into five groups: Sham operation (SO, n=5), 5/6 subtotal nephrectomy (SN, n=5), SN with exosome treatment at total protein concentration of 48.30 µg (SNE1, n=5), 96.61 µg (SNE2, n=5), and 193.21 µg (SNE3, n=5). The rat was euthanized, and the kidneys were harvested for analysis. The mRNA expression levels of NF-κB and MCP-1 were measured using RT-PCR. Macrophage infiltration was assessed using immunohistochemistry (IHC) staining with anti-CD68 antibodies.

Results: The mRNA expression of NF-κB was significantly higher in the SN group compared to the SO group. In the exosome groups (SNE1, SNE2, and SNE3), NF-κB expression was significantly lower than in the SN group (p = 0.011, 0.029, 0.026, respectively). The mRNA expression of MCP-1 in the exosome groups was not significantly different from the SN group. IHC staining showed the SN group had a more dominant macrophage infiltration compared to the SO group. The exosome group exhibited a less dominant macrophage infiltration compared to the SN group.

Conclusion: Exosomes may attenuate kidney inflammation by inhibiting inflammatory gene expression and macrophage infiltration in a 5/6 subtotal nephrectomy rat model.

KEYWORDS:
Exosome, HUC-MSC, NF-κB, MCP-1, macrophage

INTRODUCTION

Chronic kidney disease (CKD) is a non-communicable disease that contributes to the rise of global mortality rate. The condition is characterized by reduced kidney function persisting for three months or longer. CKD affects 1 in 10 people worldwide.[1,2] In Indonesia, the prevalence of CKD increased from 0.2% in 2013 to 0.38% in 2018.[3] The primary cause of CKD is kidney fibrosis, where healthy kidney tissues are replaced by extracellular matrices components, leading to diminished kidney function. The fibrosis is primarily induced by chronic inflammation.[4,5]

Inflammation is a key factor that drives the development of kidney fibrosis, making its reduction a crucial therapeutic intervention.[4] Inflammation is mediated by damage-associated molecular patterns (DAMPs), which activates nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) through toll-like receptor 4 (TLR4).[6] NF-κB acts as a transcription factor that regulates the production of cytokines and chemokines, including monocyte chemoattractant protein-1 (MCP-1).[7,8] MCP-1 is a chemokine that attracts macrophages to the injury site, where they release pro-inflammatory and pro-fibrotic cytokines. Persistent inflammation ultimately causes progressive damage to the glomeruli and tubules of the kidneys.[8,9]

Current treatments for CKD are limited to hemodialysis and kidney transplants.[10,11] Stem cell-based therapies provide a

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promising alternative due to their potential to mitigate inflammation and fibrosis.[12] However stem cell therapies also face challenges, some types of stem cells, such as induced pluripotent stem cells (iPSCs), carry a risk of tumorigenesis.[13] Previous studies have reported that mesenchymal stem cells derived from human umbilical cord (HUC-MSCs) may reduce the risk of tumorigenesis.[14] Recently, attention has shifted toward MSC-derived bioactive compounds, particularly exosomes, which are considered a safer and more stable therapeutic option with a lower risk of tumorigenesis.[15,16]

Exosomes derived from MSC offer a novel therapeutic approach with a Reno-protective effect and enhanced stability.[17] These exosomes carry bioactive molecules that are capable of repairing kidney function more effectively than MSC alone.[18,19] Previous studies have demonstrated that MSC exosomes reduce inflammation in various doses, presenting a safer and better alternative.[20,21] Specifically, exosomes containing micro RNAs, miR-26a and miR-146a-5p have been shown to downregulate inflammation by modulating NF-κB.[22-24] However, research on the effect of human umbilical cord mesenchymal stem cells (HUC-MSC) exosomes in CKD remains limited. Therefore, further investigation is needed to elucidate their impact on inflammation and kidney function in animal models. The 5/6 subtotal nephrectomy model serves as a representative CKD model due to its similarity to human kidney injury.[25]

MATERIALS AND METHODS

Animal subjects

The subjects were 25 male 3-month-old Wistar rats weighing around 150-300 grams. The rats were acclimated for 7 days before treatment. They were divided into five groups of five rats: sham operation group + exosome solvent (SO), 5/6 subtotal nephrectomy group + exosome solvent (SN), 5/6 subtotal nephrectomy group + exosome with 48.30 µg total protein (SNE1), 5/6 subtotal nephrectomy group + exosome with 96.61 µg total protein (SNE2), and 5/6 subtotal nephrectomy group + exosome with 193.21 µg total protein (SNE3).

During the experiment, the rats were kept at room temperature, 60% humidity, and 12 hours of dark-light cycle. They were given ad libitum food and drink. All procedures were conducted following the ethical clearance from The Medical and Health Research Ethics Committee (MHREC) of FK-KMK UGM number KE/FK/1964/EC/2023. The study was carried out from October 2023 to January 2024 in the Anatomy Laboratory of FK-KMK UGM, the Anatomical Pathology Laboratory of FK-KMK UGM, and the Integrated Research Laboratory of FK-KMK UGM.

Preparation of 5/6 Subtotal Nephrectomy Model

The 5/6 subtotal nephrectomy model involved two main procedures: unilateral nephrectomy and subtotal nephrectomy. The unilateral nephrectomy was performed on the right kidney, followed by the removal of the superior and inferior poles of the left kidney after seven days. rats were anesthetized with ketamine (100 mg/kg body weight, intraperitoneal) and laid on their stomach. Their lumbar hairs were shaved. An incision of 1.5 cm width was performed on the right lumbar region, followed by ligation on the renal pedicle using a 3/0 silk suture. Afterward, the right kidney was cut, and the peritoneum and skin were sutured. After 7 days, the left kidney was taken by incising the left lumbar region, followed by making cuts on the inferior and superior poles. Bleeding was stopped with a microcauter, and the peritoneum and skin were sutured.

Administration of Exosome

Exosomes were derived from human umbilical cord mesenchymal stem cells (HUC-MSC) and provided by PT. Kalbe Farma Ltd®. Exosome was dissolved with an exosome solvent and given intravenously with three variations on total protein: 48.30 µg, 96.61 µg, and 193.21 µg. Exosomes were injected twice a week for 28 days (in week 2nd, 3rd, 4th, and 5th) after 5/6 subtotal nephrectomy procedure. There were no exosome injections on week 6th in all intervention groups.

Termination and measurement of urine/serum creatinine ratio

Prior to termination, rats were placed in metabolic cages for 24-hour urine collection to measure creatinine levels. Urine samples were collected at three time points: prior to the 5/6 subtotal nephrectomy procedure, at week 2 as a mid-treatment assessment, and prior to termination. Serum samples were collected before the 5/6 nephrectomy and again prior to termination to enable calculation of the urine/serum creatinine ratio.

The rats were anesthetized with 100 mg/kg body weight of ketamine intraperitoneally. Afterward, an incision was made from the abdominal region to the thorax. NaCl 0.9% perfusion was carried out in the left ventricle while cutting the right auricular to observe perfusion flow. The kidney was taken and divided into two parts: one part was stored in a formalin fixative solution for making paraffin blocks, while the other part was stored in an RNA stabilization solution at -20°C for RNA extraction. After taking the kidneys, the carcasses were incinerated in an incinerator. Histopathological examination was performed using periodic acid–schiff (PAS) staining to visualize glomerular and tubular structural changes, thereby confirming the successful establishment of the CKD model. Representative histological images were selected from each group based on consistent and characteristic morphological features observed across all subjects.

RT-PCR and Electrophoresis

RNA was extracted using RNA isoplus (GENEzol®, Cat. No. GZR100) and quantified using nanodrop. Complementary DNA was made by mixing 3000 ng with nuclease-free water to reach a volume of 12 µL, then added to 8 µL of PCR mixture (5x RT buffer 4 µL, random primer 1 µL, dNTP 2 µL, Reverse transcriptase enzyme 1 µL). The mixture was incubated in the PCR machine (30°C for 10 minutes, 42°C for 60 minutes, and 99°C for 5 minutes). Three microliters of cDNA were inserted into a 0.2 mL microtube with 22 µL PCR mixture (0.6 µL primer forward, 0.6 µL primer reverse, 12.5 µL master mix, 8.3 µL nuclease-free water). Reverse transcriptase PCR was done for assessing the expression of following genes: NF-κB (206 bp; forward GCCTGACACCAGCATTTGA, reverse

Table I: Ratio of urine/serum creatinine in each group

Sample	*Urine/serum creatinine ratio (mean ± SD)
SO	205,823 ± 72,003
SN	9,496 ± 2,222
SNE1	34,987 ± 26,691
SNE2	43,146 ± 29,423
SNE3	42,015 ± 37,175

*Urine specimens were collected prior to termination.

Table II: Ratio of NF-κB gene expression normalized to GAPDH in each group

Group	NF-κB/GAPDH (Mean ± SD)
SO	0.574 ± 0.097
SN	0.736 ± 0.061*
SNE1	0.582 ± 0.049#
SNE2	0.614 ± 0.068#
SNE3	0.612 ± 0.088#

*P < 0.05 vs SO group; #P < 0.05 vs SN group.

Table III: Ratio of MCP-1 gene expression normalized to GAPDH in each group

Group	MCP-1/GAPDH (Mean ± SD)
SO	1.18 ± 0.122
SN	1.69 ± 0.132*
SNE1	1.377 ± 0.197
SNE2	1.481 ± 0.302
SNE3	1.469 ± 0.236

*P < 0.05 vs SO group.

CAAACCAAACAGCCTCACG); MCP-1 (150 bp; forward CAGGTCTCTGTCACGCTTCT, reverse GTAGTTCTCCAGCCGACTCA) and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) (163 bp; forward GTTACCAGGGCTGCCTTCTC, reverse TCCCGTTGATGACCAGCTTC). Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used as a control because its expression is relatively constant across different conditions. PCR was conducted with the following conditions: denaturation at 95oC for 10 seconds, annealing at 55°C for GAPDH, 60°C for MCP-1, 64°C for NF-κB for 1 minute, and extension at 72°C for 1 minute. This process is repeated for 30 cycles for GAPDH, 39 cycles for MCP-1, and 33 cycles for NF-κB. Electrophoresis was subsequently performed following RT-PCR to visualize the amplified DNA fragments, using a DNA ladder as a molecular size marker to verify fragment sizes.

Immunohistochemistry

Kidney tissue slides were deparaffinized, rehydrated, and rinsed under running water. Then, antigen retrieval was performed by heating in a citrate buffer with pH 6 for 15 minutes. After rinsing with phosphate-buffered saline (PBS), endogenous peroxidase (H2O2 3%) was inhibited for 20 minutes, then rinsed with PBS 3 times for 5 minutes. The slides were dried and background blocking was performed with immunoblock (Finetest Cat. No. IHC0009) for 30 minutes and rinsed with PBS. Afterward, the slides were dried and an anti-CD68 antibody (ABclonal A22239) was added and stored overnight at 4°C. The next day, the slides were rinsed with PBS and mouse/rabbit probe horseradish peroxidase (HRP) (Finetest Cat. No. IHC0009) was added and waited for 10 seconds to be rinsed. Then, the slides were stained with hematoxylin, dehydrated, cleared, and mounted. Immunohistochemical staining of CD68 was performed on all kidney samples, and representative images were selected to reflect consistent macrophage infiltration patterns observed across the samples. Slides were observed under a light microscope at 400x magnification and viewed in 10 fields of view.

Statistical Analysis

Data were analyzed with the Shapiro-Wilk test for normality and the Levene test for homogeneity. Normalized data were then tested with One Way ANOVA and LSD post hoc, while non-normalized data were tested with Kruskal Wallis and Mann Whitney U post hoc test. Significance was determined with $p < 0.05$.

RESULTS

Exosomes Improve Kidney Function and Protect Tubules after 5/6 Subtotal Nephrectomy

The kidneys of rats subjected to 5/6 subtotal nephrectomy exhibited a significantly lower urine/serum creatinine ratio compared to the sham operation (SO) group, as shown in Table I. This reduced creatinine ratio indicates reduced kidney function, as healthy kidneys typically filter creatinine efficiently. However, after the administration of exosomes, there was a notable improvement in kidney function. Exosomes resulted in a higher urine/serum creatinine ratio, indicating a recovery in the kidney's filtration capacity (Figure 1A).

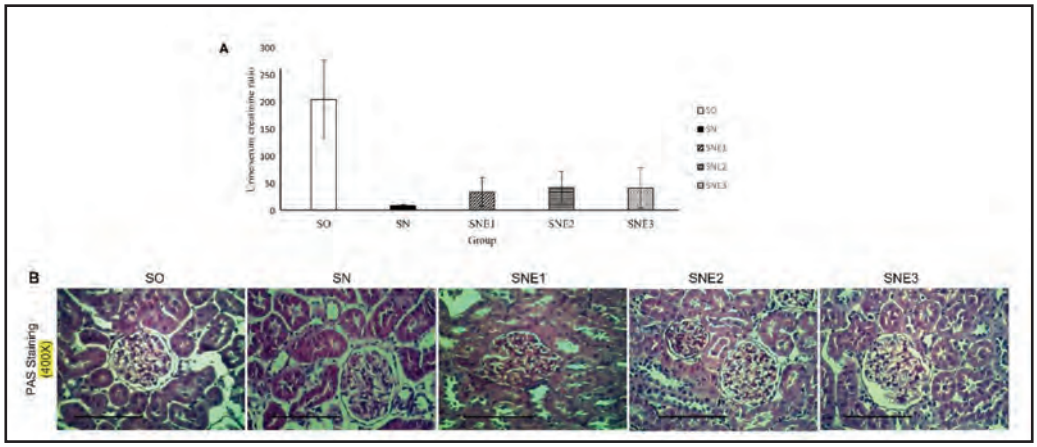

Fig. 1: Plot of urine/serum creatinine ratio in each group (A). Histological pictures (scale bar =100 µm) of kidney injury after SN model based on PAS staining (B).

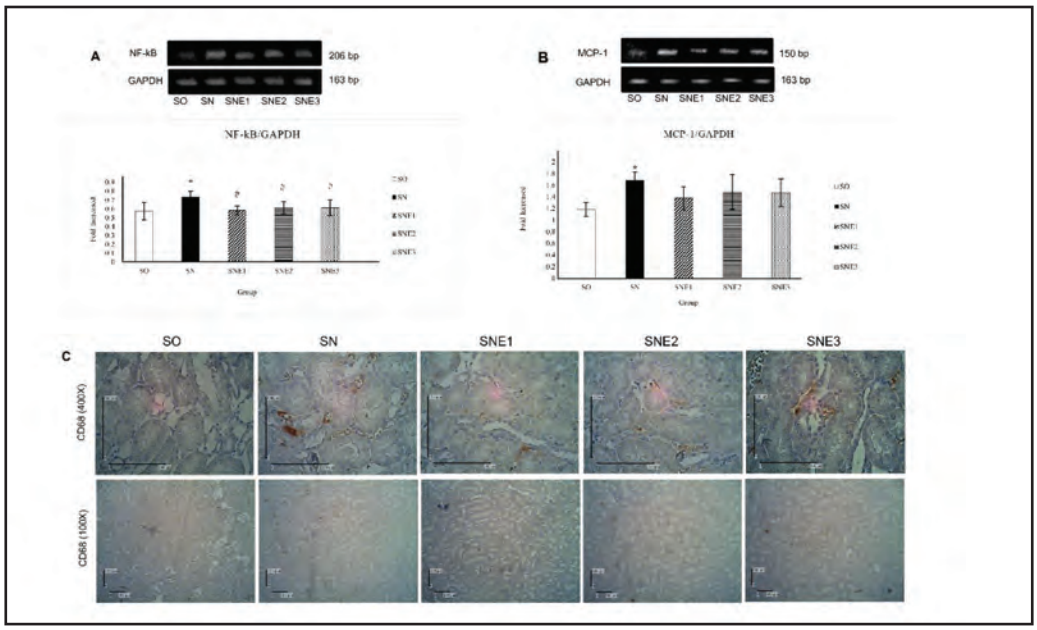

Fig. 2: Effect of Exosomes on mRNA Expression of Inflammation-Related Genes in Kidney Tissue after 5/6 Subtotal Nephrectomy. (A-B) Shows the upregulation of NF-κB and MCP-1 mRNA expression in the SN group compared to SO. NF-κB mRNA expression is significantly lower after exosome administration, while MCP-1 shows no significant change. (C) Representative image of CD-68 immunostaining shows positivity in interstitial tubules. *p<0.05 vs SO; # p<0.05 vs SN.

The 5/6 subtotal nephrectomy also caused severe tubular injury in the kidneys. This injury was characterized by several pathological changes, including interstitial inflammation, tubular dilation, and loss of the brush border, as identified through PAS staining. Figure 1B presents PAS-stained kidney sections as representative examples from each group, selected to reflect the consistent histological findings observed across all samples. The administration of exosomes showed protective effects by reducing inflammation, preventing further tubular dilation, and aiding in the recovery of the brush border.

Exosome Treatment Effects on Kidney Inflammation and Macrophage Infiltration

Gene expression related to inflammation, such as NF-κB and MCP-1, increases after CKD injury. NF-κB mRNA expression was significantly ($p < 0.05$) higher in the SN group compared to the SO group. Exosome treatment (SNE1, SNE2, SNE3) significantly reduced NF-κB mRNA expression compared to the SN group, with p-values of 0.011, 0.029, and 0.026, respectively (Table II and Figure 2A). The differences among the exosome-treated groups were not statistically significant. Figure 2B showed that MCP-1 mRNA expression was significantly higher in the SN group than in the SO group. Treatment with exosomes (SNE1, SNE2, SNE3) did not show a statistically significant difference in MCP-1 expression compared to the SN group, with p-values of 0.052, 0.178, and 0.156 (Table III).[26]

To further investigate whether exosomes can suppress inflammation, we conducted immunohistochemical staining using a CD68 antibody on kidney tissue. CD68 is a

membrane-bound glycoprotein expressed by macrophages, used to assess macrophage infiltration. Immunohistochemical staining with an anti-CD68 antibody revealed macrophage infiltration in the interstitial areas of tubules. The infiltration appeared less dominant in the exosome-treated group compared to the SN group. Exosome treatment consistently reduced macrophage infiltration across all treatment groups. As shown in Figure 2C, representative CD68-stained kidney sections from each group were selected to reflect the consistent macrophage infiltration patterns observed across samples.

DISCUSSION

This study highlights that exosome plays a vital role in inhibiting the progression of CKD by regulating inflammation in rat kidneys. Evidence supporting this includes analyses of NF-κB and MCP-1 mRNA expressions, which were involved in regulating inflammation and macrophage infiltration.

The results of this study revealed that the mRNA expressions of NF-κB and MCP-1 in the SN group were significantly higher than in the SO group. This finding aligns with a prior study that found an increased mRNA expression of NF-κB in 5/6 subtotal nephrectomy models.[27] In CKD, the expression of NF-κB increases, especially in the kidney cortex tubule cells.[7] In addition, an increase in the expression of MCP-1 was found in a 5/6 subtotal nephrectomy mouse model.28 This indicates that the model can induce kidney inflammation.

Increased mRNA expressions of NF-κB and MCP-1 as a response to injury showed that inflammation acts in the mechanism of tissue repair. Cellular injury prompts the production of signaling molecules that activate NF-κB. This activation happens through the canonical or non-canonical pathways, initiating the transcription of inflammatory genes including MCP-1, which facilitates macrophages recruitment to the site of injury for tissue repair.[29,30] However, in CKD, persistent inflammation can aggravate kidney damage.[31,32] Several studies have identified strategies to prevent kidney inflammation by targeting NF-κB. Inhibition of NF-κB can be achieved through reducing the expression of NF-κB component genes or by targeting its activating signaling pathway. For instance, exosomes derived from human umbilical cord mesenchymal stem cells (HUC-MSC) containing miR-22-3p suppress inflammation by downregulating NLRP3 expression, thereby reducing the activation and release of proinflammatory cytokines like IL-1β, which participates in the canonical pathway of NF-κB activation.33 Similarly, exosomes derived from adipose mesenchymal stem cells carrying miR-26 inhibit the NF-κB pathway by targeting TLR-4, thereby reducing the expression and phosphorylation of protein involved in NF-κB signaling.[22] Exosomes derived from HUC-MSC have also been shown to ameliorate kidney injury by inhibiting NF-κB phosphorylation.[34] Additionally, a study in a diabetic kidney disease (DKD) model reported that exosomes derived from bone marrow mesenchymal stem cells (BM-MSC) suppress NF-κB activation by reducing P65 expression.[35]

In this study, the mRNA expressions of NF-κB in SNE1, SNE2, and SNE3 groups were significantly lower than the SN group. This finding was in line with a previous study demonstrating that exosomes from MSC, which were stimulated with melatonin containing miR-26a, effectively reduce NF-κB expression in the kidney.[21] These results underscore the role of exosomes in modulating inflammation by inhibiting NF-κB activation.

The expression of MCP-1 in the exosome-treated group did not significantly differ from that in the SN group. This result may be attributed to the activity of the NF-κB inflammatory pathway, which generates various other inflammatory mediators.[36] Previous research has demonstrated that exosomes inhibit NF-κB mRNA expression, subsequently leading to a reduction in IL-6 mRNA expression in renal ischemia-reperfusion models. IL-6 plays a crucial role in the differentiation of monocytes into macrophages by upregulating the expression of the macrophage colony-stimulating factor receptor (M-CSFR).37 Furthermore, HUC-MSC exosomes have been shown to reduce TGF-β expression in the kidney, which may potentially enhance M-CSF expression.[38] M-CSF, secreted by fibroblasts, binds to M-CSFR on monocytes to promote their differentiation into macrophages.[39]

Based on immunohistochemistry observation using anti-CD68 antibodies, rat treated with exosomes exhibited lower macrophage infiltration compared to untreated rat. This finding suggests that the inhibition of NF-κB synthesis correlates with decreased macrophage infiltration, demonstrating exosomes' potential to reduce macrophage infiltration, and thus, suppress excessive inflammation.[34]

Overall, the results of this study demonstrate the positive impact of exosome administration in reducing inflammation in the kidneys of a 5/6 subtotal nephrectomy rat model. These findings align with previous research indicating that exosomes may be more effective in reducing inflammation compared to MSCs.[40]

In this study, there were no significant differences in NF-κB and MCP-1 expression among the exosome-treated groups (SNE1, SNE2, and SNE3). This suggests that while exosomes can reduce inflammation, there is no difference in effectiveness among the three groups. These results are consistent with other studies showing that exosome administration with a total protein of 50 µg and 100 µg can reduce NF-κB expression to the same extent.[22] Therefore, exploring exosomes with varying total protein contents is important to maximize their ability to suppress inflammation. While this study focused on inflammatory response, it is also important to consider the potential long-term toxicity of exosome administration in future studies to ensure their safety for therapeutic use.

CONCLUSION

Exosomes attenuate the inflammatory response in 5/6 subtotal nephrectomy rat models by reducing mRNA expression of NF-κB and macrophage infiltration.

AUTHORS' CONTRIBUTIONS

ZNZ, NA, and DC contributed substantially to the conception and design of the study. ZNZ, EY, LRA, DA, and PBS performed the animal experiments, surgical procedures, post-operative care, and tissue processing. NF, HPW, KFM, and TMS isolated the exosomes, and HM, K and MAP performed their characterization. NF, YW, and VYS carried out the biochemical assays and assisted with data interpretation. DA and RY supervised the in vivo protocols and, together with NA, contributed to experimental troubleshooting and quality control. ZNZ, NA, and RY drafted the manuscript, which was critically reviewed and revised by DA, RY, and DC for important intellectual content. NA, as the corresponding author and principal investigator, oversaw the project, secured funding, and approved the final manuscript. All authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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ORIGINAL ARTICLE

A time-to-treatment initiation analysis for treatment-naive early-stage resectable non-small cell lung cancer patients in the Malaysian private healthcare sector

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ABSTRACT

Introduction: Non-small cell lung cancer (NSCLC) remains a leading cause of cancer mortality in Malaysia, with 95% of cases diagnosed at advanced stages. Beyond screening for early detection, timely intervention is critical for optimal outcomes in early-stage, resectable NSCLC (e-NSCLC). Delays in the diagnostic, staging and referral pathway, measured as time-to-treatment initiation (TTI), are associated with poorer survival. This contemporary real-world study is the first to evaluate TTI in a cohort of Malaysian patients with e-NSCLC.

Materials and Methods: This is a retrospective study of 124 consecutive treatment-naive e-NSCLC patients who had a minimally invasive curative anatomical lung resection (lobectomy or segmentectomy) and systematic mediastinal nodal dissection between January 2021 and December 2024 at two tertiary private hospitals. Medical records were reviewed to capture key timepoints across three phases of care. The primary analysis (n=124) focused on demographics and assessed the timeline from initial general practitioner (GP) to specialist consultation, diagnosis, and definitive surgery. These patients were evaluated after surgical discharge to validation of histopathology and next-generation sequencing (NGS) reports, and oncology review. Patients who received adjuvant therapy were included in a secondary analysis to examine timelines from NGS report validation and oncology review to initiation of adjuvant therapy.

Results: The median time from the GP referral to surgery was 30.0 ± 24.5 days; GP consultation to specialist referral took 7.5 ± 17.0 days, specialist review to surgeon consultation took another 10.0 ± 16.3 days. Biopsy and staging PET-CT were completed within 3.0 ± 20.9 and 3.0 ± 20.5 days, respectively, from the initial specialist consultation. Definitive curative-intent surgery was performed 7.5 ± 13.1 days from the first cardiothoracic surgical consult and 18 ± 23.3 days following a confirmed histological diagnosis of NSCLC. The median interval from specialist review to definitive surgery was 20.0 ± 20.2 days. The median time from surgery to discharge and reporting of NGS results was 5.0 ± 2.6 days and 12.0 ± 7.7 days, respectively. Patients were seen at the first post-surgical review within 7.0 ± 3.7 days following discharge, while oncology review occurred at 19.0 ± 16.2 days post-surgery. For patients eligible for adjuvant therapy, treatment commenced 14.5 ± 11.4 days following the oncology review.

Conclusion: TTI is known to prognosticate recurrence-free and overall survival for e-NSCLC. This contemporary real-world experience from two leading tertiary cancer centres demonstrates the agility and efficiency of Malaysian private healthcare for prompt diagnosis, meticulous staging and timely, curative-intent definitive surgery for e-NSCLC, aligning with global benchmarks. Our study suggests, if prioritised, a swift TTI is highly achievable with appropriate expertise and coordinated resources, and should be incorporated as a deliverable national quality metric to drive improved outcomes for potentially curable e-NSCLC.

KEYWORDS:
Time-to-treatment initiation, non-small cell lung cancer, timely intervention, Malaysian healthcare

INTRODUCTION

Lung cancer remains a leading cause of cancer-related mortality globally, with non-small cell lung cancer (NSCLC) accounting for approximately 85% of cases.[1] In Malaysia, lung cancer ranks as the second and third most common malignancy in males and females respectively and remains the second leading cause of cancer-related mortality according to the Malaysian National Cancer Registry Report 2017–2021.[2] Notably, approximately 95% of lung cancer cases in Malaysia are diagnosed late at advanced stages III and IV, with adenocarcinoma NSCLC being the predominant histological subtype.[2]

NSCLC patients with early-stage, resectable (IA to IIIA) disease (e-NSCLC) have the highest long-term disease-free survival (DFS) and overall survival (OS), particularly when

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timely surgical resection is performed.[3] However, delays in timepoints from diagnosis to definitive treatment known as *'time-to-treatment initiation'* (TTI), including curative surgery, can adversely impact outcomes for patients with potentially curable early-stage disease. Delays in TTI have been reported by even highly developed countries, including from the European Union, United Kingdom, and United States.[4]

The impact of TTI on survival for newly diagnosed NSCLC patients of all stages is significant. According to the Mayo Clinic Cancer Center (2000-2016) multi-site registry study, median OS was markedly better for patients with a TTI ≤20 days compared to those with a TTI > 20 days (39.1 vs 28.6 months, p<0.0001).[5] The survival benefit was most pronounced for patients with stage I and II disease; OS of 103.4 vs. 63.9 months (p<0.0001) and 72.3 vs. 46.8 months (p=0.0014), respectively.[5] A recent study involving more than 80,000 NSCLC patients (SEER, 2000-2019 database, USA) concluded that a prolonged TTI > 31 days had a negative impact on OS and cancer-specific cumulative mortality for stage I disease.[6] In another study, significantly better outcomes were observed for stage III patients with a shorter TTI, in patients who survived ≥ 5 years (p=0.029).[7]

These findings reiterate the importance of a prompt diagnosis and efficient staging work-up to ensure a brief TTI to improve outcomes particularly for e-NSCLC patients. The aim of our study was to evaluate the TTI across key timepoints in the patient journey such as initial presentations to the general practitioner (GP), lung or oncology specialist and cardiothoracic surgeon, first radiological finding or histological confirmation, and clinical diagnosis leading up to definitive curative-intent surgery. This study seeks to identify real-world barriers contributing to delays in TTI and propose strategies to enhance the care pathway for patients with e-NSCLC. Such insights will guide better healthcare resource allocation and improve service delivery for more timely intervention which should translate to superior patient outcomes.

MATERIALS AND METHODS

Study Population

A total of 124 consecutive treatment-naive patients with clinical stage IA to IIIB-N2 primary NSCLC who underwent definitive curative-intent anatomical surgical lung resection between January 2021 and December 2024 from two tertiary, urban private hospitals met the inclusion criteria and were included in the study (Figure 1). All patients were clinically staged pre-operatively with a PET-CT scan, and if indicated, a contrasted MRI brain scan. The standard operation in all patients was a lobectomy or segmentectomy, with concurrent systematic mediastinal lymph node dissection, performed with a minimally invasive uniportal approach under single lung ventilation general anaesthesia and conducted by a single cardiothoracic surgeon.

Data collection

Data was extracted retrospectively from medical records and reports, including progress notes, histopathology reports, laboratory findings, and imaging studies, in compliance with ethical standards. Demographic variables collected included age, sex, and ethnicity, while smoking status was recorded as current, former, or non-smoker. Presenting symptoms were categorised as either incidental (asymptomatic) findings or symptomatic presentations, which included cough, haemoptysis, dyspnoea, weight loss and chest pain. In addition to baseline characteristics, the study focused on capturing key clinical timepoints (in days) that reflected the time-to-treatment initiation, defined as the interval from the first GP consultation to the date of definitive surgery, and where applicable, to the initiation of adjuvant therapy.

Operational definition of key clinical timepoints

The following definitions were applied in the extraction and interpretation of key clinical timepoints from patients' medical records (Figure 2).

- GP Consultation: The date of the patient's first visit to a GP for symptoms or concerns that ultimately led to the diagnosis of NSCLC.
- Specialist Consultation: The date the patient visits a relevant hospital-based specialist, e.g., respiratory physician or oncologist, for a consultation.
- Cardiothoracic Surgical Consultation: The date of the first consultation with a cardiothoracic surgeon regarding operative management for the NSCLC.
- PET-CT Scan: The date the first positron emission tomography-computer tomography (PET-CT) scan was performed for diagnostic and staging purposes.
- Brain MRI: The date the contrast-enhanced brain magnetic resonance imaging (MRI) procedure was performed to assess for potential occult brain metastases.
- Lung Biopsy Procedure: The procedural date of the first tissue biopsy which confirmed a histopathological diagnosis of NSCLC.
- Lung Biopsy Report Validation: The date the histopathology report confirming a NSCLC diagnosis was validated in the medical record by a certified pathologist.
- Surgery: The date of the definitive curative-intent surgical resection of the primary NSCLC.
- Discharge: The date the patient was formally discharged from the hospital following surgery.
- HPE Report Validation: The date the final histopathology examination (HPE) report of the resected tumour specimen was validated and made available in the medical record by a pathologist.
- NGS Report Validation: The date the next-generation sequencing (NGS) report for the surgical biopsy sample was validated by the molecular pathology laboratory and made available for clinical assessment by the oncologist.
- First Post-Surgical Review: The date of the first follow-up outpatient clinic visit with the cardiothoracic surgeon following surgery.
- Oncology Review: The date of the first formal oncology consultation for assessment, adjuvant treatment planning and follow-up.
- Adjuvant Therapy Initiation: Commencement of treatment (chemotherapy, immunotherapy and/or oral targeted therapy) within three months of the curative surgery.
- TKI Initiation: Commencement of tyrosine kinase inhibitors (TKI) as adjuvant therapy.

Data Analysis
The primary analysis (n=124) focused on demographics and assessed the timeline from the initial GP visit to specialist consultation, diagnosis and staging work-up, consultation with the cardiothoracic surgeon, to definitive surgery (Phase I). All patients were evaluated following surgical discharge to histopathology and NGS report validation, to the first post-surgical review and oncology review (Phase II) (Figure 2). A total of 66 patients eligible for adjuvant therapies were included in a secondary analysis to examine timelines from NGS report validation and oncology review to initiation of adjuvant therapy (Phase III). Further analysis was performed on the cohort of patients whose tumours harboured actionable mutations treated with a TKI, in particular oral targeted therapies, with or without chemotherapy, to evaluate the timeliness of TKI treatment initiation.

Statistical Methods
Descriptive analyses were performed to describe patients' demographics, including gender, age, ethnicity, risk factors, presenting symptoms, clinical stage at diagnosis and type of therapy received. Key clinical timepoints (from initial consultation with GPs to initiation of adjuvant therapy) were analysed using measurement of central tendency and dispersion, whereby the timeline data is presented as median ± standard deviation (SD) and range, i.e., minimum versus maximum. All statistical analyses were performed using R version 4.4.3 and Microsoft Excel 2019 (version 16).

RESULTS

Patient Demographics and Clinical Characteristics
In total, clinical data from 124 patients were retrieved in this study (Table I). The study cohort was predominantly female (52.42%), and the majority (54.84%) were aged between 40 and 64 years. Ethnic Malaysian Chinese (76.61%) were most represented in the study population, followed by foreign nationals (11.29%), Malaysian Indians (6.45%) and Malays (5.65%). In terms of risk factors, the majority were non-smokers (67.74%). A personal history of cancer and family history of cancer were reported in 14.52% and 29.84% of the population, respectively. Overall, 15.32% had a family history specifically for lung cancer.

Most cases (67.74%) were asymptomatic, discovered incidentally following opportunistic health screening. Among symptomatic patients, cough (21.77%) was the predominant symptom, followed by haemoptysis (8.87%), chest discomfort (4.03%), weight loss and shortness of breath (2.42% each). Based on the post-operative pathological TNM staging, the stages of disease were IA (33.87%), IB and IIB (20.16% each), followed by IIIA (15.32%), IIIB (5.65%) and IIA (4.84%). In total, 66 patients (53.23%) were eligible for post-surgical adjuvant therapy. Some patients with tumours that harboured targetable mutations received TKI-only therapy (18.55% of the overall study population) whilst a further 14.52% received a TKI in combination with chemotherapy. 19.35% of patients received adjuvant chemotherapy alone, and 1 patient received radiotherapy for local control for a positive R1 surgical margin.

Phase I (pre-operative care): GP consultation to Diagnosis
The median time from the first timepoint of GP consultation to treatment initiation by surgery was 30.0 ± 24.5 days (n= 58), whereby it took 7.5 ± 17.0 days from GP referral to specialist consultation (Table II). Given that many patients self-presented directly to the specialist, the median time from specialist consultation to surgery was 20.0 ± 20.2 days. During the specialist consultation, diagnostic and staging procedures including PET-CT, contrast-enhanced brain MRI, and tissue biopsy were planned and performed. The median time from the specialist consultation to the completion of the procedures, i.e., PET-CT, brain MRI, and biopsy, was 3.0 ± 20.5, 11.0 ± 19.0, and 3.0 ± 20.9 days, respectively. In particular, pathologist validation of the lung biopsy report occurred at 2.0 ± 2.2 days following the biopsy procedure, allowing for timely diagnosis and appropriate treatment planning.

Phase II (operative care): Surgical consultation to surgery and oncology care
In this analysis (n= 124), the overall median time from GP and specialist consultation to treatment initiation by surgery was 30.0 ± 24.5 and 20.0 ± 20.2 days, respectively (Table II). The specialist referral to the cardiothoracic surgeon took a median of 10.0 ± 16.3 days, and the time interval from validation of the diagnostic HPE biopsy report to surgery was 18.0 ± 23.3 days. Definitive curative surgery was performed at a median of 7.5 ± 13.1 days from the first surgical consultation, with most patients operated on within two weeks or less, of that initial surgical consultation. The majority of the patients were discharged within 5.0 ± 2.6 days with no reported in-hospital or 30-day mortality. Post-resection morbidity was minimal. The most common complications were small, self-limiting parenchymal air leaks. No patient required airway re-intubation or mechanical ventilatory support, or surgical re-exploration for bleeding or repair of air leaks or bronchopleural fistulas. Three patients (2.4%) developed a post-operative chylothorax, presumably from nodal dissection that required a prolonged hospital stay but settled fully with conservative therapy which included institution of total parenteral nutrition. Analysis and validation of HPE reports for the resected lobe/segment and mediastinal lymph nodes were available at a median of 4.0 ± 2.5 days, within the hospitalisation period for most patients. Surgical specimens were also sent for NGS testing, and genomic reports were validated at 8.0 ± 7.2 days following the resected tumour HPE validation and within 12.0 ± 7.7 days from surgery. Following hospital discharge, all patients returned for a post-surgical review within 7.0 ± 3.7 days, and all were offered an oncology referral for an independent evaluation on the need for adjuvant therapy. In total, 104 patients visited the oncologist, within 19.0 ± 16.2 days of surgery.

Phase III (post-operative care): Oncology care to adjuvant therapy initiation
66 patients were prescribed adjuvant therapy and included in the sub-analysis of adjuvant therapy initiation (Table III). Following oncology review, patients who required adjuvant therapy had their treatment initiated within 14.5 ± 11.4 days. Among patients whose tumours harboured targetable mutations and were eligible for TKI treatment, the time taken

Table I: Study population demographics and clinical characteristics

Characteristic		Total (n)	Percentage
Sex	Female	65	52.42%
	Male	59	47.58%
Age	Median (IQR)	63 (53.75-68.00)	
	Mean ± SD	60.76 ± 10.26	
	18-39	3	2.42%
	40-64	68	54.84%
	>65	53	42.74%
Ethnicity	Chinese	95	76.61%
	Foreigner	14	11.29%
	Indian	8	6.45%
	Malay	7	5.65%
Risk factors	Smoking history		
	Never	84	67.74%
	Former	26	20.97%
	Current	14	11.29%
	Cancer history		
	Personal history of cancer	18	14.52%
	Family history of cancer	37	29.84%
	Family history of lung cancer	19	15.32%
	No history of cancer	74	59.68%
Symptoms	Incidental (Asymptomatic)	84	67.74%
	Symptomatic	40	32.26%
	Cough	27	21.77%
	Haemoptysis	11	8.87%
	Loss of weight	3	2.42%
	Chest discomfort	5	4.03%
	Shortness of breath	3	2.42%
	Others*	5	4.03%
Pathological Stage	IA	42	33.87%
	IB	25	20.16%
	IIA	6	4.84%
	IIB	25	20.16%
	IIIA	19	15.32%
	IIIB	7	5.65%
Adjuvant Therapy	Tyrosine kinase inhibitor only	23	18.55%
	Osimertinib	19	15.32%
	Gefitinib	2	1.61%
	Afatinib	1	0.81%
	Alectinib	1	0.81%
	Chemotherapy only	24	19.35%
	Radiotherapy	1	0.81%
	Combination therapy	18	14.52%
	Osimertinib + chemotherapy	14	11.29%
	Alectinib + chemotherapy	3	2.42%
	Dacomitinib + chemotherapy	1	0.81%
	No adjuvant therapy	58	46.77%

*Includes symptoms like dizziness, palpitation, body aches and post-nasal drip. IQR: Interquartile range, SD: Standard deviation

from oncology review to TKI therapy initiation was 17.0 ± 37.9 days and within 26.5 ± 36.7 days from validation of the NGS report by the molecular pathologist.

DISCUSSION

This study is a comprehensive and contemporary analysis of time-to-treatment initiation among a cohort of treatment-naïve patients with resectable e-NSCLC managed in the Malaysian private healthcare sector. The median time from the initial GP visit to definitive surgery was 30.0 days, indicating timely diagnosis and relatively prompt access to pre-operative care. Our work is the first study in Malaysia to evaluate TTI exclusively for early-stage disease. It is comparable to the only prior local TTI study which reported a median interval of 1.1 months from first hospital visit to treatment initiation although > 95% of patients in this 2006 study had inoperable disease.[8] Two studies conducted in the United States reported median intervals of 27 days and 28 days from diagnosis to treatment initiation.[9-10] Similarly, a study in Singapore found a median interval of 28 days from multidisciplinary clinic visit to treatment, with a range of 4 to 111 days.[11] These comparable timelines underscore the efficiency and agility of the Malaysian private healthcare system, which aligns with regional and international standards and falls within the clinically significant window of 45 days for improved patient outcomes.[12]

The median interval from GP to specialist consultation was 8.0 days, suggesting most patients were referred promptly.

Table II: Overall timeline and key intervals from GP or specialist consultation to surgery and oncology review

Start Timepoint	End Timepoint	n	Median ± SD (days)	Min (days)	Max (days)
Overall: General practitioner	Surgery	58	30.0 ± 24.5	8	125
Overall: Specialist consultation	Surgery	123	20.0 ± 20.2	1	117
Lung biopsy report validation	Surgery	101	18.0 ± 23.3	1	174
General practitioner	Specialist consultation	58	7.5 ± 17.0	1	97
Specialist consultation	Diagnostics (Brain MRI)	73	11.0 ± 19.0	1	78
Specialist consultation	Diagnostics (PET-CT)	121	3.0 ± 20.5	1	95
Specialist consultation	Diagnostics (Biopsy)	102	3.0 ± 20.9	1	79
Lung biopsy procedure	Lung biopsy report validation	101	2.0 ± 2.2	1	13
Specialist consultation	Cardiothoracic Surgeon consultation	123	10.0 ± 16.3	1	82
Cardiothoracic Surgeon consultation	Surgery	124	7.5 ± 13.1	1	104
Surgery	Discharge	124	5.0 ± 2.6	3	24
Surgery	HPE report validation	124	4.0 ± 2.5	1	15
Surgery	NGS report validation	76	12.0 ± 7.7	2	48
HPE report validation	NGS report validation	76	8.0 ± 7.2	1	45
Discharge	First post-surgical review	124	7.0 ± 3.7	1	35
Surgery	Oncology review	104	19.0 ± 16.2	3	94

SD: Standard deviation, MRI: Magnetic resonance imaging, PET-CT: Positron emission tomography-computed tomography, HPE: Histopathology examination, NGS: Next generation sequencing

Table III: Time-to-treatment initiation for study population eligible for adjuvant therapy

Start Timepoint	End Timepoint	n	Median ± SD (days)	Min (days)	Max (days)
Overall: General practitioner	Adjuvant treatment initiation	30	62.5 ± 22.6	29	122
Overall: Specialist consultation	Adjuvant treatment initiation	54	51.0 ± 19.4	17	106
Oncology review	Adjuvant treatment initiation	54	14.5 ± 11.4	4	51
Oncology review	TKI initiation	36	17.0 ± 37.9	5	143
NGS report validation	TKI initiation	22	26.5 ± 36.7	8	154

SD: Standard deviation, NGS: Next generation sequencing, TKI: Tyrosine kinase inhibitor

However, data for the GP timepoint was only available in 58 out of 124 patients in the primary analysis. In reality, many patients either sought second opinions, were referred from other institutions, or self-presented directly to specialists or the surgeon. This latter practice is not uncommon here as the GP is not the clinical gatekeeper in Malaysian healthcare. Direct patient access or self referral to a relevant specialist especially in the private setting is allowed, and a frequent occurrence.

Detection of early-stage lung cancer remains a significant challenge. In the present study, 67.74% of cases were detected incidentally, highlighting the paucity of noticeable red-flag symptoms in early-stage disease, with asymptomatic NSCLC an incidental chance finding either from health screening or through imaging performed for other purposes. By the time symptoms such as a persistent cough, haemoptysis, or chest pain appears, the disease has often progressed to an advanced stage. Nevertheless, GPs could improve early detection by maintaining a high clinical suspicion and low threshold to investigate patients who present with a persistent cough (the predominant symptom in this series). Broadening screening criteria to include the high-risk non-smoker especially those with a family history of cancer, a personal history of cancer or most pertinently, a family history of lung cancer, either with an artificial intelligence-enhanced chest radiograph or the gold standard low-dose computed tomography (LDCT) scan will also be helpful. Our findings highlight the need to sustain and reinforce public awareness campaigns for earlier symptom recognition and encourage timely presentation to healthcare services.

The current study demonstrated upon specialist referral, essential diagnostic and staging investigations such as PET-CT scan, MRI, tissue biopsy and histopathological examination, could be conducted promptly, if prioritised, facilitating swift and appropriate treatment planning. The high efficiency in diagnosing and staging our patients is a reflection of the highly experienced and dedicated multidisciplinary teams (MDT) within the two comprehensive tertiary healthcare institutions, comprising respiratory physicians, oncologists, cardiothoracic surgeons, pathologists, nuclear medicine physicians and radiologists, all working together seamlessly, in delivering high-quality clinical care. Notably, both hospitals have regular MDT tumour board meetings. Implementing an MDT approach improved 5-year overall survival rates among patients with stage III lung cancer, for both those who underwent surgical resection and those who did not.[13] The shorter patient journey we report can be partly attributed to quicker turnaround times and shorter waiting times for various tests and services. As tertiary-level regional one-stop private cancer centres equipped with the latest state-of-the-art radiological imaging and laboratory equipment, the need to send patients or tissue samples elsewhere is mitigated.

In this study, all patients underwent PET-CT scan procedures. A contrast-enhanced brain MRI scan to exclude occult cerebral metastases was only performed for clinical stage II/III disease or if clinically indicated, in accordance with current national and international guidelines.[14-15] The data gap in the tissue biopsy procedure is attributed to patients whose tumours were not amenable to biopsy, patients who refused a pre-operative biopsy or sought care elsewhere, wherein the exact biopsy procedural dates were not traceable. In cases without histological confirmation of NSCLC pre-surgery, an intra-operative frozen section biopsy was performed prior to the curative resection.

The documented time interval from specialist visit to cardiothoracic surgeon consultation was a median of 10.0 days, during which much of the diagnostic and staging work-up was done. Following surgical consultation, the transition to surgery was prompt, with a median of 7.5 days, highlighting efficient operative scheduling practices and appropriate resource allocation in the private healthcare setting. However, ultimately this surgical urgency is driven by the singular focus and priority of the operating surgeon whose practice is largely dedicated to thoracic oncology. In this series, definitive surgery was performed at a median of 18.0 days following histological confirmation of a NSCLC.

All patients experienced an uneventful surgery with no in-hospital or 30-day mortality recorded, and median hospitalisation stay was 5.0 ± 2.6 days. Post-resection morbidity was minimal and no patient required airway re-intubation or mechanical ventilatory support, or surgical re-exploration for bleeding or repair of air leaks. The three patients who developed a post-operative chylothorax, all had prolonged hospital stays requiring total parenteral nutrition with full resolution of the chylous leak in each case. Only one patient experienced a prolonged hospital stay up to 24 days, due to a surgical wound infection requiring corrective treatment. A previous study demonstrated that for patients who received surgery-only for early-stage disease, those who had surgery between 4 and 6 weeks were associated with a 6% increased risk of death whilst a greater mortality risk (17%) was recorded for those who received surgery more than 6 weeks after diagnosis compared to patients treated immediately.[9] Presently, evaluation for cancer recurrence and survival outcomes for most patients in this study remains premature, however, we intend to continue meticulous follow-ups and correlate their DFS and OS with TTI in a future analysis.

Post-operatively, the validation of the final HPE report took a median of 4.0 days, reflecting rapid turnaround time from laboratory processing to report validation by the pathologist. This facilitates vital clinical decision-making before patient discharge, including ordering relevant genomic and biomarker tests during the index hospitalisation to guide adjuvant therapy planning. This has significantly aided the post-surgical oncology review, as shown in this study, as it took only 19.0 days from surgery to the oncologist review, and another 14.5 days for adjuvant treatment initiation.

Our study aligns with the recent shift in adjuvant therapy for early-stage, resectable NSCLC from conventional platinum-based chemotherapy and radiation therapy, either together or separately, to oral targeted therapies and immune checkpoint inhibitors. In this cohort, 31 out of 47 (65.9%) eligible EGFR-mutated NSCLC patients (data not shown) were offered standard of care osimertinib either alone or in combination with platinum-based chemotherapy, based on the significant DFS and OS benefit demonstrated in the phase III randomised ADAURA trial.[16-17] The relatively low uptake in our study suggests financial barriers to access osimertinib remain, even in an urban private setting. Notably, a few patients were prescribed an earlier generation TKI due to limited affordability. Future strategies must address such financial toxicity to ensure more equitable care.

In this study, we excluded patients exposed to neoadjuvant therapies. However, the treatment paradigm for e-NSCLC is rapidly evolving. Systemic immune checkpoint inhibitor therapy, i.e., nivolumab (CheckMate 816)[18-19], pembrolizumab (KEYNOTE-671)[20], durvalumab (AEGEAN)[21], nivolumab (CheckMate 77T)[22] for non-oncogene driven NSCLC, given as a neoadjuvant-only therapy or as part of a peri-operative 'sandwich' protocol has resulted in significant improvements in not only event-free survival (EFS), but even OS, particularly for stage III disease. Immunotherapy is fast becoming the standard of care ,and naturally this will alter the patient journey considerably, including TTI for early-stage resectable disease. Similarly, the awaited findings of neoadjuvant osimertinib use (NeoADAURA)[19] may further shift the treatment paradigm. With such advances, the timeliness of diagnosis including genomic molecular profiling and coordination between the multidisciplinary care team will become paramount to ensure patients receive optimal biomarker driven care within the appropriate timeline.

Our study demonstrates that if prioritised, a swift TTI for eNSCLC is highly feasible especially in the private healthcare setting where the necessary expertise and facilities are abundantly available and easily accessible. Although survival outcome was not the focus of this study, numerous studies confirm the association between TTI and clinical outcomes. In general, longer diagnostic intervals and treatment delays are associated with higher mortality and worse prognosis.[9,24-25] Interestingly, Loh et al.[8] found no significant association between treatment delays and long-term survival (in the only other Malaysian TTI lung cancer study to date), however, it is important to note only 5% of their patient cohort had resectable disease. Similarly, Skaug reported no significant correlation between treatment delays and long-term survival but only a minority (11%) underwent surgery.[26] In such cases, prognosis is more often driven by disease biology and stage of disease rather than timing of intervention, unlike in our study, which specifically evaluates early-stage, resectable NSCLC, where timely surgical management plays a pivotal role in achieving good outcomes. When lung cancer is diagnosed at an early, localised stage, the opportunity for a cure with surgical resection is real and possible. Hence, timely intervention is an imperative to prevent disease progression to an unresectable and incurable stage.

The small sample size of only 124 patients in the first analysis, followed by 66 patients in the second analysis, results in a low statistical power, and a greater risk of Type I and Type II errors, and reduced reliability in accurately determining the TTI for NSCLC patients in Malaysia. Ideally, TTI should encompass the interval from symptom onset to the initial GP visit, however this was precluded by the lack of reliable data on symptom onset due to challenges such as the subjective nature of symptoms, patient forgetfulness, variability in awareness and willingness to seek care, the GP's referral practices and access to tertiary medical care. Additionally, the generalisability of our findings is limited as the sample was drawn from only two private, urban tertiary hospitals, which may not represent the wider population and thus introduce selection bias. Finally, this study did not evaluate long-term cancer recurrence rates or survival following surgery or adjuvant therapy hence, we are unable to assess treatment durability and effectiveness. Future research will incorporate recurrence monitoring and survival outcomes to enable a more comprehensive understanding of how TTI impacts long-term prognosis for Malaysian patients with e-NSCLC.

CONCLUSION

This contemporary real-world study underscores the efficiency and agility of the private healthcare sector in Malaysia, in delivering timely diagnostic and high quality multi-disciplinary and multi-modal driven curative-intent surgical care for early-stage, resectable NSCLC, whilst highlighting critical gaps in the post-operative transition to adjuvant therapy. Strategies to mitigate financial toxicity are urgently required to ensure better access and more equitable adjuvant oncology care. Adopting TTI as a national performance metric (clinical key performance indictor) will help improve timeliness, equity, and long-term outcomes across lung cancer care pathways. It is unlikely such timely care can be achieved in the public sector (Ministry of Health and University) hospitals in the foreseeable future due to overwhelming clinical caseload, lengthy waiting times, limited resources and funding, and shortage of specialist staff and equipment. Leveraging on the vast expertise and resources readily available in high volume private centres of excellence through an impactful public-private collaboration seems most sensible and can quickly help close this unacceptable care gap in the provision of a timely and quality service for any Malaysian diagnosed with lung cancer.

Authors' Contributions

Anand Sachithanandan: Conceptualization, Methodology, Project administration, Supervision, Writing – review & editing. Hoh Hong Huat: Investigation, Formal analysis, Project administration, Validation, Writing – review & editing. Lee Joyin: Data curation, Formal analysis, Visualisation, Writing – original draft. Lim Yi Shwen: Data curation, Formal analysis, Visualisation, Writing – original draft. Naim Che Kamaruddin: Investigation, Data curation, Visualisation. Fatin Najihah Muhammad Lutfi: Data curation, Visualisation. Yong Wong Wai Shieh: Data curation, Visualisation. Siti Ayuni Hassanudin: Data curation. Ten Yi Yang: Data curation. Lam Mynn Dee: Data curation. Janelle Wee Chia Ern: Writing – original draft. Deva Rani Raja Sakar: Writing – review & editing. Shobana Satchithananthan: Writing – review & editing.

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ORIGINAL ARTICLE

Accuracy of the Banjarmasin prediction score for appendicitis to differentiate complicated and non-complicated appendicitis

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ABSTRACT

Introduction: Acute Appendicitis is typically felt in the right lower abdomen. Despite existing diagnostic methods to differentiate between complicated and non-complicated cases, achieving accurate diagnoses remains challenging. This study highlights the need for a reliable diagnostic tool to improve patient outcomes and inform surgical strategies, demonstrating the accuracy of the Banjarmasin Prediction Score for Appendicitis (BPSA).

Materials and Methods: This observational cross-sectional study involved patients diagnosed with acute Appendicitis at Ulin, Sultan Suriansyah, and Damanhuri Hospital in Banjarmasin, Indonesia. Data were collected through consecutive sampling and analysed using SPSS to ensure robust findings. The collected data were then compared between complicated and non-complicated appendicitis cases to evaluate the diagnostic accuracy of the BPSA and Alvarado scores.

Results: Among the 62 cases evaluated, 28 were classified as non-complicated and 34 as complicated Appendicitis. The BPSA showed a sensitivity of 71.4% and a specificity of 70.6%. The Alvarado score demonstrated lower sensitivity but a higher specificity of 79.4%. There was no significant difference in the Alvarado score (P > 0.05), while the BPSA score revealed a significant difference (P < 0.05) between complicated and non-complicated Appendicitis. Variations in histamine levels were also noted (P = 0.002), further underscoring the efficacy of the BPSA scoring system.

Conclusion: The Alvarado score is key for diagnosing acute Appendicitis, and the BPSA score helps differentiate between complicated and non-complicated cases, enhancing treatment strategies. The study's limitation was confined to a single region and a relatively small sample size, which may affect the generalisability of the findings.

KEYWORDS:
Appendicitis, BPSA Scoring, Alvarado score, Diagnostic tool, Accuracy

INTRODUCTION

Acute abdomen cases account for 7-10% of emergency department visits, with acute Appendicitis being the most common cause. Its prevalence in developed countries is 5 to 50 cases per 100,000 individuals annually, mainly affecting those aged 10 to 30. Appendiceal perforation occurs in 40% of cases, especially in adolescents and individuals over 50.[1] Non-complicated Appendicitis involves mucosal inflammation, while complicated Appendicitis includes perforation and abscess formation, increasing the risk of morbidity and mortality.[1–3]

The incidence rate of Appendicitis in Indonesia was 134 per 100,000 population. The Indonesian Department of Health reveals that Appendicitis is the fourth most common infectious disease in Indonesia, with 28,949 inpatients and 34,386 outpatients.[4] Often reported as a typical surgical emergency in Southeast Asia, Appendicitis remains a significant health concern across the region. Understanding its presentation in different local settings is, therefore, essential for optimising care. In Johor, Malaysia, Batu Pahat is the second largest city after Johor Bahru, with a population exceeding 400,000 people. The district Hospital Sultanah Nora Ismail (HSNI) has a total of 1,200 emergency surgeries. About 1/6 of emergency cases are related to appendicitis.[5]

Various scoring systems are used for diagnosing Appendicitis, each with different accuracy: the Alvarado score (24% sensitivity, 97% specificity), the Appendicitis Inflammatory Response Score (AIRS) (22% sensitivity, 97% specificity), and the Adult Appendicitis Score (AAS) (53% sensitivity, 93% specificity). These scores' positive predictive value (PPV) ranges from 81% to 82%, but negative appendectomy rates remain high at 18%-19%. Ultrasonography is limited in distinguishing between non-complicated and complicated Appendicitis, showing 81.1% sensitivity and 56.6% specificity.[6,7] Current scoring systems cannot differentiate between the two types with different treatment strategies.[8]

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Table I: The Alvarado and The Banjarmasin Prediction Score for Appendicitis (BPSA) Score

	Alvarado Score	Banjarmasin Prediction Score for Appendicitis (BPSA)
Migration or relocation of pain from paraumbilical to the right lower quadrant	1	1
Anorexia	1	1
Nausea/vomiting	1	1
Right Lower Quadrant Pain	2	2
Rebound pain	1	1
Increase the temperature > 37,50 C	1	1
Leukocytosis	2	1
Leukocyte shift to the left (>75% neutrophil)	1	1
Neutrophil Lymphocyte Ratio (NLR) > 3	-	1
Free fluid on Ultrasound	-	2
Histamine level > 1 ng/ml	-	1
TOTAL SCORE	10	13

Table II: Bi-variate Analysis Table (Difference Test) between 2 groups

Variable	Complicated Appendicitis (n = 28)	Non-complicated Appendicitis (n = 34)	p-value
Alvarado score, mean (±SD)	7.82 (±1.18)	7.44 (±1.40)	0.987a
BPSA score, mean (±SD)	10.21 (±1.57)	8.65 (±1.70)	0.009a*
Histamine level, mean (±SD)	64.99 (±43.34)	34.89(±34.83)	0.002 a*
Leucocyte, mean (±SD)	16,436.43 (±6,930.98)	13,725.59 (±4,468.32)	0.081 b
NLR, mean (±SD)	12.11 (±8.85)	7.16 (±4.84)	0.012 b*

BPSA = Banjarmasin Prediction Score for Appendicitis; NLR = Neutrophyl-Lympocyt Ratio
a = Mann-Whitney test; b = T-independent Test; c Categorical data
*Significance if p-value <0.05

Table III: Bivariate Analysis of Observation groups in the logistic regression test

Variable	Complicated Appendicitis (n = 28)	Non-Complicated Appendicitis (n = 34)	Complicated Appendicitis Crude POR (95%CI)	p-value
Alvarado score, mean (±SD)	7.82 (±1.18)	7.44 (±1.40)	1.260 (0.845-1,879)	0.256
BPSA score, mean (±SD)	10.21 (±1.57)	8,65 (±1.70)	1.831 (1.252-2.678)	0.002*
Histamine level, mean (±SD)	64.99 (±43.34)	34.89(±34.83)	1.000 (0.964-0.995)	0.009*
Leucocyte, mean (±SD)	16.436.43 (±6.930.98)	13.725.59 (±4.468.32)	1.000 (1.000-1.000)	0.075
NLR, mean (±SD)	12.11 (±8.85)	7.16 (±4.84)	1.115 (1.023-1.215)	0,014*

BPSA = Banjarmasin Prediction Score for Appendicitis; NLR = Neutrophyl-Lympocyt Ratio
*Significance if p-value <0.05

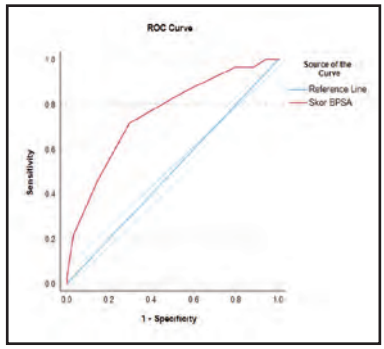
The study aims to demonstrate that combining Alvarado and BPSA scoring can effectively predict and differentiate between non-complicated and complicated appendicitis stages.

MATERIALS AND METHODS

This observational cross-sectional study evaluates how clinical findings, scoring systems, inflammatory markers, histamine levels, ultrasound results, surgical findings, and anatomical pathology effectively differentiate between non-complicated and complicated Appendicitis. The study included patients aged five and older with acute Appendicitis at Ulin, Sultan Suryansyah, and Damanhuri Hospitals in Banjarmasin, Indonesia. We analysed secondary data without intervention, excluding pregnant patients and those with non-assessable appendices, autoimmune diseases, comorbidities, malignancies, or chronic conditions.

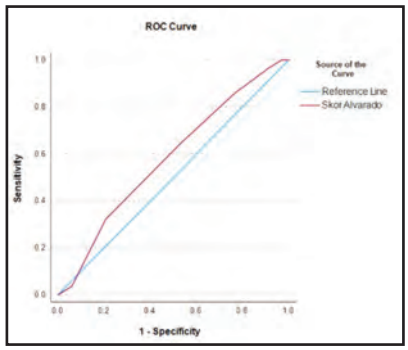
Patients were selected using consecutive sampling, in which all eligible subjects presenting during the study period and meeting the inclusion and exclusion criteria were enrolled until the required sample size was reached. This method was chosen to ensure feasibility within the available study period, minimise selection bias by including every eligible patient in sequence, and reflect the real-world distribution of cases in the participating hospitals. The minimum sample size was calculated based on a cross-sectional study design, resulting in 23 subjects per group.[9]

All acute Appendicitis patients underwent evaluation based on clinical signs, scoring systems, laboratory markers, ultrasound findings, histamine levels, and surgical results. The Alvarado and BPSA scoring considered indicators such as pain migration, anorexia, nausea/vomiting, right lower quadrant pain, rebound tenderness, fever (temperature > 37.5°C), leucocytosis, a left shift in leukocyte count (>75% neutrophils), a neutrophil-to-lymphocyte ratio (NLR) > 3, fluid accumulation on Ultrasound, and blood histamine levels > 1 ng/ml (Table I). A radiology specialist performed the Ultrasound using standardised hospital protocols to minimise variability. To control potential observer bias, all Ultrasound findings were reviewed and confirmed by a senior



Positive if Greater Than or Equal Toa	Sensitivity	1-Specificity	Specificity	Youden index
4:00	1.000	1.000	0.000	0.000
5:50	1.000	.941	0.059	0.059
6:50	0.964	.882	0.118	0.082
7:50	0.964	.794	0.206	0.170
8:50	0.857	.559	0.441	0.298
9:50	0.714	.294	0.706	0.420
10:50	0.464	.147	0.853	0.317
11:50	0.214	.029	0.971	0.185
12:50	0.036	.000	1.000	0.036
14:00	0.000	.000	1.000	0.000

Fig. 1: A. BPSA Sensitivity Curve. B. Sensitivity and Specificity of BPSA Score. The cut-off point for the area under the curve (AUC) is recorded in the table above. This conversion is based on the Youden Index. The highest value obtained is 0.42. The sensitivity of the BPSA score test is 71.4%, while its specificity is 70.6%.



Positive if Greater Than or Equal Toa	Sensitivity	1 - Specificity	Specificity	Youden Index
3.00	1	1	0.000	0.000
4.50	1	0.971	0.029	0.029
5.50	0.964	0.912	0.088	0.052
6.50	0.857	0.765	0.235	0.092
7.50	0.643	0.529	0.471	0.114
8.50	0.321	0.206	0.794	0.115
9.50	0.036	0.059	0.941	-0.023
11.00	0	0	1.000	0.000

Fig. 2: A. Alvarado Sensitivity Curve. B. Sensitivity and Specificity of Alvarado Score. The cut point of the area under the curve (AUC) is obtained in the table above with a conversion of the Youden Index. The highest value obtained is 0.115. The sensitivity value of the Alvarado score test is 32.1%, and its specificity is 79.4%

radiology specialist who was not involved in the initial scan and was blinded to the patient's histamine results and surgical findings. Histamine levels were measured in patient serum using the FineTest® Human Histamine ELISA Kit (Cat. No.: EH2552).[10]

Data analysis was used for SPSS version 26.0, reporting as frequencies and percentages for categorical data and as means and standard deviations for numerical data. We assessed data distribution using the Kolmogorov–Smirnov test and one-way ANOVA, Levene's test for homogeneity. For non-normally distributed data, we applied transformations with power transformations (exponents more significant than 1), inverse, log10, and square root to correct non-normality and non-homogeneity. The Bivariate Analysis difference test used the Mann-Whitney and Independent T-

test, and the logistic regression test results show a statistically significant relationship between the components of the BPSA scoring. The ROC curve was utilised to assess sensitivity and specificity. Data were transformed using the Youden index table, seeking the highest cut-off value.[11]

RESULTS

Subject Characteristics

This study analyses 62 cases of Appendicitis, including 28 complicated and 34 non-complicated cases. The gender distribution shows 34 males and 28 females, reflecting a balanced ratio. Patients' ages range from 5 to 67 years, with an average of 30. Most cases were treated in major hospitals in Banjarmasin, Indonesia: Ulin (37 patients), Damanhuri (24 patients), and Sultan Suriansyah (1 patient). Four patients were excluded due to positive pregnancy tests.

Comparison Test

Statistical comparison showed no significant difference in Alvarado scores between complicated and non-complicated appendicitis. In contrast, the BPSA score, histamine levels, and NLR were significantly higher in complicated cases (Table II). These findings are critical for enhancing diagnostic criteria and treatment strategies.

The logistic regression test results show a statistically significant relationship between the components of the BPSA scoring, which causes a substantial difference between complicated and non-complicated Appendicitis, with a possibility of 1.831 times greater. Histamine level (p=0.009) is the most influential component in distinguishing the two types of Appendicitis (Table III).

BPSA Score Sensitivity and Specificity Test

The area under the curve established a cut-off value of 0.42 (Figure 1). The BPSA scoring demonstrated a sensitivity of 71.4% and a specificity of 70.6% (Table IV), highlighting an impressive capacity for accurate identification. (95% CI : 1,252-2,678)

Alvarado Score Sensitivity and Specificity Test

The area under the curve cut-off value was determined to be 0.115 (Figure 2). The Alvarado scoring demonstrated a sensitivity of 32.1% and a specificity of 79.4% (Table 5). This strong performance underscores the reliability of the Alvarado score in clinical assessments. (95% CI : 0,845-1,879)

DISCUSSION

The BPSA score significantly outperforms the Alvarado score regarding sensitivity, boasting a rate of 71.4% compared to just 31.2%. The heightened sensitivity makes it especially adept at detecting complicated Appendicitis, an area where the Alvarado score often falls short, leading to a concerning number of false negatives. The key to the BPSA's effectiveness is incorporating vital parameters, including the Neutrophil-to-Lymphocyte Ratio, Histamine levels, and free fluid observed in ultrasound imaging. Despite its limitations, the Alvarado score holds a notable advantage in specificity, with rates of 79.4% versus 70.6%. This higher specificity is crucial for accurately identifying non-complicated Appendicitis, enhancing the negative rate. Therefore, while the Alvarado score remains necessary for diagnosing Appendicitis, it should be seamlessly paired with the BPSA score to classify cases as complicated or non-complicated accurately. Using both scores strategically can influence patient management, guiding therapeutic decisions, incision designs, and choices between minimally invasive or conventional surgery. This scoring system is vital in optimising postoperative care and improving patient outcomes.[6]

Previous studies indicate that NLR values greater than 7, mainly those exceeding 12, can effectively differentiate between complicated and non-complicated cases. The immunological response to perforation is both aggressive and systemic. Neutrophils, as innate immune system components, work to eliminate bacteria. In contrast, lymphocytes, part of the adaptive immune system, tend to decrease in circulation as they migrate to infected tissues. Overall, NLR serves as an easily applicable parameter.[12–14]

Supported by Camacho-Cruz et al. and Sahbaz et al., this study concluded that leucocyte counts do not significantly differentiate between complicated and non-complicated Appendicitis. Additionally, the ratios of neutrophils showed no significant difference between the two groups. Therefore, leucocyte and neutrophil counts cannot be relied upon as diagnostic tests for acute Appendicitis. Elevated leucocyte levels are non-specific, exhibit low sensitivity, and may also increase in other infections, failing to distinguish between complicated and non-complicated Appendicitis.[15,16] Another study corroborated these results, indicating that higher leucocyte counts were significant in patients with complicated Appendicitis. An increased leucocyte count is often observed in complicated and uncomplicated Appendicitis. That is because individual differences in immune responses, influenced by factors like age, immune status, and the duration of symptoms, cause WBC counts to fail to differentiate the sensitivity and specificity to distinguish between the degree of Appendicitis. They need other parameters to reveal Appendicitis.[15,17]

Several studies have shown varying sensitivity and specificity of Ultrasound. Identifying the appendix in non-complicated Appendicitis is often a challenge. Free fluid on Ultrasound is an accurate indicator of complicated Appendicitis.[6]

Research demonstrates that mastocytosis and mast cell degranulation can differentiate between complicated and uncomplicated Appendicitis, consistent with our findings of higher levels in complicated cases. Mast cells interact with the enteric nervous system via the production of nerve growth factor (NGF) and promote inflammation, potentially accelerating progression to perforated Appendicitis.[18] While direct mast cell analysis cannot occur pre-surgery, histamine—chiefly produced by these cells—can serve as a valuable alternative for pre-surgical assessment. These inflammatory processes help explain the superior sensitivity and specificity of the BPSA score observed in our study.[19]

This study had several limitations. It was conducted in a single region, which may limit its generalizability. The sample size was relatively small, and there was no blinding

in the assessment process, introducing potential observer bias. In addition, possible variability in laboratory measurements could have influenced the results. For future research with larger samples across multiple centres, applying blinding protocols and standardising laboratory methods are essential to strengthen the findings and ensure the reliability of BPSA scoring.

CONCLUSION

The Alvarado score is crucial for diagnosing acute Appendicitis, followed by the BPSA score to differentiate between complicated and uncomplicated Appendicitis, paving the way for improved treatment and management strategies. Clinically, this combination can improve decision-making for surgical intervention and reduce unnecessary delays. Future research should involve larger, more diverse, multicentre populations to validate these findings and assess the consistency of BPSA performance. Further studies comparing BPSA with other diagnostic scores, such as AIRS and AAS, are also warranted to establish its relative diagnostic accuracy.

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ETHICAL APPROVAL

The Commission of Health Research Ethics, the Faculty of Medicine and Health, Universitas Lambung Mangkurat, Banjarmasin, Indonesia, declared this study ethically feasible. (No. 031/KEPK-FK ULM/EC/II/2023)

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Factors associated with tuberculosis treatment outcome under directly observed treatment short-course in Hulu Langat district, Selangor, Malaysia

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ABSTRACT

Introduction: Tuberculosis (TB) is a significant public health concern despite being a preventable and treatable infectious disease, as indicated by the rising incidence and mortality rates. This study aims to compare treatment outcomes by different Directly Observed Treatment, Short-Course (DOTS) supervisors and to identify significant factors associated with Tuberculosis treatment outcomes under DOTS in the Hulu Langat district.

Materials and Methods: A retrospective cohort study was conducted using registry-based data from the National Tuberculosis Registry (NTBR) between 2019 and 2023. Smear-positive PTB patients' sociodemographic, clinical and DOTS supervisor factors were extracted and analysed. Logistic regression was used to determine the significant factors associated with unsuccessful treatment outcomes. The data were analysed using SPSS version 29.

Results: Out of 5225 cases of Tuberculosis during the five years (2019-2023), 2548 cases met the inclusion criteria and were added to the analysis. The treatment success rate among Tuberculosis patients who enrolled in DOTS in the Hulu Langat district was 74.5%, comprising 70.8% who were cured and 3.6% who completed treatment. In contrast, 25.5% had unsuccessful treatment outcomes; 12.7% of patients died, followed by defaulters (8%), not evaluated or transferred out (2.6%), and treatment failure (2.3%). Compared to patients supervised by other DOTS supervisors, those supervised by family members had a significantly lower risk of unsuccessful treatment outcomes (AOR 0.34, 95% CI: 0.177-0.660, p=0.001). Besides that, significant factors associated with unsuccessful treatment outcomes include adult age (19-59 years) with an AOR of 3.60 (95% CI: 1.518-8.533, p=0.004), elderly age (≥60 years) with an AOR of 5.56 (95% CI 2.297-13.438, p<0.001), male gender (AOR 1.48, 95% CI: 1.183-1.838, p<0.001), foreigners (AOR 1.92, 95% CI: 2.366-3.687, p<0.001), rural residence (AOR 1.6, 95% CI: 1.090-2.349, p=0.016), HIV-positive (AOR 2.33, 95% CI: 1.508-3.586, p<0.001), moderate changes CXR findings (AOR 2.72, 95% CI: 1.245-5.945, p=0.012) and far-advanced CXR findings (AOR 5.30, 95% CI: 2.290-12.268, p<0.001). In contrast, the study found a significant decrease in the risk of unsuccessful treatment outcomes among Chinese ethnicity (AOR 0.74, 95% CI: 0.695-1.196, p=0.044) and tertiary education (AOR 0.55, 95% CI: 0.334-0.914, p=0.021).

Conclusion: This study challenges the traditional focus on healthcare worker DOTS by highlighting the effectiveness of family-supervised DOTS in improving TB treatment outcomes. The findings underscore the potential for family-DOTS to be scaled up as a complementary strategy within the national TB programme. Thus, the study recommends that the Ministry of Health adopt a risk-stratified framework based on sociodemographic and clinical factors to guide the assignment of DOTS supervisors, ensuring each patient receives the most suitable type of supervision throughout their TB treatment. Tailored TB control strategies should also expand risk stratification beyond existing MOH high-risk groups to include males, the elderly, foreign nationals, rural residents, and those with abnormal radiological findings, with strengthened screening and supervision to improve treatment outcomes.

KEYWORDS:
Public Health, Tuberculosis, Directly Observed Therapy, Risk Factors, Treatment Outcome

INTRODUCTION

Tuberculosis (TB) remains one of the deadliest infectious diseases globally.[1] Caused by Mycobacterium tuberculosis, it is primarily transmitted through airborne droplets and mainly affects the lungs. TB exists in two forms: latent TB infection (LTBI) and active TB disease, with approximately 5–10% of those with LTBI progressing to active disease.[2] Despite advances in medical treatment, TB continues to pose a significant global health challenge.

Worldwide, TB remains a public health crisis, particularly in regions like Southeast Asia, Africa, and the Western Pacific, which together account for the majority of TB cases. In 2022, over 10 million people were infected, and TB caused more than 1.3 million deaths, making it deadlier than HIV and malaria combined.[1] High-burden countries such as India, China, and Indonesia contribute significantly to these figures, with men aged 15 years and above representing the

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majority of TB cases. While TB affects all age groups, children and people living with HIV (PLHIV) are particularly vulnerable.[1]

The World Health Organization (WHO) has spearheaded global TB control efforts with strategies like the End TB Strategy, introduced in 2014. This initiative, aligned with the Sustainable Development Goals (SDGs), aims to reduce TB incidence and mortality by 2030. Despite these global efforts, many countries, including Malaysia, have not met the initial milestones set for 2020.[3] Tuberculosis is endemic in Malaysia, with an intermediate TB burden of fewer than 100 cases per 100,000 people annually.[1] While TB notification rates have increased from 63.5 cases per 100,000 people in 2021 to 77.8 cases per 100,000 people in 2022, the success of the national TB control program has been variable.[4]

Malaysia's healthcare system, comprising a robust public sector and a thriving private sector, has made significant strides in controlling TB. The National TB Control Programme (NTP), established in 1961, introduced key strategies like the Bacillus Calmette-Guérin (BCG) vaccination, Tuberculosis Information System (TBIS) and Directly Observed Treatment Short Course (DOTS) to improve TB management.[4] However, the treatment success rate (TSR) under DOTS has yet to reach the Ministry of Health's Key Performance Indicator (KPI) target of 90%, with a reported TSR of 85% in 2022.[4] Treatment outcomes also vary depending on the type of DOTS supervisor, with healthcare workers achieving better outcomes than non-governmental organisation (NGO) volunteers or family members, as more cases of loss to follow-up are seen when patients are supervised by NGO volunteers, family members and healthcare workers (6.4%, 4.7%, and 3.5%), respectively.[4]

In 2022, the Hulu Langat district recorded a TB incidence rate of 79 cases per 100,000 population, which is higher than the national average and also reported rising trends in multidrug-resistant TB, treatment defaulters, and TB-related deaths.[4,5] Although DOTS is the cornerstone of TB control, the type of supervisor, whether a healthcare worker, family member, NGO volunteer, or others, can influence treatment adherence and outcomes. Healthcare workers, as trained professionals, are better equipped to provide consistent support, education, and early intervention when adherence issues arise, leading to improved outcomes.[6] Studies from Pakistan and India have reported higher treatment success rates under healthcare worker-supervised DOTS, while a study in Thailand shows family-supervised DOTS was not significantly associated with successful outcomes.[6-8] In contrast, Malaysian studies have not differentiated supervisor types and found no significant association between DOTS supervision and treatment outcomes.[9-12] This highlights a gap in local evidence, warranting district-level analysis that accounts for sociodemographic and clinical confounders to determine the comparative effectiveness of different DOTS supervisor categories.

This study aims to examine the relationship between DOTS supervision types and TB treatment outcomes in Hulu Langat, Selangor. It will also identify risk factors associated with TB treatment outcomes to inform future strategies for improving the management and control of TB in Malaysia.

MATERIALS AND METHODS

This study employed a retrospective cohort design, which comprised all pulmonary TB (PTB) cases reported to the Hulu Langat District Health Office between January 1, 2019, and June 30, 2023. Data were sourced from the National Tuberculosis Registry (NTBR), which is the online platform of the Tuberculosis Information System (TBIS).

The study focused on Hulu Langat, the second most populated district in Selangor, with approximately 1.4 million residents, consisting primarily of Bumiputera (63%), Chinese (28.1%), Indian (8.2%), other ethnicities and foreigners (0.7%).[13] Hulu Langat is an urban district, with six subdistricts, of which Kajang, Ampang, and Cheras are the most densely populated and report the highest TB cases. The study population included all confirmed PTB smear-positive cases, new or relapsed, who enrolled in DOTS during the study period. Excluded were patients with extra-pulmonary TB (EPTB), multidrug-resistant TB (MDR-TB), and PTB category cases after default, failed treatment and changed diagnosis. These exclusion criteria followed the World Health Organization's (WHO) criteria for calculating Treatment Success Rate (TSR).[14]

The study employed universal sampling, including all PTB cases recorded in NTBR that met the inclusion criteria. The minimum sample size was calculated using the OpenEpi sample size calculator for cohort studies (Version 3.01), referencing treatment outcome differences reported by a previous study.[9] With 95% confidence, 80% power, and an odds ratio of 2.6, the required sample size to detect a difference in unsuccessful outcomes between males (28%) and females (13%) was 332 after an estimated 30% was added to the final sample size estimates to account for potential incomplete data.

The dependent variable was TB treatment outcomes, which were defined according to the World Health Organization (WHO) standard definitions:[1]

1. Cured: A bacteriologically confirmed pulmonary TB patient who was smear- or culture-negative in the last month of treatment and on at least one previous occasion.
2. Completed treatment: A patient who finished the full course of TB treatment but lacks bacteriological confirmation of cure, although at least one earlier test was negative.
3. Treatment failure: A TB patient whose sputum smear or culture was positive at month five or later during treatment.
4. Died: A patient who died from any cause during TB treatment.
5. Treatment default: A patient who stopped TB treatment for at least two continuous months after being registered for treatment.
6. Transferred out / Not evaluated: A patient who was transferred to another facility or whose treatment outcome was unknown.

For analysis, both cured and completed treatment outcomes were categorised into successful treatment outcomes, while all other outcomes were categorised into unsuccessful treatment outcomes.

Table I: Sociodemographic and Clinical Characteristics of Patients with Tuberculosis, and Their Treatment Outcomes

Variables	n	%
Age	Mean 43.09	SD 16.5
Age group		
0-18	95	3.7
19-59	1987	78
≥60	462	18.1
Gender		
Male	1682	66
Female	866	34
Citizenship		
Citizen	2035	79.9
Non-citizen	513	20.1
Race		
Malay	1243	48.8
Chinese	453	17.8
Indian	215	8.4
Others	122	4.8
Foreigners	515	20.2
Residential Area		
Urban	2399	94.2
Rural	145	5.7
Educational Level		
No education	361	14.2
Primary	136	5.3
Secondary	1502	58.9
Tertiary	518	20.3
Monthly Income		
MYR ≤ 1500	1112	43.6
MYR 1501-3000	1392	54.6
MYR ≥3001	44	1.7
Employment status		
Employed	1868	73.3
Unemployed	680	26.7
Healthcare Worker		
Yes	23	0.9
No	2525	99.1
Smoking		
Yes	826	32.4
No	1722	67.6
Bcg scar		
Yes	2135	83.8
No	413	16.2
Diabetes		
Yes	725	28.5
No	1821	71.5
HIV status		
Yes	108	4.2
No	2431	95.4
CXR findings		
No changes	78	3.1
Minimal Changes	1244	48.8
Moderate Changes	1043	40.9
Far-Advanced Changes	167	6.6
DOTS supervisor		
Healthcare worker	1782	69.9
Family	712	27.9
NGO	6	0.2
Others	48	1.9
TB Treatment Outcomes		
Successful Treatment Outcome	1897	74.5
Cured	1804	70.8
Completed Treatment	93	3.6
Unsuccessful Treatment Outcome	651	25.5
Death	323	12.7
Treatment Failure	58	2.3
Treatment Default	205	8.0
Transferred Out/Not evaluated	65	2.6

Table II: Distribution and Simple Logistic Regression of Factors Associated With Tuberculosis Treatment Outcome

	Unsuccessful Treatment outcome n (%)	Successful Treatment Outcome n (%)	OR (95%CI)	p-value
Age group				
0-18	6 (6.3)	89 (93.7)	RC	
19-59	503 (25.3)	1484 (74.7)	5.03 (2.186, 11.563)	<0.001
≥60	141 (30.5)	321 (69.5)	6.52 (2.785, 15.245)	<0.001
Gender				
Female	163 (18.8)	703 (81.2)	RC	
Male	488 (29)	1194 (71)	1.76 (1.443, 2.154)	<0.001
Citizenship				
Citizen	427 (21)	1608 (79)	RC	
Non-citizen	224 (43.7)	289 (56.3)	2.92 (2.379, 3.581)	<0.001
Race				
Malay	257 (20.7)	986 (79.3)	RC	
Chinese	87 (19.2)	366 (80.8)	0.91 (0.695, 1.196)	0.505
Indian	56 (26)	159 (74)	1.35 (0.968, 1.887)	0.077
Others	27 (22.1)	95 (77.9)	1.09 (0.696, 1.708)	0.706
Foreigners	224 (43.5)	291 (56.5)	2.95 (2.366, 3.687)	<0.001
Residential Area				
Urban	595 (24.8)	1804 (75.2)	RC	
Rural	54 (37.2)	91 (62.8)	1.80 (1.269, 2.551)	<0.001
Educational Level				
Primary	43 (31.6)	93 (68.4)	RC	
Secondary	370 (24.6)	1132 (75.4)	0.71 (0.483, 1.034)	0.074
Tertiary	63 (12.2)	455 (87.8)	0.30 (0.191, 0.468)	<0.001
No education	166 (46)	195 (54)	1.84 (1.214, 2.792)	0.004
Monthly Income				
MYR ≥ 3001	4 (9.1)	40 (90.9)	RC	
MYR 1501-3000	263 (18.9)	1129 (81.1)	2.33 (0.826, 6.568)	0.110
MYR ≤ 1500	384 (34.5)	728 (65.5)	5.28 (1.873, 14.852)	0.002
Employment Status				
Employed	418 (22.4)	1450 (77.6)	RC	
Unemployed	233 (34.3)	447 (65.7)	1.81 (1.492, 2.191)	<0.001
Healthcare Worker				
Yes	2 (8.7)	21 (91.3)	RC	
No	649 (25.7)	1876 (74.3)	3.63 (0.849, 15.534)	0.082
Smoking				
No	408 (23.7)	1314 (76.3)	RC	
Yes	243 (29.4)	583 (70.6)	1.34 (1.114, 1.617)	0.002
BCG scar				
Yes	470 (22)	1665 (78)	RC	
No	181 (43.8)	232 (56.2)	2.76 (2.219, 3.443)	<0.001
Diabetes status				
No	464 (25.5)	1357 (74.5)	RC	
Yes	187 (25.8)	538 (74.2)	1.02 (0.835, 1.238)	0.870
HIV status				
No	600 (24.7)	1831 (75.3)	RC	
Yes	47 (43.5)	61 (56.5)	2.35 (1.590, 3.478)	<0.001
CXR Findings				
No lesion	8 (10.3)	70 (89.7)	RC	
Minimal changes	271 (21.8)	973 (78.2)	2.44 (1.158, 5.127)	0.019
Moderate changes	296 (28.4)	747 (71.6)	3.47 (1.648, 7.294)	0.001
Far-Advanced Changes	72 (43.1)	95 (56.9)	6.63 (3.001, 14.656)	<0.001
DOTS Supervisor				
Others	23 (47.9)	25 (52.1)	RC	
NGO	2 (33.3)	4 (66.7)	0.54 (0.091, 3.253)	0.504
Family	108 (15.2)	604 (84.8)	0.19 (0.106, 0.355)	<0.001
Healthcare Worker	518 (29.1)	1264 (70.9)	0.45 (0.251, 0.792)	0.006

Note: Variables with p-value < 0.25 in the simple logistic regression were selected for inclusion in the multivariable model
RC: Reference Category

Table III: Multiple Logistic Regression Analysis of Factors Associated With Unsuccessful TB Treatment Outcome

Variables	AOR	95% CI	p-value
Age group			
0-18	RC		
19-59	3.60	(1.518, 8.533)	0.004
≥60	5.56	(2.297, 13.438)	<0.001
Gender			
Female	RC		
Male	1.48	(1.183, 1.838)	<0.001
Race			
Malay	RC		
Chinese	0.74	(0.550, 0.992)	0.044
Indian	1.21	(0.848, 1.728)	0.293
Others	1.11	(0.693, 1.783)	0.660
Foreigners	1.92	(1.374, 2.669)	<0.001
Residential Area			
Urban	RC		
Rural	1.60	(1.090, 2.349)	0.016
Educational Level			
Primary	RC		
Secondary	0.92	(0.604, 1.397)	0.690
Tertiary	0.55	(0.334, 0.914)	0.021
No education	1.26	(0.788, 2.015)	0.334
Monthly Income			
MYR ≥ 3001	RC		
MYR 1501-3000	1.05	(0.356, 3.065)	0.937
MYR ≤ 1500	1.72	(0.580, 5.075)	0.329
Employment Status			
Employed	RC		
Unemployed	0.92	(0.694, 1.211)	0.542
Healthcare Worker			
Yes	RC		
No	1.05	(0.233, 4.697)	0.954
Smoking			
No	RC		
Yes	1.07	(0.851, 1.338)	0.575
BCG scar			
Yes	RC		
No	1.10	(0.726, 1.660)	0.658
HIV status			
No	RC		
Yes	2.33	(1.508, 3.586)	<0.001
CXR Findings			
No changes	RC		
Minimal changes	2.03	(0.929, 4.430)	0.076
Moderate changes	2.72	(1.245, 5.945)	0.012
Far-Advanced Changes	5.30	(2.290, 12.268)	<0.001
DOTS Supervisor			
Others	RC		
NGO	0.33	(0.053, 2.122)	0.245
Family	0.34	(0.177, 0.660)	0.001
Healthcare Worker	0.67	(0.358, 1.256)	0.212

Note: Level of significance $p < 0.05$
RC: Reference Category

Independent variables included a range of sociodemographic, clinical and DOTS supervision factors. Sociodemographic factors included age, gender, citizenship, race, residential area, education level, monthly income, employment status and healthcare worker status. Clinical factors comprised smoking status, presence of a Bacillus Calmette-Guérin (BCG) scar, diabetes status, HIV status, and chest X-ray (CXR) findings. The DOTS supervisor categories included healthcare workers, family members, NGOs or others.

The study relied on secondary data from NTBR. After obtaining approval from the Medical Research and Ethics Committee (MREC) and the Selangor State Health Department, data were downloaded from NTBR and transferred into Microsoft Excel format. A structured data collection form was used to extract relevant variables. Data were thoroughly cleaned, including identifying and correcting errors or inconsistencies. As the proportion of missing data was less than 1% across four variables, age, HIV, diabetes and CXR findings, listwise deletion was applied. Given the minimal extent of missingness, the impact on statistical power and validity of estimates was considered negligible, and advanced methods such as multiple imputation were not deemed necessary.

Data were analysed using IBM SPSS Statistics for Windows, version 29 (IBM Corp., Armonk, NY, USA). Descriptive statistics summarised continuous variables like age as means and standard deviations, while the rest of the categorical variables were presented as frequencies and percentages. For inferential statistics, bivariate analysis uses simple logistic regression to examine associations between independent variables and treatment outcomes. Variables with a p-value < 0.25 were considered for multivariate analysis to prevent premature exclusion of potential predictors.[9]

Multivariate analysis was then employed using multiple logistic regression with stepwise backwards selection to identify significant predictors of unsuccessful treatment outcomes. Variables with a p-value < 0.05 in the final model were deemed statistically significant. Model fitness was assessed using the Hosmer–Lemeshow goodness of fit test, classification tables, and the area under the ROC curve. A non-significant Hosmer–Lemeshow test (p>0.05), a classification accuracy exceeding 70%, and an area under the ROC curve > 0.5 indicated a well-fitted model.[9]

RESULTS

Table I presents the sociodemographic and clinical characteristics of 2,548 tuberculosis (TB) patients in Hulu Langat. The mean age was 43.1 years (SD: 16.5), with the majority aged 19–59 years (78.0%). Males made up 66.0% of the cases. Most patients were Malaysian citizens (79.9%) and of Malay ethnicity (48.8%). A large proportion resided in urban areas (94.2%). Regarding education, 58.9% had secondary-level education, and 54.6% had a monthly income between MYR 1,501 and MYR 3,000. The majority (73.3%) were employed. In terms of clinical characteristics, 28.5% had diabetes mellitus and 4.2% were HIV positive. Chest X-ray abnormalities were reported in 96.3% of patients, and 32.4% were smokers. Most patients (69.9%) received directly observed treatment (DOTS) supervised by healthcare workers, while others were supervised by family members (27.9%), NGOs (0.2%) or others (1.9%). Overall, the treatment success rate was 74.5%, while 25.5% experienced unsuccessful treatment outcomes, including death, default, treatment failure, or not evaluated.

Table II presents the distribution of tuberculosis (TB) treatment outcomes by sociodemographic, clinical, and DOTS supervisor factors, with p-values from simple logistic regression. Regarding DOTS supervision, patients monitored by family members (15.2%, p<0.001) had lower proportions of unsuccessful treatment outcomes compared to those supervised by healthcare workers (29.1%, p=0.006). Unsuccessful treatment outcomes were more frequent among patients aged ≥60 years (30.5%, p<0.001), males (29%, p<0.001), non-citizen (43.7%, p<0.001), the unemployed (34.3%, p<0.001), those with monthly income ≤ MYR 1500 (34.5%, p=0.002), rural residence (37.2%, p<0.001) and individuals with no formal education (46%, p=0.004). Clinically, higher proportions of unsuccessful outcomes were seen among smokers (29.4%, p=0.002), patients with no BCG scar (43.8%, p<0.001), HIV-positive individuals (43.5%, p<0.001) and far-advanced CXR changes (43.1%, p<0.001).

Table III presents the results of multiple logistic regression analysis conducted to adjust for potential confounding factors. Several variables were independently associated with unsuccessful treatment outcomes. Family-supervised DOTS remained significantly associated with a lower likelihood of unsuccessful outcomes (p=0.001). Furthermore, independent risk factors for unsuccessful treatment outcome included adults aged 19–59 years (p=0.004), elderly individuals aged ≥60 years (p<0.001), male gender (p<0.001), non-Malaysian nationality (p<0.001), and residence in rural areas (p=0.016). Clinical factors significantly associated with unsuccessful treatment outcomes included HIV positivity (p<0.001), as well as moderate (p=0.012) and far-advanced (p<0.001) chest X-ray findings. Conversely, a significantly lower likelihood of unsuccessful treatment outcome was observed among individuals of Chinese ethnicity (p=0.044) and those with tertiary education (p=0.021).

The model demonstrated a good fit, as indicated by a non-significant Hosmer–Lemeshow goodness-of-fit test (p=0.175). It correctly classified 75.6% of the cases, with an area under the ROC curve (AUC) of 0.734, reflecting acceptable discriminatory power.

DISCUSSION

The treatment success rate among TB patients who enrolled on DOTS in the Hulu Langat district was 74.5%. The success rate fell below the WHO target of more than 90%.[1] The results were comparable to prior local research, with success rates of 77.2% and 76% respectively.[9,12] However, a local study and another study in Indonesia revealed a better success rate and achieved the WHO's aim.[15,16] The comparisons revealed inadequate TB control in the Hulu Langat district, highlighting the need for improvement.

The leading cause of unsuccessful treatment outcomes in our study was death (12.7%), which is higher than the 10% reported in the national studies.[10,11] This growing trend contradicts the World Health Organization's End TB plan milestone, which seeks to reduce mortality by 90% by 2030.[3] The rest of the unsuccessful outcomes are treatment default (8%), not evaluated or transferred out (2.6%), and treatment failure (2.3%). Previous research in Ethiopia and Morocco found that the defaulter group had the largest rate of unsuccessful treatment outcomes.[17,18] Previous literature consistently demonstrates that gaps in the TB care cascade, especially at diagnosis and treatment, high rates of treatment interruption and loss to follow-up, persistent barriers among high-risk groups (such as prisoners, migrants, and people living with HIV), and the growing threat of drug-resistant TB.[10,11,19,20] Socioeconomic factors, health system limitations, knowledge gaps, and stigma further hinder program effectiveness.[21-23] Interventions that are patient-centred, community-based, and leverage technology have shown the most significant promise in improving outcomes, particularly when tailored to local contexts and vulnerable populations.[24]

Given the unachievable success and mortality rates from 2019 to 2023, it is crucial to investigate the evidence on the most effective DOTS supervisors and the significant factors leading to unsuccessful treatment outcomes. This will help develop effective interventions and strategies to reduce TB morbidity and mortality. Based on the final model of the multiple logistic regression, this study found that a significant decrease in the risk of unsuccessful treatment outcomes among family-DOTS supervisors as compared with other DOTS supervisors. Besides that, unsuccessful treatment outcomes were significantly associated with the adult and elderly age group, male gender, foreigners, rural residential area, HIV-positive, moderate and far-advanced changes in CXR findings. In contrast, the study also found a significant decrease in the risk of unsuccessful treatment outcomes among individuals of Chinese ethnicity and those with tertiary education.

Regarding the comparison of DOTS supervisors, DOTS by healthcare workers reduced the odds of unsuccessful outcomes by 55% (OR: 0.45), while family-supervised DOTS showed an 81% reduction (OR: 0.19). NGO-supervised DOTS (OR: 0.54) was not statistically significant. However, multivariate analysis confirmed that only family-supervised DOTS remained significant, with an AOR of 0.34, reducing the risk of unsuccessful outcomes by 66%. Most of the study's findings, locally and abroad, show that DOTS supervisors were not significantly associated with treatment outcomes.[6,7,9-11] Our study suggests that family-supervised DOTS is more effective in Hulu Langat or other similar settings in Malaysia, as family members provide consistent support to enhance adherence and outcomes. The reduced significance of DOTS by healthcare workers in the multivariate analysis implies that other factors, such as patient-provider relationships and socioeconomic status, play a more crucial role in determining treatment success.

Culturally, strong family ties in Malaysia provide emotional support, reminders, and encouragement that help patients adhere to and complete their TB treatment.[25] Structurally, family involvement serves as a vital link between patients and healthcare providers, assisting with overcoming stigma, financial difficulties, and ensuring timely access to care for better treatment outcomes.[25] While family-supervised DOTS shows better outcomes, healthcare worker-supervised DOTS remains crucial, particularly for non-compliant patients. In contrast, family DOTS may benefit well-educated patients with work commitments. Enhancing both supervision types to complement each other and incorporating family-centred approaches into TB programs through routine counselling sessions, training family members, and recognising their role can further strengthen treatment success in Malaysia's culturally diverse settings.[25]

Prior research has indicated that older individuals diagnosed with TB exhibited a significant mortality rate.[9,10,17,26] Older age was found to be a significant factor associated with unsuccessful treatment outcomes in this study. Adult patients aged 19-59 had 3.6 times higher odds for unsuccessful treatment outcomes compared to those aged 0-18. For elderly patients aged over 60 years, the odds increase to 5.6 times, indicating a higher likelihood of unsuccessful outcomes as age increases. The elderly's susceptibility to TB treatment failure is driven by immune system decline due to ageing and is powerfully compounded by comorbidities like malnutrition, diabetes, and cancer. These factors increase the risk of initial infection, progression to active disease, and failure to respond effectively to standard TB therapies.[27] To reduce unsuccessful TB outcomes in the elderly, need to focus on infection control to stop the transmission, systematic screening and preventive therapy for high-risk groups, rapid diagnosis with effective treatment and close monitoring, and tailored programmatic management addressing their specific needs and comorbidities.[28]

Besides that, the adult group also show a significant association with unsuccessful outcomes, and these findings are similar to a study done in Brazil that shows young adults are associated with unsuccessful treatment outcomes.[29] A possible explanation is that the young adult group are more likely to be non-compliant and may miss follow-up appointments due to work or other commitments.[9,11] Public health strategies should support older adults by improving healthcare access, managing comorbidities, and providing nutritional aid. For young adults, efforts should focus on enhancing treatment adherence through flexible scheduling, workplace or family support, and technology-based tools like reminders or telemedicine.[24]

The male predominance in the unsuccessful treatment outcomes in our study concurs with the TB burden and mortality trend observed nationally and worldwide.[1,9-11] Men were found to be a significant factor associated with unsuccessful treatment outcomes in this study, with 1.5 times higher odds as compared to women. Men face a higher TB burden and unsuccessful outcomes due to risk behaviours and barriers like stigma and financial constraints.[30] To address these disparities, gender-sensitive interventions such as risk reduction campaigns and strategies to improve healthcare access are essential and recommended by frameworks advocating for gender-responsive TB programs.[30]

This study also found that non-citizens were significantly associated with unsuccessful TB treatment outcomes, with a 1.9 times higher risk as compared to the local citizens, aligning with multiple studies from Malaysia and Busan.[9-11,31] Malaysia's industrialisation has attracted many job-seeking immigrants, increasing TB transmission risks. These individuals often face barriers like low income, limited healthcare access, and poor education, leading to inadequate treatment adherence.[9] Public health policies must ensure inclusive TB services, offering culturally appropriate education, legal protections, and social support for migrants to improve outcomes and reduce transmission.[32]

Our findings of ethnicity show that Chinese ethnicity had significantly lower odds (26.2%) of experiencing unsuccessful treatment outcomes for TB compared to other ethnic groups, such as Malays and Indians, who did not show significant differences in treatment outcomes. Another study conducted in Malaysia and the neighbouring country that shares the same ethnicities as Singapore indicates that non-Malay patients, including Chinese, had lower odds of recurrent TB and better treatment outcomes, possibly due to factors such as healthcare access and cultural attitudes towards treatment adherence.[10,32-34]

Besides that, our study indicates that patients living in rural areas had 1.6 times higher odds of experiencing unsuccessful treatment outcomes for tuberculosis compared to those in urban areas. The national study and other countries in India, England and Africa also showed that rural populations often face greater challenges in TB management that can lead to unsuccessful outcomes compared to their urban counterparts.[11,22,35,36] Public health strategies should focus on improving healthcare infrastructure in rural areas, training healthcare workers to manage TB more effectively, and implementing community-based TB programs that can reach remote populations.[11,22,35,36]

Educational attainment is also a significant factor associated with TB treatment outcomes in Hulu Langat District, Selangor. Patients with tertiary education had 44.8% lower odds of unsuccessful treatment outcomes compared to those with primary education. This finding is similar to the national study that shows a higher risk of unsuccessful outcomes among low-education patients.[10,11] Higher education's link to better TB outcomes highlights the importance of health literacy. Public health efforts should focus on educating patients and the public about treatment adherence, early symptom recognition, and the risks of non-compliance, especially for those with lower education levels.[19,21]

TB-HIV co-infection also had significant impacts on TB treatment outcomes, as the findings of our study indicate that HIV-positive patients had 2.3 times higher odds of experiencing unsuccessful TB treatment outcomes compared to HIV-negative patients. Previous studies in Malaysia, South Korea and Africa also show similar significant findings of association between HIV-positive patients and unsuccessful treatment outcomes.[9-11,22,37-39] HIV co-infection significantly worsens TB treatment outcomes due to impaired immunity, higher drug resistance, and reduced adherence.[40] This underscores the need for integrated TB-HIV care, early HIV diagnosis, and continuous monitoring of collaborative efforts to improve outcomes.[22]

CXR findings were significantly associated with TB outcomes, with moderate changes increasing odds by 2.7 times and far-advanced changes by 5.3 times. Consistent with previous studies, these findings highlight that extensive lung damage and higher bacterial loads complicate treatment.[9-11,37] Early diagnosis, close monitoring of significant CXR abnormalities, and routine use of radiological assessments to guide treatment decisions are crucial for improving outcomes.[37]

This study had certain limitations. Since this is a retrospective cohort study using secondary data from a surveillance database, some variables, such as underlying chronic illness like malnutrition, and some behavioural traits like alcohol or drug intake, were not easily accessible for examination. Apart from that, the study included only PTB Smear Positive cases; therefore, the outcome cannot be applied to other types of TB. Furthermore, using secondary data limits the ability to establish causality, as it only allows for analysis of associations without confirming cause-and-effect relationships; thus, recommendations for future studies are to consider a longitudinal design to assess causality better.

CONCLUSION

This study challenges the traditional focus on healthcare worker DOTS by highlighting the effectiveness of family-supervised DOTS in improving TB treatment outcomes. The findings underscore the potential for family-DOTS to be scaled up as a complementary strategy within the national TB programme. Thus, this study proposes that the Ministry of Health adopt a risk-stratification framework based on sociodemographic and clinical factors to guide the assignment of DOTS supervisors, ensuring each patient receives the most suitable type of supervision throughout their TB treatment. This study also showed that unsuccessful treatment outcomes were significantly associated with the adult and elderly age group, male gender, foreigners, rural residential area, HIV-positive, moderate and far-advanced changes in CXR findings, but a significant decrease in the risk of unsuccessful treatment outcomes among the Chinese ethnicity and tertiary education. Tailored TB control strategies should expand risk stratification beyond existing MOH high-risk groups to include males, the elderly, foreign nationals, rural residents, and those with abnormal radiological findings, with strengthened screening and supervision to improve treatment outcomes.[4]

ETHICS APPROVAL

Ethics approval was obtained from Medical Research & Ethics Committee Ministry of Health, Malaysia (NMRR ID-24-00625-IVT(IIR).

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AUTHOR CONTRIBUTIONS

MHSAJ and RAZ conceptualized and designed the study. ZS, NAH, and MKHZ were responsible for data acquisition. MHSAJ conducted the data analysis and prepared the initial draft of the manuscript. All authors critically revised the manuscript and approved the final version for submission.

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eDenguev2 Database: Factors associated with the occurrence of dengue hotspot localities in the Selangor State in 2022

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ABSTRACT

Introduction: The dengue outbreak in Selangor, Malaysia, has been a significant concern in recent years. Selangor has reported the highest number of dengue cases in the country, with over 22,000 cases in 2023 alone. The outbreak in Selangor has been overwhelming, and the outbreak was divided into controlled outbreaks, uncontrolled outbreaks, and hotspots according to the onset of the outbreak. Multiple factors have contributed to the occurrence of dengue hotspots in Selangor. This study aims to determine the factors associated with the occurrence of dengue hotspot localities in Selangor for the year 2022.

Materials and Methods: This is a cross-sectional study among dengue outbreak localities in Selangor that utilized data from the eDenguev2 database from the Selangor State Health Department for the year 2022. Data collection and analysis were conducted from April 2024 until June 2024. The first (index) case from each dengue outbreak localities of controlled outbreak and hotspot localities in Selangor for 2022 were identified and analyzed to determine the factors associated with the occurrence of hotspot localities.

Results: 391 (14%) out of 2751 dengue outbreak localities as hotspot localities. According to the demographic analysis of patients in these hotspot localities, the majority were adults aged 26–35 years old (24.04%), with a mean age of 33 years. The majority were female (57.30%), employed (58.57%), Malaysian nationals (93.09%), and of Malay ethnicity (62.15%). Geographically, the Petaling District reported a significant portion of hotspot localities (40.4%). A large number of cases originated in strata housing (67.8%) and urban areas (93.5%), with a delay of more than 48 hours for the commencement of source elimination activities. Notably, most hotspot areas did not have any possible breeding sites (99.2%), had low entomological parameters: Aedes Index (AI), Bruteu Index (BI), and Container Index (CI), and there were no delays in reporting cases, investigating them, verifying them, and registering them. The occurrence of hotspot localities was significantly associated with cases originating from urban areas, with a p-value of 0.048 and an adjusted odds ratio (aOR) of 2.343 (95% CI: 1.006, 5.456).

Conclusion: Urban areas are significantly more likely to become a hotspot for dengue outbreaks. Public health implications highlight the need for urban-focused interventions and rapid response. Broader strategies, such as GIS mapping and community engagement, remain relevant, though not directly assessed here.

KEYWORDS:
Dengue, dengue outbreak, hotspot localities, Selangor

INTRODUCTION

Dengue fever is escalating as a critical global health challenge, particularly in tropical and subtropical urban regions.[1] In 2023, it caused over 5 million reported infections and 5,500 deaths worldwide, with record highs continuing into 2024 over 12 million cases reported to date.[2] The disease spread primarily by Aedes aegypti and Aedes albopictus, concentrated in dense human habitats and is intensified by climate change and rapid urbanization.[3] Without a specific antiviral treatment, dengue management relies heavily on vector control, early detection, and proper clinical care to reduce fatalities. In Southeast Asia, especially Malaysia, dengue remains endemic with significant public health consequences. In 2023, Malaysia recorded 123,133 dengue cases an 86% increase compared to 2022, with approximately 100 deaths.[4] Selangor state consistently bears the national burden of dengue, characterized by persistently high incidence and challenges in outbreak control.[5] Despite efforts under the National Dengue Control Plan 2022–2026, Selangor has struggled to meet the goal of containing 95% of outbreaks within 14 days.[6]

In Malaysia, a dengue outbreak is defined as two or more cases occurring within 200 meters and 14 days; localities are subsequently classified as controlled (no new cases after 14 days), uncontrolled (cases persist beyond 14 days), or hotspots (cases continue for at least 30 days).[7] In Selangor in 2021 alone, there were 2,888 controlled, 492 uncontrolled, and 434 hotspot outbreak localities.[5] Several recent studies have examined factors contributing to dengue outbreaks. Timeliness of notification and response is key, as delays in initiating vector control can allow wider transmission.[8] Urban ecological factors, such as high-rise living and dense residential clusters, have been shown to facilitate breeding of Aedes mosquitoes.[9-11] Additionally, land-use practices like unmanaged open spaces, stagnant water areas, and construction zones are frequently associated with prolonged outbreaks.[5,12] Human-related factors such as gender and

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activity patterns also play a role. Studies show that adult males, particularly those involved in outdoor or mobile occupations, are more likely to be exposed to infected mosquitoes, contributing to transmission in certain localities.[5,13]

Despite this growing body of literature, few studies focus specifically on the localities where outbreaks persist beyond the national control threshold of 14 days. Understanding what differentiates short-duration outbreaks from long-lasting hotspot localities can inform targeted public health responses. Therefore, this study aims to investigate the characteristics that differentiate hotspot localities in Selangor during 2022. By evaluating variables across four domains which are patient demographics, vector control practices, environmental conditions, and land-use patterns, it can explain why some localities rebound from outbreaks swiftly, while others continue long-term transmission beyond 30 days.

MATERIALS AND METHODS

Study design and study population

This is retrospective case-control design study used Selangor eDenguev2 database. The eDenguev2 database is an online system consisting of patient data, vector control data, and environmental data that was developed in January 2009. It aims to systematically and in real-time manage dengue case registrations in Malaysia, ensuring effective surveillance at district, state, and national levels.

The study population consisted of localities with the status of controlled outbreaks and hotspots in Selangor for the year 2022. The sampling unit included is the first (index) case of controlled outbreak localities and hotspot localities in Selangor for the year 2022 that were thoroughly investigated by the district health offices, with complete investigation reports submitted to the Selangor State Health Department. The study period was from 1 March 2024 until 1 July 2024, which was the most recent data available at the time of the research permission application.

Sample size

Based on the study by Priya et al. (2023), which noted that the odds ratio for students to contribute to the dengue outbreak was 1.729 compared to the unemployed population.[14] The estimated sample size using an odds ratio sample size calculator (Fleiss with continuity correction) was 310 cases and 310 controls. This calculation assumed a significance level of 0.05 (two-tailed analysis) and 80% power. Adjusting for a 20% data loss due to redundant or missing data, the required sample size for this study was 372 per group. Universal sampling was employed to select eligible cases for hotspots, and simple random sampling was employed to select eligible cases from controlled outbreaks. Within controlled outbreak localities, simple random sampling was done using SPSS, and the amount yielded was as large as the hotspot localities.

Data collection and data management

According to National Dengue Strategic Plan 2022-2026, the controlled outbreak was defined as the localities where there is no dengue case is notified after the 14th day from the notification date of the second case, while hotspot is a locality that lasts for more than 30 days from the date the outbreak started.[15]

The independent variables in this study were grouped into four domains: patient factors, which include age group, gender, occupational status, and the time taken to seek treatment; vector control factors, consisting the time taken for case notification, the initiation of case investigation, and the start of source reduction activities; environmental factors, involving the type of housing and population density in the outbreak areas; and land use factors, focusing on the presence of high-risk breeding sites. The operational definitions of the variables studied are presented in Table I. Data management procedures are illustrated in Figure 1.

Statistical analysis

All statistical analyses were conducted using IBM SPSS Statistics version 29. Continuous variables were described using means and standard deviations, while categorical variables were summarized as frequencies and percentages. Group comparisons were performed using independent t-tests for continuous variables and Chi-square or Fisher's exact tests for categorical variables, where appropriate.

To identify factors associated with hotspot localities, simple logistic regression was first applied to calculate crude odds ratios (cORs) and 95% confidence intervals (CIs). Variables with a p-value < 0.25 in the univariate analysis were included in the multivariable logistic regression model. A backward stepwise selection approach was used, and variables with a p-value < 0.05 were retained in the final model. Adjusted odds ratios (aORs) with 95% CIs were reported. Multicollinearity among predictor variables was assessed using collinearity diagnostics, with no evidence of multicollinearity observed. Interaction terms were tested but found to be non-significant. Model fit was evaluated using the Hosmer–Lemeshow goodness-of-fit test (p=0.499), and explanatory power was assessed using the Pseudo R^2 (Cox & Snell). Model discrimination was evaluated using the area under the receiver operating characteristic (ROC) curve, which was 52.3%. No influential outliers were identified based on Cook's distance.

Ethics Application

This study was registered with the National Medical Research Register (Ref. No: NMRR ID- 24-00237-IF2). Ethical approval was obtained from Medical Research Ethics Committee (Ref. No: NMRR ID- 24-00237-IF2) and the Faculty Research Ethics Committee (Ref. No: 100 - FPR (PT.9/19) (FERC-EX-24-09)). Selangor State Health Department granted permission to utilise data in eDenguev2 registry for this study. This study adhered to the Malaysian Code of Responsible Conduct in Research to ensure data confidentiality and compliance with ethical standards throughout the research. This study utilized anonymized, de-identified secondary data, aggregated to prevent re-identification. This method preserves confidentiality and aligns with ethical research standards, eliminating the need for informed consent.

Table I: Operational Definition

No.	Variables	Definition
1.	District Population Density	a) Less density population district Districts of less than 500,000 population which are Hulu Selangor, Kuala Selangor, Kuala Langat,Sepang, Sabak Bernam. b) High density population district Districts of more than 500,000 population which are Petaling, Hulu Langat, Klang, Gombak
2.	Duration taken to seek treatment	Data is determined by subtracting the date of diagnosis from the date of onset.
3.	Duration taken for case notification	Data is determined by subtracting the notification date to the date of diagnosis
4.	Duration taken for initiation of case investigation, case verification and case registration in eDengueV2	Data is determined by subtracting the date of case investigation to the date of case notification
5.	Duration taken for commencement of vector control activities	Data is determined by subtracting the date of first source elimination activity to the date of case registered in eDengueV2 database
6.	Aedes Index (AI)	Is defined as the percentage of premises positive for Aedes larval breeding in a locality with < 1 % (low transmission and ≥ 1% (high transmission). Number of house positive dengue breeding divided with number of house inspected x 100 %
7.	Bruteau Index (BI)	Number of container positive with dengue breeding divided with number of house inspected x 100 house
8.	Container Index (CI)	Number of container positive with dengue breeding divided with number of container inspected x 100%
9.	Presence of potential breeding sites	Presence of places that have the potential to become breeding ground - construction site, abandoned housing project, cemetery, dumping ground, land/empty land, recreational park
10.	Residential Area	Urban area: Gazette areas with their adjoining built-up areas, which had a combined population of 10,000 or more 16

RESULTS

Of the 782 dengue outbreak localities reported in Selangor in 2022, 50.8% were classified as hotspot areas. Most cases involved individuals aged 26–35 years (24.0%), with a mean age of 33 years. Most patients were female (57.3%), employed (58.6%), and of Malay ethnicity (62.2%). Geographically, a significant proportion of cases originated from the Petaling district (37.2%), with a high concentration in urban localities (93.5%) and strata housing areas (67.8%). Although entomological indicators such as the Aedes Index and Container Index were generally low across all localities, hotspot areas were more frequently associated with delays in case notification and vector control activities.

Univariable logistic regression identified three variables with statistically significant associations with hotspot classification. Urban residential areas exhibited higher odds of being classified as hotspots (COR=2.29, 95% CI: 0.99–5.34, p=0.048). Delayed case notification, defined as notification occurring more than 24 hours after diagnosis, was also associated with an increased likelihood of hotspot status (COR=0.33, 95% CI: 0.11–1.02, p=0.055). In the multivariable logistic regression model, urban residential areas remained a significant predictor (aOR=2.34, 95% CI: 1.01–5.47, p=0.048), and delayed notification continued to show a negative association with controlled outbreak classification (aOR=0.32, 95% CI: 0.10–1.00, p=0.052), indicating potential weaknesses in timely outbreak response.

These findings show the influence of urbanisation and the timeliness of public health response on the persistence of dengue transmission in hotspot areas. While demographic and entomological characteristics did not show significant associations with hotspot classification, operational delays which particularly in case notification and initiation of vector control activities, emerged as critical contributing factors. These results highlight the need for targeted interventions in urban settings, with an emphasis on strengthening early detection and rapid response mechanisms to mitigate the escalation of dengue outbreaks.

DISCUSSION

This study examined factors associated with dengue hotspot localities in Selangor for the year 2022. Urban residence emerged as the only statistically significant predictor in the multivariable model (aOR=2.34, 95% CI: 1.01–5.47, p=0.048). However, the significance was marginal, and the model demonstrated poor discrimination (ROC AUC=52.3%), indicating limited predictive utility. These findings should therefore be interpreted with caution and are unlikely to serve as robust predictors across different settings or time periods.

The association between urban residence and dengue hotspot classification is consistent with prior evidence in Malaysia and Southeast Asia, where dengue is disproportionately concentrated in urban and densely populated areas. Urban environments provide abundant vector breeding habitats and facilitate human–mosquito contact, amplifying transmission risk [17,18]. In Malaysia, urbanization has been consistently linked to dengue transmission, but other determinants have also been highlighted. Similar patterns were observed in Singapore, where neighbourhood-level urban density was a strong determinant of dengue clustering[19,20]. However, other Malaysian studies identified additional key predictors. For instance, Abdullah et al. (2022) reported significant associations between rainfall, temperature, and dengue incidence [21], while Mohd-Zaki et al. (2014) emphasized the role of notification delays in

Table II: Patient's Factors Characteristics with Hotspots and Controlled Outbreak Localities in Selangor for the year 2022 (N:782)

Variables	Total (n=782) n (%) [a]	Hotspot Localities (n=391) n (%) [b]	Controlled Outbreak Localities (n=391) n (%) [b]	p-value
Patient's Factors				
Age (in years)[d]				
<15 year old	134 (17.1)	62 (15.9)	72 (18.4)	0.211
16 to 25 years old	138 (17.6)	63 (16.1)	75 (19.2)	
26 to 35 years old	181 (23.1)	94 (24.0)	87 (22.3)	
36 to 45 years old	155 (19.8)	89 (22.8)	66 (16.9)	
≥46 years old	174 (22.3)	83 (21.2)	91 (23.3)	
Gender[d]				0.424
Female	459 (58.7)	224 (57.3)	235 (60.1)	
Male	323 (41.3)	167 (42.7)	156 (39.9)	
Occupation Status[d]				0.725
Unemployed	175 (22.4)	83 (21.2)	92 (23.5)	
Employed	449 (57.4)	229 (58.6)	220 (56.3)	
Student	158 (20.2)	79 (20.2)	79 (20.2)	
Nationality[d]				0.585
Malaysian	724 (92.6)	364 (93.1)	360 (92.1)	
Non-Malaysian	58 (7.4)	27 (6.9)	31 (7.9)	
Ethnicity[d]				0.837
Chinese	140 (17.9)	66 (16.9)	74 (18.9)	
Indian	102 (13.0)	51 (13.0)	51 (13.0)	
Malay	475 (60.7)	243 (62.1)	232 (59.3)	
Others	65 (8.3)	31 (7.9)	34 (8.7)	
District[d]			< 0.001*	
Sabak Bernam	1 (0.0)	0 (0.0)	1 (0.3)	
Gombak	24 (3.1)	1 (0.3)	23 (5.9)	
Hulu Langat	234 (29.9)	108 (27.6)	126 (32.2)	
Hulu Selangor	26 (3.3)	16 (4.1)	10 (2.6)	
Klang	154 (19.7)	78 (19.9)	76 (19.4)	
Kuala Langat	25 (3.2)	13 (3.3)	12 (3.1)	
Kuala Selangor	10 (1.3)	5 (1.3)	5 (1.3)	
Petaling	291 (37.2)	158 (40.4)	133 (34.0)	
Sepang	17 (2.2)	12 (3.1)	5 (1.3)	
District Population Density[d]				
Less Density Population District	79 (10.1)	46 (11.8)	33 (8.4)	0.123
High Density Population District	703 (89.9)	345 (88.2)	358 (91.6)	
Notification Source[d]				
Private hospital	220 (28.1)	118 (30.2)	102 (26.1)	0.517
Government Hospital	111 (14.2)	57 (14.6)	54 (13.8)	
GP Clinic	262 (33.5)	128 (32.7)	134 (34.3)	
Government Health Cinic	189 (24.2)	88 (22.5)	101 (25.8)	
Duration Taken To Seek Treatment (days)[e]	782 (100)	2.91 ± 1.670	3.19 ± 3.02	0.111
Environmental Factors				
Type of Housing[d]				0.394
Landed	241 (30.8)	126 (32.2%)	115 (29.4)	
Strata	541 (69.2)	265 (67.8%)	276 (70.6)	
Residential Area[d]				0.048*
Rural	28 (3.6)	10 (2.6 %)	18 (4.6)	
Urban	754 (96.4)	381 (97.4 %)	373 (95.4)	
Land Use Factor				**0.477**
Presence of Total Potential Breeding Sites[d]				
No	774 (99.0)	388 (99.2 %)	386 (98.7)	
Yes	8 (1.0)	3 (0.77%)	5 (1.28)	
Vector Control Factors				0.043*
Duration taken for case notification[d]				
≤ 24 hours	766 (98.0)	387 (99 %)	379 (96.9)	
> 24 hours	16 (2.0)	4 (1 %)	12 (3.1)	
Duration Taken for Initiation of case investigation, case verification and case registration[d]				0.808
≤ 24 hours	575 (73.5)	286(73.1)	289(73.9)	
> 24 hours	207 (26.5)	105(26.9)	102(26.1)	
Duration Taken for Commencement of Source Elimination Activity[d]				0.243
≤ 48 hours	237 (30.3)	111(28.4)	126(32.2)	
> 48 hours	545 (69.7)	280(71.6)	265(67.8)	

Table II: Patient's Factors Characteristics with Hotspots and Controlled Outbreak Localities in Selangor for the year 2022 (N:782)

Variables	Total (n=782) n (%) [a]	Hotspot Localities (n=391) n (%) [b]	Controlled Outbreak Localities (n=391) n (%) [b]	p-value
Aedes Index[d]				0.362
< 1 %	771 (98.6)	387 (99)	384 (98.2)	
≥ 1 %	11 (1.4)	4 (1.02)	7 (1.79)	
Bruteau Index (BI)[d]				0.563
< 5 %	448 (57.3)	228 (58.3)	220 (56.3)	
≥ 5 %	334 (42.7)	163 (41.7)	171 (43.7)	
Container Index (CI)[d]				.
< 10 %	782 (100)	391 (100)	391 (100)	
≥ 10 %	0 (0)	0 (0)	0 (0)	

[a]Within total sample.
[b]Within the hotspot localities and controlled outbreak localities
[c]Mean±Standard Deviation
*level of significance at α = 0.05
[d]Chi-Square test was used to calculate the p-value
[e]Independent t-test was used to calculate the p-value

Table III: Univariable analysis of factors associated with hotspot localities in Selangor for the year (n:782)

Variables	β (SE)	Wald (df)	cOR (95% CI) [a]	p-value [b]
Patient's Factors				
Age (in years)				
<15 year old	0.39(0.22)	3.09	1.478(0.96,2.29)	0.079
16 to 25 years old	0.17(0.21)	0.64	1.185 (0.78,1.80)	0.425
26 to 35 years old	-0.08(0.23)	0.13	0.921 (0.59,1.44)	0.719
36 to 45 years old	-0.06(0.23)	0.37	0.944 (0.60,1.48)	0.803
≥46 years old			1	ref.
Gender				
Female			1	ref.
Male	0.12(0.15)	0.69	1.13 (0.85,1.50)	0.407
Occupation Status				
Unemployed			1	ref.
Employed	0.14(0.18)	0.6	1.15 (0.81,1.63)	0.437
Student	0.10(0.15)	0.22	1.11 (0.72,1.71)	0.639
Nationality				
Malaysian	0.15(0.27)	0.29	1.16 (0.68,1.98)	0.592
Non-Malaysian			1	ref.
Ethnicity				
Chinese			1	ref.
Indian	0.13 (0.26)	0.24	1.14 (0.68,1.90)	0.623
Malay	0.17 (0.19)	0.82	1.19 (0.82,1.73)	0.365
Others	0.04 (0.30)	0.01	1.04 (0.58,1.87)	0.906
District Population Density				
Less Density Population District	0.37(0.24)	2.36	1.45 (0.90,2.32)	0.124
High Density Population District			1	ref.
Notification Source				
Private Hospital	0.09(0.19)	0.23	1.10 (0.75,1.60)	0.63
Government Hospital	0.19(0.24)	2.03	1.21 (0.76,1.94)	0.423
GP Clinic	0.28(0.20)	2.03	1.33(0.90,1.97)	0.154
Government Health Clinic		2.27	1	ref.
Duration Taken To Seek Treatment (days) [c]	-0.05	2.41	0.95(0.89,1.01)	0.121
Environmental Factors				
Type of Housing				
Landed			1	ref
Strata	0.14 (0.16)	0.77	1.15 (0.85,1.55)	0.381
Residential Area				
Rural			1	ref
Urban	0.83(0.43)	3.7	2.29 (0.99,5.34)	0.054

Table III: Univariable analysis of factors associated with hotspot localities in Selangor for the year (n:782)

Variables	β (SE)	Wald (df)	cOR (95% CI) [a]	p-value [b]
Land Use Factor				
Presence of Total Potential Breeding Sites				
No			1	ref
Yes	-0.52(0.73)	0.49	0.60 (0.14,2.52)	0.482
Vector Control Factors				
Duration taken for case notification				
≤ 24 hours			1	ref
> 24 hours	-1.12 (0.58)	3.69	0.33 (0.11,1.02)	0.055
Duration Taken for Initiation of case investigation, case verification and case registration				
≤ 24 hours			1	ref
> 24 hours	0.03 (0.16)	0.03	1.03 (0.75,1.42)	0.855
Duration Taken for Commencement of Source Elimination Activity				
≤ 48 hours			1	ref
> 48 hours	-0.18 (-0.156)	1.31	1.20 (0.88,1.62)	0.253
Aedes Index				
< 1 %			1	ref
≥ 1 %	-0.57(0.63)	0.8	0.57 (0.17,1.96)	0.371
Bruteau Index (BI)				
< 5 %			1	ref
≥ 5 %	-0.08(0.15)	0.3	0.92 (0.70, 1.23)	0.584

Note: COR = crude odds ratio, AOR = adjusted odds ratio, CI = confidence interval, [a]simple logistic regression, [b]multiple logistic regression, *level of significance at α = 0.05. Variables with p-value < 0.25 in [a]simple logistic regression were further analyzed in [b]multiple logistic regression.

Table IV: Multivariable analysis of factors associated with hotspot localities in Selangor for the year (n:782)

Variables	β (SE)	Wald (df)	aOR (95% CI) [a]	p-value [b]
Patient's Factors				
Age (in years)				
<15 year old	-0.413(0.241)	2.93	0.443 (0.221,0.892)	0.087
16 to 25 years old	-0.425(0.241)	3.121	0.654 (0.408,1.048)	0.077
26 to 35 years old	-0.228(0.224)	1.041	0.796 (0.513,1.234)	0.307
36 to 45 years old	-0.387(0.225)	2.947	0.679 (0.437,1.056)	0.086
≥46 years old		0.4731	1	ref
District Population Density				
Less Density Population District	-0.389(0.246)	2.504	0.678 (0.418,1.097)	0.114
High Density Population District			1	ref
Notification Source				
Private Hospital	-0.260(0.206)	1.588	0.771 (0.514,1.155)	0.208
Government Hospital	0.001(0.245)	0	1.001 (0.620,1.619)	0.995
GP Clinic	-0.223(0.189)	1.391	0.800 (0.553,1.159)	0.238
Government Health Clinic		2.566	1	ref
Duration Taken To Seek Treatment (days) [c]	-0.051(0.033)	2.442	0.950 (0.892,1.013)	0.118
Environmental Factors				
Residential Area				
Rural			1	ref
Urban	0.852(0.431)	3.899	2.343 (1.006,5.456)	0.048
Vector Control Factors				
Duration taken for case notification				
≤ 24 hours			1	ref
> 24 hours	-1.139(0.582)	3.831	0.320 (0.102,1.002)	0.05

Notes: No interaction. No multicollinearity among variables was detected in the final model. The Hosmer-Lemeshow goodness-of-fit test signified a good model fit (p = 0.499). Pseudo R square (Cox & Snell) = 1.1%. The area under the Receiver Operating Characteristic (ROC) curve was 52.3%.

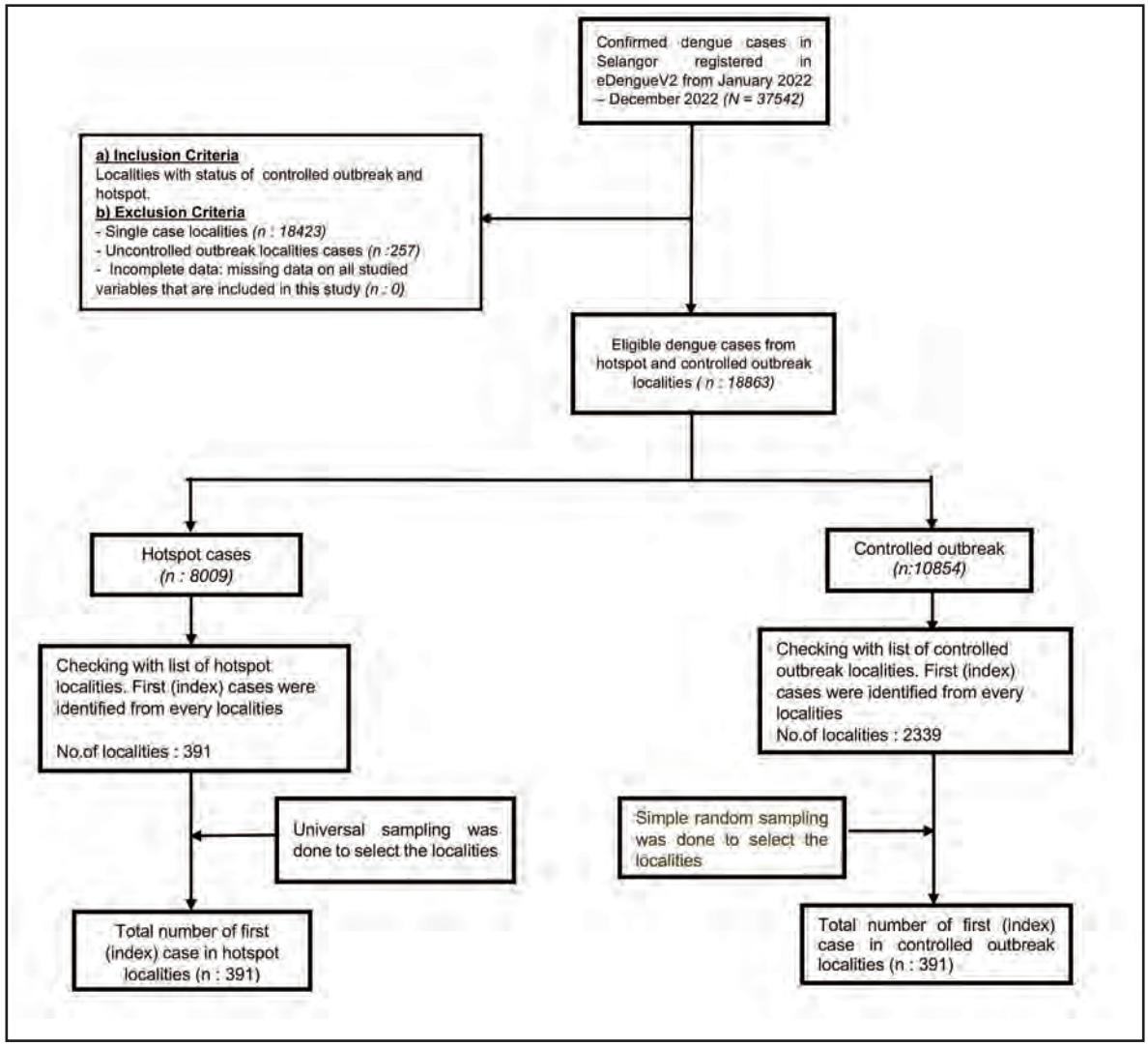

Fig. 1: Flow diagram of data extraction process and sampling

sustaining outbreaks.[22] Whereas another study has further demonstrated that larval population dynamics strongly influence epidemic potential.[23] These findings suggest that dengue hotspots are shaped by multiple interacting ecological, operational, and social factors, which may explain the modest performance of the present model.

Operationally, delayed case notification (>24 hours) showed a borderline association with hotspot classification, indicating potential gaps in outbreak response timeliness. This aligns with earlier research that highlighted prompt reporting as critical to effective vector control and containment.[24,25] Other factors, such as strata housing, male gender, and student status, exhibited elevated odds ratios but were not statistically significant. These should be interpreted as unconfirmed trends rather than established predictors and require further investigation before being integrated into policy or practice.

On the other hand, the public health implications of this study emphasize two priorities: (i) urban-focused interventions and (ii) timely outbreak response. Strengthening case notification systems, accelerating early vector control deployment, and tailoring dengue control to high-density environments are directly supported by the present findings. Broader strategies such as GIS-based risk mapping, community engagement, and resource optimization remain relevant but were not directly assessed here and should therefore be considered supplementary recommendations, guided by previous literature. [26-28]

Finally, the findings should be viewed within the context of post-COVID-19 dengue surveillance. The data analyzed were from 2022 but reviewed in 2024, a period during which surveillance operations, health system priorities, and dengue transmission patterns may have shifted. Moreover, the one-year observation period offers only a snapshot of dengue dynamics and may not capture seasonal or inter-annual variations that are critical in dengue epidemiology.

Strengths and Limitations

A notable strength of this study is the use of statewide eDengueV2 surveillance data, which integrates epidemiological, entomological, and operational

information. This comprehensive database enabled a multifactorial exploration of dengue hotspots in Selangor. The case–control design with standardized outbreak classification criteria also enhanced methodological consistency and reduced potential misclassification between hotspot and non-hotspot localities. Another strength lies in the statewide coverage, which provides a population-level perspective rather than being limited to a single district. This enhances the relevance of the findings for public health planning and resource allocation at the state level.

Nonetheless, several limitations must be acknowledged. The model showed only marginal significance for the main predictor and poor discriminatory capacity (ROC AUC=52.3%), which limits its value for prediction. Some potentially relevant environmental and operational variables, such as rainfall, temperature, entomological indices, and vector control response time, could not be included due to data constraints. Their absence may have contributed to the modest model performance. In addition, reliance on routine surveillance data introduces risks of underreporting, delayed reporting, and potential misclassification of cases. Finally, the study was limited to a one-year period (2022), which may not adequately capture seasonal or inter-annual variations in dengue epidemiology. The time lag between data collection and analysis (2022–2024) also means that the results may not fully reflect the most current outbreak dynamics in the post-COVID-19 context.

CONCLUSION

Dengue outbreaks are still worrying in Selangor despite all prevention and control measures being conducted as per ministry guidelines. Identifying factors that contribute to the occurrence of dengue hotspot localities helps to understand the overall impact of dengue outbreaks on public health and helps future interventions to be more targeted, proactive, and cost-effective, which eventually lead to a better dengue control plan in the future.

CONFLICT OF INTEREST

The authors did not have a conflict of interest.

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ORIGINAL ARTICLE

Cross-sectional study on association of autoantibodies and organ involvement in systemic sclerosis patients

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ABSTRACT

Introduction: Systemic sclerosis (SSc) is a connective tissue disease characterised by inflammation, fibrosis, and vascular abnormalities affecting multiple organs, including the skin, lungs, heart and kidneys. Between 75% and 95% of SSc patients have positive SSc-associated autoantibodies. The 2013 European League Against Rheumatism/American College of Rheumatology classification criteria for SSc includes autoantibodies as an important domain, highlighting their importance when clinical manifestations are subtle. However, the association of autoantibodies and specific clinical manifestations vary across different geographical regions and ethnicities, warranting further study across diverse populations. Hence, the objective of this study is to evaluate the association between autoantibodies and organ involvement in SSc patients at a tertiary centre in Malaysia.

Materials and Methods: This cross-sectional study included 48 SSc patients who received follow-up care at a tertiary centre in Malaysia from July 2013 to June 2023 (a ten-year period). Demographic, clinical, laboratory and radiological information were extracted from patient records.

Results: A total of 48 patients were enrolled in our study. Forty-five (93.8%) patients were female and 3 (6.2%) patients were male. Regarding ethnicity, 26 (54.2%) patients were Malay, 17 (35.4%) patients were Chinese and 5 (10.4%) patients were Indian. Mean age at diagnosis was 52.96 years (SD ± 13.99). Thirty-nine (81.2%) patients had limited subtype and 9 (18.8%) patients had diffuse subtype. The most common clinical manifestations were sclerodactyly (97.9%) and Raynaud's phenomenon (79.2%). The most commonly found autoantibodies were anti-Ro-60 (37.5%) and anti-Scl-70 (33.3%) while anti-Jo-1 (2.1%) was the least detected. Antinuclear antibody (ANA) was detected in 87.5% of our cohort. Anti-Scl-70 was significantly associated with interstitial lung disease (ILD) and ILD progression. Anti-Centromere was significantly associated with telangiectasia and gastroesophageal reflux disease (GERD). Meanwhile, anti-La was associated with synovitis and anti-Ribonucleoprotein (RNP) was associated with microstomia. Twenty-nine (60.4%) patients had evidence of ILD and 11 (22.9%) patients had progressive ILD. Additionally, pulmonary hypertension of varying severity was observed in 14 (29.2%) patients.

Conclusion: This study supports the well-established association of anti-Scl-70 with ILD and ILD progression. Other unique associations observed in this study could be due to the distinct ethnic and genetic background in the Malaysian population. To gain a more comprehensive understanding of these unique autoantibody-clinical manifestation patterns in Malaysian SSc patients, larger multicentre studies are recommended.

KEYWORDS:
Autoantibodies, organ involvement, systemic sclerosis

INTRODUCTION

Systemic sclerosis (SSc) is a connective tissue disease characterised by inflammation, fibrosis, and vascular abnormalities affecting multiple organs, including the skin, lungs, heart and kidneys. The two main subtypes of SSc are limited SSc and diffuse SSc based on the extent of the skin involvement. Between 75% and 95% of SSc patients have positive SSc-associated autoantibodies. The 2013 European League Against Rheumatism/American College of Rheumatology classification criteria for SSc includes autoantibodies as an important domain, highlighting their importance when clinical manifestations are subtle. However, the association of autoantibodies and specific clinical manifestations vary across different geographical regions and ethnicities, warranting further study across diverse populations.[1] Hence, the objective of this study is to evaluate the association between autoantibodies and organ involvement in SSc patients at a tertiary centre in Malaysia.

MATERIALS AND METHODS

This cross-sectional study included 48 SSc patients who received follow-up care at a tertiary centre in Malaysia from July 2013 to June 2023 (a ten-year period). Patients with overlap syndrome were included, while patients with mixed connective tissue disease were excluded. Demographic, clinical, laboratory and radiological information were extracted from patient records. The definitions and measurements of organ involvement are summarised in Table I. The autoantibodies analysed include anti-Ro-52, anti-Ro-60, anti-Jo-1, anti-Smith, anti-Centromere, anti-La, anti-Ribosomal P, anti-Scl-70 and anti-Ribonucleoprotein (RNP). These antibodies were recorded as dichotomous variables based on their positivity and assessed for

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Table I: The definitions of organ involvement

Organ involvement	Types of involvement	Definition	Assessment
Cutaneous involvement	Sclerodactyly	Skin thickening and tightening.	Physical examination
	Microstomia	Mouth opening limited to the patient's three middle fingers.	Physical examination
	Raynaud's phenomenon	A history of excessive cold sensitivity and recurrent events of sharply demarcated pallor and/or cyanosis of the digits.	History or physical examination
	Telangiectasia	Erythematous matted skin lesions of vascular origin, thus they blanch after local pressure.	Physical examination
	Digital ulceration	Active ulcers are defined as denuded areas with defined borders, loss of epidermis and dermis distal to the proximal interphalangeal joint on the volar aspect of a finger.	Physical examination
	Calcinosis	Calcium deposition in any soft tissue.	Physical examination or radiological study
Musculoskeletal involvement	Synovitis	Joint inflammation.	History or physical examination
	Myopathy	Decreased proximal muscle power.	Physical examination
Pulmonary involvement	ILD	NSIP, UIP, organising pneumonia (OP) attributable to SSc.	Physical examination, radiological study and lung function test
	Progressive ILD	Defined as at least two of the following three criteria occurring within the past year with no alternative explanation: 1. Worsening respiratory symptoms. 2. Physiological evidence of disease progression (either of the following): a. Absolute decline in forced vital capacity (FVC) ≥5% predicted b. Absolute decline in diffusing capacity of the lungs for carbon monoxide (DLCO) ≥10% predicted 3. Radiological evidence of disease progression.	History or physical examination, lung function test and radiological study
Cardiac involvement	Pulmonary hypertension	Mean pulmonary arterial pressure ≥ 25mmHg based on right heart catheterisation or pulmonary artery systolic pressure ≥ 30mmHg based on echocardiogram.	Echocardiogram, right heart catheterisation
	Cardiomyopathy	Evidence of myocarditis, cardiac arrhythmia or heart failure attributable to SSc.	History, physical examination, laboratory tests and echocardiogram
	Pericarditis	Pericardial effusion	Echocardiogram
Gastrointestinal involvement	GERD	Symptoms of heart burn or gastritis.	History
	Chronic constipation	Fewer than three bowel movements a week for more than 3 months.	History
	Chronic diarrhoea	Persistent alteration in stool consistency, with loose stools and increased frequency for a duration exceeding four weeks.	History
Renal involvement	Renal crisis	A sudden onset of hypertension (above 140/90 mmHg, a 30 mmHg increase in systolic blood pressure, or a 20 mmHg increase in diastolic blood pressure) and associated disorders, including an increase of more than 50% in serum creatinine or above 120% of normal range, proteinuria, microscopic haematuria, thrombocytopenia, haemolysis or hypertensive encephalopathy.	History, physical examination and laboratory tests

Note: Adapted from Motaghi P, Daneshbodi M, Karimifar M. Correlation between autoantibodies and internal organs involvement in Iranian systemic sclerosis patients. Immunopathol Persa 2022; x(x): e24238.

correlation with clinical findings using Fisher's exact test and two-by-two tables; p-value of ≤ 0.05 was considered significant.

RESULTS

A total of 48 patients were enrolled in our study. Forty-five (93.8%) patients were female and 3 (6.2%) patients were male. Regarding ethnicity, 26 (54.2%) patients were Malay, 17 (35.4%) patients were Chinese and 5 (10.4%) patients were Indian. Mean age at diagnosis was 52.96 years (SD ± 13.99). Thirty-nine (81.2%) patients had limited subtype and 9 (18.8%) patients had diffuse subtype. Eighteen (37.5%) patients in the cohort had overlap syndrome with other rheumatic diseases. The most common clinical manifestations were sclerodactyly (97.9%) and Raynaud's phenomenon (79.2%). The demographic characteristics and clinical manifestations are summarised in Table II.

Forty (83.3%) patients had at least one positive autoantibody and 24 (50%) patients had more than one autoantibody. The most commonly found autoantibodies were anti-Ro-60

Table II: Demographic, clinical, and serologic characteristics (n=48)

Gender, n (%)	
Male	3 (6.2)
Female	45 (93.8)
Age at diagnosis, mean ± SD (years)	52.96 ± 13.99
Ethnic, n (%)	
Malay	26 (54.2)
Chinese	17 (35.4)
Indian	5 (10.4)
Disease subtype, n (%)	
Limited	39 (81.2)
Diffuse	9 (18.8)
Clinical Manifestation/Organ involvement, n (%)	
Sclerodactyly	47 (97.9)
Microstomia	25 (52.1)
Raynaud's phenomenon	38 (79.2)
Telangiectasia	24 (50)
Digital ulceration	10 (20.8)
Calcinosis	4 (8.3)
Synovitis	19 (39.6)
Myopathy	6 (12.5)
ILD	29 (60.4)
Progressive ILD	11 (22.9)
Pulmonary hypertension	14 (29.2)
Cardiomyopathy	1 (2.1)
Pericarditis	2 (4.2)
GERD	19 (39.6)
Chronic constipation	0 (0)
Chronic diarrhoea	2 (4.2)
Renal crisis	0 (0)
Antibody positivity, n (%)	
ANA	42 (87.5)
Anti-Ro-52	14 (29.2)
Anti-Ro-60	18 (37.5)
Anti-Jo-1	1 (2.1)
Anti-Smith	4 (8.3)
Anti-Centromere	10 (20.8)
Anti-La	4 (8.3)
Anti-Ribosomal P	2 (4.2)
Anti-Scl-70	16 (33.3)
Anti-RNP	15 (31.3)

Table III: The correlation and predictive values of autoantibodies for organ involvement

Autoantibodies	Organ involvement	p-value	Odds/Risk ratio
Anti-Ro-52	None	-	-
Anti-Ro-60	None	-	-
Anti-Jo-1	None	-	-
Anti-Smith	None	-	-
Anti-Centromere	Telangiectasia	0.004	13.800
	GERD	0.036	5.506
Anti-La	Synovitis	0.020	2.933
Anti-Ribosomal P	None	-	-
Anti-Scl-70	ILD	0.007	0.027
	ILD progression	7.933	5.444
Anti-RNP	Microstomia	0.047	3.732

(p-value of ≤ 0.05 was considered significant.)

(37.5%) and anti-Scl-70 (33.3%) while anti-Jo-1 (2.1%) was the least detected. Antinuclear antibody (ANA) was detected in 87.5% of our patient cohort. Anti-Scl-70 was significantly associated with interstitial lung disease (ILD) and ILD progression. Anti-Centromere was significantly associated with telangiectasia and gastroesophageal reflux disease (GERD). Meanwhile, anti-La was associated with synovitis and anti-RNP was associated with microstomia. Table III summarised these correlations and predictive values of autoantibodies for organ involvement.

Twenty-nine (60.4%) patients had ILD and 11 (22.9%) patients had progressive ILD. For patients with ILD, 16 (55.2%) patients had non-specific interstitial pneumonia (NSIP) ILD pattern, 8 (27.6%) patients had usual interstitial pneumonia (UIP) ILD pattern and 5 (17.2%) patients had other or non-specific pattern. Out of the 11 patients with progressive ILD, 4 (36.4%) patients received mycophenolate mofetil, 4 (36.4%) patients received cyclophosphamide and 3 (27.2%) patients received azathioprine as first line immunosuppressive therapy. Additionally, pulmonary hypertension of varying severity was observed in 14 (29.2%) patients.

DISCUSSION

According to the 2024 Malaysia national census, the ethnic composition of the population comprises 70.3% Malay and indigenous groups, 22.4% Chinese, 6.5% Indian and 0.8% other races.[2] The ethnic distribution in our cohort, with Malays (54.2%), Chinese (35.4%), and Indians (10.4%), was broadly similar to that of the overall population. The higher prevalence of SSc among the Chinese population could be due to genetic factors, as certain human leucocyte antigens have been closely linked to SSc susceptibility in China.[3]

In our study, limited SSc (81.3%) was the predominant subtype, which was consistent with a study conducted in Malaysia in 2014.[4] This finding was also similar to studies from Japan and India but contrary to studies from Thailand, Singapore and China.[5-9] The two most common clinical presentations were sclerodactyly and Raynaud's phenomenon, which were consistent with the European Scleroderma Trials and Research group (EUSTAR) cohort.[10] A lower proportion of our patients (79.2%) had Raynaud's phenomenon compared to the EUSTAR cohort (96.3%). This could be attributed to Malaysia's warm climate and possible underreporting of symptoms. Sixty percent of our SSc patients had evidence of ILD and 29% had evidence of pulmonary hypertension. These findings were broadly similar to those in the EUSTAR cohort. As expected, NSIP (55.2%) was the major ILD pattern in our cohort.

In the EUSTAR cohort, the most common SSc associated antibodies were anti-Scl-70 (36.8%), followed by anti-Centromere (32.3%).[10] In our cohort, the most commonly found autoantibodies were anti-Ro-60 (37.5%) and anti-Scl-70 (33.3%). Only 18.6% of our patients tested positive for anti-Centromere antibody. These findings are consistent with data from our neighbouring country, Singapore.[5] Anti-Scl-70 is widely recognised for its association with ILD and ILD progression, which was also reflected in our cohort. The significance of associations between anti-Centromere with telangiectasia and GERD, anti-La with synovitis, anti-RNP with microstomia are not well established. Hence, larger multicentre studies are needed to confirm these associations found in our cohort. Anti-RNA polymerase III antibodies are specific markers for SSc and are known to be associated with diffuse skin involvement and severe internal organ complications.[11] However, this marker is not routinely tested in Malaysia due to unavailability in the commercial panels.

LIMITATIONS

There are some limitations in our study. First, the study was based on retrospective data and some data were incomplete. Secondly, the study only involved a single tertiary centre in Malaysia and might not fully reflect the diverse ethnic and genetic background of our population. Thirdly, the detection of organ involvement relied on patient-reported symptoms and the initiative of the attending clinician to actively screen for them. As a result, the true frequency of organ involvement might be underestimated.

CONCLUSION

This study supports the well-established association of anti-Scl-70 with ILD and ILD progression. Other unique associations observed in this study could be due to the distinct ethnic and genetic background in the Malaysian population. To gain a more comprehensive understanding of these unique autoantibody-clinical manifestation patterns in Malaysian SSc patients, larger multicentre studies are recommended.

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ETHICAL APPROVAL

This study involved human participants and was registered via National Medical Research Register Malaysia with a Research ID of NMRR ID-23-02432-GBB.

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Postpartum glucose intolerance following gestational diabetes mellitus: A retrospective cohort analysis of prevalence and clinical predictors in Malaysia.

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ABSTRACT

Introduction: Postpartum glucose intolerance significantly increases the risk of developing type 2 diabetes mellitus (T2DM) in women with prior gestational diabetes mellitus (GDM). This study assessed the prevalence and identified clinical predictors of postpartum glucose intolerance among Malaysian women.

Materials and Methods: This retrospective cohort study included 600 women with previous GDM attending postpartum oral glucose tolerance testing (OGTT) at 16 primary health clinics in Terengganu, Malaysia. Data collected encompassed sociodemographic details, antenatal clinical characteristics, and postpartum OGTT outcomes. Multivariable logistic regression analyses identified significant predictors.

Results: The overall prevalence of postpartum glucose intolerance was 19%, with impaired glucose tolerance (IGT) predominant (76%). Significant predictors included family history of diabetes (aOR=2.110; 95% CI: 1.324–3.365), previous GDM history (aOR=1.874; 95% CI: 1.137–3.090), primiparity (aOR=1.804; 95% CI: 1.122–2.898), elevated fasting plasma glucose at GDM diagnosis (aOR=1.636; 95% CI: 1.196–2.238), and elevated 2-hour plasma glucose at GDM diagnosis (aOR=1.452; 95% CI: 1.267–1.663).

Conclusion: The study highlights a substantial prevalence of postpartum glucose intolerance among Malaysian women with prior GDM. Identifying high-risk individuals based on family history, parity, and antenatal glucose levels may enable targeted preventive strategies to reduce the risk of progressing to T2DM.

KEYWORDS:
Diabetes, Gestational; Glucose Intolerance; Postpartum Period; Risk Factors; Prevalence

INTRODUCTION

Postpartum glucose intolerance is an emerging global health concern, particularly among women with prior gestational diabetes mellitus (GDM), which affects 6% to 13% of pregnancies worldwide.[1,2] In Terengganu, Malaysia, GDM prevalence has reached 27.3%, significantly exceeding the national average.[3] Women with GDM have a six to tenfold higher risk of developing type 2 diabetes mellitus (T2DM),[4, 5] and this risk persists for up to 35 years postpartum.[6] In South and Southeast Asia, postpartum prevalences reach 29.9% for T2DM and 25.9% for prediabetes, reflecting a 13-fold higher diabetes risk.[7]

Factors influencing postpartum glucose intolerance include obesity, maternal age, ethnicity, and family history of diabetes.[8,9] Malays, the predominant ethnic group in Terengganu, show increased susceptibility.[10] Regional disparities in healthcare access and sociocultural practices may further affect postpartum outcomes, particularly in rural areas.[11,12] Postpartum glucose intolerance also has intergenerational implications, with offspring facing increased risk of cardiovascular and metabolic diseases.[13,14] While research on GDM is expanding, data from Southeast Asia remain limited.[7] Without timely postpartum screening, many women remain undiagnosed, missing opportunities for prevention.

This study aims to assess the prevalence and identify clinical predictors of postpartum glucose intolerance among women with previous GDM in Terengganu. The findings are expected to guide targeted screening and preventive strategies, inform policy and contribute to improve maternal metabolic health in Southeast Asia.

MATERIALS AND METHODS

Study Design

This retrospective cohort study involved 16 primary health clinics across eight districts in Terengganu, Malaysia, providing Maternal and Child Health (MCH) services.

Study Population

Eligible participants were Malaysian women aged 18 years or older, with documented GDM history, who underwent postpartum oral glucose tolerance testing (OGTT) six weeks postpartum between January 2021 and December 2022. Women with pre-existing diabetes, on diabetes medication, medical conditions affecting glucose metabolism (e.g., thyrotoxicosis or acromegaly) or who relocated postpartum were excluded.

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Sample Size
Sample size calculation utilized the two-proportions formula based on previously reported family history proportion among GDM populations.15 Here, the proportion of family history of DM among GDM women with normal postpartum glucose (Po) was 58%, the estimated proportion of family history of DM among GDM women with abnormal postpartum glucose (P1) was 66.7% with level of significance (α) was 0.05 and the power of the study (β) was 80%. A calculated sample size of 475, with additional 20% to account for potential data loss, resulted in 570 participants. 600 participants were recruited to enhance precision.

Sampling Method
A stratified multistage approach was used to select study clinics, after which eligible participants were retrospectively identified from antenatal diabetes registries. Although clinic selection was random, individual sampling depended on available medical records.

Data Collection Procedures
Secondary data were extracted from the clinic copies of the Maternal Health Records, which document antenatal care, delivery and postpartum information. GDM diagnosis followed the Malaysian Clinical Practice Guidelines, using a 75g OGTT with either FPG ≥ 5.1 mmol/L or 2hPG ≥ 7.8 mmol/L as diagnostic thresholds.16 Standardized national care protocols ensure all women with GDM undergo postpartum glucose screening at six weeks.

Data were collected using a standardized proforma and entered into an Excel database. Completeness was verified, and participants with missing postpartum glucose measurements or essential variables were excluded from the analysis.

Data Categories Collected
Data were extracted from the Maternal Health Records according to the following categories:

1. Sociodemographic Data: Age, ethnicity, educational level (categorized as primary, secondary, or tertiary), and occupation.
2. Antenatal Clinical Data: Family history of diabetes (first-degree relatives), parity (primiparous or multiparous), previous GDM diagnosis, gestational age at the first prenatal booking, BMI at booking (categorized as underweight, normal, overweight, or obese), total gestational weight gain, and the gestational age at which GDM was diagnosed (first, second, or third trimester). Details on the treatment for GDM (diet control, metformin alone, insulin alone, or combined therapy) were also recorded. Additional clinical data included antenatal OGTT results (fasting plasma glucose [FPG] and 2-hour plasma glucose [2hPG]) and foetal ultrasound findings (presence of polyhydramnios or congenital abnormalities).
3. Postpartum Clinical Data: Postpartum glucose tolerance status was classified as normal or abnormal using World Health Organization (WHO) criteria.17 Women with FPG ≥ 6.1 mmol/L and 2hPG ≥ 7.8 mmol/L after ingestion of 75 g of oral glucose load were considered to have abnormal glucose tolerance.[17] Abnormal glucose tolerance was categorized as postpartum diabetes mellitus and prediabetes, which includes impaired fasting glucose (IFG), impaired glucose tolerance (IGT) or both. The WHO criteria were used in accordance with Malaysia's national guidelines.[16]

Study Variables
The variables under study were divided into dependent and independent variables:

- Dependent Variable:
  Postpartum OGTT results (FPG and 2hPG), categorized as:
  a. Normal glucose tolerance
  b. Abnormal glucose tolerance (prediabetes or diabetes)

- Independent Variables:
  a. Sociodemographic Data: Age, ethnicity, educational level and occupation.
  b. Antenatal Clinical Information: Parity, BMI at booking, previous diagnosis of GDM, family history of diabetes (first-degree relative), gestational age at GDM diagnosis, treatment for GDM, total gestational weight gain, antenatal OGTT results (FPG and 2hPG), and foetal ultrasound findings.

Data Analysis
Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS version 26.0). Descriptive statistics summarized participant characteristics and glucose intolerance prevalence. Data were expressed as frequency and percentages for categorical variables. Associations were determined using logistic regression. Simple logistic regression was first performed, in which variables with p-value less than 0.25 or clinically significant variables were included further for multivariable logistic regression. Variables with a p-value less than 0.25 in the univariate analysis were selected for inclusion in the multivariable logistic regression model to ensure that potentially important predictors were not excluded prematurely. From the multivariable logistic regression, final adjusted model was produced, in which variables with p-value less than 0.05 considered as statistically significant. Interaction, multi-collinearity test and model fit based on Hosmer Lemeshow test were checked on the final adjusted model. The finding association for each factor was reported using crude and adjusted OR (aOR).

Ethical Approval
Ethical approval for this study was granted by Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia (MOH) (NMRR ID-23-00409-TPH) and Universiti Sultan Zainal Abidin (UniSZA) Research Ethics Committee (approval No. UniSZA/UHREC/2023/521).

RESULTS

Prevalence of Postpartum Glucose Intolerance
Out of the 600 women diagnosed with GDM and tested postpartum, 114 (19.0%) were found to have abnormal OGTT results at six weeks postpartum. Of those with abnormal postpartum glucose tolerance, 15% had IFG, 76% had IGT, 4% had both IFG and IGT and 5% were diagnosed with T2DM. This prevalence highlights the considerable risk of abnormal glucose regulation among women with previous GDM.

Table I: Sociodemographic and clinical characteristics of GDM women who underwent postpartum glucose testing at six weeks postpartum (N=600)

Characteristics	Normal OGTT postpartum (N=486)			Abnormal OGTT postpartum (N=114)		
	Median (IQR)	N	%	Median (IQR)	N	%
Ethnicity						
Malay		479	98.6		113	99.1
Chinese		3	0.6		0	0
Others		4	0.8		1	0.9
Education level						
Primary school		6	1.2		3	2.6
Secondary school		240	49.4		49	43.0
Tertiary education		240	49.4		62	54.4
Employment status						
Employed		233	47.9		63	55.3
Unemployed		253	52.1		51	44.7
Parity						
Primiparous		166	34.2		50	43.9
Multiparous		320	65.8		64	56.1
History of GDM in previous pregnancies						
Yes		103	21.2		43	37.7
No		383	78.8		71	62.3
First degree relatives with DM						
Yes		237	48.8		78	68.4
No		249	51.2		36	31.6
Gestational age GDM was diagnosed						
1st trimester		182	37.4		57	50.0
2nd trimester		213	43.8		45	39.5
3rd trimester		91	18.7		12	10.5
Results of foetal ultrasound						
Normal		471	96.9		110	96.5
Abnormal		15	3.1		4	3.5
Treatment of GDM during pregnancy						
Diet		348	71.6		74	64.9
Insulin only		91	18.7		26	22.8
Metformin and insulin		9	1.9		4	3.5
Metformin only		38	7.8		10	8.8
BMI at booking						
Underweight		22	4.5		3	2.6
Normal		84	17.3		19	16.7
Overweight		148	30.5		25	21.9
Obese		232	47.7		67	58.8
OGTT upon diagnosed GDM						
Fasting plasma glucose	Median = 5.0 Minimum = 3.4 Maximum = 10.1 IQR =0.8			Median = 5.1 Minimum = 3.6 Maximum = 8.4 IQR =0.9		
2 hours plasma glucose	Median = 8.2 Minimum = 3.5 Maximum = 14.6 IQR =1.6			Median = 9.1 Minimum = 3.7 Maximum = 13.9 IQR =2.2		
Weight increase during pregnancy (kg)	Median = 7.0 Minimum = -13.0 Maximum = 20 IQR =5.5			Median = 7.0 Minimum = -6.0 Maximum = 19 IQR =6.0		

IQR: interquartile range

Table II: Simple logistic regression for factors associated with postpartum glucose intolerance

Characteristics	crude OR	95% CI	p-value
Education level			
Primary/Secondary school	1.00	(ref)	
Tertiary education	1.222	(0.812, 1.840)	0.337
Employment status			
Unemployed	1.00	(ref)	
Employed	1.341	(0.890, 2.021)	0.160
Parity			
Multiparous	1.00	(ref)	
Primiparous	1.506	(0.995, 2.280)	0.053
History of GDM in previous pregnancies			
No	1.00	(ref)	
Yes	2.252	(1.455, 3.485)	< 0.001
First degree relatives with DM			
No	1.00	(ref)	
Yes	2.276	(1.476, 3.510)	< 0.001
Gestational age GDM was diagnosed			0.024
1st trimester	1.00	(ref)	
2nd trimester	0.675	(0.435, 1.045)	0.078
3rd trimester	0.421	(0.215, 0.824)	0.012
Results of foetal ultrasound			
Normal	1.00	(ref)	
Abnormal	0.876	(0.285, 2.690)	0.817
Treatment of GDM during pregnancy			0.370
Diet	1.00	(ref)	
Insulin only	0.714	(0.374, 1.364)	0.308
Metformin with/without insulin	0.959	(0. .458, 2.008)	0.912
BMI at booking			0.150
Underweight	1.00	ref	
Normal	1.659	(0.450, 6.117)	0.447
Overweight	1.239	(0.345, 4.449)	0.743
Obese	2.118	(0.615, 7.293)	0.234
OGTT upon diagnosed GDM			
Fasting plasma glucose	1.716	(1.295, 2.274)	< 0.001
2 hours plasma glucose	1.459	(1.278, 1.665)	< 0.001
Weight increase during pregnancy	0.985	(0.942, 1.030)	0.511

OR = odd ratio, 95% CI = 95% Confident Interval

Table III: Multivariate logistic regression for factors significantly associated with postpartum glucose intolerance

Characteristics	aOR*	95% CI	p-value
Employment status			
Unemployed			
Employed	1.470	(0. 936, 2.309)	0.094
Parity			
Multiparous			
Primiparous	1.804	(1.122, 2.898)	0.015
History of GDM in previous pregnancies			
No			
Yes	1.874	(1.137, 3.090)	0.014
First degree relatives with DM			
No			
Yes	2.110	(1.324, 3.365)	0.002
Gestational age GDM was diagnosed			0.328
1st trimester			
2nd trimester	0.998	(0.610, 1.633)	0.995
3rd trimester	0.590	(0.282, 1.235)	0.162
OGTT upon diagnosed GDM			
Fasting plasma glucose	1.636	(1.196, 2.238)	0.002
2 hours plasma glucose	1.452	(1.267, 1.663)	< 0.001

aOR = Adjusted odd ratio, 95% CI = 95% Confident Interval
*Multiple Logistic Regression model using Enter method was applied
Multicollinearity and interaction term were checked and not found
Hosmer-Lemeshow test (p>0.05), classification table (overall correctly classified percentage=82.8%) and area under the ROC curve (73.1%) were applied to check the model fitness

Sociodemographic and Clinical Characteristics
Most participants were Malay, comprising 98.6% of women with normal OGTT results and 99.1% with abnormal results. Educational attainment was evenly distributed between secondary and tertiary levels, with slightly more tertiary-educated women in abnormal OGTT group (54.4%) than in the normal group (49.4%). Employment was also more common among women with abnormal OGTT results (55.3%) compared to those with normal results (47.9%).

Primiparous women were more frequent in the abnormal group (43.9%) compared to the normal group (34.2%). A previous history of GDM was reported in 37.7% of women with abnormal group versus 21.2% in the normal group. Similarly, a family history of diabetes among first-degree relatives was higher in the abnormal group (68.4%) compared with the normal group (48.8%).

Half of the women with abnormal OGTT results were diagnosed with GDM during the first trimester (50.0%), compared to 37.4% in the normal group. Conversely, fewer women in the abnormal group were diagnosed in the third trimester (10.5%) compared to the normal group (18.7%). Obesity at booking was also more prevalent in the abnormal group (58.8%) compared to the normal group (47.7%).
Table I summarizes these findings.

Predictors of Postpartum Glucose Intolerance
From the simple logistic regression, only employment status, parity, history of GDM in previous pregnancies, first degree relatives with DM, gestational age when GDM was diagnosed, FPG and 2hPG during antenatal OGTT were statistically significant at 0.25 and added to the final model. Notably, a history of GDM in previous pregnancy (OR = 2.252, 95% CI: 1.455–3.485, $p < 0.001$) and a family history of diabetes (OR = 2.276, 95% CI: 1.476–3.510, $p < 0.001$) showed the strongest association in the univariate analysis (Table II).

In the multivariable logistic regression (Table III), the model was adjusted for employment status, parity, history of GDM, family history of diabetes, gestational age at GDM diagnosis, and both antenatal glucose measures (FPG and 2hPG). Five predictors were statistically significant at 0.05, namely first-degree relatives with DM, history of GDM in previous pregnancies, parity, FPG and 2hPG level on the antenatal OGTT.

Those with first degree relatives with DM had 2.110 times the odds of having postpartum glucose intolerance, as compared to those without history of first-degree relatives with DM (aOR=2.110; 95% CI (1.324, 3.365), $p = 0.002$). Those with history of GDM in previous pregnancies had 1.874 times the odds of having postpartum glucose intolerance, as compared to those without history of GDM (aOR=1.874; 95% CI (1.137, 3.090), $p = 0.014$). Primiparous women had 1.804 times the odds of having postpartum glucose intolerance as compared to multiparous (aOR=1.804; 95% CI (1.122, 2.898), $p = 0.015$).

For each unit increase of FPG level on the antenatal OGTT, the odds of having postpartum glucose intolerance increased by 1.636 (aOR=1.636; 95% CI (1.196, 2.238), $p = 0.002$).

For each unit increase of 2hPG level on the antenatal OGTT, the odds of having postpartum glucose intolerance increased by 1.452 (aOR=1.452; 95% CI (1.267, 1.663), $p = < 0.001$).

No multicollinearity (highest VIF 1.054) and interactions were detected. Hosmer Lemeshow test revealed p-value of more than 0.05 ($p = 0.179$), with overall classified percentage of 82.8%. Area under the ROC curve was 73.1% ($p < 0.05$), indicating good fit of the model.

DISCUSSION

Prevalence of Postpartum Glucose Intolerance
In our study, 19.0% of women demonstrated postpartum glucose intolerance at six weeks, with IGT as the predominant abnormality. This aligns with global estimates ranging from 20% to 60% and regional findings of 27% at 6–12 weeks postpartum.[7,8,15] The slightly lower prevalence observed may reflect differences in healthcare access and postpartum behaviours in this population. Malaysian studies report similar short-term prevalences of 12–20%,[15,18-20] while long-term follow-up shows rates exceeding 50% within a decade.[13,21] These findings underscore the need for continued monitoring beyond routine postpartum testing. The predominance of IGT highlights a key opportunity for preventive lifestyle or pharmacological interventions, and the 5% immediate progression to diabetes further emphasises the urgency of early postpartum screening.

Key Predictors of Postpartum Glucose Intolerance
Our multivariable analysis identified family history of diabetes mellitus, previous history of GDM, primiparity, and elevated fasting and 2hPG at GDM diagnosis as significant predictors of postpartum glucose intolerance.

Family History of Diabetes
A family history of diabetes in first-degree relatives doubled the risk of postpartum glucose intolerance, consistent with meta-analyses showing familial predisposition as strong independent factor.[22,23] Genetic susceptibility, shared lifestyle patterns and environmental influences likely contribute. While genetic predisposition is non-modifiable, early identification and personalized lifestyle interventions could substantially mitigate long-term risks.

History of GDM in Previous Pregnancies
A previous GDM diagnosis significantly increases the likelihood of postpartum glucose intolerance, a finding consistent with global literature. Our study found out that women with a prior GDM had approximately 1.87 times higher odds of postpartum glucose intolerance, supporting international findings of increased recurrence risk.[5,24,25] Persistent insulin resistance and inadequate pancreatic beta-cell compensation may underlie this association.26 Recognizing prior GDM as a red flag can prompt preventive interventions which could delay or prevent the onset of T2DM.

Parity
Interestingly, our study found that the association between primiparity and higher risk differs from most studies that link multiparity with increased risk.[27-29] This may relate to behavioural or physiological differences during a first

pregnancy, including stress and limited experience with glucose management. Regardless, this reinforces the need for universal postpartum screening, irrespective of parity.

FPG at GDM Diagnosis
Elevated antenatal FPG independently predicted postpartum glucose intolerance, supporting previous studies showing its strong prognostic value.30 High FPG levels during pregnancy indicate substantial insulin resistance, which may persist into the postpartum period, increasing the risk of sustained glucose dysregulation.21 Clinically, women with elevated FPG should be prioritized for early postpartum glucose testing and intensive lifestyle counselling.

2hPG at GDM Diagnosis
Similarly, higher 2hPG value predicted increased postpartum glucose intolerance, consistent with studies demonstrating that post-load glucose reflects peripheral insulin resistance and delayed glucose clearance.30, 31 Therefore, an elevated 2hPG level during the antenatal OGTT should not be overlooked, even if fasting glucose was near-normal. Including both fasting and 2h values in antenatal assessment improves risk stratification and guides postpartum surveillance.

BMI and Weight Gain During Pregnancy
Although BMI and weight gain during pregnancy are clinically important indicators, neither was significantly associated with postpartum glucose intolerance in this cohort. The high baseline prevalence of overweight and obesity may have reduced variability between groups, while antenatal dietary counselling and treatment may have attenuated metabolic differences.

Clinical Implications and Practical Applications
All significant predictors were detectable during pregnancy, highlighting antenatal care as a key opportunity for early risk stratification. Linking antenatal risk factors to structured postpartum follow-up, lifestyle counselling and digital or community-based reminder systems may improve postpartum screening uptake. A simple risk-prediction tool could assist primary-care clinicians, especially in resource-limited settings.

Study Limitations and Recommendations
This retrospective design and reliance on secondary data limit certain variables' control and completeness. The predominantly Malay cohort may restrict generalizability. Further longitudinal studies, multi-ethnic cohorts, and longer-term follow-up research are recommended to confirm these findings and explore effective interventions.

CONCLUSION

This study reveals a significant prevalence of postpartum glucose intolerance in women with previous GDM, highlighting critical predictors useful for targeted intervention and preventive strategies. Strengthened antenatal risk assessment, structured postpartum screening, and lifestyle counselling may reduce long-term diabetes risk.

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ORIGINAL ARTICLE

Postoperative spondylodiscitis: Five-year, single-center retrospective analysis. Is it really postoperative?

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ABSTRACT

Introduction: Postoperative spondylodiscitis (POSD) is not uncommon. The incidence of POSD varies between 0.21–3.6% In this study, it was aimed to examine the clinical findings, diagnosis and treatment of postoperative spondylodiscitis (POSD).

Materials and Methods: Between September 2017 and October 2022, 37 patients were included in the study, who applied to the Infectious Diseases and Clinical Microbiology Clinic of the XXX Hospital and had POSD infection and were followed-up/treated as outpatients or inpatients. The following were examined: symptoms, physical examination findings, contrast-enhanced spinal MRI (magnetic resonance imaging) findings of the patients, laboratory findings, PPD (purified protein derivative) and QuantiFERON TB-Gold test and blood cultures. The antibiotics that were started and the clinical and radiological response of the patients to the treatment were evaluated.

Results: Of the patients 25 (67.6%) were female and 12 (32.3%) were male. The mean time to develop POSD after surgery was 44.8 months. In our study, we found that laboratory tests were not significant in diagnosing POSD other than C-reactive protein(CRP). Teicoplanin and ciprofloxacin were given to all patients except one patient with positive brucella slide and tube agglutination. With this treatment, clinical and radiological improvement was observed in 24 patients. The treatment of 13 patients, including the patient who was given Brucella treatment, was changed due to the lack of clinical and radiological improvement, and anti-tuberculosis treatment was started and recovery was achieved. The mean duration of the treatment was 3.5 months in the pyogenic POSD group and 9.5 months in the POSD patient group that recovered with anti-tuberculosis therapy.

Conclusion: It Should be kept in mind that in cases where the POSD patients do not benefit from empirical treatment, the causative agent may be an agent other than the common microorganisms, for example M. tuberculosis, and if the agent cannot be detected, finding the diagnosis from treatment is also an option.

KEYWORDS:
Postoperative spondylodiscitis; tuberculous spondylodiscitis; spinal infection; acute phase reactants; paravertebral abcess

INTRODUCTION

Spondylodiscitis (SD) is defined as infection of the vertebral body, intervertebral disc, and posterior vertebral arch Postoperative spondylodiscitis (POSD) is an infection of the vertebral bone, disc, and nucleus pulposus. The incidence of POSD varies between 0.21–3.6% and may cause serious sequelae The first discectomy surgery, performed approximately 100 years ago, is now one of the most frequently performed surgical procedures, and its frequency is steadily increasing.[2] The causes of POSD may include iatrogenic factors resulting from inadequate aseptic technique during surgery, as well as infections transmitted hematogenously or via contiguous spread.[2] The frequency of implant application in spinal surgery is increasing today, and the success rate of medical treatment alone without surgical intervention in implanted spondylodiscitis is relatively low.[3] Although the most common cause is Gram-positive cocci (especially Staphylococcus aureus), Gram-negative bacteria also play a role in the POSD infections. Fever, spinal pain, difficulty in walking, neurological symptoms (such as sensory loss and neurological deficits) may also be present.[4] Diagnosis is mainly based on clinical signs and symptoms and supported by laboratory tests and radiological imaging.[5] Leukocytosis, elevated C-reactive protein (CRP) and erythrocyte sedimentation rate(ESR) and positive blood cultures may be present.[4] It has been stated that Magnetic resonance imaging (MRI) has an important role in the diagnosis and differential diagnosis of postoperative spinal complications.[6] Surgical treatment is indicated if neurological disorders, spinal deformities, septic conditions or extensive abscess formations are present.[7] Antibiotic therapy in combination with spinal immobilization has been shown to produce good long-term results in the majority of patients. When the causative organism is determined, specific intravenous antibiotics for the causative agent should be administered followed by appropriate oral antibiotics. If the causative agent cannot be identified, broad-spectrum antibiotics with anti-staphylococcal coverage are recommended.[8] However, studies with POSD are often conducted in countries where infected tissue sampling is performed; this study may be useful in determining treatment protocols in hospitals where interventional biopsy is not performed, such as our centre.

In this study, it was aimed to examine the clinical findings, diagnosis and treatment of patients who applied to XXX Hospital Infectious Diseases and Clinical Microbiology clinic between September 2017 and October 2022 and had POSD

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infection and were followed up/treated as outpatients or inpatients.

MATERIALS AND METHODS

Between September 2017 and October 2022, 37 patients were included in the study, who applied to the Infectious Diseases and Clinical Microbiology clinic of the XXX Hospital and who developed POSD and were followed-up/treated as outpatients or inpatients. All patients had undergone vertebral surgery but had not undergone internal fixation. No tissue samples were taken from any patients except for two patients who underwent biopsy using an open surgical technique. The files of these patients were scanned retrospectively through the information processing system of our hospital. In the file screening, we examined the patients' complaints and physical examination findings, spinal MRI findings with contrast, routine blood tests before treatment, hemogram, ESR, CRP, procalcitonin, brucella slide and tube agglutination, purified protein derivative (PPD) and QuantiFERON TB-Gold test results and blood culture results. Monthly contrast-enhanced spinal MRIs of the patients were reviewed retrospectively, and radiological recovery times, and, if a change was made in the initial antibiotic therapy, the time and shape of the change were noted. Results with a Brucella serum tube agglutination test (SAT) of 1/160 and above and a PPD test of 15 mm and above were considered positive. With the exception of open biopsies performed on two patients in the postoperative period, the absence of discharge in the lumbar region of the patients and the non-performance of invasive biopsies, and consequently the inability to obtain wound cultures, are limiting factors in our study. No pathology other than chronic inflammation was detected in patients who underwent bone biopsy, and caseous necrosis was not observed. In these patients, the diagnosis of tuberculosis is presumptive based on treatment.

This study was conducted in accordance with the ethical standards of the Declaration of Helsinki and was approved by the XXX University Non-Invasive Clinical Research Ethics Committee (Date: 12.04.2023, Resolution no: 2023/233).

RESULTS

All 37 patients with POSD included in the study, who were followed up, had a history of lumbar spine surgery. Operations were carried out in different centers and provinces, and there was no clustering in a single center. Of the patients included in the research, 25 (67.6%) were female and 12 (32.3%) were male. Their mean age was 52.8 (range: 35-71 years). The mean age of female patients was 56.5 (range: 35-75 years), while the mean age of men was 49.2 (range: 40-61 years). The mean time to develop pyogenic POSD after surgery was 44.8 months (range: 3 weeks-23 years). The mean time after surgery was found to be 40.6 months (range: 3 weeks-18 years) in the POSD group that recovered with anti-tuberculosis (anti-TBC) therapy.

All of the patients complained of severe limitation in crouching and right-left and prone-supine rotational movements while lying down. On physical examination, the main finding was lumbar tenderness and pain during leg internal rotations. Apart from this, fever in three patients, sweating in nine patients, and weight loss in one patient in the last six months, such as losing 5% or more of their weight, were observed.

At the time of diagnosis, 27 patients did not have any chronic disease. Six patients had hypertension (HT), two patients had diabetes mellitus (DM), and two patients had chronic obstructive pulmonary disease (COPD). Laboratory findings of the patients are given in Table I.

Blood cultures were taken from 30 of 37 patients included in the study. *Methicillin-susceptible coagulase-negative staphylococci* (MSCNS) developed in five patients, *methicillin-resistant coagulase-negative staphylococci* (MRCNS) in two patients, and *methicillin-resistant S. aureus* (MRSA) in two patients. There was no growth in the blood cultures of the other 21 patients.

In the initial treatment of the patients in our study, treatment for Brucella SD infection (doxycycline 2x100 mg tablet (tb), rifampicin 1x600 mg tb, streptomycin 1x1 g intramuscular (IM)) was initiated in one patient because the Brucella slide agglutination test was positive and the tube agglutination test was >1/160, and treatment for pyogenic POSD (teicoplanin 1x600 mg intravenous (IV) and ciprofloxacin 2x500 mg tb) was initiated in 36 patients. Since clinical and radiological improvement was observed in 24 patients (66.7%) with teicoplanin and ciprofloxacin treatment, the treatment was continued. In 12 patients (33.7%) who did not improve clinically and radiologically, treatment was changed and daptomycin 1x500 mg IV/linezolid 2x600 mg IV and meropenem 3x1 gr IV were started. Anti-TBC therapy (isoniazide 1x300 mg, rifampicin 1x600 mg, ethambutol 15-20 mg/kg, pyrazinamide 20-25 mg/kg, oral) was initiated in 12 patients who received this treatment due to lack of clinical and radiological response. The only patient who was treated for Brucella infection was treated by switching to anti-TB treatment due to no response to treatment. The initial treatments and the times of treatment change are shown in Table II. The mean duration of treatment was 3.5 months (range: 2-7 months) in the pyogenic POSD group and 9.5 months (range: 6-13 months) in the POSD patient group that recovered with anti-TBC therapy.

QuantiFERON TB-Gold test was performed on eight of 37 patients included in the study, and it was found to be positive in three patients and negative in five patients. There was no growth in the blood culture of all three patients with QuantiFERON TB-Gold test positive and it was observed that three patients recovered with the anti-TBC treatment. It was determined that the final treatment of only one of the five patients with QuantiFERON TB-Gold test negative was the anti-TBC treatment. PPD was found to be negative in three patients with QuantiFERON TB-Gold test positive. Of the 13 patients who achieved full cure with the anti-TBC treatment, four were PPD positive, eight were PPD negative, and one patient was PPD anergic. In our study, we found that laboratory tests other than CRP were not significant in diagnosing POSD ($p>0.05$).

When the contrast-enhanced lumbar MRIs of the patients in our study were evaluated, 11 patients had paravertebral soft tissue involvement, seven patients had abscesses (various sizes from phlegmon to 6 cm), and four patients had soft tissue involvement. Five of the patients with paravertebral involvement had pyogenic POSD, and six had POSD that improved with the anti-TBC therapy. One patient with POSD who recovered with the anti-TBC therapy had soft tissue involvement, one had phlegmon, and four had abscess greater than 1 cm. Two of the patients with pyogenic POSD had abscesses (1 and 3 cm), and three patients had soft tissue involvement.

DISCUSSION

POSD is a complication that develops following spinal disc surgery.[5] The incidence of postoperative discitis after lumbar discectomy has been reported to be 0.7% to 2.8%.[9] In one study, POSD developed in 47 (1%) of 4698 patients who underwent lumbar surgery. Spinal stiffness and fever were observed most frequently after low back and hip pain.[2] In another study, it was stated that fever was observed the most after lumbar pain.[10] Lumbar pain, difficulty in walking and fever were the most common findings in our study. Advanced age, immunosuppression, spinal trauma, DM, obesity, smoking, indwelling catheters, malnutrition, and prolonged hospital stay are risk factors for POSD. High infection rates have been observed in elderly patients and patients with spinal trauma.[2] The mean age of the patients included in our study was 52 and two patients had DM.

Gram-positive cocci (such as *S. aureus, Staphylococcus epidermidis*, and beta-hemolytic streptococci) are the most common pathogens. Gram-negative bacteria also play a role in POSD infections and may be associated with systemic disease and multi-system organ failure.[11] In a study, blood culture grew in four of 12 POSD cases, and *S. aureus* was detected in three and *Pseudomonas aeruginosa* in one.[5] In another study, according to the culture results of 20 POSD cases, the most common microorganism was *S. aureus* in three (42%) cases, and *Escherichia coli* (14.5%), *S. epidermidis* (14.5%), *Streptococcus viridans* and (14.5%) *Acinetobacter baumanii* (14.5%) each in one case.[12] In our study, unlike the literature, MSCNS was detected most frequently in five patients, MRCNS in two patients, and MRSA in two patients. It is a rare condition that the causative agent is *Mycobacterium tuberculosis* in patients who develop POSD. It was reported that a patient who had been treated for pulmonary tuberculosis 20 years ago and had a full recovery underwent an operation for lumbar disc herniation and that patient developed POSD 3 weeks later, and the anti-TBC treatment was initiated for the patient whose PCR test was positive for *Mycobacterium tuberculosis* in two of the vertebral biopsies performed for the second time, who did not respond to broad-spectrum antibiotic treatment, and the patient benefited from this treatment.[13] There are other case reports of tuberculous spondylodiscitis after lumbar spine surgery.[14,15] Vertebral sampling could not be performed on the patients included in our study, so histological and microbiological diagnosis or PCR test (polymerase chain reaction) could not be performed for the diagnosis of tuberculosis POSD. In cases where the agent cannot be detected in the treatment of POSD, it should be kept in mind that the agent may be *M. tuberculosis* when broad-spectrum antibiotics for possible agents are given in a sufficient time and no response is obtained.

While CRP is a predictable serum parameter in patients with spondylodiscitis, the leukocyte count is not specific.[16,17] Similar to leukocyte count, ESR is not thought to be useful as a definitive indicator for POSD.[18] Similarly, in our study, it was seen that CRP was significant in the diagnosis of POSD, while the leukocyte count and ESR were not significant in the diagnosis.

Direct graphs are usually the first diagnostic method in the diagnosis of POSD, but they are not sensitive for discitis. Computed tomography (CT), MR, and radionuclide imaging methods can be used for diagnosis.[8] On MRI, it is not easy to diagnose because changes caused by the postoperative inflammatory response at the level of the operated disc and bone marrow edema in the adjacent end-plates are frequently seen in postoperative patients, even in the absence of infection.[19,20] MRI is the most sensitive (93-96%) and specific (92.5-97%) method for the early detection of spondylodiscitis. It can differentiate between pyogenic discitis, neoplasia, and tuberculosis, allowing better identification of the paravertebral and epidural spaces. For patients for whom MRI is contraindicated, radioisotope scanning followed by CT with contrast is recommended. The earliest MRI abnormalities appear when edema and inflammatory cells infiltrate the vertebral body and disc space.[21] As MRI findings of POSD, it was stated that the signal intensity decreased on T1-weighted images in the disc space due to edema (Modic I changes) caused by inflammation and infection and that the signal intensity increased on T2-weighted images and decreased in the adjacent bone marrow on T1-weighted images after gadolinium injection.[2] In our study, MRI was used in the radiological diagnosis and follow-up of the patients, and abscess and paravertebral tissue involvement were also detected, apart from discitis.

Antibiotherapy and bed rest were reported to be effective treatment modalities for POSD without internal fixation, and surgical treatment was recommended in case this treatment failed.[23] It has been stated that surgical treatment using one-stage posterior debridement, fusion, and instrumentation followed by continuous closed irrigation and drainage may be an effective treatment option for POSD.[23] It has been determined that the agent-directed antibiotic given intravenously for 6 weeks and then orally for 6 weeks is effective. If the causative agent cannot be identified, antibiotics with broad-spectrum anti staphylococcal coverage are recommended.[8] In our study, teicoplanin and ciprofloxacin treatment was given in cases where no causative agent could be detected. While 24 patients benefited from this treatment, 12 patients received broad-spectrum antibiotics due to the lack of clinical and laboratory improvements, but the anti-TBC treatment was started because there was no improvement and our country is an endemic country in terms of tuberculosis. These patients showed clinical and radiological improvement with the anti-TBC treatment.

A limitation of our study is the inability to perform postoperative biopsies, which prevented histopathological diagnosis and tissue microorganism identification. Furthermore, due to the single-center nature of the study, the generalizability of the results is limited, and multicenter, prospective studies are needed. Another limitation of the study is that QuantiFERON TB-Gold test and PPD could not be performed on all patients.

CONCLUSION

In cases where the POSD patients do not benefit from empirical treatment, it should be considered that the causative agent may be other than common microorganisms, for example *M. tuberculosis* Since interventional procedures aimed at identifying the causative microorganisms are not performed in every center, we believe that diagnosis based on treatment could be considered as an alternative approach.

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ORIGINAL ARTICLE

The accuracy of intraoperative assessment of myometrial invasion in early-stage endometrial cancer and its association with lymph nodes metastasis

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ABSTRACT

Introduction: Assessment of the depth of myometrial invasion is important for optimal surgical strategies and treatments. This study aims to assess the accuracy of intraoperative evaluation of myometrial invasion in FIGO early-stage endometrial cancer and its association with lymph node metastasis, impacting treatment decisions and patient outcomes.

Materials and Methods: This is a retrospective study analysis of 150 patients diagnosed preoperatively with early-stage endometrial cancer who underwent surgical staging in Institut Kanser Negara (IKN), Putrajaya from January 2018 until December 2022. After the hysterectomy procedure, all uterine specimens will be opened for intraoperative assessment of the depth of myometrial invasion by a gynae oncology surgeon. According to FIGO classification, the depth was assessed to be either greater or less than 50% of myometrial thickness. Gross estimation during operation will be compared with the final histopathological result. This study aims to evaluate the accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of intraoperative myometrial invasion compared to the final histology. Secondly, this research aims to explore the association between depth of myometrial invasion and lymph nodes involvement.

Results: A total of 150 patients were recruited, the sensitivity and specificity of intraoperative assessment in detecting depth of myometrial invasion were 42% and 94%, respectively and the PPV and NPV were 78% and 76%. The overall accuracy was 77%. The sensitivity of only 42% in this study suggested that intraoperative myometrial assessment missed as many as 58% of patients who had deep myometrial invasion. A total of 9 (6%) patients were found to have lymph nodes involvement with 5 of them showing deeper myometrial invasion. Although there was a higher number of lymph node involvement observed in cases with deeper myometrial invasion, the difference was not statistically significant (p > 0.05).

Conclusion: We conclude that intraoperative assessment of myometrial invasion is still reliable and inexpensive method to practice. Accuracy of assessment can be improved in integrate MRI and transvaginal ultrasound in preoperative assessment.

KEYWORDS:
Endometrial Carcinoma, Intraoperative assessment, Myometrial Invasion, Lymph Nodes Metastasis

INTRODUCTION

Endometrial cancer ranks as the sixth most common cancer globally among women, with a notable surge in its incidence observed over the last two decades.[1] According to the summary Malaysia National Cancer Report 2017 – 2021, endometrial cancer stands as the fourth most prevalent malignancy among women in Malaysia.[2] The incidence rate in Malaysia shown an upward trend, increasing from 3.8 to 4.6 cases per 100 000 population, highlighting the growing concern surrounding this form of cancer among women.[2]

Approximately 48.6 % of women in Malaysia were diagnosed with Stage 1 endometrial cancer at presentation.[2] The mainstay of treatment for early-stage endometrial cancer is hysterectomy and bilateral salpingo-oophorectomy with or without systematic lymphadenectomy.[3] Lymphadenectomy has been associated with several postoperative complications such as lymphoedema, deep vein thrombosis (DVT), and paralytic ileus due to autonomic nerve injuries. In more extensive procedures, it can even result in life-threatening conditions such as major vessels injuries.[4]

According to European Society of Gynecology Oncology (ESGO) guideline, Grade 1 and Grade 2 endometrioid tumors and myometrial invasion less than 50% is considered as low-risk endometrial cancer and the risk of lymph node involvement is less than 5%.5 Based on the European Society for Medical Oncology (ESMO) guideline, in low-risk endometrioid Adenocarcinoma FIGO Stage 1A, lymphadenectomy can be omitted.[3] Several studies also showed that there is no benefit of systematic lymphadenectomy in Stage 1a endometrial cancer.[6,7] It is also widely opinion that systematic lymphadenectomy is recommended for cases involving Grade 2 to Grade 3 endometrioid tumors that infiltrate over half of the myometrial thickness and non-endometrioid histological types.[3,5]

Several methods available for evaluation of myometrial invasion either preoperative or intraoperative assessment. Preoperatively, magnetic resonance imaging (MRI) and

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transvaginal sonography (TVS) had been widely used to assess myometrial invasion.[8] However, not all centers can provide ultrasound experts and some limitation in medical imaging such as MRI, include challenges in securing timely appointments. Therefore, not all centers especially in Malaysia government hospital settings are able to offer early MRI appointment, which can potentially impact the scheduling surgeries.[8,9] Intraoperative frozen section is one of the accurate methods for evaluation of myometrial invasion and consider as high accuracy.[8] Unfortunately, not all centers can provide trained pathologist specifically experts in gynecologic oncology that can interpret intraoperative frozen section specimen.[10] Therefore, the accuracy of assessment of myometrial invasion is important to avoid unnecessary lymphadenectomy and overtreatment in patient diagnosed with early endometrial cancer.

Our hospital at the Institut Kanser Negara (IKN), Putrajaya serves as a prominent referral center, handling a substantial volume of endometrial cancer cases per year. The primary objective of this study is to measure the accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of our routine practice of gross intraoperative assessment of myometrial invasion compared to the final histology in early stage of endometrial cancer. Our secondary objective is to assess and compare the association between superficial and deep myometrial invasion with lymph node metastasis.

MATERIALS AND METHODS

Approval from the Medical Research and Ethics Committee (MREC) was obtained prior to the commencement of this study (NMRR ID-24-00793-OOS).

Study Design and Participants

This retrospective study involved 150 patients with pre-operative histopathological diagnosis of endometrial carcinoma based on either dilatation and curettage or hysteroscopic specimens. All the newly diagnosed patients with endometrial cancer FIGO Stage 1 were operated and continued treatment and follow up in IKN between January 2018 to December 2022. All the detailed information were reviewed from IKN's Hospital Information System 'Fisicien' such as patient characteristics, histology, treatment, intraoperative gross examination results of the uterine specimens and final histopathological report.

The eligible patients were aged 18 and older with newly diagnosed preoperatively Endometrial Cancer (FIGO) Stage 1 that underwent surgical procedures and continued follow up in IKN. Exclusion criteria encompassed patients with Endometrial Cancer Stage 2 and above diagnosed preoperatively, synchronous tumour or more than one primary cancer and those with incomplete medical record.

There is no routine preoperative assessment in IKN Hospital for preoperative staging of early endometrial cancer. Diagnostic imaging such as transvaginal ultrasound, computed tomography, or magnetic resonance imaging are used differently depending in the physician's decision and option of treatment. All patients decided and agreed for operation will undergo comprehensive surgical staging including hysterectomy and bilateral salpingo-oophorectomy either by abdominal approach or laparoscopy. Pelvic lymphadenectomy was performed in all patients. Intraoperatively, after the hysterectomy procedure, anterior wall of uterus was incised using scalpel or Mayo Scissor and opened vertically along the uterine fundus to cervix to assess the depth of myometrial invasion. Full thickness incisions were made through the tumour, myometrium and cervix. The assessment process is shown in Fig. 1. Intraoperative gross assessment of depth of myometrial invasion was carried out by the gynaecologic oncologist in each case, which were noted to be less than or equal to 50% or more than 50% involvement of myometrial invasion. All the parameters were described in the operative notes and were compared with the final histopathology report.

Statistical Analysis

The data analysis will be done using the SPSS version 27. Accuracy, sensitivity, specificity, positive predictive value and negative predictive value were calculated. Descriptive statistics were done for qualitative data as number and percentage. Analysis for independent variables were done using the Chi Square test or Fisher's exact test as appropriate. The p-value of <0.05 was considered significant.

RESULTS

A total of 330 patients newly diagnosed with endometrial cancer between January 2018 until December 2022. Out of these, 180 patients were excluded due to Stage 2 and above (n=71), patients with synchronous tumour or with more than one primary cancer (n=21), patients with incomplete operative findings (n=11), and another 36 patients were also excluded, in view of during COVID-19 period, the patients underwent surgery at IKN and subsequently received postoperative follow-up at their respective hospitals for review of the final histopathology results. As a result, 150 patients were recruited in the study (Fig.1).

The baseline characteristics of patients are summarized in Table 1. The mean age was 55 ⌖ 11.7 years old and majority of them are among the postmenopausal group (60%). Mean body mass index was 31 ⌖ 6.56 kg/m2. Low parity among the highest risk in early endometrial cancer (46%). Majority of them had multiple comorbidities, which comprised 43% of the patients.

The procedure and histologic information are summarized in Table II. Majority of the patients had endometrioid histology (97.3%) and grade 1 tumour (54%). 97 patients underwent open laparotomy (64.7%), and others had minimally invasive surgical approach (35.3%).

Intraoperative assessment of depth of myometrial invasion was correctly correspond with final histopathological report in 115 (76.7%) out of 150 patients. Table 3 compare the intraoperative myometrial assessment to final histopathology results. The sensitivity in detecting myometrial invasion was only 42% and specificity was 94% (Table IV). The PPV and NPV was 77.7 % and 76.4 % respectively. False gross intraoperative assessment was found

Table I: Baseline characteristics of patients

	n	%
Age (years; mean ± SD)	55 ± 11.7	
Body Mass Index	31 ± 6.56	
Menopausal State		
- Pre-menopause	60	40%
- Post-menopause	90	60%
Parity		
- Low parity	69	46%
- Para 2 – 4	60	40%
- More than 4	21	14%
Comorbidities		
- Diabetes Mellitus	8	5.3%
- Hypertension	23	15%
- Multiple	65	43%
- Others	6	4%
- No medical illness	48	32%

Table II: Procedure and histopathologic information

Characteristic	n	%
Pre-operative Endometrial Sampling		
- Office endometrial sampling	72	48%
- Hysteroscopy and curettage	78	54%
Operation mode		
- Laparotomy	97	64.7%
- Laparoscopy	53	35.3%
Histological Cell type		
- Endometrioid	146	97.3%
- Non-endometrioid	4	2.7%
Tumor grading (preop)		
- Grade 1	81	54%
- Grade 2	61	40.7%
- Grade 3	8	5.3%

Table III: Comparison of Intraoperative Assessment of Myometrial Invasion versus Final Histopathologic Results

Intraoperative gross assessment	Final Histopathology Result	
	Less than 50% invasion	More than 50% invasion
Myometrial invasion < 50 %	94 (94%)	29 (58%)
Myometrial invasion > 50 %	6 (6%)	21 (42%)

Table IV: Diagnostic test related to intraoperative gross assessment of depth of myometrial invasion in endometrial cance

Sensitivity	42%
Specificity	94%
Negative predictive value	76.4%
Positive predictive value	77.7%
Accuracy	76.7%

in 35 patients (23.3%). The depth of myometrial invasion was underestimated in 29 patients, and it was overestimated in 6 patients.

Regarding relation between myometrial invasion and positive lymph nodes metastasis, it was found that there was no significant relation between lymph nodes metastasis and the depth of myometrial invasion. A total of 9 (6%) patients were found to have lymph nodes involvement with 5 of them showing deeper myometrial invasion based on final histopathology report. Although there was a higher number of lymph node involvement observed in cases with deeper myometrial invasion, the difference was not statistically significant ($p > 0.05$).

DISCUSSION

According to the World Health Organization (WHO), the increasing prevalence of overweight is a concerning issue in many countries, including middle and lower-income countries such as Malaysia.[11] Based on the data collected from the National Health and Morbidity Survey (NHMS) 2019, the prevalence of overweight among adults in Malaysia was reported to be 50.1% and it was significantly higher among females.[11] As the prevalence of obesity among women in Malaysia continues to rise, it serves as one of the contributing factors to the increasing trend of endometrial cancer within Malaysian population.[2]

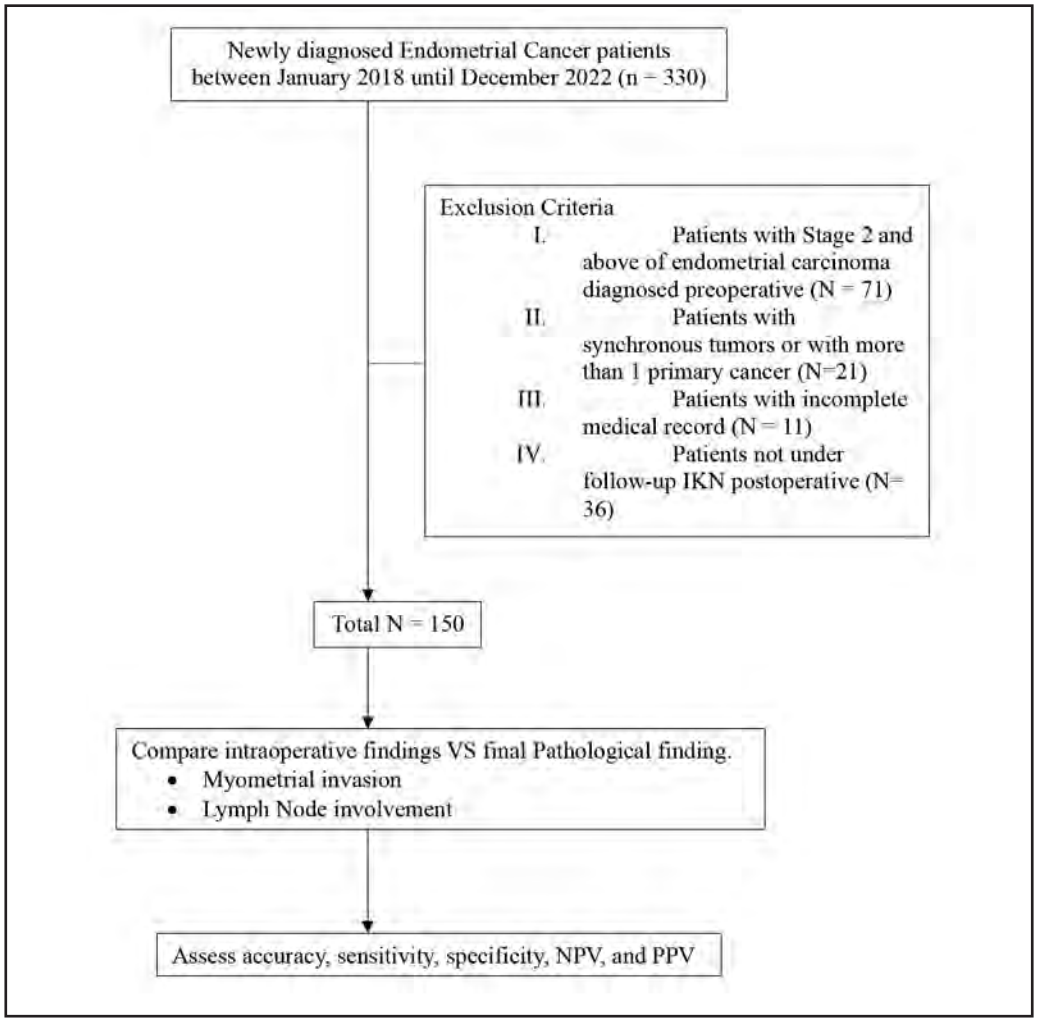

Fig. 1: Flow chart

Majority of women diagnosed with early-stage endometrial cancer are obese and have multiple comorbidities such as diabetes mellitus and hypertension.[12] Obese women undergoing prolong and extensive surgery such as systematic lymphadenectomy may be at increased risk of perioperative complications.[12] Certainly, lymphadenectomy is deemed important for comprehensive staging in endometrial cancer due to its significance in postoperative adjuvant therapy and prognosis.[13] Based on the latest FIGO staging of endometrial cancer 2023, lymph node staging should be performed in intermediate or high-risk endometrial cancer.[14] Hence, a selective approach of lymphadenectomy should be considered in low-risk early stage endometrial cancer, to balance between benefits of complete staging and the risks associated with the surgical procedure.[13]

Apart from tumor grading and histological type, depth of myometrial invasion is one of the most important risk factors for lymph node metastases.[15] Deeper myometrial invasion has been found to be associated with lymph nodes involvement.[15,24] There are several preoperative and intraoperative tools for surgical staging to identify the depth of myometrial invasion such as transvaginal ultrasound, magnetic resonance imaging (MRI), intraoperative gross assessment and intraoperative frozen section.[15] Each method exhibited varying levels of accuracy in identifying the depth of myometrial invasion.[16-18,22] Predictive value of transvaginal ultrasound in determination of depth of myometrial invasion is 80-87%.[15]

The sensitivity and specificity of MRI in detecting depth of myometrial invasion were 65.6% and 88.5%, respectively.[18] Unfortunately, not all government hospital were equipped with MRI facilities offering early appointment availability.[16] Intraoperative gross examination has been proposed as simple and inexpensive tools to visualize the depth of myometrial invasion.[16] Studies have shown that myometrial invasion is a strong predictor of node metastasis, with a sensitivity rate reaching up to 86%.[19] Various methods, whether used individually or in combination, preoperatively or intraoperatively are used to categorize patients into low or high-risk groups of endometrial cancer for complete surgical staging.[22]

Based on our study, we found that intraoperative gross assessment had good specificity (94%) and accuracy (76.7%) but relatively poor sensitivity (42%). Compared to previous meta-analysis, the pooled sensitivity and specificity of intraoperative gross examination compared with final histology were 71% and 91% respectively.[17] The study

conducted by Cem Yagmur Ozdemir et al, demonstrated a low sensitivity of 34 % and a specificity of 100% in predicting deep myometrial invasion.[20] Differences in the expertise and abilities of the surgeons could be a potential explanation for the comparatively reduced sensitivity observed during intraoperative macroscopic examinations in their research.[20]

The sensitivity of only 42% in our study showed that intraoperative myometrial assessment missed as many as 58% of patients who had deep myometrial invasion. The detection of myometrial invasion by gross examination exhibits poor sensitivity, which can be attributed to several factors. These factors include the experience of the surgeon, the infiltrative pattern and grading of the disease, as well as retrospective design method employed.

Nowadays, intraoperative frozen section analysis serves as a valuable tool in assessing the depth of myometrial invasion.[21] Based on the systemic review, intraoperative frozen section had higher accuracy in detecting the depth of myometrial invasion.[21] In contrast, ESGO guideline did not agree frozen section analysis due to poor reproducibility.[5] Apart from that, it is also not widely available in all facilities in view of inadequate specialized, skilled and available gynae pathologist to interpret the frozen section specimen.[21]

Many studies shown correlation between deeper myometrial invasion and lymph nodes metastasis.[4,23] In low-risk endometrial cancer cases, comprising superficial myometrial invasion and low-grade endometrioid histology, lymph node involvement was observed in 6% of patients.[5] This figure closely aligns with our study population, where 6% of the 150 recruited patients had lymph node metastasis.

Our institute is considered to have one of the largest numbers of cancer cases per year in Peninsular Malaysia, highlighting the strength of our study. In addition, our institute has appropriate human resources, including skilled oncologists, a resident training system and pathologists. Our limitation of this study was data collection. Some of the cases were continue follow-up postoperatively in other institution. Another limitation was the study was retrospective in nature. Lastly, for the best results, a change of study design to a prospective data collection approach and the level of operator who examined the uterine specimen each case, might be more suitable to achieve higher accuracy of intraoperative gross assessment in this study.

CONCLUSION

Intraoperative myometrial assessment during surgical staging showed good specificity and accuracy but limited sensitivity. These findings suggest that it remains a valuable clinical tool to guide surgeon to decide the best surgical treatment for each individual. However, combination of other modalities such as transvaginal ultrasound and MRI should be implemented accordingly to maximize the diagnostic accuracy.

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ORIGINAL ARTICLE

Leptospirosis in Perak state for the year 2024: Hospitalisation rate and its associated factors

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ABSTRACT

Introduction: Leptospirosis remains a public health concern in Malaysia, particularly in high-burden states like Perak. Understanding the hospitalisation rate and its associated factors is important for informing early intervention strategies and optimising disease management; however, local data on these aspects remain scarce. This study seeks to address this gap by determining the hospitalisation rate and identifying the risk factors associated with hospitalisation among probable and confirmed leptospirosis cases in Perak.

Materials and Methods: This is a retrospective cohort study using secondary data from two data sources obtained from the e-Notifikasi system database and laboratory reports of all registered leptospirosis cases in Perak from January to December 2024. The outcome variable, which was hospitalisation status, was determined by the treating team based on clinical manifestation and disease severity. Multiple logistic regression was applied to identify factors associated with hospitalisation cases. Data was analysed using SPSS version 29.

Results: A total of 764 registered leptospirosis cases were included in the study, with 75.5% (n=577) required hospital admission (95% CI: 72%,79%). The average age of patients was 32 years (SD: 20.5), with two-thirds (67.8%) being male. Kinta district reported the highest proportion of cases (30.4%). Factors significantly associated with hospitalisation included: presence of complications (aOR: 8.06, 95% CI: 1.57,41.48), vomiting (aOR: 11.00, 95% CI: 6.63,18.25), headache (aOR: 4.44, 95% CI: 2.70,7.32), onset-to-diagnosis (aOR: 1.37, 95% CI: 1.23,1.52), histories of recreational activity exposure (aOR: 3.41, 95% CI: 2.07,5.62), soil exposure (aOR: 2.60, 95% CI: 1.11,6.07) and types of occupation; student (aOR: 2.79, 95% CI: 1.58,4.93), agriculture (aOR: 5.06, 95% CI: 2.20,11.63), military personnel (aOR: 4.87, 95% CI: 1.08,21.92) and pensioners (aOR: 5.96, 95% CI: 3.31,10.74).

Conclusion: This study adds to the existing knowledge on the hospitalisation rate and its associated factors among registered leptospirosis cases in Perak. These findings highlight the importance of targeted health education, enhanced clinical vigilance and risk-based interventions tailored to local exposure patterns. While the study's strengths include comprehensive case capture and validated data, limitations include the absence of meteorological, socioeconomic status and health literacy data. These limitations emphasise the need for future longitudinal and behavioural studies.

KEYWORDS:
Leptospirosis, Hospitalisation, Environmental Exposure

INTRODUCTION

Leptospirosis, caused by bacteria of the genus Leptospira, is the most prevalent zoonotic disease worldwide.[1] Globally, leptospirosis contributes to nearly one million cases and 59,000 deaths each year, often peaking during rainy seasons and in areas with poor sanitation or occupational exposure.[2] Human leptospiral infections primarily result from direct or indirect exposure to the urine of infected animals, which gain entry into the body through the skin via a cut or abrasion, or through the mucous membranes of the conjunctivae or oral cavity.[3]

Leptospirosis, an emerging infectious disease, has been a public health concern in Malaysia due to its association with flooding, agriculture, and urban environments. Its incidence rates fluctuated between 13 and 17 cases per 100,000 population from 2011 to 2022, which is higher than those of neighbouring countries such as Thailand and the Philippines.[4] The increase in cases is possibly associated with changes in population behaviours and surveillance activities during the COVID-19 pandemic.[5] In Malaysia, leptospirosis is most commonly diagnosed using serological tests, such as the Microscopic Agglutination Test (MAT), which identifies serovar-specific antibodies, and solid-phase assays that detect Immunoglobulin M (IgM) antibodies. A patient's serum is expected to test positive for the IgM serology test within five to 10 days after the onset of symptoms, while MAT is likely to yield positive results between 10 and 12 days from the onset of the illness.[6]

Perak, a state in the northwest of Peninsular Malaysia, has shown a persistently high incidence and mortality rate over the years. The incidence varied between 11.41 and 13.60 per 100,000 for the years 2016 and 2017,[7] with case fatality rates ranging from 3.14% to 14.3% from 2011 to 2016.[8] Research has shown that 57% of environmental samples from

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recreational forests in Perak were contaminated with pathogenic Leptospira,[9] thereby providing favourable environments for the bacteria, which contribute to the persistence of the disease. Moreover, Perak has a diverse economic structure with agriculture remaining one of the important sectors, thus exposing workers to soil and water potentially contaminated by Leptospira.[10] The state's unique geographical and economic profile makes it a noteworthy area for studying leptospirosis.

Leptospirosis presents with a wide range of clinical symptoms, varying from a mild, self-resolving febrile illness that can be managed as an outpatient to a severe, potentially fatal condition involving multiple organ failure and requiring inpatient treatment. Leptospirosis hospitalisation rates vary globally, reflecting differences in disease severity and health-seeking behaviour. In Netherlands, hospitalisation was required in 74.4% cases,[11] whereas in Sri Lanka, an annual hospitalisation incidence of 52.1 per 100,000 population,[12] and an average of 0.6 hospitalisations per 1,000,000 population was observed in the United States.[13]

Several studies has been conducted to identify factors associated with hospitalisation including sociodemographic variables (e.g. age, gender, economic status, types of residency, education level),[12,14-15] clinical characteristics (e.g. presence of complication, late onset diagnosis, types of serovar, MAT titre level),[14,16-17] and environmental exposure (e.g. occupation, history of recreational activity and exposure to animal).[14,18] However, most of these research were done globally, for example in New Zealand, Sri Lanka, and Columbia, which have different health system and surveillance structure and their findings may not fully be applicable in endemic region like Malaysia, where exposure and health-seeking attitude could vary.

Ideally, leptospirosis cases should be promptly identified through effective diagnosis and thorough understanding of risk factors in order to prevent severe disease progression which requires hospitalisation. However, despite leptospirosis being gazetted as a notifiable disease in Malaysia, the incidence remain inconsistent indicating that existing preventive strategies are not optimized.[4] The majority of existing studies in Malaysia focus on the severity of cases based on clinical and laboratory parameters,[19] with less emphasis on sociodemographic and environmental influences. This research gap delays the early identification of high-risk cases and the implementation of targeted intervention. Consequently, preventable complications, overburdened healthcare and reduced job productivity will occur. Understanding these gaps is important for improving disease management, guiding targeted public health interventions and optimizing resource allocation. This study seeks to address this gap by determining the hospitalisation rate and identifying risk factors associated with hospitalisation among probable and confirmed leptospirosis cases in Perak.

MATERIALS AND METHODS

A state-level retrospective cohort study using secondary data from January to December 2024 was conducted. It involved the registered leptospirosis case reported to the Perak State Health Department (*Jabatan Kesihatan Negeri Perak,* JKNP). Perak is a state located on the northwest of Peninsular Malaysia, comprising 12 administrative districts. As of 2024, there are approximately 2.57 million multi-racial communities residing in Perak, making it the fourth most densely populated state in Malaysia.[20]

Data Source

The present study obtained data from two sources using name and identification number as the common identifier. Data sources included: (i) the e-Notifikasi Database System, recorded and maintained by the Communicable Disease Control Unit to obtain patients' demographic information, clinical presentations, and epidemiological histories; and (ii) laboratory reports from the Ipoh Public Health Laboratory (Makmal Kesihatan Awam Ipoh, MKAI) to determine the Leptospira serogroup based on the MAT results.

Leptospirosis is a notifiable disease in Malaysia, mandated under the Prevention and Control of Infectious Diseases Act 1988 (Act 342). Medical practitioners notified all probable and confirmed leptospirosis cases at clinics or hospitals through the e-Notifikasi system. Upon notification, the case was reviewed and verified at the district level by a trained health inspector from the District Health Office (DHO), who completed the required case details in the system, including patient demographic data, clinical symptoms, and epidemiological exposure history. The health inspector investigated the notification via hospital visits for inpatients and phone calls or home visits to those treated as outpatient cases.

The district epidemiologist reviewed the data before submission to the JKNP, where they are centrally managed and monitored by the Communicable Disease Control Unit (CDC Unit) to ensure accuracy, completeness, and timely reporting. Laboratory data, which included Leptospira serogroup identification through MAT, were recorded by MKAI-trained laboratory personnel. All procedures were conducted based on the Standard Operating Procedures (SOP) outlined in the Guidelines for the Diagnosis, Management and Prevention of Leptospirosis by the Ministry of Health Malaysia (2011).

Study Population and Sampling

The study population comprised all registered leptospirosis cases in the state of Perak, including both confirmed and probable cases. In this study, a probable leptospirosis case is defined as a patient who presents with clinical features consistent with leptospirosis and a positive rapid test or ELISA (IgM serology) for *Leptospira*. A confirmed case is defined as an individual with a Microscopic Agglutination Test (MAT) titre ≥1:400 based on a single serum sample. Cases were included if the patients resided in Perak during the notification period. To ensure the accuracy and completeness of the data, subjects with incomplete laboratory diagnosis results for Leptospirosis (IgM serology and MAT), those with co-infections, and those transferred in from another state during the notification period were excluded from the study. The sample size for this study was calculated using OpenEpi software version 3.01. The percentage of unexposed

Table I: Sociodemographic Characteristics of Leptospirosis Cases in Perak for Year 2024 (n=764)

Variables	Total (N=764) Mean (SD) / n (%)	Leptospirosis Cases		p-value
		Outpatient (n=187)	Inpatient (n=577)	
		n (%) Mean (SD)	n (%) Mean (SD)	
Sociodemographic				
Age (years)	32.0 (20.50)	31.0 (13.90)	32.0 (22.30)	0.638[a]
Gender				
Female	246 (32.2)	60 (32.1)	186 (32.2)	0.970[b]
Male	518 (67.8)	127 (67.9)	391 (67.8)	
Ethnicity				
Malay	545 (71.3)	132 (70.6)	413 (71.6)	0.298[b]
Chinese	35 (4.6)	5 (2.7)	30 (5.2)	
Indian	53 (6.9)	17 (9.1)	36 (6.2)	
Others	131 (17.1)	33 (17.6)	98 (17.0)	
Nationality				
Malaysian	726 (95.0)	174 (93.0)	552 (95.7)	0.152[b]
Non-Malaysian	38 (5.0)	13 (7.0)	25 (4.3)	
District				
Bagan Datuk	7 (0.9)	1 (0.5)	6 (1.0)	
Batang Padang	65 (8.5)	18 (9.6)	47 (8.1)	
Hilir Perak	14 (1.8)	1 (0.5)	13 (2.3)	
Hulu Perak	88 (11.5)	21 (11.2)	67 (11.6)	
Kampar	28 (3.7)	4 (2.1)	24 (4.2)	
Kerian	17 (2.2)	1 (0.5)	16 (2.8)	
Kinta	232 (30.4)	78 (41.7)	154 (26.7)	
Kuala Kangsar	146 (19.1)	27 (14.4)	119 (20.6)	
Larut, Matang, Selama	122 (16.0)	24 (12.8)	98 (17.0)	
Manjung	20 (2.6)	6 (3.2)	14 (2.4)	
Mualim	6 (0.8)	1 (0.5)	5 (0.9)	
Perak Tengah	19 (2.5)	5 (2.7)	14 (2.4)	

Notes: [a]Independent t-test/ [b]Pearson Chi-square/ [c]Others:Indigeneous group from Penisular and East Malaysia, and non-Malaysian; *level of significance set at 0.05

individuals with outcome was based on Sokolova, Marshall & Benschop (2021), who discovered that the prevalence of outpatient leptospirosis cases is 47%. The odds ratio for the risk factors associated with recreational activity was 2.36. By setting alpha at 0.05 and achieving a power of 80%, the minimum sample size required was 180. However, present analysis included all eligible cases to ensure good representativeness and high external validity.

Study Variables

A total of twenty-five variables were extracted from these two data sources (twenty-four variables from e-Notifikasi and one from the MKAI laboratory reports for analysis. The outcome variable was the hospitalisation status of leptospirosis cases, categorised as either outpatient or inpatient. The decision to admit relied on the clinical manifestations and their severity, as determined by the treating team.

The independent variables were selected based on relevance in previous studies and availability in the e-Notifikasi database system. The variables were classified into three domains, they were (i) socio-demographic (age, gender, ethnicity, nationality, and district of residency), (ii) clinical, and (iii) environmental factors. For clinical domain, eleven variables were included seven self-reported symptoms of leptospirosis such as fever, upper respiratory tract infection (cough, sore throat, flu), gastrointestinal symptoms (abdominal pain, vomiting, diarrhea), headache, myalgia; duration between symptom onset to diagnosis by medical doctor (days); MAT titre value (<1:400 or ≥1:400); number of serovar detected by each case (one or more than one type); and presence of leptospirosis complication e.g., sepsis/septic shock, meningitis, pulmonary haemorrhage, Weil's Syndrome and multi-organ failure.[6] For environmental domain, five variables related to patients' environmental exposure within 21 days before symptoms were included, they were: (i) job exposure (e.g., agriculture, student, military personnel, pensioner, others); (ii) animal exposure such as rodents, livestock, cats, dogs; (iii) history of flooding/exposure to flood water; (iv) history of recreational water activity; and (v) history of direct contact with soil such as gardening, landscaping, farming.

Data Management

Figure 1 illustrates the process of data extraction and management for this study. JKNP downloaded the data into Microsoft Excel Open XML Spreadsheet (.xlsx) format, and all personal identifiers were removed before release to the researcher to maintain participants' confidentiality. Data cleaning was performed using the final dataset (n=780). After applying the inclusion and exclusion criteria, 764 (98%) eligible cases were retained for final analysis. The final dataset (n=764) was then imported into Statistical Package for the Social Sciences (SPSS), version 29.0, to screen for missing data and perform statistical analysis. No missing data was found in this study. To maintain confidentiality and secure the data, all anonymous data was stored in a password-protected folder, accessible only to members of the research team.

Table II: Clinical and Environmental Characteristics of Leptospirosis Cases in Perak for Year 2024 (n=764)

Variables	Total (N=764) Mean (SD) / n (%)	Leptospirosis Cases Status		p-value
		Outpatient (n=187) n (%) / Mean (SD)	Inpatient (n=577) n (%) / Mean (SD)	
CLINICAL FACTORS				
Fever				
No	25 (3.3)	10 (5.3)	15 (2.6)	0.066[b]
Yes	739 (96.7)	177 (94.7)	562 (97.4)	
URTI				
No	623 (81.5)	134 (71.7)	489 (84.7)	< 0.001[b]
Yes	141 (18.5)	53 (28.3)	88 (15.3)	
Gastrointestinal Symptoms				
i) Abdominal Pain				
No	629 (82.3)	177 (94.7)	452 (78.3)	<0.001[b]
Yes	135 (17.7)	10 (5.3)	125 (17.7)	
ii) Vomiting				
No	371 (48.6)	153 (81.8)	218 (37.8)	<0.001[b]
Yes	393 (51.4)	34 (18.2)	359 (62.2)	
iii) Diarrhea				
No	480 (62.8)	159 (85.0)	321 (55.6)	<0.001[b]
Yes	284 (37.2)	28 (15.0)	256 (44.4)	
Headache				
No	477 (62.4)	139 (74.3)	338 (58.6)	<0.001[b]
Yes	287 (37.6)	48 (25.7)	239 (41.4)	
Myalgia				
No	463 (60.6)	121 (64.7)	342 (59.3)	0.186[b]
Yes	301 (39.4)	66 (35.3)	235 (40.7)	
Presence of complication				
No	707 (92.5)	185 (98.9)	522 (90.5)	<0.001[b]
Yes	57 (7.5)	2 (1.1)	55 (9.5)	
Onset-to-Diagnosis (Days)	4.0 (3.12)	3.0 (1.65)	5.0 (3.34)	<0.001[a]
MAT titre level				
<1:400	475 (62.2)	136 (72.7)	339 (58.8)	<0.001[b]
≥1:400	289 (37.8)	51 (27.3)	238 (41.2)	
Total Number of Serovar				
1	168 (22)	41 (21.9)	127 (22.0)	0.980[b]
>1	596 (78)	146 (78.1)	450 (78.0)	
ENVIRONMENTAL FACTORS				
Animal Exposure				
No	360 (47.1)	54 (28.9)	306 (53.0)	<0.001[b]
Yes	404 (52.9)	133 (71.1)	271 (47.0)	
Flood Exposure				
No	757 (99.1)	187 (100.0)	570 (98.8)	0.284[c]
Yes	7 (0.9)	0 (0.0)	7 (1.2)	
History of Recreational Activity				
No	443 (58.0)	146 (78.1)	297 (51.5)	<0.001[b]
Yes	321 (42.0)	41 (21.9)	280 (48.5)	
Soil Exposure				
No	687 (89.9)	176 (94.1)	511 (88.6)	0.028[b]
Yes	77 (10.1)	11 (5.9)	66 (11.4)	
Occupation				
Others[d]	199 (26.0)	83 (44.4)	116 (20.1)	<0.001[b]
Agriculture	85 (11.1)	12 (6.4)	73 (12.7)	
Military Personnel	14 (1.8)	4 (2.1)	10 (1.7)	
Student	230 (30.1)	43 (23.0)	187 (32.4)	
Sewage worker	12 (1.6)	6 (3.2)	6 (1.0)	
Pensioners	224 (29.3)	39 (20.9)	185 (32.1)	

Notes: URTI= Upper Respiratory Tract Infection; MAT= Microscopic Agglutination Test;
[a]Independent t-test/ [b]Pearson Chi-square/ [c]Continuity Correction (Yates correction)
[d]Others : occupation other than involving agriculture, military personnel, student, sewage worker, housewife and pensioner *level of significance set at 0.05

Table III: Factors associated with hospitalisation among Leptospirosis Cases in Perak using simple logistic regression (n=764)

Variables	B (SE)	Wald (df)	Crude OR (95% CI)	p-value
Age	0.002 (0.004)	0.141 (1)	1.002 (0.993, 1.010)	0.708
Gender				
Female	ref		1.000	
Male	-0.007 (0.180)	0.001 (1)	0.993 (0.698, 1.414)	0.970
Ethnicity				
Malay	ref		1.000	
Chinese	0.651 (0.493)	1.742 (1)	1.918 (0.729, 5.043)	0.187
Indian	-0.390 (0.311)	1.577 (1)	0.677 (0.368, 1.245)	0.209
Others	-0.520 (0.225)	0.054 (1)	0.949 (0.611, 1.474)	0.949
Nationality				
Malaysian	ref		1.000	
Non-Malaysian	-0.501 (0.353)	2.013 (1)	0.606 (0.304, 1.210)	0.156
Fever				
No	ref		1.000	
Yes	0.750 (0.417)	3.230 (1)	2.117 (0.934, 4.795)	0.720
URTI				
No	ref		1.000	
Yes	-0.787 (0.199)	15.605 (1)	0.455 (0.308, 0.672)	<0.001
Vomiting				
No	ref		1.000	
Yes	2.003 (0.208)	92.604 (1)	7.411 (4.928, 11.143)	<0.001
Headache				
No	ref		1.000	
Yes	0.717 (0.188)	14.605 (1)	2.048 (1.418, 2.957)	<0.001
Myalgia				
No	ref		1.000	
Yes	0.231 (0.173)	1.743 (1)	1.260 (0.894, 1.775)	0.187
Presence of Complication				
No	ref		1.000	
Yes	2.277 (0.725)	9.865 (1)	9.746 (2.354, 40.354)	0.002
Onset-to-Diagnosis (Days)	0.295 (0.044)	45.806 (1)	1.344 (1.233, 1.464)	<0.001
MAT titre level				
<1:400	ref		1.000	
≥1:400	0.627 (0.185)	11.528 (1)	1.872 (1.304, 2.689)	<0.001
Total Number of Serovar				
1	ref		1.000	
> 1	0.014 (0.204)	0.004 (1)	1.014 (0.680, 1.511)	0.947
Animal Exposure				
No	ref		1.000	
Yes	-1.023 (0.182)	31.707 (1)	0.360 (0.252, 0.513)	<0.001
History of Recreational Activity				
No	ref		1.000	
Yes	1.211 (0.195)	38.419 (1)	3.357 (2.289, 4.924)	<0.001
Soil Exposure				
No	ref		1.000	
Yes	0.726 (0.337)	4.634 (1)	2.067 (1.067, 4.002)	0.031
Occupation				
Others	ref		1.000	
Agriculture	1.471 (0.343)	18.379 (1)	4.353 (2.222, 8.527)	<0.001
Military Personnel	0.582 (0.609)	0.912 (1)	1.789 (0.542, 5.899)	0.339
Student	1.135 (0.222)	26.152 (1)	3.112 (2.014, 4.808)	<0.001
Sewage worker	-0.335 (0.595)	0.317 (1)	0.716 (0.223, 2.297)	0.574
Pensioners	1.222 (0.227)	28.877 (1)	3.394 (2.173, 5.300)	<0.001

Note: OR=Odds Ratio ; SE=standard error; df = degree of freedom; CI; Confidence interval; B=unstandardised regression weight *level of significance at 0.25

Table IV: Factors Associated with Hospitalisation among Leptospirosis Cases in Perak using multiple logistic regression (n=764)

Variables	B (SE)	Wald (df)	Adj OR(95% CI)	p-value
Clinical Factors				
Vomiting (Yes)	2.398 (0.258)	86.256 (1)	11.001 (6.632, 18.248)	<0.001
Headache (Yes)	1.491 (0.255)	34.241 (1)	4.443 (2.696, 7.322)	<0.001
Presence of Complication (Yes)	2.087 (0.836)	6.240 (1)	8.064 (1.568, 41.483)	0.012
Onset-to-Diagnosis (Days)	0.311 (0.054)	33.546 (1)	1.365 (1.229, 1.517)	<0.001
Environmental Factors (History of Exposure)				
Recreational Activity Exposure	1.227 (0.255)	23.108 (1)	3.410 (2.068, 5.624)	<0.001
Soil Exposure	0.954 (0.433)	4.854 (1)	2.596 (1.111, 6.067)	0.028
Types of Occupation				
Agriculture	1.620 (0.425)	14.534 (1)	5.055 (2.197, 11.627)	<0.001
Military Personnel	1.586 (0.768)	4.248 (1)	4.868 (1.081, 21.923)	0.039
Student	1.027 (0.290)	12.493 (1)	2.792 (1.580, 4.934)	<0.001
Pensioners	1.785 (0.301)	35.268 (1)	5.958 (3.306, 10.737)	<0.001

Note: AOR= Adjusted Odds Ratio; SE = standard error; B= unstandardised regression weight; d.f = degree of freedom; CI; Confidence interval; *level of significance at 0.05
Backward LR method was applied; No multicollinearity and no interaction; Hosmer Lemeshow test, p-value = 0.471; Area under Receiver Operating Characteristics (ROC) Curve = 0.88

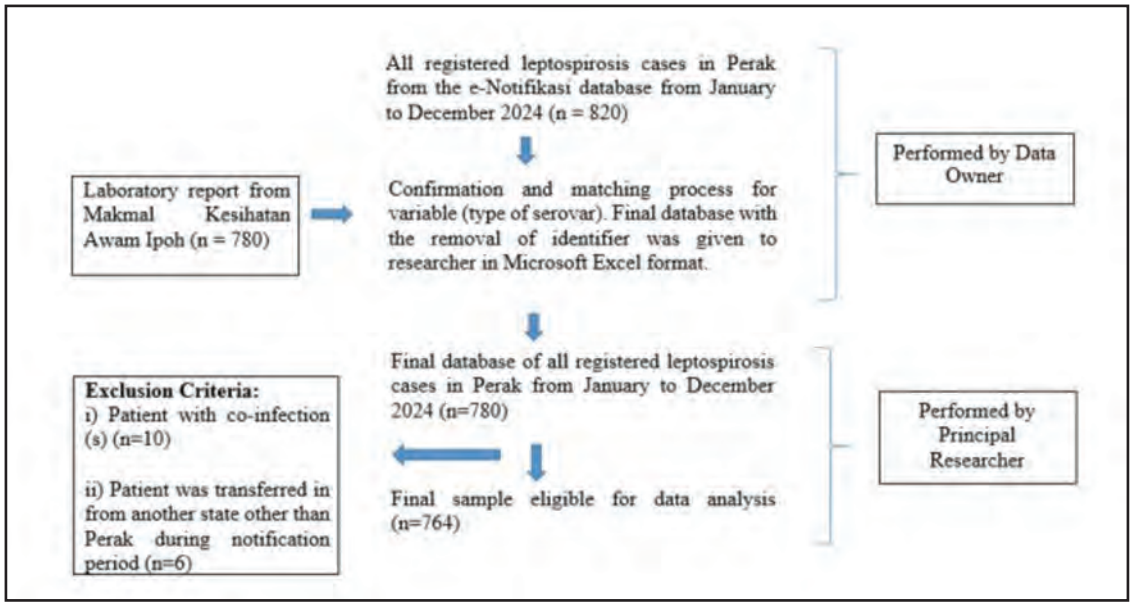

Fig. 1: Flowchart of data extraction

Statistical Analysis

All data were analysed using SPSS version 29.0. The leptospirosis hospitalisation rate was calculated by using the formula as followed:

$$\text{Hospitalisation Rate of Registred Leptospirosis Cases} = \frac{\text{Total number of registered leptospirosis cases require hospitalisation}}{\text{Total number of registered leptospirosis cases from January 2024 – December 2024}}$$

Estimation of the hospitalisation rate (95% confidence interval (CI) of the proportion interval was measured using the following formula: $95\%CI = p \pm z\ (\sqrt{(p(1-p)/n)}\ )$.

Descriptive analysis was performed to summarise the sociodemographic, clinical, and environmental characteristics of leptospirosis cases. Categorical variables were reported using frequencies and percentages, while continuous variables were summarised using mean and standard deviation (SD). A univariate analysis was conducted between in-patient and out-patient group characteristics, using the Pearson Chi-square test or continuity correction test for categorical variables and the independent t-test for continuous variables. To identify risk factors associated with hospitalisation, simple and multiple logistic regression analyses were conducted. Variables with clinical importance and a p-value less than 0.25 in simple logistic regression analysis were included in the preliminary multivariable model. The Backwards Likelihood Ratio method was used for variable selection. No interaction and

multicollinearity were observed in the final model. Model fitness was confirmed using the Hosmer–Lemeshow goodness-of-fit test, classification table and the Receiver Operating Characteristic (ROC) curve. Results were presented as crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) and corresponding p-values.

RESULTS

A total of 764 registered leptospirosis cases were included in the study, comprising 37.8% confirmed cases and 62.2% probable cases. The majority of cases (n=577, 75.5%) required hospital admission (95% CI 72%,79%). Among confirmed cases, 82.3% (n=238) required hospitalisation, while 71.0% (n=339) of probable cases were also hospitalised.

The mean (SD) age of cases was 32 (20.5) years, and two-thirds of them were male (67.8%). The majority of cases were Malaysians (95.0%). The highest number of cases was reported from the Kinta district (30.4%), followed by the Larut, Matang and Selama districts (16.0%). Tables I and II demonstrated the sociodemographic, clinical and environmental characteristics of leptospirosis cases, respectively. The sociodemographic characteristics were comparable between outpatient and inpatient cases, with no statistically significant difference in their distributions.

To investigate the association between sociodemographic factors, clinical presentations and environmental exposures with hospitalisation status, simple logistic regression analysis was conducted, in which 13 out of 24 variables were statistically significant at $p<0.25$, including ethnicity, nationality, vomiting, headache, presence of complications, timing of diagnosis, MAT titre level, history of animal exposure, recreational activity, soil exposure and occupation (Table III). These variables were subsequently included in the multivariable binary logistic regression model. Seven significant risk factors associated with hospitalisation among leptospirosis cases were identified (Table IV). These included: presence of complications (aOR: 8.06, 95% CI: 1.57,41.48), vomiting (aOR: 11.00, 95% CI: 6.63,18.25), headache (aOR: 4.44, 95% CI: 2.70,7.32), onset-to-diagnosis (aOR: 1.37, 95% CI: 1.23,1.52), histories of recreational activity exposure (aOR: 3.41, 95% CI: 2.07,5.62), soil exposure (aOR: 2.60, 95% CI: 1.11,6.07) and types of occupation; student (aOR: 2.79, 95% CI: 1.58,4.93), agriculture (aOR: 5.06, 95% CI: 2.20,11.63), military personnel (aOR: 4.87, 95% CI: 1.08,21.92) and pensioners (aOR: 5.96, 95% CI: 3.31,10.74).

DISCUSSION

By analysing Leptospirosis cases notified to JKNP in 2024, this study aimed to investigate the hospitalisation rate among leptospirosis cases, the characteristics of leptospirosis cases overall and based on hospitalisation status, and to determine the risk factors associated with hospitalisation. Analysis revealed three main findings, they were (i) the hospitalisation rate was reported 75.5% (95% CI: 72%, 79%) among registered leptospirosis cases; (ii) leptospirosis cases involved young age group (in their thirties on average), mostly male and majority were from the Kinta district, and (iii) seven risk factors associated with hospitalisation included presence of vomiting, headache, leptospirosis complication, longer onset-to-diagnosis duration, presence of recreational activity and soil exposure, and occupation.

The hospitalisation rate revealed in the present study was similar to that in the Netherlands (74.4%) and New Zealand (53.0%), where the same inclusion criteria were used to recruit leptospirosis cases as in the present study.[11,14] Conversely, the United States reported a lower rate of 0.6 hospitalisations per 1,000,000 population annually.[13] This lower rate could be attributed to differences in case definition and surveillance system. In that study, hospitalised leptospirosis cases were included based on hospital discharge data where diagnosis was made by a physician using an ICD-Code without requiring laboratory confirmation as well as leptospirosis was not nationally notifiable until 2012. This led to underreporting and underestimation of hospitalised cases.[21]

It was demonstrated that the mean (SD) age of leptospirosis cases in Perak was 32 (20.5) years, with the majority of cases affecting the male population. This finding was in line with previous studies, where Malaysians aged 30-39 years and Thai young adults aged 15-34 years have been identified as the most affected group, attributed to greater exposure to environmental and occupational risk factors.[22-23] Apart from that, males had a higher risk of contracting leptospirosis due to behavioural factors, such as lower adherence to personal protective measures and increased outdoor activity, thereby increasing their susceptibility to infection.[24] Moreover, another study reported that post-pubertal males had a much greater incidence of leptospirosis, most likely due to a combination of increased environmental exposure and a weakened immune system impacted by testosterone.[25]

The Kinta district reported the highest proportion of leptospirosis cases, at 30.4%. This could be attributed to being the most populous district in Perak with an estimated population of 908,900 in 2023, accounting for approximately 35.8% of the state's total population of 2.54 million.[10] The high population density, especially in urban areas, increases the risk of exposure to contaminated environments, particularly in urban settings.26 Furthermore, the majority of the population in Kinta belongs to the working-age group (15-64), with 22% (140,000) ranging from 30 to 39 years old.[10] They are typically more engaged in occupational or outdoor activities that increase the risk of leptospirosis. These findings highlight the Kinta district as a hotspot area for Leptospirosis transmission in Perak, emphasising the need for local authorities to focus on strategic preventive public health measures and enhance disease surveillance in this district.

Furthermore, it was found that the sociodemographic characteristics were comparable between outpatient and inpatient leptospirosis cases. Clinical factors and environmental exposures were the important risk factors associated with leptospirosis cases in Perak. Leptospirosis cases that presented with vomiting, headache, and complications (such as meningitis, organ failure, and sepsis) had higher odds of getting hospitalised. Vomiting and headache may be warning signs of leptospirosis, requiring close observation to prevent further deterioration. These

symptoms were reported to be the most common clinical manifestations among hospitalised leptospirosis cases in previous studies.[27-31]

Vomiting may reflect hepatic involvement or electrolyte disturbances or early sepsis, and headache may reflect early neurological involvement or meningitis. To avoid serious complications such as seizure, altered mental status and intracranial hypertension, which have been reported in complicated cases, attending doctors should be vigilant in recognising this cardinal symptom.[32]

Leptospirosis cases presented with a longer onset-to-diagnosis duration had higher odds of hospitalisation, which was consistent with a study conducted in New Caledonia.[17] Pathogenetically, a late diagnosis would prolong the duration of bacterial replication and vascular damage, allowing the infection to shift from the leptospiremic to the immune phase, where complications are more likely to occur.[33] The patient and the healthcare provider can cause these delays. Leptospirosis cases might misinterpret the early symptoms of leptospirosis as mild or work-related fatigue, especially those working in high-risk jobs such as agriculture, which is linked to our finding that agriculture is a significant factor related to hospitalisation.[34] Apart from that, non-specific early symptoms of leptospirosis can mirror common viral infections, leading to under-recognition or misdiagnosis by primary healthcare providers.[35] Therefore, enhancing public awareness and provider training are important in reducing diagnosis delay to prevent hospitalisation that could jeopardise job productivity.

On top of that, environmental exposures, particularly those engaged in recreational activities or exposure to soil, were significantly linked to a higher risk of hospitalisation. The demographics of affected cases may explain this. Firstly, the majority reside in the Kinta district, which is known for its accessible rivers and recreational forests, and many of these sites are located near leptospira-contaminated water sources.[9] Secondly, young males, being the highly affected population, were more likely to engage in outdoor activities such as hiking, camping or swimming.[11,36] Additionally, farmers and students were at a higher risk of hospitalisation, possibly attributed to their relatively lower socio-economic status and/or lower health literacy, as highlighted in previous studies.[14,37] Farmers are often exposed to contaminated soil and infected animal urine during agricultural work or paddy field activities.[38] Similarly, students may engage in outdoor activities such as swimming or community clean-up events without adequate protective measures due to lack of awareness.[37] Consequently, prolonged exposure to contaminated water or soil, whether through recreational or job-related activities, may increase the risk of more severe disease manifestations, necessitating hospital admission.[39]

These findings offer several actionable insights and public health implications. While factors such as age and gender are non-modifiable, other factors, including the timing of diagnosis, occupational, recreational, and soil exposure, as well as clinical symptom recognition, can be addressed through targeted interventions. Delayed diagnosis and limited health literacy, particularly among students and farmers, underscore the need to strengthen health education campaigns on leptospirosis in the community, as well as among recreational centre owners/operators and local authorities, and to enhance clinical vigilance in healthcare settings.[40] Future behavioural studies are highly recommended to explore the public risk perception and preventive practices related to leptospirosis among the high-risk groups.

Overall, several strengths were demonstrated in the present study. Firstly, the inclusion of all serology-positive leptospirosis cases, regardless of MAT titre (including probable and confirmed cases), reflects the real-world clinical spectrum of leptospirosis, allowing for a broader representation of cases and reflect the overall burden of the disease. Secondly, data was primarily collected and verified in the national e-Notifikasi system by trained and experienced health inspectors working in the communicable disease unit. One-to-one interviews conducted through hospital visits or home interviews during the case investigation reduced the risk of information bias, particularly in documenting exposures and clinical presentations. Lastly, retrospective cohort study improves the ability to examine possible causal relationship between exposures and hospitalisation using available surveillance data.

Nevertheless, individual health literacy levels, comorbidities, socioeconomic status, healthcare access, and meteorological indicators such as rainfall or soil humidity were not captured in this study. These unmeasured factors may significantly influence both exposure and health-seeking behaviour, potentially leading to residual confounding. Despite efforts to minimise information bias through one-to-one interviews, some exposure data were self-reported and could introduce recall bias. Furthermore, hospital admission criteria were not standardised across facilities and may have resulted in variations in hospitalisation outcomes. Nonetheless, the findings still offer a better understanding of hospitalisation trends observed in routine clinical practice.

CONCLUSION

In conclusion, three in four leptospirosis cases were hospitalised. Leptospirosis primarily affected males, particularly those in their thirties, who resided in the Kinta district. Risk factors associated with hospitalisation included clinical factors (presence of vomiting, headache, and leptospirosis complication, as well as longer onset-to-diagnosis duration) and environmental factors (history of recreational activity or soil exposure within the past 21 days preceding the onset). Targeted leptospirosis awareness campaigns, particularly among recreational site operators and frequent visitors, should be prioritised to improve awareness and promote protective behaviours. As leptospirosis continues to pose a significant health threat in Malaysia, a multi-agency collaboration shall be strengthened to employ the One Health approach for prevention and control efforts.

ETHICAL APPROVAL

This study was conducted according to the guidelines of the Declaration of Helsinki and approved by two Institutional Review Boards. Ethical clearance was obtained from:
i) Research Ethics Committee (REC), UiTM (FERC-EX-25-04), and ii) Medical Research Ethics Committee (MREC), Ministry of Health Malaysia (NMRR ID-25-01199-484).

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ORIGINAL ARTICLE

Isotretinoin-induced severe dry eye disease and meibomian gland alterations in patients with acne vulgaris: A noncontact ocular surface analysis

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ABSTRACT

Introduction: Although isotretinoin causes various potentially vision-threatening ocular side effects, it remains widely prescribed for acne vulgaris (AV) globally due to its proven efficacy, particularly in severe or treatment-resistant cases. This study evaluated the effect of isotretinoin on ocular surface parameters to elucidate the underlying mechanisms of isotretinoin-associated dry eye disease (DED).

Materials and Methods: A comparative cross-sectional observational study was conducted at two tertiary hospitals between August 2022 and May 2023. A total of 48 patients with AV were recruited and categorised into the isotretinoin-treated (n=19) and isotretinoin-naive (n=29) groups. A LacryDiag® ocular surface analyser was used to evaluate meibomian gland loss (MGL) and tear film parameters. The Ocular Surface Disease Index (OSDI) questionnaire was administered to evaluate dry eye symptom, severity and functional effects.

Results: At enrollment, the mean duration of AV was 5.26 ± 3.28 and 6.39 ± 5.63 years in the treated and naive groups, respectively. Treated participants had completed at least a minimum of 16 weeks of daily isotretinoin therapy at the time of examination (mean: 16.89 ± 3.2 weeks). The OSDI score was markedly higher in the treated group than that in the naive group (43.20 ± 18.79 vs 18.15 ± 19.24). The isotretinoin-treated group had a significantly greater MGL percentage than the naive group (p<0.001), significantly lower noninvasive break-up time (NIBUT) (p=0.046) and lipid layer thickness (p<0.001). The mean tear meniscus height was also lower in the treated group, although the difference was not statistically significant (p = 0.462). Pearson's correlation analysis revealed a significantly moderate positive correlation between the MGL percentage and OSDI score (r=0.417, p=0.003) and a significantly moderate negative correlation between MGL percentage and NIBUT (r=−0.348, p=0.015).

Conclusion: Isotretinoin therapy in patients with AV is remarkably associated with greater MGL, severe dry eye symptoms, and reduced tear film stability, supporting a lipid-deficient mechanism in isotretinoin-induced DED. Routine ocular surface evaluations are recommended for the early detection and management of ocular complications in patients receiving isotretinoin.

KEYWORDS:
Isotretinoin, meibomian gland disease, meibography, noninvasive break-up time, OSDI

INTRODUCTION

Acne vulgaris (AV) is the most common dermatological condition among adolescents, affecting approximately 85% of individuals aged 12–24 years.[1] Its pathogenesis is multifactorial, involving androgen-mediated stimulation of sebaceous glands, which promotes follicular hyperkeratinization and colonization by *Propionibacterium acnes*, leading to chronic inflammation and eventual scar formation.[2,3] The Global Burden of Disease Study 2019 documented a 47.9% increase in global cases from 1990 to 2019, culminating in 117.4 million cases worldwide.[4] Although AV is commonly observed during adolescence, it may persist into adulthood. A recent study involving 1,167 patients with acne reported that 41.3% were adults, among whom 85% were women, highlighting both the continued burden of AV beyond teenage years and its higher prevalence among adult women.[5]

Beyond cutaneous manifestations, AV may also affect the eye, particularly the ocular surface, primarily through its effect on meibomian glands (MGs).[6] Altered MG activity disrupts meibum quality and secretion, predisposing patients to MG dysfunction (MGD) and resultant evaporative dry eye disease (DED).[6] DED, previously referred to as dry eye syndromes (DES), is now classified according to TFOS DEWS II criteria, which emphasise tear film instability, hyperosmolarity, and ocular surface damage.[7] Clinically, these ocular changes are often subjectively detected through fluorescein staining, which reveals corneal or conjunctival staining and reduced tear break-up time (TBUT). However, objective evaluation is superior and currently can be performed using ocular surface analyser (OSA) to quantify MG loss (MGL) and tear film parameters, including noninvasive break-up time (NIBUT), lipid layer thickness (LLT), and tear meniscus height (TMH).[8]

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Isotretinoin, a systemic vitamin A derivative, is indicated for treating nodulocystic and severe AV, as well as moderate cases that are refractory to conventional therapies.[9,10] Although its dermatological efficacy is well established, isotretinoin has also been implicated in inducing apoptosis in sebocytes, including those within MGs, potentially leading to noncicatricial MGD and subsequent tear film instability, ocular consequences that remain underrecognized.[11] The current Malaysian guidelines for AV management exclude recommendations for ophthalmological referral or screening.[10] This study objectively evaluated MG and tear film parameters in isotretinoin-treated patients using a noncontact ocular surface analyser, providing evidence of remarkable DED and addressing a critical gap in local clinical data to support more integrated patient care.

MATERIALS AND METHODS

This comparative cross-sectional observational study was conducted at two tertiary hospitals between August 2022 and May 2023: the Ophthalmology Clinic of Hospital Pakar Universiti Sains Malaysia and the Dermatology Clinic of Hospital Raja Perempuan Zainab II. The Human Research Ethics Committee of Universiti Sains Malaysia (USM/JEPeM/21060488] and the Medical Research and Ethics Committee of the Ministry of Health [NMRR ID-22-00453-J83] approved this study. Written informed consent was obtained from all patients.

Selection and Recruitment of the Participants

A total of 48 patients with AV were recruited via convenience sampling and categorised into two groups: the isotretinoin-treated (n=19), consisting of individuals who had completed at least 16 weeks of daily 20 mg isotretinoin therapy, and the isotretinoin-naive group (n=29), with no prior exposure to oral isotretinoin. Eligibility for the treated group required completion of at least a 16-week course of oral isotretinoin at a fixed daily dose of 20 mg. The exclusion criteria included the presence of anterior segment pathology, history of corneal or refractive surgery, chronic use of topical corticosteroid eye drops, current or prior intake of estrogen-containing medications, and diagnosis of trigeminal neuropathy. Demographic and clinical data, including age, gender, race, education level, duration of AV, and duration of isotretinoin therapy, as well as systemic and ocular history were obtained through patient interviews and review of medical records. A comprehensive ophthalmic examination, including visual acuity testing, anterior segment evaluation, and fundus assessment, was performed for all participants.

Sample Size Determination

The minimum required sample size for this study was calculated a priori for the primary outcome, MGL, using PS Power and Sample Size Software for an independent t-test (α=0.05, power=0.95). Based on a standard deviation of 0.7 and an expected difference of 1.01 between groups, [12] 14 participants per group were needed. Accounting for a 10% dropout, the total minimum sample size was 32 (16 per group).

Assessment of Dry Eye Symptoms

The severity and functional effects of dry eye symptoms were assessed using a 12-item OSDI questionnaire. Depending on participant literacy and language preference, either the original English version or the validated Malay translation was used.[13] Responses were obtained through self-completion or interviewer assistance. OSDI scores were categorised as follows: normal (0–12 points), mild (13–22 points), moderate (23–32 points), and severe (33–100 points).[14]

Noncontact Analysis of Tear Film Parameters

Tear film assessments were performed following the OSA protocol, using a LacryDiag® analyser (Quantel Medical, Cournon-d'Auvergne, France), ensuring standardised and reproducible evaluations.[8,15,16] A single masked and trained research assistant performed these procedures in the following sequence to ensure consistency, minimise potential bias, and reduce procedural variability: (1) TMH, (2) LLT, (3) NIBUT, and (4) meibography. Examinations were conducted in a temperature-controlled room with air-conditioning maintained at a comfortable level.[16] To prevent airflow-related interference, the patient's face was positioned away from direct ventilation, and no fans were used during examination.[16] Each parameter was measured three times, with the mean value used for analysis to enhance repeatability and precision.

TMH was measured at the inferior lid margin (in millimeters) to estimate the aqueous tear volume.[16,17] LLT was evaluated via interferometric analysis and categorised using a simplified version of the Guillon classification system: lipid-deficient (grades 0–2), normal lipid levels (grades 3–5), and excessive lipid presence (grade 6).[16,17] NIBUT was automatically recorded in seconds over three consecutive trials, with the median value used for analysis; readings ≤12 s were considered indicative of DED.[16,17] MG loss (MGL) was assessed using noncontact infrared meibography of the upper eyelid.[18] The captured images were automatically analysed using proprietary software to quantify the MGL percentage, defined as the proportion of gland dropout relative to the total tarsal area.[15] MGL was subsequently graded using the meiboscale system based on quantified percentage MGL: grade 0 (no loss), grade 1 (<25%), grade 2 (26%–50%), grade 3 (51%–75%), and grade 4 (>75%).[19]

Statistical Analysis

All demographic and clinical data were entered into IBM SPSS Statistics, version 27.0 (IBM Corp., Armonk, NY, USA). All entries were reviewed for completeness and accuracy. The Shapiro–Wilk test was used to assess data normality, which confirmed a normal distribution.

Descriptive statistics were used to summarise the demographic characteristics, MGL percentage and clinical parameters of DED, including OSDI scores and tear film parameters (TMH, LLT, and NIBUT). Numerical variables were expressed as means and standard deviations, whereas categorical variables were expressed as frequencies and percentages.

Comparative analyses of OSDI scores, NIBUT, TMH, and MGL between isotretinoin-treated and naive participants were performed using an independent samples t-test. Differences in LLT category distribution, OSDI severity level, and meiboscale grading were evaluated using Fisher's exact test. Correlation analysis was conducted using Pearson's correlation coefficient to explore the relationships between MGL percentages and clinical parameters of DED (OSDI, NIBUT, LLT, and TMH). A p-value <0.05 was considered statistically significant in all tests, with the correlation strength interpreted on the basis of standard r-value guidelines.

RESULTS

The participants' demographic characteristics are summarised in Table I. The cohort was predominantly Malay (n = 45), with a smaller proportion of Chinese participants (n = 3). The mean age of the patients was 21.6 ± 3.15 and 25.7 ± 9.89 years in the isotretinoin-treated and isotretinoin-naive groups, respectively. Although statistically remarkable, the wide standard deviation in the naive group indicates age variability and potential overlap between cohorts. There was higher female than male, with a ratio of 1.82:1. Most patients (79.1%) were nonsmokers. Almost half (47.9%) of the patients were students. The mean duration of AV at baseline enrollment was 5.26 ± 3.28 and 6.39 ± 5.63 years in the treated and naive groups, respectively. The isotretinoin-treated participants had completed at least a minimum of 16 weeks of isotretinoin therapy at a daily dose of 20 mg at the time of examination (mean: 16.89 ± 3.2 weeks).

The objective profiles of MG and dry eye parameters are presented in Table II. The isotretinoin-treated group had a considerably higher mean OSDI score than the naive group (43.20 ± 18.79 vs 18.15 ± 19.24). The isotretinoin-treated group had lower mean values of NIBUT (p=0.046), LLT (p< 0.001), and TMH (p=0.462). A threefold higher mean MGL percentage was observed in the isotretinoin-treated group (p<0.001), with a more frequent higher dropout, meiboscale grade 2–3 in this group (p<0.001), consistent with more advanced structural compromise than in the isotretinoin-naive group (Figure 1).

Post-hoc analysis using observed means and pooled SDs demonstrated high statistical power for the primary outcomes (MGL: Cohen's d=2.02, Power (1–β)=1.00; OSDI: Cohen's d=1.31, Power (1 – β) = 0.99). For the secondary outcomes, power was lower (NIBUT: Cohen's d=0.71, Power (1–β)=0.62; TMH: Cohen's d=0.12, Power (1–β)=0.06), indicating that non-significant findings should be interpreted cautiously. These results support the robustness of significant findings while highlighting limited power for certain parameters.

The relationships between MGL and clinical parameters of DED were analysed using Pearson's correlation (Table III). There was a significant moderate positive correlation between the MGL percentage and OSDI score (r=0.417, p=0.003) and a significant moderate negative correlation between the MGL percentage and NIBUT (r=–0.348, p=0.015) (Fig. 2).

Table I: Demographic Profile of Patients with Acne Vulgaris

Variables	Total (n=48)	Isotretinoin-Treated (n=19)	Isotretinoin-Naïve (n=29)	p-value
Age (years)				
(Mean ± SD)		21.6 ± 3.15	25.7 ± 9.89	0.008[a]
Gender (n, %)				0.653[b]
Male	17 (35.4)	6 (31.6)	11 (38)	
Female	31 (64.6)	13 (68.4)	18 (62)	
Race (n, %)				0.148[b]
Malay	45 (93.8)	19 (42.2)	26 (57.8)	
Chinese	3 (6.2)	0 (0.0)	3 (100)	
Smoking (n, %)				0.276[b]
Yes	10 (20.9)	2 (10.5)	8 (27.6)	
No	38 (79.1)	17 (89.5)	21(72.4)	
Occupation (n, %)				0.452[b]
Student	23 (47.9)	12 (63.2)	11 (37.9)	
Government	4 (8.4)	1 (5.3)	3 (10.3)	
Others	16 (33.3)	5 (26.3)	11 (37.9)	
Unemployed	5 (10.4)	1 (5.3)	4 (13.8)	
Duration of acne (years)				
(Mean ± SD)		5.26 ± 3.28	6.39 ± 5.63	0.385[a]
Duration of oral isotretinoin (years)				
(Mean ± SD)		16.89 (3.2)		

[†] [a]Independent t-test; [b]Chi-square test, p-value < 0.05 significant

Table II: Meibomian Gland Loss and Clinical Parameters of Dry Eye Disease in Patients with Acne Vulgaris

Variables	Isotretinoin-Treated (n=19)	Isotretinoin-Naïve (n=29)	p-value
Meibomian Gland Loss			
Percentage Loss (Mean ± SD)	33.89 ± 16.1	11.21± 6.4	<0.001[a]
Meiboscale (n, %)			
Grade 0 (No MGL)	0 (0.00)	3 (10.3)	<0.001[b]
Grade 1 (< 33% MGL)	5 (26.3)	26 (89.7)	
Grade 2 (33% – 66% MGL)	11 (57.9)	0 (0.00)	
Grade 3 (> 66% MGL)	3 (15.8)	0 (0.00)	
OSDI Score			
Overall score (Mean ± SD)	43.20 ± 18.79	18.15 ± 19.24	<0.001[a]
Severity (n, %)			
Normal (0 – 12 points)	0 (0.00)	3 (10.3)	<0.001[b]
Mild (13 – 22 points)	5 (26.3)	26 (89.7)	
Moderate (23 – 32 points)	11 (57.9)	0 (0.00)	
Severe (33 – 100 points)	3 (15.8)	0 (0.00)	
NIBUT			
Overall score (Mean ± SD)	10.64 ± 2.96	13.02 ± 3.62	0.046[a]
TMH			
Overall score (Mean ± SD)	0.22 ± 0.10	0.23 ± 0.07	0.462[a]
Lipid Layer Thickness (n, %)			<0.001[b]
Grade 0 – 2 (Deficient)	13 (68.4)	1 (3.4)	
Grade 3 – 5 (Normal)	6 (31.6)	26 (89.7)	
Grade 6 (Excessive)	0 (0.0)	2 (6.9)	

† Abbreviations: OSDI, Ocular Surface Disease Index; NIBUT, non-invasive break-up time; TMH, tear meniscus height; MGL, meibomian gland loss
‡ [a]Independent t-test; [b]Fisher's exact test. p-value < 0.05 significant

Table III: Correlation Between Meibomian Gland Loss and Clinical Parameters of Dry Eye Disease Among Patients with Acne Vulgaris

	Meibomian Gland Loss	
	(r value)	p-value
Clinical Parameters of DED		
OSDI Score	0.417	0.003
NIBUT	0.348	0.015
TMH - 0.201	0.171	

† Abbreviations: OSDI, Ocular Surface Disease Index; NIBUT, non-invasive break-up time; TMH, tear meniscus height; DED, dry eye disease.
‡ Pearson correlation: r, correlation coefficient (r > 0.75 strong-perfect correlation). p-value < 0.05 significant

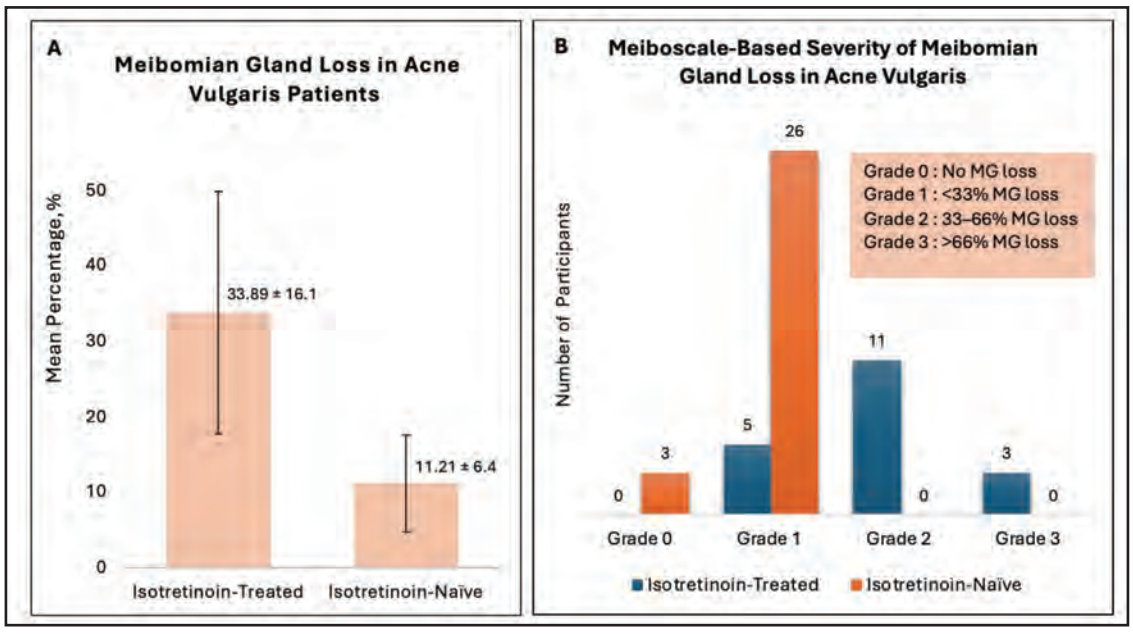

Fig. 1: Quantitative and qualitative assessment of meibomian gland loss in isotretinoin-treated vs. isotretinoin-naïve groups. (A) Mean percentage of meibomian gland loss was significantly greater in the treated group (p<0.001, independent t-test). (B) Meiboscale[29] scores indicated more severe dropout in the treated group (p<0.001, Fisher's exact test)

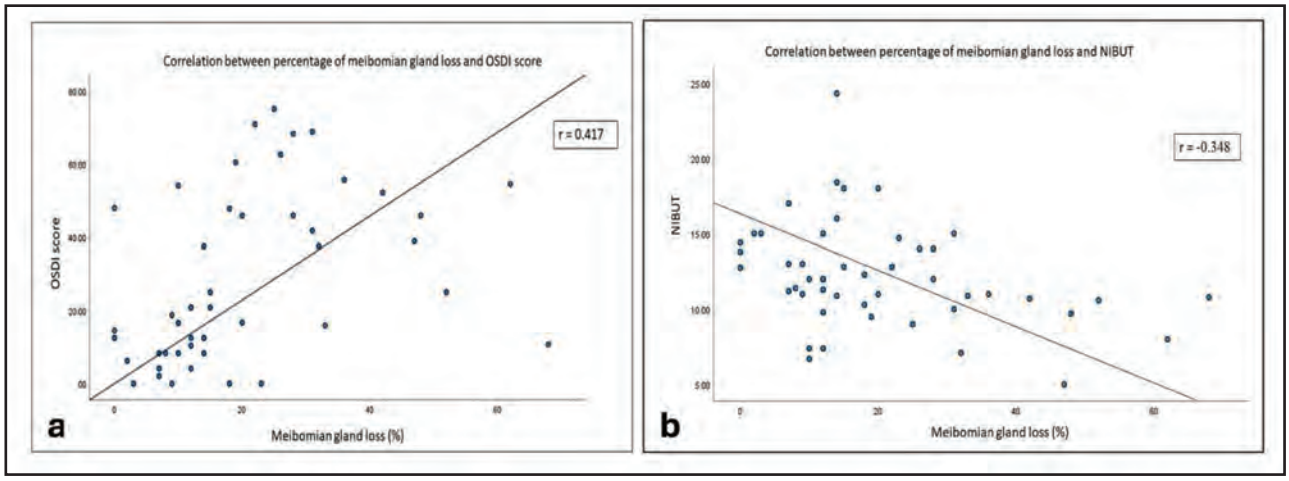

Fig. 2: Scatter plots showing (a) a moderate positive correlation between meibomian gland loss and OSDI score (r=0.417, p=0.003) and (b) a moderate negative (inverse) correlation between the meibomian gland loss percentage and NIBUT (r=–0.348, p=0.015)

DISCUSSION

Malaysian authorities and regulatory advisories emphasise that isotretinoin should be prescribed only by registered dermatologists,[10] with safety communications primarily focused on psychiatric and sexual complications.[20] However, its potential effects on ocular and visual functions remain largely overlooked, despite mounting evidence of MGD, evaporative DED, blepharitis, conjunctival irritation, contact lens intolerance, optic neuropathy, and isotretinoin-associated intracranial hypertension with papilloedema.[21–23] This gap in awareness presents a critical blind spot, particularly as isotretinoin prescriptions, commonly marketed as Accutane, continue to rise across dermatologic, aesthetic, and general practice settings.[24–26] To address this oversight, our study investigated the impact of isotretinoin on MG integrity and tear film stability in a Malaysian patient cohort.

AV predominantly affects adolescents and young adults, a trend reflected in our study cohort. Although a statistically remarkable age difference was observed between the isotretinoin-treated and naive groups, both cohorts largely overlapped in age and were composed primarily of individuals in their teenage and early adulthood years, consistent with global demographic patterns.[27] A recent Malaysian study involving high school and university students in Sarawak reported an AV prevalence of 75.8% among 441 subjects, with the highest rates among those aged 16–18 years.[28] Females accounted for 65.8% of the cases,[28] as observed in our cohort. These findings underscore the importance of early AV intervention with routine ocular screening in adolescents and young adults undergoing isotretinoin therapy, particularly among females, who often seek timely acne treatment to prevent scarring and address appearance-related concerns.

It is well established that isotretinoin alters sebaceous glands, and MG, being of the same histological type, are similarly affected, leading to MGD and associated DED.[23,29] In our study, isotretinoin-treated patients exhibited greater MGL, substantially reduced NIBUT, and deficient LLT consistent with classic MGD features and previous literature.[11,30] A correlation between greater MGL and reduced TBUT, as well as thinner LLT, has also been documented.[30] Isotretinoin reduces wax ester production in sebaceous glands, which likely disrupts lipid secretion from MGs.[31] Because MG lipids, known as meibum, form the nonpolar sublayer of the tear film, a deficiency in these lipids accelerates tear evaporation and contributes to the development of evaporative DED.[31]

Objective MG assessment and tear film measurements using a noncontact OSA provided reliable and reproducible data that strongly support the diagnosis of MGD and tear film instability.[8,16] However, symptom assessment using the OSDI remains essential for evaluating patient-reported discomfort and exploring correlations between MG changes and DED.[32] In our study, isotretinoin-treated individuals exhibited substantially elevated OSDI scores, with a positive correlation between symptom severity and MGL, indicating a greater symptom burden associated with increased gland dropout. These findings are consistent with previous reports of heightened OSDI scores during isotretinoin therapy.[32,33] Notably, each 10-mg increase in isotretinoin dose was associated with a 0.20-point increase in the OSDI score,[32] reinforcing the need for routine symptom monitoring.

Our findings underscore the urgent need to update and strengthen current management guidelines and treatment frameworks for AV by incorporating DED screening using the OSDI, a widely accessible tool that can be easily administered by patients, general practitioners, pharmacists, or other healthcare personnel.[37–40] With the rising number of isotretinoin prescriptions issued by general practitioners and aesthetic physicians globally, including in Malaysia, ocular health vigilance is essential.[24–26] Individuals initiating isotretinoin therapy should be promptly referred for ophthalmology assessment to mitigate potential ocular complications. Although dermatologic outcomes are rightly prioritized, particularly in appearance-conscious adolescents, ocular side effects and dry eye complications from

isotretinoin therapy can significantly impact quality of life.[4,34,35] Even at a relatively low daily dose (20 mg/day)[36] and brief 16-week treatment duration, features consistent with MGD and evaporative DED were already evident, suggesting that ocular effects may manifest rapidly and potentially persist with prolonged use.

This study has several limitations. Its cross-sectional design captured only the short-term ocular effects of isotretinoin on MGs and tear film parameters. Longitudinal data would better characterize the persistence of these changes, particularly given reports of sustained NIBUT reduction up to one-year post-treatment.[11] Baseline ocular surface parameters prior to isotretinoin initiation were unavailable, limiting the precision in attributing observed changes solely to isotretinoin, as AV itself may cause MGD. Cumulative and weight-adjusted doses were not analyzed, and treatment adherence relied on patient interviews rather than verified records, introducing possible recall bias. The convenience sampling and relatively small, uneven sample size between groups may also introduce selection bias, however consecutive recruitment of eligible participants helped reduce this risk. Lastly, as most participants were Malay, generalizability to other ethnic groups may be limited. Future studies should include baseline assessments, verified dosing and adherence data, longitudinal follow-up, and more diverse sampling to clarify isotretinoin's long-term ocular effects.

CONCLUSION

Oral isotretinoin therapy in patients with AV is associated with substantial structural and functional changes in MGs, contributing to tear film instability, MGD, and evaporative DED. Early recognition of dry eye symptoms and ophthalmologic assessments should be integrated into acne management to preserve vision, ocular comfort, and overall quality of life.

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ETHICAL APPROVAL

USM Human Research and Ethical Committee [USM/JEPeM/21060488] and the National Medical Research Registry [NMRR ID-22-00453-J83].

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High expression of vascular endothelial growth factor is a risk factor for poor response to neoadjuvant Paclitaxel – carboplatin chemotherapy in stage IB3, IIA2, and IIB cervical cancer

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ABSTRACT

Introduction: Cervical cancer ranks among the top causes of death worldwide in gynecological cancers and is among the most prevalent cancers worldwide, particularly in Indonesia. This study aims to prove that high expression of Vascular Endothelial Growth Factor (VEGF) is a risk factor for a poor response to neoadjuvant paclitaxel-carboplatin chemotherapy in cervical cancer stages IB3, IIA2, and IIB.

Materials and Methods: This nested case-control study was conducted in Prof. I G.N.G. Ngoerah General Hospital, Denpasar. All medical data were collected from October 2022 to April 2023. The case group consisted of 28 patients with cervical cancer stages IB3, IIA2, and IIB who showed a poor response to three cycles of neoadjuvant paclitaxel-carboplatin chemotherapy, while the control group consisted of 28 patients who had a good response to the same treatment. The variables were the expression of VEGF protein, response to neoadjuvant chemotherapy, and baseline characteristics (primary tumor size, histopathological grading, histopathological type, age, parity, and BMI). Data analysis was performed descriptively and analytically using Chi-square tests and logistic regression.

Results: There was no significant differences in age, parity, BMI, primary tumor size, degree of differentiation, and histopathological type between the case and control groups. High VEGF expression was found in 78.5% of the case group and 25% of the control group. Further analysis showed that high VEGF expression was significantly associated with a poor chemotherapy response, with an odds ratio (OR) of 16.97 (95% CI 3.17 – 38.15, p = 0.001).

Conclusion: High VEGF expression is a significant risk factor for a poor response to neoadjuvant paclitaxel-carboplatin chemotherapy in cervical cancer stages IB3, IIA2, and IIB.

KEYWORDS:
Vascular Endothelial Growth Factor, Cervical Cancer, Neoadjuvant Chemotherapy, Paclitaxel-Carboplatin, Chemotherapy Response

INTRODUCTION

Cervical cancer ranks among the top causes of death worldwide in gynecological cancers and is among the most prevalent cancers worldwide, particularly in Indonesia. Appropriate management strategies and good therapeutic responses can reduce recurrence, morbidity, and mortality rates. Various studies have reported a relationship between angiogenesis and tumor infiltration and metastasis. One important pro-angiogenic factor is Vascular Endothelial Growth Factor (VEGF). However, research results on VEGF expression concerning the prognosis and therapeutic response of cervical cancer have been inconsistent.

In 2020, cervical cancer ranked second in new cases and cancer-related deaths in Indonesia. Approximately 36,633 new cervical cancer cases are diagnosed annually, with around 21,003 deaths attributed to cervical cancer in Indonesia.[1] Bali ranks 16th in the number of cancer cases (1,438 cases) and 9th in the prevalence of cervical cancer (0.7%).[2] From 2018 to 2019, the Central General Hospital (RSUP) I.G.N.G. Ngoerah received 649 patients, with the most common stages being stage IIB (31%), stage IIIB (26%), and stage IB1 (11%).[3] The primary cause of cervical cancer is the

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Human Papillomavirus (HPV). The main oncoproteins of HPV, E6 and E7, target p53 and retinoblastoma protein (pRb), leading to uncontrolled cell proliferation, genomic instability, and inhibition of cell apoptosis. Cervical cancer management strategies are determined according to the Federation Internationale de Gynecologie et d'Obstetrique (FIGO) staging classification.[4,5]

Therapeutic modalities for cervical cancer include primary surgery, primary radiotherapy, chemotherapy, and combination therapy. Surgery is performed on patients with stage IA and IB1 cervical cancer. Radiotherapy and chemoradiation are provided for stages IIB to IVA. Adjuvant therapy is indicated after radical hysterectomy, depending on the disease stage. In regions where radiotherapy facilities are unavailable, neoadjuvant chemotherapy followed by surgery is an alternative option.[6,7] Due to limited radiotherapy equipment at RSUP I.G.N.G. Ngoerah, the management of stage IIB patients with cervical cancer is modified by providing platinum-based neoadjuvant chemotherapy than followed by total hysterectomy (for operable cases) or radiotherapy (for inoperable cases). The response of stage IB3, IIA2, and IIB cervical cancer patients to neoadjuvant chemotherapy before radical hysterectomy is crucial. This is because patients who do not respond well may delay selecting a more appropriate therapy modality, leading to suboptimal management or a loss of the window of opportunity.[8]

The response to chemotherapy is determined by factors such as angiogenesis or tumor vascularization, cellular proliferative activity, and genetic instability of cervical cancer. Angiogenesis is a critical biological process for the growth and metastasis of primary cancer.[9] VEGF is a pro-angiogenic factor that plays a crucial role in vasculogenesis and angiogenesis in both physiological and pathological processes.[10] Several studies have indicated that excessive VEGF expression in tumor tissue samples can be used as a diagnostic or prognostic marker for cervical cancer.[11,12]

The question remains whether high VEGF expression is a risk factor for a poor response to neoadjuvant paclitaxel-carboplatin chemotherapy in cervical cancer stages IB3, IIA2, and IIB.

MATERIALS AND METHODS

Study Design

The study design is a nested case-control study. In a case-control study, researchers conduct analytical observations to examine the relationship between an effect and a specific risk factor. The case group includes patients with cervical cancer stages IB3, IIA2, and IIB who showed a poor response to three cycles of neoadjuvant paclitaxel-carboplatin chemotherapy. The control group includes patients with stages IB3, IIA2, and IIB of cervical cancer who showed a good response to the same chemotherapy regimen. The study was conducted in the Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, and the Department of Anatomic Pathology. Medical data were collected from October 2022 to April 2023.

This study has received ethical approval from the Ethics Committee of the Faculty of Medicine, Udayana University/Prof. I G.N.G. Ngoerah General Hospital, Denpasar, in accordance with Research Permit No: DP.04.03/D.XVII.22.2/24477/2023.

Population and Sample

The target population of this study is patients with stages IB3, IIA2, and IIB of cervical cancer. The accessible population is patients with stages IB3, IIA2, and IIB of cervical cancer who were treated at the Gynecologic Oncology Clinic, Department of Obstetrics and Gynecology. The study sample consists of patients treated at the Gynecologic Oncology Clinic who meet the inclusion and exclusion criteria. The sample size for the case-control study design was calculated with the minimum sample size required for this study is 56 patients.

The following were the study's inclusion criteria: as follows: all patients with cervical cancer stages IB3, IIA2, and IIB; those who received three cycles of neoadjuvant paclitaxel-carboplatin chemotherapy at intervals of 3 to 4 weeks; patients with AUC 5 with serum creatinine ≤1.1 and SGOT/SGPT ≤100; both poor and good responders; paraffin blocks suitable for immunohistochemistry examination; and patients who agreed and signed consent to participate as research subjects. The exclusion criteria included patients who had previously undergone surgery, chemotherapy, or radiotherapy, whether related to gynecological malignancies or not. The dropout criteria were as follows: patients who received three cycles of neoadjuvant paclitaxel-carboplatin chemotherapy at intervals greater than 4 weeks; those with serum creatinine >1.1 before or during chemotherapy (before completing three cycles); patients with SGOT/SGPT >100 before or during chemotherapy (before completing three cycles); patients with anemia (HB <10) and/or leukopenia (WBC <4.1), and/or thrombocytopenia (PLT <140,000) before or during chemotherapy (before completing three cycles); and patients with hypoalbuminemia (ALB <3) before or during chemotherapy (before completing three cycles).

Data and Variables

The independent variable in this study is VEGF protein expression. The dependent variable is the response to neoadjuvant chemotherapy. Control variables include primary tumor size, histopathological grading, histopathological type, age, parity, and BMI.

Procedure

Patients with stages IB3, IIA2, and IIB of cervical cancer who visit the Gynecologic Oncology Clinic, Department of Obstetrics and Gynecology, FK UNUD/RSUP I.G.N.G. Ngoerah Denpasar, were included in the study. Selected samples were patients with histopathological examination results indicating squamous or non-squamous cell carcinoma of the cervix and clinically classified as stage IB3, IIA2, and IIB according to FIGO staging (2018). Data collected included basic data, clinical data, pathology data, chemotherapy administration forms, and response data to three cycles of neoadjuvant paclitaxel-carboplatin chemotherapy.

Table I: Distribution of Characteristics: Age, Parity, BMI, Primary Tumor Size, Degree of Differentiation, and Histopathological Type in Case and Control Groups

Variable	Group				p-value
	Case (n=28)		Control (n=28)		
	Mean	SD	Mean	SD	
Age	43.46	8,492	45.68	11.116	0.406
Parity	2.21	1,031	2.46	1.170	0.400
Body Mass Index	23.47	3,88	24.67	3.85	0.251
Primary Tumor Size	4.50	0,509	4.68	0.476	0.181
Degree of Differentiation n (%)					
Good	16 (57.14)		13 (46.43)		0.432
Poor	12 (42.86)		15 (53.57		
Histopathological Type n (%)					
SCC	20 (71.43)		23 (82.14)		0.351
Non-SCC	8 (28.57)		5 (17.86)		

Table II: VEGF Expression in Case and Control Groups

		Group		Odds Ratio (OR)	95% CI	p-value
		Case	Control			
VEGF expression	High VEGF	22	7	16,974	3,17 – 38,15	0,001
	Low VEGF	6	21			

According to RECIST version 1.1, chemotherapy response is classified as good when patients achieve either complete response or partial response, and poor when outcomes are progressive disease or stable disease.

- Complete Response (CR) : disappearance of all target lesions.
- Partial Response (PR) : at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD) : at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study.
- Stable Disease (SD) : neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.[13]

Data Analysis

Collected data will be analyzed descriptively and analytically. Descriptive analysis will use research characteristics and calculate statistical elements such as mean, standard deviation, median, and range, as well as count and percentage. Inferential analysis will use odds ratio analysis with the Chi-square test. Data precision will be expressed with a 95% CI and a significance level accepted if $p < 0.05$. Control variables that may influence chemotherapy response, such as primary tumor size, histological grading, histopathological type, age, and parity, will undergo multivariate analysis with Logistic Regression analysis. Given the sample size is less than 100 cases, unconditional Logistic Regression testing will be performed.

RESULTS

Patient characteristics

An observational case-control study was conducted on 56 paraffin blocks of cervical cancer stages IB3, IIA2, and IIB at the Gynecologic Oncology Clinic, Department of Obstetrics and Gynecology, Faculty of Medicine, Udayana University/Prof. Dr. I.G.N.G. Ngoerah General Hospital from September 2022 to August 2023. The paraffin block samples of cervical cancer that received three cycles of neoadjuvant paclitaxel-carboplatin chemotherapy at the Department of Anatomic Pathology, Faculty of Medicine, Udayana University/Prof. Dr. I.G.N.G. Ngoerah General Hospital Denpasar, were selected through random sampling (simple). A total of 56 samples were divided into 28 samples with poor chemotherapy response as the case group and 28 samples with good chemotherapy response as the control group. VEGF expression was examined using immunohistochemistry techniques at the Department of Anatomic Pathology, Faculty of Medicine, Udayana University/Prof. Dr. I.G.N.G. Ngoerah General Hospital Denpasar.

Based on Table I, the numerical variables such as age, parity, BMI, and primary tumor size, when tested for normality using the Kolmogorov-Smirnov test ($p > 0.05$), were found to be normally distributed. The comparison between case and control groups, evaluated using the chi-square test, shows no significant differences.

Risk of Poor Chemotherapy Response with High VEGF Expression

The study results show that VEGF expression is higher in the poor chemotherapy response group compared to the good chemotherapy response group, with p=0.04.

Based on Table II, in the case group, 22 (78.5%) had high VEGF expression, while in the control group, 7 (25.0%) had high VEGF expression. Therefore, high VEGF expression is a significant risk factor for poor response to neoadjuvant paclitaxel-carboplatin chemotherapy in stages IB3, IIA2, and IIB patients with cervical cancer, with an odds ratio of 16.974 (OR=16.974, 95% CI 3.17 – 38.15, p=0.001) compared to low VEGF expression.

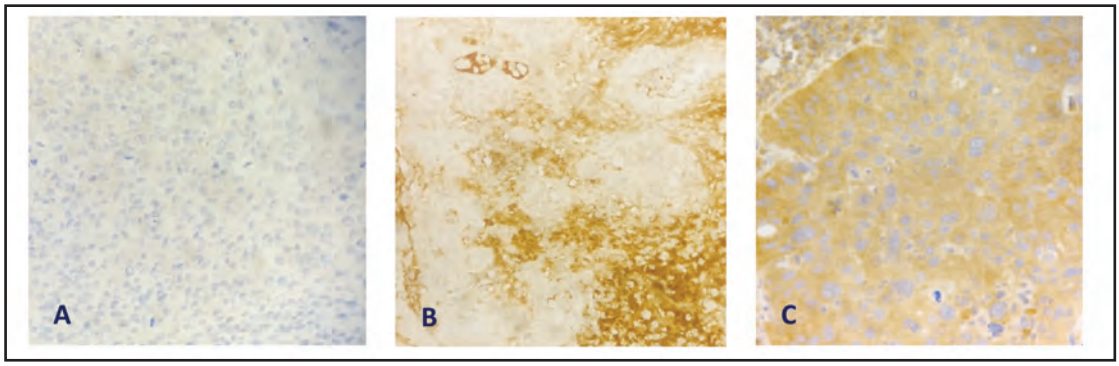

Fig. 1: VEGF Expression in Case Group with Poor Chemotherapy Response. Description: Image (A) Staining in Non-SCC with a score of 3 (low) (VEGF, 100x), Image (B) Staining in SCC with a score of 6 (high) (VEGF, 400x), Image (C) Staining in SCC with a score of 9 (high) (VEGF, 100x)

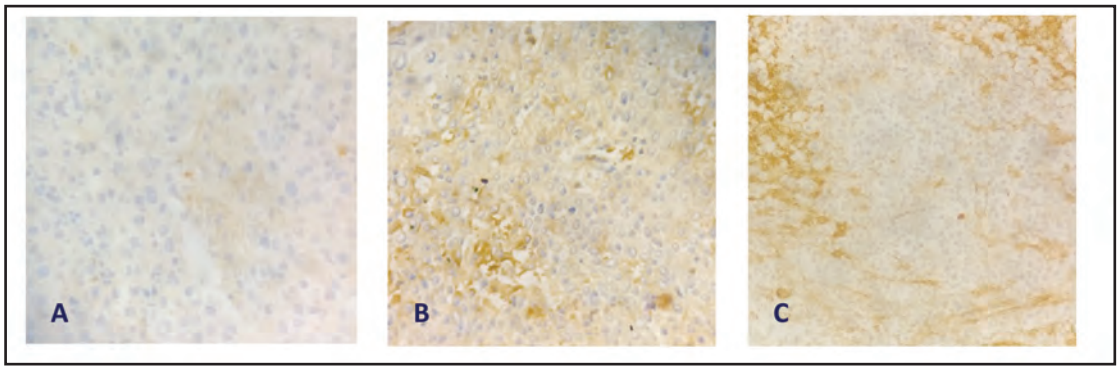

Fig. 2: VEGF Expression in Control Group with Poor Chemotherapy Response. Description: IHC VEGF staining at 400x magnification in SCC. Image (A) Score 1 (low), Image (B) Score 2 (low), Image (C) Score 6 (high)

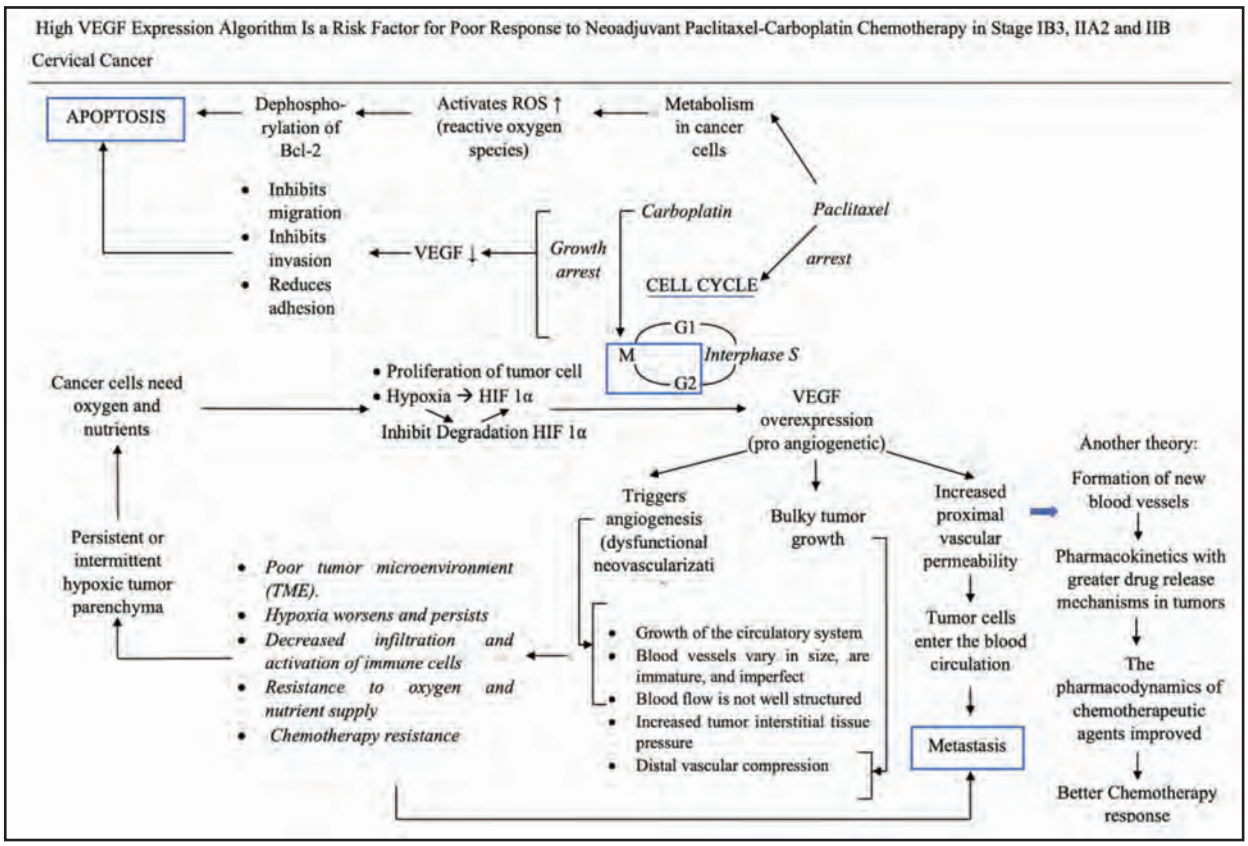

Fig. 3: VEGF Expression Cascade on Response to Neoadjuvant Paclitaxel Carboplatin Chemotherapy in Cervical Cancer

Analysis of VEGF Expression in Chemotherapy Response
The assessment of IHC intensity is divided into 4 categories: 0 (negative), 1 (weak), 2 (moderate), and 3 (strong). The intensity score (0–3) is multiplied by the percentage score (0–3), and the final score is grouped into 0–1 (negative), 2-3 (+, weak expression), 4-5 (++, moderate expression), and 6 (+++, strong expression).[14] The final immunohistochemistry score or histoscore is calculated from the combination of the intensity and percentage scores, ranging from 0 to 12. A histoscore is considered negative if the final score is < 4 and positive if > 4.[14]

DISCUSSION

In this study, there was no statistically significant difference between age, body mass index (BMI), primary tumor size, degree of differentiation, and histopathological type within the case and control groups. This is supported by previous studies by Huang et al. (2020), Kaabia et al. (2019), Mossa et al. (2003), Matsuo et al. (2018), and Muhammad et al. (2020).[15-19] However, we found out that group with higher risk of poor chemotherapy has higher VEGF expression by 16.974 times compared to low VEGF expression (OR=16.974, 95% CI=3.17–38.15, p=0.001). Among the case group, 20 samples (71.4%) showed high VEGF protein expression, while only 5 samples (17.8%) in the control group did.

This study involved 40 patients with stage IB2 to IVA cervical carcinoma who received neoadjuvant chemotherapy. Biopsies taken before treatment analyzed VEGF and VEGFR-2 expression. Eighteen patients had a good clinical response to chemotherapy, with tumor regression greater than 50%, while 22 had a poor response. Sixteen patients were VEGF positive and 24 negative. Only positive VEGF expression was significantly associated with a good response clinically to chemotherapy. VEGFR-2 expression did not show a significant relationship with the response. A one-year prospective study involving 54 samples found that VEGF expression could predict chemotherapy response; higher VEGF expression correlated with poorer response.[20] Furthermore, a case-control study of 45 patients diagnosed with stage I to IV cervical cancer found a relationship between VEGF and tumor size ($p<0.05$) and chemoradiation response ($p<0.03$).[21] Multivariate analysis found that VEGF expression alone increased the likelihood of a good response more than sixfold, confirming its role as an independent prognostic factor for response.[22]

VEGF promotes neovascularization in hypoxic tumor areas, the neovascular structure of tumors is considered immature and dysfunctional. This is characterized by increased proximal vascular permeability, increased interstitial tumor tissue pressure, and distal vascular compression due to tumor mass growth. These dysfunctional neovessels disrupt the TME, exacerbating hypoxia, reducing infiltration of the immune cell and activity, increasing the risk of metastasis spread, and resistance to oxygen, nutrient, and chemotherapy supply. Tumor neovessels have a different morphology compared to normal tissue blood vessels. The tumor neovascular lumen is enlarged, tortuous, and irregular. With immaturity and lack of mural cell association, excessive permeability and poor perfusion occur. This worsens tumor parenchyma hypoxia and triggers the formation of pro-angiogenesis factors. Additionally, a more fragile basement membrane disrupts endothelial cell function, increasing vascular permeability, blood flow resistance, and bleeding risk. These factors cause pharmacokinetic and dynamic disturbances, resulting in decreased chemotherapy drug efficacy due to inadequate blood flow to the tumor tissue.[23]

Uncontrolled cell proliferation without adequate perfusion and oxygenation leads to hypoxic conditions, which are common in solid tumors. Excessive tumor growth will outstrip the surrounding blood vessels' capacity. As a result, oxygen expression in the tumor drops by 2-9%. Under hypoxic conditions, the hypoxia-inducible factor-1α (HIF-1α) transcription factor is activated. This will increase the transcription of pro-angiogenic factors, such as VEGF.[24] VEGF binds to its receptor on the cell membrane to trigger proliferation, migration, invasion, and microtubule formation. This reduces the likelihood of microvascular and macrovascular chemotherapy efficacy on endothelial cells.25 Three factors can influence cancer cell response to chemotherapy: drug pharmacokinetics, intrinsic tumor cell factors, and extrinsic tumor factors, namely the microenvironment or TME.[24]

Theoretically, increased VEGF is associated with poor chemotherapy response through its mechanisms. However, one study showed that increased VEGF alone could indicate a good chemotherapy response through pharmacokinetic mechanisms related to greater drug release in tumor areas with newly formed blood vessels with greater vascular permeability and better pharmacodynamics of chemotherapeutic agents. Tumor cells can secrete abundant pro-angiogenic factors, contributing to the formation of abnormal vascular networks characterized by irregular, immature blood vessels with high permeability, worsening tumor perfusion. The resulting hypoxic environment can also further impair perfusion with more invasive and aggressive tumor properties, inhibiting tumor cell degradation activity of the vascular system.[23]

This study has several limitations. First, the trial design reflects regional characteristics, particularly the adjustment of the neoadjuvant treatment plan due to incomplete radiotherapy equipment at our center. While this highlights an innovative approach within our setting, it may limit the generalizability of our findings, as radiotherapy remains a cornerstone in the global management of locally advanced cervical cancer. Second, although the exploration of VEGF expression as a predictive factor would be valuable, we were unable to establish a logistic regression model with response as the outcome variable due to the limited sample size. Consequently, the potential influence of VEGF expression, while discussed, could not be fully clarified.

CONCLUSION

High VEGF expression increases the risk factor for poor response to neoadjuvant paclitaxel-carboplatin chemotherapy in patients with stages IB3, IIA2, and IIB of cervical cancer. VEGF expression indicates a risk factor in

assessing the response to neoadjuvant paclitaxel-carboplatin chemotherapy in patients with stages IB3, IIA2, and IIB of cervical cancer. Therefore, additional angiogenesis markers are needed to complement and strengthen the evaluation of the response to neoadjuvant paclitaxel-carboplatin chemotherapy in patients with stages IB3, IIA2, and IIB of cervical cancer. The findings of this study could be used as an additional parameter for the risk assessment of neoadjuvant paclitaxel-carboplatin chemotherapy response in patients with stages IB3, IIA2, and IIB of cervical cancer.

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Hepatoprotective effect of medicinal plant in nanoemulsions form

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ABSTRACT

Introduction: Clove extract (CE) and grape seed oil (GSO) are medicinal plant compounds. Clove (*Syzygium aromaticum*) and grape (Vitis vinifera) are widely recognized botanical species with established therapeutic benefits. This study aims to assess the hepatoprotective effect of nanoemulsions containing CE and GSO in acute liver injury induced by carbon tetrachloride (CCl4) in rats (*Rattus norvegicus*).

Materials and Methods: Twenty laboratory mice with criteria were healthy, male, and weighing around 250 mg. Liver damage was induced in experimental animals using carbon tetrachloride (CCl4) on days 20 and 21 of treatment. The experimental animals were divided into four groups, the group 1 (G1) was a negative control group which was not induced and given standard feed, the group 2 (G2) was a positive control group which was induced and given standard feed, the 3 (G3) was induced and given CE nanoemulsion pretreatment and GSO formula A, the group 4 (G4) was induced and given pretreatment of nanoemulsion CE and GSO formula B. Giving nanoemulsion according to the group for 21 consecutive days. Next, on day 22, serum and liver tissue samples were taken to assess the condition of the liver tissue.

Results: The study's findings demonstrated that the administration of nanoemulsions containing CE and GSO exhibited a dose-dependent reduction in acute liver injury induced by CCl4. Liver function based on levels of serum *aspartate aminotransferase* (AST) and *alanine aminotransferase* (ALT) has a significant difference in group 2 compared to group 4 with a P value of 0.006 and 0.01. The liver histopathology showed a healing process in the group treated with clove and grape nanoemulsion therapy. In group 4 there was no vacuole degeneration, reduced inflammatory cell infiltration, and increased neovascularization compared to group 2.

Conclusion: The hepatoprotective effect of nanoemulsions containing CE and GSO was observed to have antioxidant, antibacterial, and anti-inflammatory properties resulting in significant improvements in serum biomarkers related to hepatotoxicity and histopathological analysis of liver injury.

KEYWORDS:
Hepatoprotective, liver injury, nanoemulsion

INTRODUCTION

Injury to the liver can be caused by the consequences of oxidative stress, which arises when oxidants and antioxidants are not balanced. Hepatocyte proteins, lipids, and DNA are significantly impacted by reactive oxygen species (ROS) and reactive nitrogen species. These processes lead to defects in the liver's structure and function.[1] The size and anatomical positioning of the liver contribute to the persistent challenge posed by liver injuries in the context of achieving favorable treatment outcomes. The necessity of surgical intervention should be primarily determined by clinical characteristics, with particular emphasis on the assessment of hemodynamic condition. In this study, we endeavored to elucidate our methodology for addressing hepatic injuries. Furthermore, we emphasized the importance of careful management, considering the elevated mortality rates linked to liver trauma interventions.[2,3] Routine and excessive administration of analgesic and antipyretic drugs leads to hepatotoxicity.[4,5] Liver injury serves as a prevalent pathophysiological foundation for several liver diseases, with prolonged liver injury often playing a significant role in initiating liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC).[6,7]

The research that has been done extensively supports the employment of herbal medicines as a prominent avenue for developing innovative pharmaceutical substances to address serious diseases. Numerous research indicates that many plant species include phytoconstituents, including glycosides, saponins, flavonoids, steroids, tannins, alkaloids, terpenes, and other compounds that possess pharmacological properties. Clove, scientifically referred to as *Syzygium aromaticum*, is a conventional spice that has been historically employed for food preservation and contains a range of therapeutic attributes. *S. aromaticum* exhibits a high abundance of sesquiterpenes, monoterpenes, hydrocarbons, phenolic compounds, and several other phytochemicals. The composition of clove extract (CE) primarily consists of three crucial phytochemical compounds, namely eugenyl acetate, eugenol, and -caryophyllene. Multiple investigations have demonstrated that eugenol possesses antiviral, antifungal,

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anticancer, antiseptic, antidepressant, antispasmodic, and antibacterial attributes, rendering it efficacious against a diverse range of pathogenic bacteria.8–12 The efficacy of clove essential oil (*Syzygium aromaticum*, L.) in inhibiting the growth of many pathogenic microbes has been extensively established.[13,14]

In along with cloves, grape seeds have been extensively utilized in the healthcare industry. Grape seed oil (GSO) possesses a notable abundance of phenolic compounds, fatty acids, and vitamins, rendering it of considerable commercial significance within the medicinal, cosmetic, and food sectors. The suggestion of utilizing it as a consumable oil has also been put out, mostly due to its favorable sensory attributes. GSO possesses advantageous attributes for human health, including anti-inflammatory, cardioprotective, antibacterial, and anticancer qualities. Additionally, it has the potential to interact with several cellular and molecular pathways. The observed impacts have been attributed to the elements found in GSO, including tocopherol, linolenic acid, resveratrol, quercetin, procyanidins, carotenoids, and phytosterols.[15,16]

Carbon tetrachloride (CCl4) therapy can cause steatosis in mice, which is a model for both alcoholic and non-alcoholic fatty liver disease in humans. Compared to animals treated with CCl4, proanthocyanidins successfully reduced lipid buildup, liver injury, and DNA damage while also restoring antioxidant enzyme levels. Further research indicated that proanthocyanidins reduced CYP2E1 production in the liver, preventing the first step in free radical synthesis from CCl4. Proanthocyanidins isolated from grape seeds were administered orally to reduce CCl4-induced hepatic steatosis and liver damage by lowering oxidative stress and inhibiting cytochrome CYP2E1.[17]

Due to the above, it has been suggested that the combination of cloves and grape seeds exhibits considerable promise. The nanoemulsion preparation mixture has been extensively refined due to its exceptional ability for absorption. They improve the solubility and bioavailability of medications that are weakly water soluble by creating a large interfacial area for drug dissolution with their small droplet size, which is typically between 20 and 200 nanometers. Additionally, because nanoemulsions can encapsulate both hydrophilic and hydrophobic medications. Nanoemulsions are regarded as thermodynamically stable isotropic systems, in which the input energy is produced mechanically or physiochemically, and the two immiscible liquids mix to form a single phase that aids emulsifying agents like cosurfactants and surfactants.[18,19]

This study aims to analyze the hepatoprotective effect of nanoemulsion containing CE and GSO induced by carbon tetrachloride (CCL_4) in animal models. Hepatotoxic agents commonly used to induce liver damage are acetaminophen, galactosamine, acetaminophen, thioacetamide, and azoxymethane.[20] In this study, CCL4 was used, since it is a potent hepatoxic, nephrotoxic, and prooxidant agent that is commonly used to induce hepatotoxicity in experimental animals. It is also a model that is frequently used to screen for the hepatoprotective activity of medications and natural products. Histopathological analysis and the quantity of cytoplasmic enzymes released into the bloodstream are typically used to determine the severity of injury to the liver.2[1] The CCl4-induced hepatotoxicity process occurs due to biotransformation into trichloromethyl free radicals (CCl3) or trichloroperoxyl radicals (CCl3O2-) produced by the mixed-function cytochrome P450 oxygenase system of the endoplasmic reticulum, which causes oxidative stress and membrane damage.[22]

Determining the architectural alteration is one of the most important aspects of the histological evaluation of liver biopsies in the context of liver disease.[23] The mitigation of liver damage caused by CCl4 has long been regarded as an indication of liver protective action, as the alterations associated with CCl4-induced liver damage are similar to those seen in acute viral hepatitis. In this work, attenuation of carbon tetrachloride-induced hepatotoxicity is an excellent technique to evaluate the liver protective capabilities of CE and GSO.[24] This study aims to assess the hepatoprotective effect of nanoemulsions containing CE and GSO on the level of acute liver damage using histopathological evaluation and increased levels of certain enzymes released into the circulation induced by carbon tetrachloride (CCl4).

MATERIALS AND METHODS

Plants and nanoemulsions preparation

Clove (Syzygium aromaticum L.) samples were obtained from the agricultural region of West Java, Indonesia. The clove samples were analyzed at the Bandungense Herbarium, School of Life Technology (SITH), Bandung Institute of Technology Indonesia. The process of plant determination is carried out by identifying the shape, color, and texture of plant parts. The color and texture of both the front and back sides of the plant sample contain deterministic parameters to obtain a unique optimum combination of features that maximize the identification rate. The plant database is created from commonly used front and back scan images of plants. Plants are classified based on a combination of shape and dimensions. The GSO used in this study was sourced from Tabanan Regency, Bali, Indonesia. An examination using Gas Chromatography-Mass Spectrometry (GC-MS) was conducted to ascertain the precise composition of the GSO.

Based on the comparison of GCMS analysis results of grape seed oil, it can be seen that grape seed oil contains fatty acids in the form of Hexadecanoic acid (CAS) Palmitic acid, 9-Octadecenoic acid (Z)-, methyl ester (CAS) Methyl oleate, Tetradecanoic acid (CAS) Myristic acid (table 1). Palmitic acid is a saturated fatty acid that also shows antibacterial activity against gram-positive and gram-negative bacteria. The production of clove flower ethanol extract involves utilizing the maceration process. Initially, a mass of 300 grams of simplicia was measured. The extraction process was conducted using the maceration technique, employing a solvent consisting of 96% ethanol. The ratio of simplicia to solvent was maintained at 1:10, and the extraction duration spanned three days. Subsequently, the filtrate is gathered and subjected to evaporation utilizing a rotating vacuum evaporator, maintaining a temperature below 50℃. This is then succeeded by concentrating the resulting extract by applying a water bath at a temperature of 60℃ till it attains the state of a concentrated clove extract.

The composition analysis of the extracted portions of clove Phytochemical screening aims to determine the content of compounds contained in both the simple and extract that will produce pharmacological effects.

The nanoemulsion formulation was prepared through the precise measurement of each constituent. The ethanol extract derived from clove flowers was dissolved in ethanol of analytical grade with the assistance of ultrasonic equipment. The dissolved extract is afterward combined with grape seed oil, tween 80, and PEG 400. The mixture is then stirred using a magnetic stirrer on a hotplate, operating at 750 revolutions per minute for 15 minutes. The stirring process is conducted at a temperature of 40℃ to ensure homogeneity. The water phase, specifically distilled water, should be gradually incorporated into the mixture while employing a magnetic stirrer operating at a speed of 750 revolutions per minute (rpm) for 30 minutes at 40℃. Subsequently, the sample was subjected to sonication for 60 minutes, with the application of plastic wrap to ensure proper containment. Several nanoemulsion formulas were made, then the two best formulas were taken for further testing, namely formulas A and B with clove extract content of 25% and 50% respectively.

Histopathology assessment

A biopsy of the rat's liver tissue was performed then the sample was soaked in 10% formol salt solution for 24 hours to fix it. These samples were then immersed in a 10% formol saline solution for 24 hours to fix them. The samples underwent a washing process using tap water, followed by a series of dilutions with several types of alcohol (methyl, ethyl, and 100% ethyl) to remove moisture. The specimens underwent a rinsing process using xylene, followed by embedding in paraffin at a temperature of 56 °C within a hot air oven for 24 hours. The tissue blocks, composed of paraffin and beeswax, were prepared for sectioning using a sled microtome at a thickness of 4 µm. The tissue slices that were acquired were carefully placed onto glass slides. These slides were then subjected to a deparaffinization process to remove the paraffin wax. Subsequently, the sections were stained using hematoxylin and eosin stain, a commonly used method for routine examination. The stained slides were then observed using a Leica light microscope. Analysis by assess the score of Hepatocyte vacuolar degeneration, Fatty change in hepatocytes, Fibroblastic cells proliferation, number of inflammatory cells, and neovascularisation. Histoscore from 0-3 (nill, mild, moderate, severe).

Blood sampling and biochemical evaluation

Blood samples were collected at the final stage of the experiment. They were retrieved from the cardiovascular veins of each rat using fine capillary. Serum samples were utilized to examine several biochemical parameters, explicitly focusing on liver function tests. The activities of hepatic enzymes, specifically alanine transaminase (ALT) and aspartate transaminase (AST), were examined.

Experimental animals

Healthy adult male rats (Rattus norvegicus Strain) of approximately the three months of age, weighing around 250 gram, were purchased from Animal Laboratory BandungThe animals were maintained in a controlled environment with a 12-hour light-dark cycle, a relative humidity of 50 ± 5%, and an ambient temperature of 25 ± 2 °C. Rats received a standard pellet diet and water ad libitum.

Experimental design

A total of twenty mice were utilised in a research investigation aimed at examining the potential protective properties of CE and GSO against hepatotoxicity induced by CCl4 in rats. The animals were randomly allocated into four groups of equal size, each consisting of five rats. The animals were then subjected to the following treatments:25,26

i. Group 1: serving as the negative control group, consisted of rats that were provided with a typical synthetic food for 3 weeks.
ii. Group 2: positive control group, were administered a regular meal and intramuscularly injected with CCl4 (twice) through split injection at a dosage of 1 mL/kg (body weight) on the last two days of 21 days experimental period.
iii. Group 3: treatment group formula A, rats were administered a conventional meal and intramuscularly injected with CCl4 (twice) using a split injection technique at 1 mL/kg (body weight) on the last two days of 21 days experimental period and they were orally administered nanoemulsion CE and GSO formula A at a 1 mL/kg dosage, for three weeks.
iv. Group 4: treatment group formula B, rats were administered a conventional meal and intramuscularly injected with CCl4 (twice) using a split injection technique at 1 mL/kg (body weight) on the last two days of 21 days experimental period and they were orally administered nanoemulsion CE and GSO formula B at a 1 mL/kg dosage, for three weeks.

Statistical analysis

The statistical analysis was performed using the GraphPad Prism software, specifically GraphPad 9 Software. The statistical significance of the data was evaluated by employing a one-way analysis of variance (ANOVA), followed by doing Tukey test as a post-hoc test to identify which particular means of several groups differ significantly from one another. A P-value below the threshold of 0.05 ($P < 0.05$) was considered to have statistical significance.

Ethics statement

The experimental procedures pertaining to the animals and their welfare were carried out in accordance with the ARRIVE 2.0 guidelines for Laboratory Animals in Research, as authorised and disseminated by the World Health Organisation. The Ethical Committee of the Faculty of Medicine at Unisba Bandung, Indonesia, granted clearance (102/KEPK-Unisba/V/2023) for the procedures applied and the welfare of the animals involved in the study.

RESULTS

Histological examination

Histopathological examination is still the gold standard in assessing liver damage. The liver is susceptible to many toxins and pollutants such as CCl4. Exposure to CCl4 can cause the formation of ROS and cause liver damage. The liver histopathology showed a healing process in the group treated with clove (Syzygium aromaticum) and grape (Vitis vinifera)

Table I: Analysis of Gas Chromatography-Mass Spectrometry

Compounds	GCMS (%)
Hexadecanoic acid (CAS) Palmitic acid	63.65
9-Octadecenoic acid (Z)-, methyl ester (CAS) Methyl oleate	5,03
Tetradecanoic acid (CAS) Myristic acid	31.32

Table II: The score of histological changes observed in the liver tissue of the experimental groups

Component	PC	NC	FA	FB
Hepatocyte vacuolar degeneration	+	-	-	-
Fatty change in hepatocytes	+	-	-	-
Fibroblastic cells proliferation	-	-	+	+
Inflammatory cell infiltration in the portal area	++	-	+	-
Neovascularisation	-	-	+	++

PC: positive control, NC: Negative control.
FA: Nanoemulsion formula A, FB: Nanoemulsion formula B
+++ Severe, ++: Moderate, +: mild, -: nil.

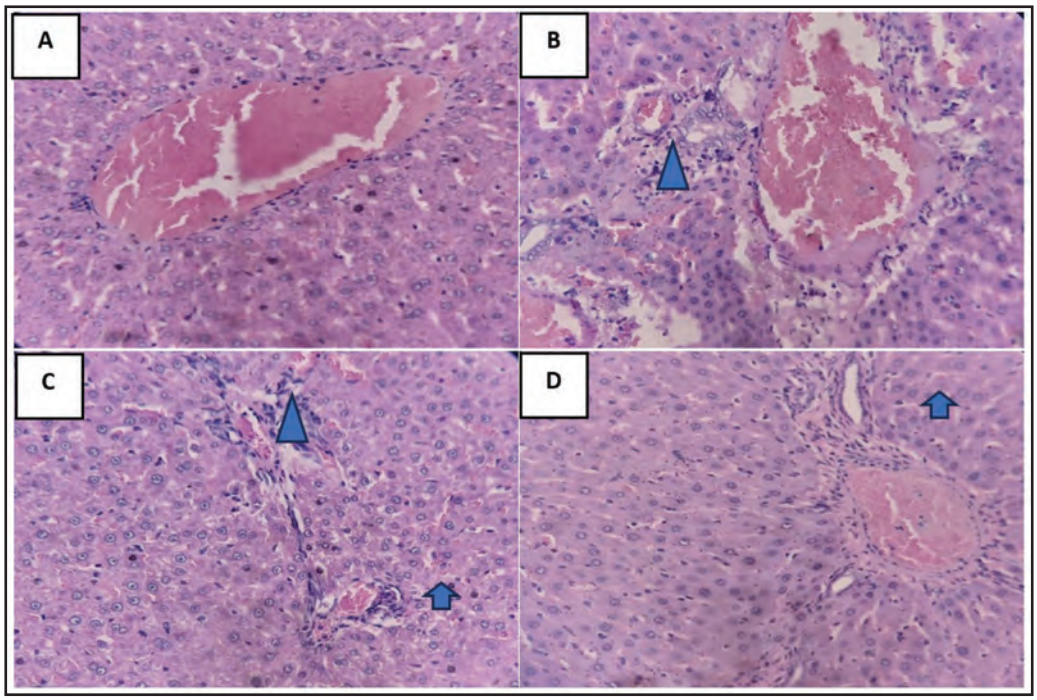

Fig. 1: (A) Group 1: No histopathological changes were seen; (B) Group: There is vacuolar generation of hepatocytes, fatty changes in hepatocytes, and many inflammatory cells ( ); (C) Group 3: The presence of neovascularisation ( )in the portal vein, accompanied with limited infiltration of inflammatory cells ( ), was seen in the portal area; (D) Group 4: The increase of neovascularisation ( ) in the portal vein was seen in the portal area. (H&E.X40)

nanoemulsion therapy. In group 4 (nanoemulsion formula B) there was no vacuole degeneration, reduced inflammatory cell infiltration, and increased neovascularization compared to group 2 (Fig. 1, Table IV).

Liver function

To investigate liver function, serum levels of AST and ALT were examined, with results as depicted in Figures 2 and 3. These findings indicate that the positive control group of mice induced with CCl4 experienced a significant increase in AST and ALT levels compared with the negative control group. However, administration of nanoemulsion before treatment succeeded in reducing the increase in blood AST and ALT activities. The findings of this study indicate that the nanoemulsion formulation, containing CE and GSO, has hepatoprotective properties in the context of acute liver damage caused by CCl4. Liver function based on levels of serum AST and ALT has a significant difference in group 2 (positive control) compared to group 4 (nanoemulsion formula B) with a p-value = 0.01.

Despite both G1 and G2 were given the same standard feed in this study, G1 is a negative control group that does not experience an acute liver injury caused by carbon tetrachloride, whereas G2 is a positive control group that experiences an acute liver injury caused by carbon

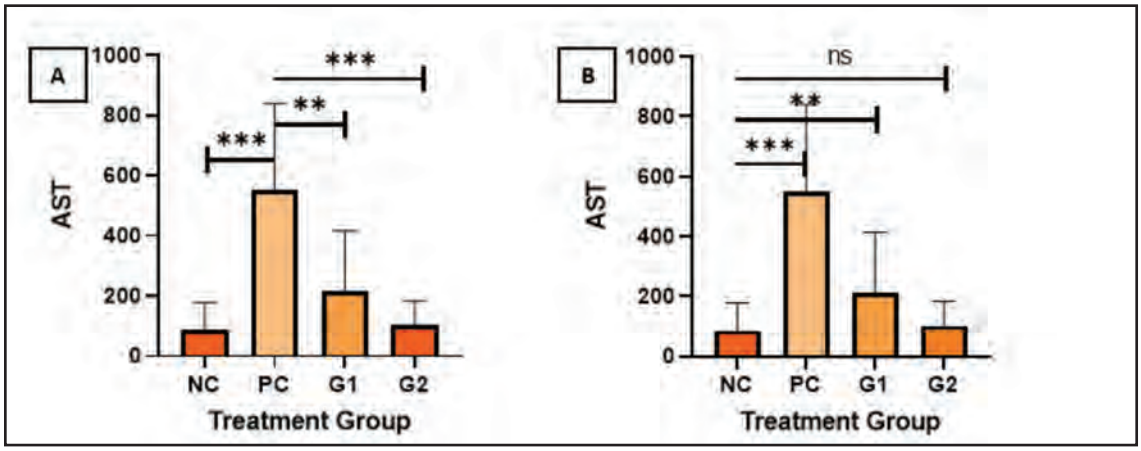

Fig. 2: Pretreatment of CCL4-induced acute liver damage of mice treated with nanoemulsion. AST values were measured 48 hours after CCl4 injection. (A) G2 (***) shows significant differences compared to the PC group (P=0.006) while G1 (*) indicates no significant differences compared to the PC group (P=0.052). (B) G1 and G2 (ns) show no significant differences compared to the NC group (P>0.05)

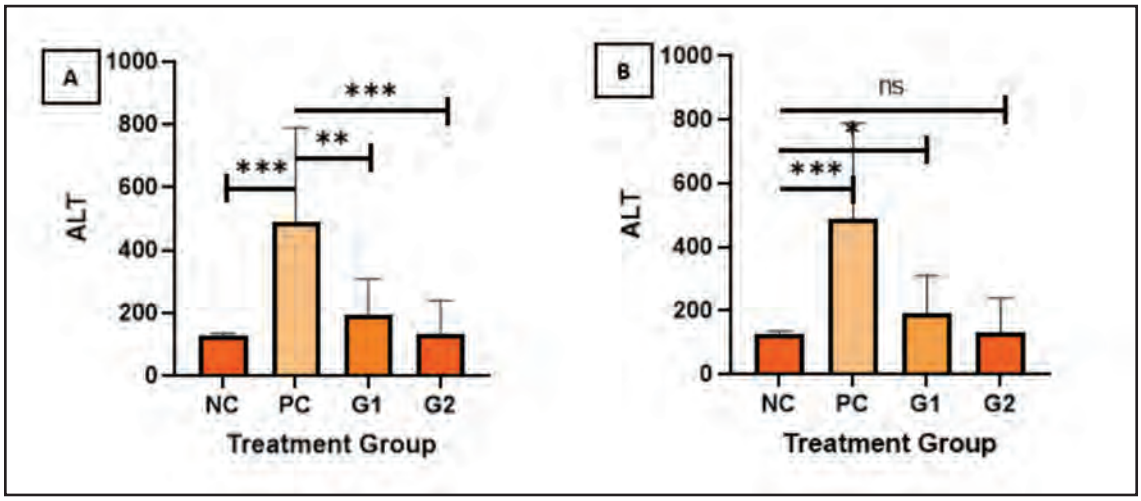

Fig. 3: Pretreatment of acute liver damage in rats induced by CCl4 by administration of nanoemulsion. ALT values were measured 48 hours after CCl4 injection. (A) G2 (***) showed a significant difference compared to the PC group (p=0.01) while G1 (*) showed no significant difference compared to the PC group (p=0.9). (B) G1 and G2 (ns) did not show significant differences compared to the NC group (p>0.05)

tetrachloride but does not receive any hepatoprotective agents. This makes figure 2 more clearly illustrate the hepatotoxic effect caused by carbon tetrachloride. G1 did not exhibit a significant difference from PC, while G2 had shown a substantial difference.

Aspartate aminotransferase

According to the data presented in Figure 2, the group treated with CCl4 (referred to as PC) exhibited a notable increase in AST activity (551,4 IU/L) as compared to the normal control group (referred to as NC, with a value of 102,8). The groups treated with nanoemulsions exhibited a notable reduction in AST activity, with values of 214 and 112,6, respectively, in comparison to the CCl4 control group (AST activity of 551,4). This indicates the efficacy of both nanoemulsions in ameliorating the impact of CCl4 by preserving the hepatocytes' integrity.

Alanine aminotransferase

ALT activity observed in the animals subjected to testing exhibited a range of 126,5 to 428 IU/L, as depicted in Figure 3. The PC group had the highest significant value of ALT activity, which was reported as 428 IU/L. The application of nanoemulsions containing CE and GSO has been found to exhibit a substantial reduction in the activity of ALT levels, with values of 192,2 and 170,6 respectively, effectively restoring them to normal levels observed in the control (NC) group, which recorded a value of 126,5.

DISCUSSION

This study shows that a medicinal plant, specifically synthesized into nanoemulsions containing CE and GSO, exhibited a hepatoprotective effect, as evidenced by the assessment of liver injury using histopathology examination.

The levels of AST and ALT also demonstrate normal values compared to positive control groups. The aim of this study was to assess the phytochemical composition of this nanoemulsion, as well as its potential to mitigate hepatic damage and toxicity generated by CCl4 in rats. CCl4 is a highly potent and widely recognized poisonous substance that elicits liver injury by promoting the production of reactive oxidative stress. This study demonstrates the hepatotoxic effects caused by carbon tetrachloride. G2 has shown significant differences from PC and G1 has no significant differences from PC as shown in figure 2.

Liver injury can be caused by environmental contaminants, such as CCl4. The animals exposed to CCl4 showed various types of alterations like lymphocytes infiltration, edema and congestion.[27] Hepatotoxins, such carbon tetrachloride and paracetamol, are frequently used to induce hepatotoxicity in rats in experiments.[28] The hepatotoxic effects in rats are most indicative of similar hepatotoxic effects in human hepatocytes. Similar concentration-dependent Glutathione depletion, oxidative stress, and mild cytotoxicity are reported in rat and human hepatocytes.2[9]

AST and ALT levels correspond well with the severity of acute liver injury generated by carbon tetrachloride during the time span studied, implying that blood AST and ALT levels should be increased in all samples 24 hours after causing acute liver injury with carbon tetrachloride.[30]

According to current literature, it has been suggested that extracts derived from *Syzygium aromaticum* have potential protective properties against these specific problems. As an essential component of metabolic and excretory processes, the liver is consistently responsible for detoxifying substances. Hepatotoxic substances comprise a variety of agents, including viruses, fungal byproducts, bacterial metabolites, minerals, environmental pollutants, and chemotherapeutic drugs. These agents have the potential to generate a wide spectrum of organ dysfunctions. Liver unjury including hepatocellular carcinoma, fibrosis, cirrhosis, and hepatitis, encompass a collection of highly significant medical disorders.[31,32]

Hepatotoxins, including ethanol, acetaminophen, and CCl4, have been demonstrated to induce hepatic damage, characterized by diverse levels of hepatocyte degeneration and cellular fatality. Reactive oxygen species (ROS), including superoxide and hydroxyl radicals, have also been associated with carbon tetrachloride toxicity. Based on the available evidence, it can be observed that CCl4 was frequently used as a hepatotoxin in experimental hepatopathy. The initial stage in a sequence of events that culminates in the oxidation of membrane lipids and subsequent cell death is believed to include the covalent attachment of metabolites of CCl4, specifically trichloromethyl-free radicals, to cellular proteins.[33,34]

Carbon tetrachloride (CCl4) causes hepatotoxicity in model species because it closely resembles human liver damage. This toxicity results from the activation of several cytochromes, including CYP2E1, CYP2B1, CYP2B2, and perhaps CYP3A, which produce the trichloromethyl radical (CCl3*). CCl3* can bind to biological molecules such lipids, proteins, and nucleic acids, altering lipid metabolism and resulting in fatty degeneration. It can also combine with DNA to cause liver cancer. When exposed to oxygen, CCl3* degrades into the more reactive CCl3OO*, resulting in lipid peroxidation and membrane damage. At the molecular level, CCl4 causes the release of various inflammatory cytokines, including TNF-α and NO, which can aid or hinder hepatotoxicity through cellular death.[35]

Drug-induced liver injury (DILI) encompasses a wide array of clinical presentations, from instances of elevated liver enzymes without accompanying symptoms to cirrhosis. The potential for hepatotoxicity could perhaps be mitigated through the utilization of herbal dietary supplements. The liver, the primary organ responsible for detoxification, is susceptible to damage caused ROS, which lead to a depletion of the body's antioxidant reserves. Oxidative stress is a common consequence of chronic liver diseases, as ROS are consistently observed in these conditions.[9]

Eugenol, a fragrant oil derived from cloves, is commonly utilized as a culinary additive to enhance the taste of food and beverages. Additionally, it is a topical herbal medicine for alleviating toothaches and, to a lesser extent, as an oral prescription for gastrointestinal and respiratory conditions. There is currently no evidence to suggest that therapeutic amounts of eugenol are associated with increased blood enzyme levels or clinically observable liver damage. However, it is essential to note that ingesting excessive doses, such as in overdose cases, can lead to significant liver damage. Clove essential oil is composed of eugenol, a volatile phenolic chemical extracted from the buds and leaves of Eugenia caryophyllata. It serves as a valuable constituent in several products, where it has been employed in limited quantities within gastronomy, cosmetics, and pharmaceuticals. The derivatives of this substance have been used in medicine as a local anesthetic and antiseptic agent. Eugenol exhibits a diverse range of biological actions, encompassing antioxidant, analgesic, and anti-inflammatory characteristics.[36,37] Shahavi MH., et al.'s study on the evaluation of critical parameters for the preparation of stable clove oil nanoemulsion demonstrated that pulsed ultrasound at the right intervals was more effective than continuous ultrasonication, while the average droplet size of the clove oil nanoemulsion decreased as the work cycle increased.[38]

S. aromaticum exhibits a high abundance of sesquiterpenes, monoterpenes, hydrocarbons, phenolic compounds, and other phytochemicals. The three primary phytochemical constituents in clove oil are eugenyl acetate, eugenol, and β-caryophyllene. The pharmacological properties of S. aromaticum have been extensively investigated concerning several pathogenic bacteria, parasites, and microorganisms, such as Plasmodium, Babesia, Theileria, Herpes simplex, and hepatitis C viruses. Multiple research investigations indicate that eugenol possesses various beneficial properties, such as antiviral, antifungal, anticancer, antiseptic, antidepressant, antispasmodic, and antibacterial activities. These features enable eugenol to effectively combat pathogenic bacteria, including methicillin-resistant S. aureus and Staphylococcus

epidermidis. Furthermore, it has been determined that eugenol demonstrates promising lethality against the growth of many parasites, such as Giardia lamblia, Fasciola gigantica, Haemonchus contortus, and Schistosoma mansoni. Additionally, eugenol has shown protective effects against hepatotoxicity generated by CCl_4.[8]

A review conducted by Gaber ESB, et al., in 2020 investigate the phytochemical composition and biological activity of clove extracts, as well as clove essential oil and its primary active ingredient, eugenol. The study also made use of gas chromatography-mass spectrometry (GC-MS) analysis to uncover novel findings.8 The radical scavenging activity of clove extract was shown to be greater in comparison to that of honey extracts. Both subjects successfully alleviated the negative effects of oxidative stress and liver damage caused by CCl_4.[9] The application of clove extract effectively inhibited the growth of hepatocytes into fibroblasts.[8]

The present investigation demonstrated the synergistic hepatoprotective benefits of a combination of clove and grape seed. The pharmacological effects of the active constituents found in various portions of V. vinifera, including hepatoprotective, anticancer, antioxidant, antibacterial, anticancer, and anti-inflammatory properties.[39] The study conducted Abdelsalam, H. M., et al., (2019) states that synergistic therapeutic effect of combining *Vitis vinifera* extract with Silymarin on an experimental cardiorenal damage model can be attributed mostly to the facilitation of the Keap1/Nrf2 signaling pathway. *Vitis vinifera* exhibits a range of mechanisms in its capacity as an antioxidant, antimicrobial, and anti-inflammatory agent. These mechanisms encompass the augmentation of superoxide dismutase, hemeoxygenase-1, and glutathione peroxidase activity, alongside the reduction of glutathione levels and malondialdehyde (MDA) concentrations. Additionally, Vitis vinifera activates the factor2/ARE pathway, which is linked to nuclear erythroid2. There exist multiple papers that discuss the possible application of these substances in the prevention of diverse diseases, such as cardiovascular disease, cancer, degenerative diseases, and inflammatory disorders.[40]

Research conducted by Amel et al., in 2016, used grape seed oil against carbon tetrachloride-induced oxidative stress in the liver of γ-irradiated rats shows that rats exposed to CCl4 demonstrated increased blood levels of ALT, AST activity, IL-6, and TNF-α. The GSO demonstrated protective benefits against acute liver injury generated by CCl4 in rats that were exposed to γ-irradiation. These effects can be related to the potent antioxidant, anti-inflammatory, and anti-apoptotic actions of GSO. The activation of antioxidant enzyme activity. Phenolic chemicals, fatty acids, and vitamins in grape seed oil are valuable to pharmaceuticals. Among grape seed oil's potential interactions with cellular and molecular pathways are its anti-inflammatory, cardioprotective, antibacterial, and anticancer actions, as demonstrated in in vitro investigations. These advantages are caused by the phytosterols, tocopherols, linolenic acid, resveratrol, quercetin, procyanidins, and carotenoids found in grape seed oil.[16]

The limitations of this study include the possibility of wide variations in sensitivity to the hepatotoxic effects of carbon tetrachloride due to differences in the developmental stage and efficacy of cytochrome P450, which are also ultimately species and age dependent. The use of carbon tetrachloride to induce acute liver injury may cause damage to other organs such as the central nervous system and kidneys. CCl4 primarily affects the central zone of the liver, which does not correspond to the massive necrosis typically seen in human liver failure. Therefore, the CCl4-induced hepatotoxicity picture in this study may not be fully representative of human liver failure.

CONCLUSION

The hepatoprotective effect of nanoemulsions containing CE and GSO was observed to have antioxidant, antibacterial, and anti-inflammatory properties resulting in significant improvements in serum biomarkers related to hepatotoxicity and histopathological analysis of liver damage.

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Influenza vaccination uptake among public primary healthcare workers in Seberang Perai Tengah district, Penang

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ABSTRACT

Introduction: Influenza poses a significant public health burden globally, contributing to substantial morbidity and mortality, particularly among vulnerable populations. Healthcare workers (HCWs) are at increased risk of contracting and transmitting influenza, making vaccination a key preventive strategy. Despite the well-established benefits and strong recommendations advocating influenza vaccination for all HCWs, only a few studies have examined vaccination uptake among HCWs in Malaysia. This study aimed to determine the prevalence of influenza vaccination among public primary HCWs in Seberang Perai Tengah district, Penang, reasons for vaccination or non- vaccination and to identify its associated factors.

Material and Methods: A cross-sectional study was conducted from January to March 2025 inviting all HCWs from nine health clinics and six dental clinics in the district. Data for socio-demography, work-related characteristics, history of influenza vaccination, reason to vaccinate or non-vaccination for influenza, knowledge and attitude towards influenza and its vaccination were collected using a validated self-administered questionnaire in a Google form. Knowledge and attitudes towards influenza and its vaccination were assessed using an 18-item questionnaire on a five-point Likert scale. A higher score for each component, knowledge (0-15) and attitude (0-3), indicates better knowledge and more positive attitudes, respectively. Descriptive statistics were used for demographic data and prevalence. Multiple logistic regression was performed to identify factors associated with vaccination uptake.

Results: A total of 359 HCWs participated. The participants had a mean age of 37.9 years (SD=7.09), with females comprising 77.7% of the sample. Nurses represented the largest proportion (33.7%), followed by assistant or aide (24.2%), and doctors (11.7%). The prevalence of influenza vaccination uptake was 97%, with only 12 participants reported never being vaccinated. The primary reasons for vaccination were self-protection (94.2%), followed by protecting family and friends (70.9%) and the availability of free vaccination at work (50.7%). Among the unvaccinated participants, 58.3% expressed concerns about side effects and 25% stated reasons for fear of getting sick from the vaccine and personal reluctance. Multiple logistic regression revealed that the attitude score was significantly associated with influenza vaccination uptake (Adjusted OR: 2.12, 95% CI: 1.30-3.44, p=0.002). Vaccinated participants had a higher median knowledge score (11.0, IQR 4.00), and attitude score (3.0, IQR 1.00) compared to non-vaccinated participants suggesting better knowledge and attitude towards influenza or its vaccinations. While most participants held positive views, misconceptions persisted; 30.4% believed the vaccine might cause influenza, and 39.3% believed influenza could be transmitted via blood.

Conclusion: The high vaccination rate reflects strong acceptance and awareness among HCWs. Misconceptions regarding vaccine safety persist, and necessitate targeted educational efforts. Although high uptake suggests favourable attitudes, further longitudinal studies are needed to explore motivational factors and causality more definitely. Targeted education can address misconceptions and side effects, supporting sustained high vaccination rates and reducing hesitancy.

KEYWORDS:
Influenza, vaccination, primary healthcare, healthcare workers, Malaysia

INTRODUCTION

Seasonal influenza affects around one billion cases annually, including 3-5 million severe cases and causes 290,000 to 650,000 respiratory deaths worldwide.[1] During influenza pandemics, the emergence of novel, rapidly evolving strains resulted in millions of deaths worldwide, with multiple strains often circulating concurrently.[2] This acute viral respiratory infection contributes to substantial morbidity and mortality each year, particularly among older adults.[3] Consequently, vaccination is a key component of pandemic preparedness, safeguarding HCWs and ensuring the continuity of essential health services during outbreaks. According to the Centers for Disease Control and Prevention, individuals aged 65 and above account for 50-70% of influenza-related hospitalisations and 70-85% of influenza-related deaths.[4]

Influenza is caused by RNA viruses of the Orthomyxoviridae family, with three main subtypes: A, B, and C.[5] Influenza type A and B cause seasonal epidemics. Typical symptoms

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include fever, cough, sore throat, headache, myalgia, malaise and coryza. In Malaysia, influenza occurs throughout the year as indicated by WHO bi-weekly influenza update.[6] It should not be mistaken for the common cold, as it may lead to complications such as bronchitis, pneumonia, sinusitis, otitis media, encephalitis, pericarditis, and Reye's syndrome.[7] Transmission primarily occurs through respiratory droplets and aerosols. The incubation period ranges from one to four days. Individuals may be infectious from one day before symptom onset to up to seven days thereafter.[7]

Uncomplicated influenza is generally self-limiting and managed with supportive care, including antipyretics and hydration. However, complications involving the lower respiratory tract may require hospitalisation, further straining healthcare resources. HCWs are at elevated risk of contracting and transmitting influenza due to occupational exposure.[8] Primary healthcare providers, as the initial point of patient contact, are particularly crucial in breaking the chain of transmission and safeguarding high-risk populations.[9]

Globally, influenza vaccination uptake among HCWs varies considerably. A recent meta-analysis included data from 26 countries, reporting an overall HCWs vaccination uptake of 41.7%.[10] A more detailed breakdown revealed regional vaccination coverage was highest in the Americas at 67.1%, followed by the Middle East at 51.3%, Oceania at 48.7%, Europe at 42.5%, Asia at 28.5%, and lowest in Africa at 6.5%.[10] Despite the availability of free influenza vaccinations for public HCWs in Malaysia, its uptake remains suboptimal, ranging from 7.2%-67.2%.[9,11-13] A study conducted in local university reported a declining trend in influenza vaccination uptake: 23.8% in 2009, 18.8% in 2010, and 7.2% in 2011.[12] The highest reported rate of 67.2% vaccination uptake was among primary HCWs in Klang Valley, Malaysia, following influenza A H1N1 pandemic in 2009.[9] At post COVID-19 pandemic era, we would expect a higher acceptance of vaccination among HCWs as part of preventive effort.

A study carried out among HCWs in Turkey found that the primary reason for receiving the influenza vaccine was "to protect myself and my family".[14] The main reasons cited for non-vaccination included the belief that "Influenza vaccination is unnecessary and ineffective", as well as past experiences with the vaccine.[14] Similarly, a local study reported that protection against influenza infection was the most common motivator for vaccination, while time constraints were the most frequently cited barrier.[12] Their study also found that influenza vaccination uptake was significantly associated with older age and a history of previous vaccination.[12] In another study in Saudi Arabia, the perception of being at own risk was seen as a major deterrent to vaccination.[15] Factors associated with vaccine uptake in their study included prior vaccination and availability of the vaccine in the workplace.[15]

Influenza vaccination is primarily administered via intramuscular injection. However, an alternative option is intranasal live attenuated influenza vaccine (LAIV), which may be suitable for specific populations, such as healthy and non-pregnant individuals aged 2-49 years.[16] This limits LAIV's utility in mass vaccination campaigns. In Malaysia, various inactivated influenza vaccines are available, including egg-based quadrivalent vaccines such as Fluarix Tetra, Influvac, FluQuadri Quadrivalent, Vaxigrip Tetra, as well as cell-based vaccine such as SKYCellflu Quadrivalent.[17] Malaysia does not include the live attenuated influenza vaccine in the national immunisation program.

Influenza vaccination provides protection to approximately 54% to 67% of the vaccinated population for up to 12 months.[18] Though adverse effects such as local pain, fever, malaise and irritability are common, the benefits outweigh the risks.[19] Rare but serious side effects, such as anaphylaxis, Guillain-Barre syndrome, and pericarditis, have been reported but occur infrequently. Scientific evidence supports the safety and efficacy of influenza vaccination.[20]

According to the Malaysian guidelines for adult immunisation, the annual influenza vaccine is recommended for all individuals wishing to reduce their risk and for specific target groups. These include HCWs, individuals aged 50 and above, those aged 18-49 with underlying medical conditions, pregnant women, individuals living in institutional settings, and persons with obesity.[17] Other high-risk groups include immunocompromised individuals, such as those with HIV, those undergoing chemotherapy or corticosteroid therapy, and patients with malignancy.[1]

This study aimed to determine the prevalence of influenza vaccination uptake among public primary HCWs in Seberang Perai Tengah District, Penang, reasons for accepting or refusing vaccination and to identify factors associated with vaccine acceptance.

MATERIALS AND METHODS

A cross-sectional study was conducted from January to March 2025 involving HCWs from all fifteen public primary care clinics consisting of nine health clinics and six dental clinics in Seberang Perai Tengah district of Penang, Malaysia. All HCWs in the fifteen public primary care clinics in Seberang Perai Tengah district were invited to participate in the study. Recruitment was coordinated by the Family Medicine Specialist in each respective clinic, who disseminated the invitation message through their clinic's official WhatsApp group. A participant information sheet, informed consent and a self-administered questionnaire were disseminated via a Google forms link. A follow-up reminder was sent two weeks after the initial distribution for two rounds.

Participants were required to log in with a unique Google account to avoid duplicate responses. Data were manually reviewed to check for completion, inconsistency or suspicious entry. The inclusion criteria encompassed all HCWs who could comprehend either in English or Malay and provided informed consent. Cleaners were excluded from participation as they were outsourced from private companies. A total of 982 HCWs were invited, and 360 responded, yielding a response rate of 36.6%. However, one participant was excluded due to contradictory responses, resulting in 359 participants for further analysis.

For objective 1 prevalence estimation, sample size calculation was performed using the population proportion formula,[21] based on a previous estimated vaccination prevalence of 51.4% among HCWs.[11] The population size was 982 (the total number of HCWs in Seberang Perai Tengah in March 2025). The calculation assumed a Type 1 error probability of 0.05 and precision of 0.05. The calculated sample size was 277 samples. Accounting for a 20% potential dropout rate, the minimum required sample size was 347.

For objective 2 risk factor analysis, sample size was calculated using G*Power software for logistic regression analysis. To detect a predictor with a large effect size (odds ratio=12.49)[12], with 80% power, 5% significance level, and baseline complication prevalence of 7.2%, the minimum required sample size was 51 participants after accounting for covariates.

The final sample size of 347 participants was chosen as it provides adequate power for both objectives, ensuring robust analysis for prevalence estimation and sufficient power to detect clinically meaningful risk factors.

Study Instrument

This study utilised a self-administered questionnaire adapted with permission from an instrument developed and validated by Hudu et al. for use among Malaysian healthcare workers.[11] The choice of this instrument was based on its established validity and relevance to our target population. The original validation by Hudu et al. included a pilot survey with HCWs in Malaysia, which affirmed its content validity and linguistic appropriateness for the local context.[11] For our study, the questionnaire was deployed via Google Forms and was pre-tested by a small group of primary care HCWs for clarity and technical functionality. The questionnaire comprises of 33 questions across six key domains: i) socio-demographic data, ii) work-related characteristics, iii) history of influenza vaccination, iv) reason for vaccination or non-vaccination, v) knowledge and attitude towards influenza and its vaccination, and vi) presence of comorbidities associated with increased influenza risk.[11]

Knowledge and attitude related to influenza and its vaccination were assessed using 18-item questions originally developed by Hudu et al.[11] For our study, the scale demonstrated good internal consistency with a Cronbach's alpha of 0.91. Each statement was assessed using a five-point Likert scale, ranging from "Strongly agree to Strongly disagree". Responses were scored as follows: *1-strongly agree, 2- agree, 3-not sure, 4- disagree, 5- strongly disagree*. We simplified the scoring into dichotomization as most statements assessed factual knowledge. For positively worded statements, "Strongly agree" or "Agree" responses were scored as 1, while "Not sure", "Disagree" and "Strongly disagree" were scored as 0. Items 12,14,17 were reverse- coded to ensure that a higher total score consistently reflected better knowledge and more positive attitudes toward influenza and its vaccination. Knowledge-related items included Q1-Q7 and Q11-Q18, while attitude-related items were Q8-Q10. There were no missing data points among the participants in this study.

Ethical Consideration

This study was approved by Medical Research and Ethics Committee (MREC) of the Ministry of Health Malaysia (NMRR ID-24-02381-TQE) and the Research Ethics Committee of University Kebangsaan Malaysia (UKM) (JEP-2024-589). Permissions were obtained from Penang State Health Department (JKN Pulau Pinang), Seberang Perai Tengah District Health Office (PKD), and Seberang Perai Tengah Dental Health Office (PPD) prior to study commencement. All participants provided informed consent before answering the questionnaire. Participation was voluntary, and confidentiality was assured throughout the study. The questionnaires used in this study was adapted with permission from the original authors.[11]

Statistical Analysis

Data entry and analysis were conducted using IBM SPSS Statistics version 26. Prior to analysis, data cleaning was performed to check for any missing values, data entry errors, or inconsistencies. Categorical variables were presented as frequencies and percentages, whereas continuous variables were described using means and standard deviations (SD) for normally distributed data or medians with interquartile ranges (IQR) for skewed data.

The prevalence of influenza vaccination uptake among the HCWs was calculated and expressed as a percentage. Reasons for receiving or not receiving the influenza vaccination were presented in frequency tables. To assess knowledge and attitude, two separate scores were calculated from the 18-item Likert-scale questionnaire. A knowledge score was derived from 15 specific questions (possible range: 0-15), while a distinct attitude score was derived from the remaining three questions (possible range: 0-3). Each score was analysed independently and summarized using either the mean and standard deviation (SD) for normally distributed data or the median with interquartile range (IQR) for skewed data.

Multiple logistic regression analysis was performed to identify factors that were independently associated with influenza vaccination uptake among primary HCWs. Both Backward Likelihood Ratio and Forward Likelihood Ratio methods were initially applied during the model-building process to assess the best-fitting model. The variables that showed a p-value of less than 0.25 in the univariate analysis were included in the multivariate logistic regression analysis. After comparison, the Forward Likelihood Ratio method was chosen for the final model, as it retained the most statistically significant variables while achieving a better model fit. The results of the logistic regression analysis were presented as crude odds ratios (OR) and adjusted odds ratios (Adj. OR) with their corresponding 95% confidence intervals (CI). To assess model assumptions, multicollinearity was examined using Variance Inflation Factor (VIF). A VIF of less than 10 and tolerance above 0.1 were considered acceptable. The model's goodness-of-fit was evaluated using the Hosmer-Lemeshow test, and the Nagelkerke R^2 was reported to indicate the model's explanatory power. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Characteristic of Participants

The study involved participants aged 22 to 57 years, (mean=37.9 years, SD=7.09). Three-quarters of the participants were female, and nurses constituted the largest occupational group (33.7%). The duration of service ranged from 1 to 34 years, with a mean of 13.0 years (SD = 7.31), and 90.8% reported direct patient exposure (Table 1). A small percentage reported pre-existing medical illnesses, including asthma (3.6%) and heart disease (1.6%).

Influenza Vaccination Uptake

The majority of participants (97%) reported previous influenza vaccination, with only 12 HCWs in Seberang Perai Tengah reporting no prior vaccination (Table I). This small number of unvaccinated participants (n=12) may limit the model's discriminatory power and stability, and a low event rate could affect generalizability and precision of estimates.

Among the 347 vaccinated participants, the most frequently reported reasons were self-protection (94.2%), protecting family and friends (70.9%) and the availability of free vaccination at the workplace (50.7%) (Figure 1). For the 12 unvaccinated HCWs, the most common reason cited was concern about side effects (58.3%), followed by fear of getting sick from the vaccine and personal reluctance (each 25%) (Figure 2).

Knowledge and Attitude Towards Influenza and Its Vaccination

Table II presents the responses of HCWs to 18 knowledge and attitude statements. Most participants (over 60%) agreed that influenza is a serious health threat, and that vaccination is safe and worthwhile. However, misconceptions persisted, particularly regarding transmission routes (item 12), with 39.3% incorrectly believing influenza is blood or bodily fluid-borne, and vaccine side effects (item 17), where 30.4% believed the vaccine could cause infection. Additionally, 27.6% mistakenly believed they were not at increased risk (item 14), despite their direct patient contact.

The knowledge scores of participants ranged from 0 to 15, with a median score of 11.0 (IQR 4.0). Two participants achieved the maximum score of 15. In contrast, 20 participants had a knowledge score of zero. The median knowledge score for vaccinated participants was 11.0 (IQR 4.00) while for not vaccinated participants the mean score was 6.2 (SD 3.46). The score distribution for vaccinated participants was slightly skewed to the left (skewness=-1.135), indicating a concentration of higher scores. In contrast, the non-vaccinated group's distribution was approximately symmetrical (skewness=0.037). A Mann-Whitney test indicated a significant difference in knowledge scores between the two groups (Z=-3.142, p=0.002).

Attitude scores ranged from 0 to 3, with an overall mean score of 2.1 (SD 1.12). Majority of participants (n=191) achieved the maximum score of 3, while 60 participants scored zero. These participants with zero marks for attitude most often selected "Neutral" for their answers. The median score for vaccinated participants was 3.0 (IQR 1.00), while the means score for not vaccinated participants was 1.1 (SD 1.31). The score distribution for vaccinated participants was left-skewed (skewness=-1.049), while the not vaccinated group's distribution was slightly right-skewed (skewness=0.690). The Mann-Whitney test showed that vaccinated participants had a significantly higher attitude score than the not vaccinated participants (Z=-2.834, p=0.005).

Factors Associated with Influenza Vaccination Uptake

Prior to interpreting regression findings, model assumptions were assessed. Multicollinearity was not a serious issue, with all included variables having VIF values below 6.1 and tolerance values above 0.16. The Hosmer-Lemeshow test indicated good model fit (χ^2 = 4.321, df = 7, p=0.742). The overall model was statistically significant (p<0.05) and explained 14.8% of the variance in vaccination uptake (Nagelkerke R^2 = 0.148).

Multiple logistic regression analysis revealed that total attitude score was a significant predictor of influenza vaccination uptake (p=0.002). Each one-point increase in a participant's attitude score was associated with a more than two-fold increase in the odds of vaccinated (Adj. OR: 2.12; 95% CI: 1.30–3.44). The total knowledge score was not a significant predictor in the final model (p=0.645).

Subgroup analysis for Knowledge and Attitude Scores

Knowledge and attitude scores varied significantly by occupation. Doctors had the highest median knowledge score (13.00, IQR 2.00), closely followed by pharmacists (mean = 11.33, SD = 2.23). Conversely, nurses exhibited the lowest mean knowledge score (8.64, SD 4.30). For attitudes, pharmacist had the highest mean score (2.75 SD 0.62), and nurses again had the lowest mean score (1.99 SD 1.25). Further subgroup analysis of participants with low knowledge scores (defined as ≤10) and low attitude scores (defined as ≤2). Of the 164 low-knowledge scoring participants, the highest proportion of participants with poor knowledge were assistants or aides (54.0%, n=47), followed by nurses (52.9%, n=64) and medical assistants (51.3%, n=20). In contrast, doctors had the lowest proportion of poor knowledge (14.3%, n=6). Of the 168 low-attitude scoring participants, the highest proportion of participants with a poor attitude were technicians (66.7%, n=4), followed by allied health professionals (57.1%, n = 8), and dentist (52.6%, n=20). Pharmacists had the lowest proportion of poor attitude (16.7%, n=2).

A Spearman correlation analysis showed no significant correlation between years of service and either knowledge scores (r=-0.018, p=0.740) or attitude scores (r=0.016, p=0.756). Consistent proportions of low-scoring participants were observed across all years of service categories. For this analysis, year of service was categorized into five groups: 0-5 years, 6-10 years, 11-15 years, 16-20 years, and more than 20 years. For knowledge scores, the percentage of participants with poor knowledge ranged from 41.8% to 49.3%. Similarly, for attitude scores, the percentage of participants with a poor attitude ranged from 43.3% to 48.9%, showing no strong differentiation across year of service categories.

Table I: Sociodemographic characteristics and influenza vaccination uptake (n=359)

Characteristics	Numbers (n)	Percentage (%)
Age(year)		
Mean (SD)	37.9	7.09
Gender		
Male	80	22.3
Female	279	77.7
Ethnic		
Malay	273	76
Chinese	42	11.7
Indian	34	9.5
Others	10	2.8
Education Level		
Primary education	3	0.8
Secondary education	89	24.8
Diploma	155	43.2
Bachelor's degree	90	25.1
Master's degree	12	3.3
Professional degree	10	2.8
Job categories		
Doctor	42	11.7
Dentist	38	10.6
Medical Assistant	39	10.9
Nurse	121	33.7
Allied Health Professional	14	3.9
Pharmacist	12	3.3
Technician	6	1.7
Assistant or aide	87	24.2
Years of service (years)		
Mean (SD)	13.0	7.31
Exposure to patients	326	90.8
Medical Illness	61	17.0
Asthma	13	3.6
Endocrine	17	4.5
Heart Disease	6	1.6
Kidney Disease	1	0.3
Others	29	7.7
Vaccination uptake:		
Ever vaccinated	347	97
Never vaccinated	12	3

DISCUSSION

Vaccination uptake rates

This study revealed an exceptionally high influenza vaccination uptake rate of 97% among HCWs in Malaysian public primary care settings. This remarkable figure highlights the successful implementation of influenza vaccination initiatives within this healthcare district. The high coverage rate can be attributed to institutional strategies, including the provision of free and accessible vaccination services, and favourable attitude among HCWs. Notably, the observed coverage exceeded the World Health Organization's target of 75% vaccination among HCWs.[22] A recent report from Occupational and Environmental Health Unit reported 85% of the HCWs in the district agreed for the vaccination in 2024 (unpublished data). The vaccination process in the district was still ongoing during the data collection period and the latest registration for the health district showed (76.9%) of HCW had been vaccinated (unpublished data).

These findings are in stark contrast to previous local studies, which reported a lower uptake ranging from 7.2%-67.2%.[9, 11-13] Internationally, similar challenges are evident. Studies from India and Turkey have reported low-4.4% to 9.2% uptake rates.[23,24] The decision to vaccinate is often influenced by a perceived risk of disease severity and concerns over vaccine-related side effects.[25] Sun et al reported that the COVID-19 pandemic led to a sustained increase in influenza vaccination rate, driven by heightened public awareness of disease prevention and control, as well as changes in health-related behaviours, thus enhanced willingness to receive vaccination.[26] This post-COVID pandemic impact could partly contributed to the high vaccination uptake in our study.

Studies have reported a high acceptance rate in Mexico, United States and Singapore. In Mexico, a survey found an 80% acceptance rate among HCWs in three urban hospitals, with key motivators being the perceived safety and the efficacy of the vaccine.[27] Similarly, in the United States, 78.6% of participants reported receiving an influenza vaccine during the 2016-2017 season,[28] bolstered by mandatory vaccination policies in some states. Singapore, a neighbouring country, has also achieved a high vaccination rate of 82% among HCWs.[29] Like Malaysia, influenza vaccination in Singapore is free and encouraged by the

Table II: Knowledge and attitude towards influenza vaccination among HCWs (n=359)

No	About Influenza Vaccination	Strongly Agree N (%)	Agree N (%)	Neutral N (%)	Disagree N (%)	Strongly disagree N (%)
1	I am at risk of getting flu	142 (39.6)	80 (22.3)	85 (23.7)	29 (8.1)	23 (6.4)
2	People around me are at risk of getting flu	154 (42.9)	80 (22.3)	86 (24.0)	21 (5.8)	18 (5.0)
3	Flu is a serious threat to my health	120 (33.4)	103 (28.7)	101 (28.1)	22 (6.1)	13 (3.6)
4	Flu is a serious threat to the health of people around me	124 (34.5)	105 (29.2)	99 (27.6)	16 (4.5)	15 (4.2)
5	Flu vaccination can protect me from getting the flu	139 (38.7)	127 (35.4)	62 (17.3)	16 (4.5)	15 (4.2)
6	If I get a flu vaccination, people around me will be better protected from flu	142 (39.6)	112 (31.2)	79 (22.0)	13 (3.6)	13 (3.6)
7	Flu vaccination is safe	160 (44.6)	116 (32.3)	57 (15.9)	14 (3.9)	12 (3.3)
8	Getting vaccinated for flu is worth the time and expense	150 (41.8)	120 (33.4)	64 (17.8)	11 (3.1)	14 (3.9)
9	Health care workers should be rewarded for getting vaccinated for flu	149 (41.5)	89 (24.8)	75 (20.9)	21 (5.8)	25 (7.0)
10	Health care workers should be required to be vaccinated for flu	167 (46.5)	90 (25.1)	72 (20.1)	12 (3.3)	18 (5.0)
11	Influenza is more serious than a bad cold	192 (53.5)	94 (26.2)	53 (14.8)	7 (1.9)	13 (3.6)
12	Influenza virus is transmitted by contact with blood and body fluids	75 (20.9)	66 (18.4)	66 (18.4)	55 (15.3)	97 (27.0)
13	Influenza virus is transmitted by coughing and sneezing	211 (58.8)	89 (24.8)	33 (9.2)	11 (3.1)	15 (4.2)
14	Healthcare workers are less susceptible to influenza infections than other people	39 (10.9)	60 (16.7)	64 (17.8)	65 (18.1)	131 (36.5)
15	The signs and symptoms of influenza include fever, headache, sore throat, cough, nasal congestion, and aches and pains	229 (63.8)	77 (21.4)	31 (8.6)	6 (1.7)	16 (4.5)
16	People with influenza can transmit the virus before they experience symptoms	146 (40.7)	118 (32.9)	66 (18.4)	17 (4.7)	12 (3.3)
17	The influenza vaccination may cause some people to get influenza	55 (15.3)	54 (15.0)	121 (33.7)	58 (16.2)	71 (19.8)
18	You can get vaccinated for influenza without an injection	26 (7.2)	35 (9.7)	85 (23.7)	76 (21.2)	137 (38.2)

Table III: Simple and multiple logistic regression analysis of factors associated with influenza vaccination uptake (n=359)

Variable	Not vaccinated n=12		Vaccinated n=347		Simple Logistic Regression		Multiple Logistic Regression	
	Mean (SD)	n (%)	Mean (SD)	n (SD)	Crude OR (95% CI)	p-value	Adj OR (95% CI)	p-value
Age(year)	32.0 (9.25)[a]		38.0 (7.08)		1.09 (0.99, 1.20)	0.079		
Gender						0.636		
Male		2 (2.5)		78 (97.5)	1.00 (ref.)			
Female		10 (3.6)		269 (96.4)	1.45 (0.31, 6.76)			
Ethnic								
Malay		11 (4.0)		262 (96.0)	-			
non-Malay		1 (1.2)		85 (98.8)	-			
Education Level						0.205		
Secondary and below		5 (5.4)		87 (94.6)	1.00 (ref)			
Tertiary		7 (2.6)		260 (97.4)	2.14 (0.66, 6.90)			
Job categories								
Professional		1 (1.1)		91 (98.9)	-			
Paramedics		7 (3.8)		175 (96.2)	-			
Non-clinical		4 (4.7)		81 (95.3)	-			
Years of service (years)	7.0 (10.50)[a]		13.2 (7.30)		1.10 (1.00, 1.21)	0.063	1.10 (1.00, 1.22)	0.053
Exposure to patients						0.372		
Yes		10 (3.1)		316 (96.9)	0.49 (0.10, 2.34)			
No		2 (6.1)		31 (93.9)	1.00 (ref)			
Medical Illness						0.976		
Yes		2 (3.3)		59 (96.7)	0.98 (0.21, 4.57)			
No		10 (3.4)		288 (96.6)	1.00 (ref)			
Knowledge score	6.2 (3.46)		11.0 (4.00)[a]		1.19 (1.05, 1.35)	0.006		
Attitude score	1.1 (1.31)		3.0 (1.00)[a]		2.06 (1.28, 3.30)	0.003	2.12 (1.30, 3.44)	0.002

Note: Multiple Logistic Regression analysis using the Forward method
Nagelkerke R square 14.8%
SD = Standard Deviation; OR = Odds Ratio; Adj. OR= Adjusted Odds Ratio; 95% CI = 95% Confidence Interval
[a] Median (Interquartile range, IQR)

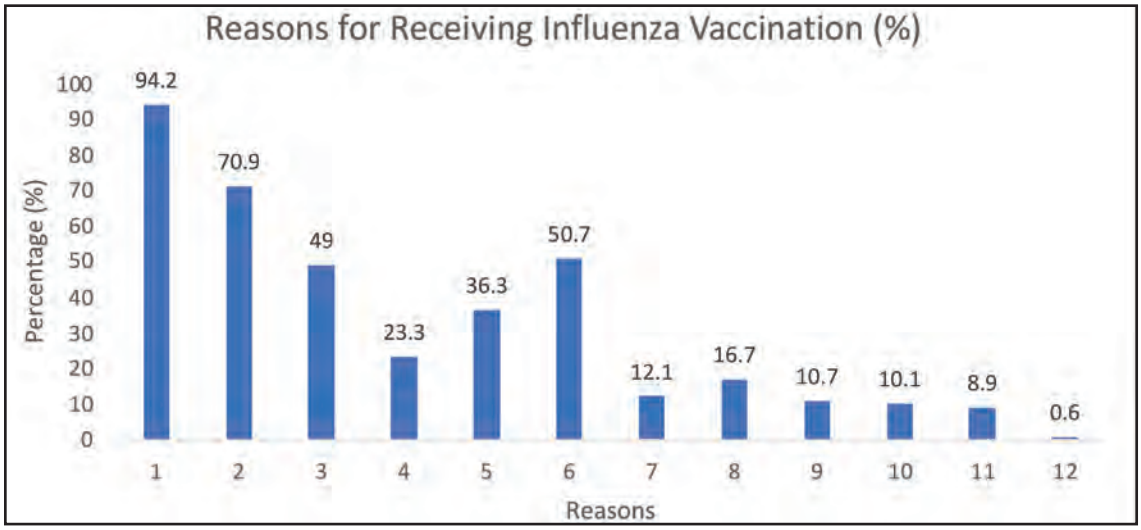

Fig. 1: Percentage of the reasons for receiving influenza vaccination among vaccinated HCWs (n = 347) 1. To protect myself from flu, 2. To protect my friends or family from flu, 3. To protect patients from getting flu, 4 Avoid missing work, 5. It is easy to get flu vaccination at work, 6. Flu vaccine was offered free of charge at work, 7. My employer pays for the time used to get a flu vaccination, 8. My employer recommends that I get a flu vaccination, 9. My employer requires me to be vaccinated for flu, 10. A physician or nurse recommended flu vaccination to me, 11. My colleagues at work recommended flu vaccination to me, 12. To travel

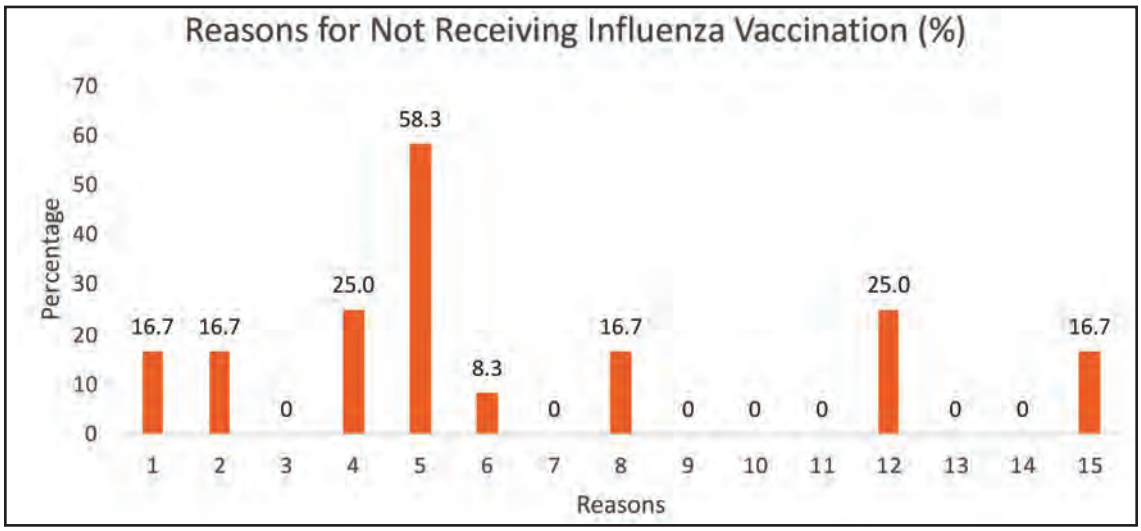

Fig. 2: Percentage of reasons for not receiving influenza vaccination among non-vaccinated HCWs (n= 12) 1. I don't need it, 2. Others need to be vaccinated more than I do, 3. I already had the flu, 4. I might get sick from the vaccine, 5. I may experience side effects, 6. I am allergic to the vaccine, 7. I dislike needles, 8. I haven't gotten around to it / I don't have the time, 9. I don't think that flu vaccines work, 10. There was no vaccine available, 11. Flu vaccines cost too much, 12. I just don't want the vaccine, 13. My employer didn't require me to have a vaccination, 14. My medical care provider recommended that I not get the vaccine, 15. Pregnant

health authorities. Key motivators included higher educational level, belief in the influenza severity, and vaccine safety. Barriers such as fear of adverse effects and doubts about vaccine efficacy were also noted, findings that mirror our local data.[29]

Reasons for vaccination

Among vaccinated participants, the primary motivations included self-protection (94.2%), protecting family and friends (70.9%), and access to free workplace vaccination (50.7%). This reflects Malaysia's collectivist culture, in which family-oriented values strongly influence health decisions. Kegl et al reported similar motivators in a study in Slovenia, such as self-protection and the protection of family and patients.[30] Likewise, Hollmeyer et al emphasised the importance of self-protection and convenience as key determinants of vaccine acceptance.[31] The availability of free and easily accessible vaccination services, such as mobile carts or on-site options, has been shown to significantly enhance vaccination rates,[32] and likely played a major role in the high uptake observed in this study.

Reasons for non-vaccination

Among the small proportion of unvaccinated HCWs, the most cited reason for non-vaccination was concern about side effects (58.3%), followed by fear of illness caused by the vaccine and general reluctance (25% each). These reasons are consistent with reports from Qatar and China, where concerns over vaccine safety remain significant barriers, even among medical professionals.[33,34] For example, Kegl et al reported that HCWs declined vaccination due to personal health beliefs and concerns about potential adverse effects of the vaccine.[30] This suggests that medical training alone does not guarantee vaccine literacy or confidence.

In our study, 16.7% of unvaccinated participants cited pregnancy as a reason for declining the vaccine. Inactivated vaccines are generally safe. Vila-Candel et al reported that the vaccine rejection among pregnant women was attributed to a lack of knowledge and insufficient information regarding influenza vaccination.[35] The WHO strongly recommends influenza vaccination during pregnancy to reduce maternal and neonatal complications.[1] Similarly, the Centers for Disease Control and Prevention (CDC) confirms the safety and importance of vaccination during any trimester, as pregnancy increases the risk of severe influenza outcomes.[36] The fact that such misconceptions exist among HCWs who are expected to educate and counsel patients, raises concerns about the potential downstream impact on community health behaviours.

Knowledge and attitude scores and misconceptions

A crucial finding of this study is the distinction between the roles of knowledge and attitude in influencing vaccination behaviour. While both knowledge and attitude scores were significantly higher among vaccinated participants in initial comparisons, only the attitude score emerged as a statistically significant predictor in the multivariate analysis. This suggests that while factual knowledge is important, it may not be the primary driver for vaccination in this cohort. The decision to get vaccinated appears more strongly influenced by underlying beliefs, trust in vaccine safety, and the perceived value of vaccination. This is consistent with literature supporting the Health Belief Model, where perceived susceptibility, severity, benefits, and barriers are strong determinants of preventive health behaviour.[37]

Knowledge of vaccines, including their efficacy and safety, plays a critical role in strengthening HCWs confidence in communicating the risks and benefits of vaccination. HCWs who trust the safety and efficacy of influenza vaccination were more likely to recommend it to their patients.[32] However, their capacity and confidence can be undermined when they are not adequately equipped with the necessary information to address patients' questions or engage in informed discussions about vaccination.

Targeted educational intervention should be developed to address specific misconceptions and promote evidence- based understanding of vaccine benefits and safety. Educational interventions could be tailored to the primary care setting, such as workplace seminars and e-learning modules with quiz-based reinforcement. Targeted informational posters or infographics is crucial for addressing key misconceptions about influenza vaccination: emphasizing its inactivated nature to dispel fears of causing flu (a misconception held by 30.3% of participants), clarifying that influenza is not transmitted through blood (incorrectly believed by 39.3% of respondents), and reinforcing its safety profile while debunking concerns about side effects. Misconceptions concerning transmission mode and influenza vaccination may drive lower scores. Integrating digital technologies such as vaccine tracking systems and automated reminder platforms can also streamline processes and improve adherence.

Local studies found that increasing age was significantly associated with influenza vaccination uptake, but not other socio-demographic characteristics.[12,13] However, our study did not identify statistically significant associations with socio-demographic characteristics, similar to another local study.[9]

LIMITATIONS

Despite 36.6% of response rate, the participants were from all 15 clinics in the health district and from various health professions. We acknowledge that recruitment via WhatsApp groups and voluntary participation may introduce a degree of self-selection bias. HCWs who are more engaged, tech-savvy, or have a greater interest in influenza vaccination may have been more inclined to participate. However, this approach was chosen for its practicality in reaching a dispersed population across multiple clinics.

Social desirability bias may have influenced participants' self-reported vaccination status, potentially leading them to report higher vaccination rates than actual. The reliance on self-reported data without verification against official immunisation records may introduce recall bias. The voluntary nature of participation and the non-respondents – those who declined participation or did not provide consent may differ systematically from respondents, which could limit the generalizability of the findings. Vaccine hesitancy can be fueled by misinformation within healthcare settings and may have impacted participants' responses. This study is limited by its cross-sectional design which precludes causal inference. Weak explanatory model (Nagelkerke $R^2 = 14.8\%$), suggested that other unmeasured factors may also influence vaccination uptake. Longitudinal studies would be invaluable to track vaccination behaviour over time. Intervention assessment studies are also warranted to evaluate the effectiveness of targeted educational programs designed to address specific misconceptions and enhance vaccine confidence. Furthermore, cross-regional comparisons of influenza vaccination uptake rates and associated factors within Malaysia and across Southeast Asia could provide broader insights into the effectiveness of different institutional strategies.

CONCLUSION

This study provides an assessment of influenza vaccination uptake among HCWs in Seberang Perai Tengah, Penang, revealing a remarkably high coverage rate of 97%. The findings highlight the critical role of institutional strategies, particularly the provision of free and easily accessible

workplace vaccination in facilitating vaccine uptake. These system-level facilitators, coupled with generally positive health beliefs among HCWs, were associated with the high compliance observed. Despite this, a small proportion of HCWs remain hesitant, with concerns mainly related to vaccine safety and potential side effects, underscoring the persistent influence of misinformation and vaccine mistrust, even within healthcare settings. This study offers valuable insights into influenza vaccination among HCWs. Continued investment in staff education, vaccine availability, and supportive policies may further consolidate these gains while protecting both HCWs and the communities they serve.

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Prevalence, risk factors and etiologies of onychomycosis in patients with psoriasis

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ABSTRACT

Introduction: Psoriasis is a chronic immune mediated inflammatory disease often involving nails, presenting significant physical and psychological impacts. Onychomycosis, frequently coexists with psoriatic nail manifestations, complicating diagnosis and treatment. This study aims to evaluate the prevalence, etiology, and risk factors for onychomycosis among psoriasis patients in a tertiary public hospital in Malaysia.

Materials and Methods: A prospective cross-sectional study was conducted involving 191 psoriasis patients from October 2023 to August 2024. Nail involvement was assessed using the Nail Psoriasis Severity Index (NAPSI), and fungal diagnostics included potassium hydroxide microscopy, fungal cultures, and polymerase chain reaction. Associations between clinical variables and onychomycosis were analyzed.

Results: The prevalence of onychomycosis was 13.6%, with dermatophytes being the most common etiological agent (69%), followed by moulds (23%) and yeasts (8%). Higher NAPSI scores were significantly associated with increased odds of onychomycosis (Adj. OR: 1.02, p=0.001). Smoking also emerged as a potential risk factor (p=0.054). Other variables, including diabetes, treatment for psoriasis and BMI, were not significantly associated with onychomycosis in this study.

Conclusion: Onychomycosis is prevalent among psoriasis patients, particularly those with severe nail involvement. Dermatophytes remain the primary pathogens, although moulds account for a notable proportion in this tropical setting. These findings underscore the importance of incorporating fungal diagnostics in psoriasis management to optimize outcomes and break the cycle of worsening disease.

KEYWORDS:
Psoriasis, Onychomycosis, Nail Psoriasis, Dermatophyte, Mould, Yeast, Nail dystrophy

INTRODUCTION

Psoriasis (PsO) is a chronic immune mediated inflammatory disease characterized by aberrant immune activation and accelerated epidermal cell proliferation. It affects approximately 2% of the population. In Malaysia, the prevalence of PsO is estimated to be 0.3% with an incidence of 34.2/100,000 person-year.[1] This condition primarily affects the skin, although it can also involve the nails and joints. Nail involvement, known as psoriatic nail dystrophy, is a common manifestation of psoriasis, occurring in approximately 57% of patients.[2-3] This condition not only leads to physical discomfort and pain but also has a significant impact on the quality of life and psychological well-being of affected individuals.[3-4]

Onychomycosis, a fungal infection of the nail unit, is a prevalent nail disorder worldwide. There are higher prevalence rates among older individuals (aged above 60 years old), immunocompromised patients, immunosuppressed patients i.e, Patients with Human immunodeficiency Virus (HIV), kidney transplant and dialysis patients. Obese patients and smokers are also at increased risk of onychomycosis.[5-7] Psoriasis may also be a risk factor for onychomycosis, the affected nails are prone to develop fungal infection.[8-10]

The clinical presentations of onychomycosis include onycholysis, nail plate thickening, crumbling, ridging, onychocryptosis, and partial or complete nail loss. These symptoms can lead to physical pain, functional impairment, and cosmetic concerns. These features share many similarities with the clinical presentation of nail psoriasis, and there may be an overlap between onychomycosis and psoriatic nail changes.

This study aimed to investigate the prevalence and etiological distribution of onychomycosis in psoriasis patients in a tertiary public hospital in Malaysia. We also hope to find out the risk factors for onychomycosis among patients with psoriasis.

This study provides valuable insights into the burden of onychomycosis in this specific patient population and contribute to the existing knowledge on onychomycosis as a disease itself.

MATERIALS AND METHODS

A prospective cross sectional study was conducted on patients with psoriasis who visited the dermatology clinic in Hospital Pulau Pinang (which serves as the public tertiary referral

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hospital for northern Malaysia) from October 2023 to August 2024.

Approval from the Malaysian Research and Ethics Committee was obtained on 27 October 2023, before study commencement (MRR ID-23-02480-SGV). The study was conducted in accordance with the Declaration of Helsinki.

A voluntary recruitment process was used to recruit all adult patients (over the age of 18) who had psoriasis. Patients with uncertain diagnosis, have acquired HIV infections and active malignancy were excluded.

The diagnosis of psoriasis was made through clinical evaluation by a dermatologist based on history and clinical examination of chronic, recurrent, multiple well demarcated erythematous scaly plaques with silvery scales over extensor surfaces of the body lasting at least 6 months.

Subsequently, data was collected using direct interview via structured data collection forms and questionnaires on quality of life (Dermatology Life Quality Index [DLQI]). Nail psoriasis severity index (NAPSI) scoring was used to assess the severity of nail psoriasis. Psoriasis area and severity index (PASI) and body surface area (BSA) assessment were used to assess the severity of psoriasis.

Nails with abnormalities such as nail dystrophy, leukonychia, onycholysis, pachyonychia and subungual hyperkeratosis, were sent for fungal culture and sensitivity. A maximum of two nails with the above changes were chosen for clipping. Selected nails were clipped with a sterilized 13cm nail nipper (Tekno-Medical, Germany) after cleaning the nail with alcohol swab containing 70% isopropyl alcohol. A fragment of at least 5 mm transversely and 2mm longitudinally of the chosen nail were cut. After each patient use, all nail nippers were autoclaved to ensure sterility to minimize the risk of transmission of infections.

The harvested clippings were sent to the microbiology lab in hospital Pulau Pinang for Potassium hydroxide (KOH) examinations and fungal cultures by the resident microbiologists. All nail clippings sent were innoculated on Sebouraud dextrose agar (SDA), Mycosel agar (containing chloramphenicol and cyclohexine asantimicrobial) and SDA + chloramphenicol. These clippings will be innoculated on all 3 agars at 25 degrees celcius +/- 2 degrees celcius for 3 weeks. The samples were read for a minimum of once a week for any growth for a duration of 3 weeks. Fungal identification was based on macroscopy and microscopy. (after staining with lactophenol cotton blue stain), and were sent for identification using polymerase chain reaction in Institute of Medical Research Malaysia.

Diagnosis of onychomycosis were based on clinical features (discoloured, deformed, hypertrophic, or hyperkeratotic, or has subungual debris) with either a positive KOH examination and/or suggestive culture results.

In the event that the cultures were suggestive of mould, a repeated culture was obtained from the same nail and the diagnosis of non-dermatophyte mould (NDM) onychomycosis were based on fulfilling at least 3 of the following criteria: Positive direct microscopy; Absence of a dermatophyte in culture; growth of non-dermatophyte mould in culture; similar growth of the causative agent in repeat culture.

All statistical analyses were performed using the Statistical Package for Social Sciences for Windows, SPSS 22.0 (SPSS Inc, Chicago, Illinois). Continuous variables are presented as means and standard deviations if they were normally distributed or median and interquartile range if not. Categorical variables are reported as proportions and percentages. Comparisons were made between those with and with- out nail psoriasis. Categorical data were analyzed using χ^2 or Fisher's exact test. Analysis of continuous data was performed using the independent t test. A multiple logistic regression model was applied with adjustment for confounders to determine the risk factors for nail onychomycosis. A p-value of < 0.05 was considered statistically significant.

RESULTS

A total of 191 patients were recruited. The mean age of psoriasis onset was 35.2 years (±16.0). The mean onset of psoriatic nail changes were 40.2 years (±15.3). The demographics and clinical characteristics of the patients are shown in Table I.

A total of 131 (68.6%) patients were found to have nail involvement. The mean age of patients who develop psoriatic nail changes was 51.5 years (SD 16.3). The majority of patients were male (81; 61.8%), and the predominant ethnic group was Chinese (63; 48.1%), followed by Malay (54; 41.2%) and Indian (14; 10.7%). A family history of psoriasis was present in 34 patients (26.0%). Smokers made up 21 patients (15.3%). The mean body mass index (BMI) was 27.3 kg/m² (SD 6.6). Common comorbidities included dyslipidemia (58; 44.3%), hypertension (46; 35.1%), and diabetes mellitus (37; 28.2%). Psoriatic arthropathy was observed in 35 patients (26.7%), while scalp involvement affected 119 patients (90.8%). The mean body surface area (BSA) affected was 5.9% (SD 10.2), with a mean Dermatology Life Quality Index (DLQI) score of 4.3 (SD 5.3). The mean Nail Psoriasis Severity Index (NAPSI) was 29.9 (SD 32.2), and the mean Psoriasis Area and Severity Index (PASI) was 3.8 (SD 6.1) in patients with psoriatic nail involvement. In this group of patients, all were on topical therapy (131; 100%), while one patient (0.8%) underwent phototherapy. Systemic therapy was administered to 62 patients (47.3%), with methotrexate (35; 26.7%) and acitretin (14; 10.7%) being the commonest treatments. The clinical characteristics of patients with nail involvement in psoriasis is detailed in Table II.

The prevalence of onychomycosis in our study population was 13.6%. Out of that figure, dermatophyte onychomycosis had a prevalence of 9.4%, mould onychomycosis stood at 3.1%, and yeast onychomycosis showed a prevalence of 1.1%. Within the dermatophyte category, we detected 18 cases, with *Trichophyton spp.* being the most prevalent species of dermatophyte affecting patients with psoriasis. In

Table I: Clinical characteristics of subjects

Variables	Mean±SD
Age of disease onset with nail involvement	40.22±15.26
Age of disease onset without nail involvement	48.53±17.39
PASI score	
With onychomycosis	5.7±6.76
Without onychomycosis	2.92±4.81
NAPSI	
With onychomycosis	45.23±37.35
Without onychomycosis	16.58±26.84
BSA	
With onychomycosis	8.88±10.85
Without onychomycosis	4.33±8.80
DLQI	3.97±4.88
BMI	27.08±6.27

Table II: Clinical characteristics of patients with nail involvement in psoriasis

Variables	Mean (SD)
Mean age, years (SD)	51.5 (16.3)
Mean age of psoriasis onset, years (SD)	35.7 (16.0)
Gender	
Male, n (%)	81 (61.8)
Female, n (%)	50 (38.2)
Ethnicity	
Malay, n (%)	54 (41.2)
Chinese, n (%)	63 (48.1)
Indian, n (%)	14 (10.7)
Family history of psoriasis	
Yes, n (%)	34 (26.0)
No, n (%)	97 (74.0)
Smoker	21 (15.3)
No, n (%)	111 (84.7)
BMI, kg/m2 (SD)	27.3 (6.6)
Comorbidities	
Diabetes Mellitus	
Yes, n (%)	37 (28.2)
No, n (%)	94 (71.8)
Hypertension	
Yes, n (%)	46 (35.1)
No, n (%)	85 (64.9)
Dyslipidaemia	
Yes, n (%)	58 (44.3)
No, n (%)	73 (55.7)
Arthropathy	
Yes, n (%)	35 (26.7)
No, n (%)	96 (73.3)
Scalp involvement	
Yes, n (%)	119 (90.8)
No, n (%)	12 (9.2)
BSA	5.9 (10.2)
DLQI	4.3 (5.3)
NAPSI	29.9(32.2)
PASI	3.8 (6.1)
Treatment	
Topical	
Yes, n (%)	131 (100)
No, n (%)	0 (0)
Phototherapy	
Yes, n (%)	1 (0.8)
No, n (%)	130 (99.2)
Systemic	
Yes, n (%)	62 (47.3)
No, n (%)	69 (52.7)
Methotrexate, n (%)	35 (26.7)
Acitretin, n (%)	14 (10.7)

Table III: Culture results

	N=26
Dermatophyte	18
Non dermatophyte	
Yeast	2
Mould	6
Etiology	N=26
Dermatophyte	
Trichophyton spp.	11
Trichophyton interdigitale	1
Microsporum spp.	3
Microsporum canis	1
Epidermophyton spp.	2
Non dermatophyte	
Yeast	
Trichosporon asahii	1
Candida albicans	1
Mould	
Fusarium incarnatum	1
Aspergillus niger	4
Penicillum spp.	1

Table IV: Factors associated with onychomycosis (simple logistic regression)

Variable		Crude OR	(95% CI OR)	X^2 stat. (df)[a]	p-value[a]
Age(years)		1.01	(0.98;1.0)	0.34(1)	0.558
Gender	Male	2.21	(0.88;5.5)	3.09(1)	0.091
	Female	1.00			
DM	Yes	1.15	(0.45;2.9)	0.09(1)	0.768
	No	1.00			
NAPSI		1.02	(1.01;1.0)	15.78(1)	<0.001
BMI		1.02	(0.96;1.0)	0.41(1)	0.519
BSA		1.04	(1.00;1.0)	4.36(1)	0.053
Treatment				0.73(2)	0.693
	Biologics	1.18	(0.30;4.6)	0.06(1)[b]	0.807[b]
	Non biologics	1.47	(0.61;3.5)	0.74(1)[b]	0.390[b]
	No systemic treatement	1.00			
Smoking	Yes	3.21	(1.18;8.7)	4.66(1)	0.023
	No	1.00			

[a]Likelihood Ratio(LR) test
[b]Wald test

Table V: Factors associated with onychomycosis (multiple logistic regression)

Variable		Adj. OR	(95% CI OR)	X^2 stat. (df)	p-value
Age (years)		1.01	(0.97;1.04)	0.11(1)	0.737
Gender		1.32	(0.46;3.78)	0.28(1)	0.600
DM		0.76	(0.25;2.28)	0.24(1)	0.625
NAPSI		1.02	(1.01;1.04)	10.73(1)	0.001
BMI		1.05	(0.98;1.13)	1.76(1)	0.184
BSA		1.02	(0.98;1.07)	0.75(1)	0.387
Treatment				0.52(2)	0.771
	Biologics	0.81	(0.15;4.50)	0.06(1)b	0.809b
	Non biologics	1.33	(0.51;3.53)	0.34(1)b	0.561b
Smoking		3.06	(0.98;9.53)	3.72(1)	0.054

*Adj. OR=Adjusted odds ratio
[a]Likelihood Ratio(LR) test
[b]Wald test

addition, we identified *Trichophyton interdigitale,* and *Microsporum spp.* among the dermatophytes. Among the mould infections, Aspergillus niger was the predominant species, observed in 4 patients. Only two patients had yeast onychomycosis caused by Candida albicans and *Tonsurans asahii.* The nail fungal culture results are summarized in Table III.

Among patients with dermatophyte onychomycosis, 12 had positive cultures for *Trichophyton spp.* and in this group, six patients were on systemic treatments : four were on methotrexate, one on Guselkumab, and one on sulphasalazine. The other six patients positive for *Trichophyton spp.* were on topical treatment only. Among the two patients who grew *Epidermophyton spp.*, one was on methotrexate while the other received only topical medications. Of the four patients who had onychomycosis due to *microsporum spp.*, two were on methotrexate, one was on acitretin and another on topical treatment only. Among the six positive cultures for mould, the patient positive for *Fusarium incarnatum* was treated with methotrexate for his psoriasis, while in the *Aspergillus spp.* patients, two were on methotrexate and the other two were on topical therapy. The patient who grew *penicillum spp.* was on topical treatment. In our patients who had yeast onychomycosis, the patient with *Trichosporon asahii* was taking methotrexate, while the patient with candida albicans was on topical medications.

We performed a simple logistic regression analysis to investigate the association between onychomycosis and various independent variables, including age, gender, diabetes mellitus (DM), NAPSI, smoking, BMI, body surface area (BSA) as a severity marker in psoriasis patients, and treatments. The results of this analysis are presented in Table V. The analysis indicated that NAPSI was a significant predictor of onychomycosis, with higher NAPSI scores correlating with increased odds of the condition. Additionally, smoking emerged as a significant factor, with smokers having over three times the odds of developing onychomycosis compared to non-smokers.

In this multiple logistic regression analysis, NAPSI score was a significant predictor of onychomycosis, with an Adj. OR of 1.02 (95% CI: 1.01–1.04; p=0.001). Smoking was associated with increased odds of onychomycosis with a borderline significance (p=0.054). Other factors, including age, gender, diabetes mellitus, BMI, BSA, and treatment type, did not show statistically significant associations with onychomycosis in this analysis and is summarized in Table V.

DISCUSSION

Nail involvement is a common finding in psoriasis that occurs in up to 60% of patients with psoriasis.1 The lifetime incidence of nail psoriasis has been reported to be 80% to 90%. Approximately 5% to 10% of patients may have exclusive nail psoriasis.[11-12] The nail changes in psoriasis include pitting, leukonychia, red lunula and nail dystrophy which are nail matrix abnormalities, while nail bed involvement causes splinter hemorrhages, onycholysis, oil spots (salmon patches), and subungual hyperkeratosis. These clinical manifestations associated with nail psoriasis may morphologically resemble onychomycosis.

In 2012, B. Sigurgeirsson et al. (13) conducted a population based study where a systematic review was done on 21 studies investigating the prevalence of onychomycosis in the general population and found that the prevalence of onychomycosis was 11.4%.[13]

Onychomycosis is encountered in psoriatic patients with an incidence that is reported to range from 13% up to 47%.[14] This tallied with our study prevalence of 13.6%. While this figure sits at the lower end of the range among psoriasis patients, it still shows that there is a higher prevalence of onychomycosis among patients with psoriasis compared to the general population. Klaassen et al. (15) reviewed all the available literature concerning the prevalence of onychomycosis in patients with and without nail psoriasis from January 1980 to April 2012 and found the prevalence of onychomycosis in psoriatic patients was 18%, while in the normal population, it was 9.1%.[15] The wide range in prevalence of onychomycosis among patients with psoriasis found in various studies could be attributed to factors such as variations in study design, population demographics, diagnostic methods, and geographical location.

In 2021, a study from thailand by Chularojanamontri L et al (16) found that treatment with methotrexate was a statistically significant risk factor for onychomycosis in psoriasis patients.[16] However, there was no increase risk of onychomycosis found among our studied population. This could be due to a difference in demographics as well as fungal distribution in the country as in that study, candida infection was found to be the commonest pathogen causing onychomycosis, which differed from our most prevalent causative organisms, which were dermatophytes.[16]

Nail involvement is strongly associated with the presence of onychomycosis, indicating that individuals with nail involvement are more likely to have onychomycosis than those without.

Among those with psoriatic nail changes, we found a positive correlation between more severe nail psoriasis, quantified using NAPSI score, and a risk of onychomycosis. NAPSI is a significant predictor of onychomycosis after adjusting for other variables with each unit increase in NAPSI associated with a 2% increase in the odds of developing onychomycosis. This highly significant p-value suggests that nail involvement is strongly associated with the presence of onychomycosis, underscoring the importance of NAPSI as a clinical indicator. A study by Rizzo at al. (17) also found worse NAPSI scores among psoriasis patients with onychomycosis than those without, however it was not statistically significant.[17]

We also noted that higher body surface areas of psoriasis skin involvement also increased the risk of onychomycosis. These factors show that, at least in the confines of our study population, an increased risk of onychomycosis is seen with increased severity of both skin disease and nail changes in psoriasis.

However, it is known that psoriatic nail changes themselves may not necessarily predispose to higher risks of onychomycosis. One of the functions of the nail plate is to provide protection against invading organisms.[18] This protection may be compromised in patients with psoriatic nail changes. Also onycholysis provides a moist subungual space that can be easily colonised by pathogens.[19] Therefore, nail psoriasis could contribute to the development of fungal infection of the nail. On the other hand, the rapid growth of the affected nails in psoriasis may inhibit the development of onychomycosis, due to the fast turnover and elimination of the distal nail plate, may reduce the opportunity for fungi to invade the nail keratin.[20] Serum- like glucoprotein material that was found in psoriatic oil drop spots may also have an inhibitory effect against dermatophytes.[21] It is known that peptides like psoriasins are being up-regulated in psoriasis and are antimicrobial in nature.[22] Dermatophytes do also seem to grow slower on the keratin of psoriatic nails compared to the growth on healthy nails.[23] The duality between the aggravating factors and the protective factors for and against microorganism invasion may explain the prevalence of onychomycosis among our study population.

It is interesting to note that in our study, smoking is found to be a significant risk factor for onychomycosis in psoriasis patients. A study in Turkey found that cigarette smoking is significantly associated with nail changes in psoriasis.[24] As we gathered in this present study, a worse NAPSI score indicating more severe nail involvement in psoriasis correlates with an increased risk of psoriasis. It is therefore important to address this risk factor among patients with psoriasis and nail involvement in clinical practice.

This study did not find a significant difference in risk factor among our patients across gender, diabetic status and body mass index (BMI). In the general population, onychomycosis seems to be more prevalent among male patients.[13] However, it seems that gender difference did not affect the risk of onychomycosis in psoriasis patients in our study. BMI, while a risk factor for having more severe psoriasis, did not affect the predilection for developing onychomycosis in this study. Diabetes, a known risk factor of reduced immunity to infections in general, does not seem to be a factor for developing onychomycosis in patients with psoriasis in this study.

Our study found dermatophytes to be the most common fungal agent which accounts for 69% of onychomycosis in this study, followed by mould which accounts for 23% and yeasts at 8% of the total etiological agents. This aligns with the findings of some studies, such as Gupta et al., 2024 (25) who reported dermatophytes as the predominant cause in psoriatic onychomycosis.[25] However, the significant proportion of mould infections in our study is noteworthy and differs from some previous reports where yeasts were found to be more prevalent.9 This discrepancy could be attributed to several factors, including variations in diagnostic methods, geographical differences in fungal flora, or underlying patient characteristics.

It is noted that some local studies in Malaysia that found mould to be the dominant aetiological agent in onychomycosis were done with single culture positive results on pre collected nail specimens.[26] These may represent environmental contamination or commensals rather than actual pathogenic mould or yeast onychomycosis. This may give a false perception of mould being a more common aetiological agent for onychomycosis in tropical countries. Further studies with a more controlled methodology in the local context will help shed more light on the fungal flora distribution in this region. Repeated isolation of the same mould is crucial from at least two different time points/patient visits in the absence of a dermatophyte growth in culture prior to confirming a diagnosis of NDM onychomycosis. Repeated cultures of the same NDM minimizes the possibility of it being a contaminant according to Koch's first postulate of pathogenicity, which states it is highly unlikely to isolate a contaminant consistently.[27-28] However, it should also be noted that the lower prevalence of NDM onychomycosis in our study could not be extrapolated to the general population as this could potentially be due to other patient and environmental factors, such as patient demographics, underlying psoriasis and treatment with systemic therapy. It is also limited by our relatively small sample size and study population of patients with underlying psoriasis as opposed to the general population.

This study also found some interesting fungal organisms that were cultured from the nails of 2 patients ie. *trichosporon asahii*, and *microsporom canis* which were organisms rarely attributed to onychomycosis.

T. asahii is a yeast that is more commonly found in immunodeficient and immunocompromised patients, and individuals with hematological malignancies29-30 An epidemiological study of *T. asahii* conducted in China, published in 2020 found that antifungal effect of triazoles, such as voriconazole, fluconazole and itraconazole was the most effective in the treatment of *T. asahii* infection.[31]

Microsporum canis is a zoophilic fungus and it is widely isolated from the hair coat of cats with dermatophytosis. It more frequently cause tinea capitis and tinea corporis in humans, although there have been case reports of onychomycosis caused by *microsporum canis* which were succesfully treated with oral terbinafine.[32-33]

The potential relationship between psoriasis and onychomycosis is very important as it influences patient management. The presence of undetected and untreated fungi in the nail plate may increase the severity of nail psoriasis through Koebner phenomenon and be the cause of the treatment failure.[15] While uncontrolled psoriasis could also manifest as uncontrolled nail psoriasis and larger BSA therefore giving a more severe NAPSI score. This severity in NAPSI score is correlated with increased risk of onychomycosis, and so does an increased BSA, as seen in our study. This may create a vicious cycle where onychomycosis increases severity of psoriasis and uncontrolled psoriasis predisposes to onychomycosis.

While treatment of psoriasis is thought to potentially alter the susceptibility of onychomycosis among patients with psoriasis, literature on the role of immunosuppressive medications on risk of acquiring onychomycosis is sparse. [34] Treatment of psoriasis includes topical therapy with corticosteroids, immunosuppresants like methotrexate and cyclosporin as well as biological agents including tumour necrosis factor (TNF) alpha inhibihors and interleukins 17 and 23 inhibitors. In 2022, Alves et al. (35) found that patients who received systemic treatment with methotrexate for their psoriasis had a 92.8% positivity rate for onychomycosis ($p < 0.05$). Increased rates of onychomycosis were also reported in patients treated with the TNF alpha inhibitors adalimumab and infliximab. The study provided some evidence that certain systemic treatments in psoriasis may predispose to onychomycosis.[35] Another study by Al Mutaifi (37) also found an increased risk of onychomycosis among patients who are on TNF alpha inhibitors with the highest preponderance among patients on infliximab.36 Methotrexate could also cause slowing of nail growth, which could predispose to fungal infection.[37] However, our study failed to find correlations between psoriasis treatment types including conventional systemic treatments as well as biological agents, and onychomycosis.

Onychomycosis in psoriasis patients with nail involvement also presented unique clinical considerations. The presence of pre-existing nail dystrophy and structural changes associated with psoriasis, such as nail pitting, subungual hyperkeratosis, and onycholysis, may influence the clinical presentation, severity, and treatment response of onychomycosis. These interactions between onychomycosis and psoriasis contribute to the complexity of managing both conditions simultaneously.

A diagnosis of onychomycosis may be missed due to the similarities in clinical features. Also, patients who present with nail changes associated with psoriasis may be mistakenly treated for onychomycosis thereby delaying a diagnosis of psoriasis, especially if their diseases manifest with predominantly nail presentations. The presence of both conditions can mask the true extent of either disease, making it difficult to accurately assess the severity and appropriate management strategies.

Differentiating onychomycosis from psoriatic nail dystrophy can be challenging due to overlapping clinical manifestations. Psoriatic nails often exhibit onycholysis, thickening, and discolouration, which can mimic the appearance of onychomycosis. This diagnostic dilemma can lead to delays in appropriate treatment, exacerbating the condition and impacting the patient's quality of life. The coexistence of psoriasis and onychomycosis can further complicate the diagnostic process.

The findings from this study underscore the importance of incorporating fungal screening in psoriasis patients, especially those exhibiting significant nail involvement as indicated by high NAPSI scores. Early identification of onychomycosis is crucial, as it can exacerbate psoriatic nail disease and complicate treatment regimens. Clinicians should consider a multidisciplinary approach, integrating dermatology and mycology expertise, to ensure accurate diagnosis and management.

For patients diagnosed with onychomycosis, tailored antifungal therapy should be initiated promptly. Systemic antifungal agents, such as terbinafine or itraconazole, may be indicated, particularly for dermatophyte infections, while localized treatment may be sufficient for mild cases. Moreover, treatment plans should address the underlying psoriatic condition, as effective control of psoriasis could potentially improve nail health and reduce the incidence of fungal infections.

Furthermore, education on nail care and hygiene practices can empower patients to manage their conditions better and minimize the risk of fungal infections. Clinicians should also remain vigilant for any recurrence of onychomycosis, considering it as part of a comprehensive management strategy for psoriasis patients.

CONCLUSION

This study highlights the significant prevalence of onychomycosis among psoriasis patients, particularly in those with severe nail involvement. A higher NAPSI score was a significant predictor of onychomycosis, emphasizing the relationship between the severity of nail psoriasis and fungal infection risk. While dermatophytes remained the predominant cause, the presence of non-dermatophyte mould in a notable proportion of cases underlines the need for thorough diagnostic approaches, particularly in regions with tropical climates where mould are more prevalent.

Given the diagnostic challenges in differentiating onychomycosis from psoriatic nail dystrophy, clinicians should maintain a high index of suspicion and pursue appropriate fungal investigations. Early detection and management of onychomycosis in psoriasis patients may prevent treatment failures and improve both nail and skin outcomes, contributing to better overall disease control and patient quality of life.

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Effectiveness of a developed module for colorectal cancer patients receiving chemotherapy in reducing depression at the National Cancer Institute, Malaysia

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ABSTRACT

Introduction: Colorectal cancer (CRC) is one of the most common cancers globally. The burden continues to grow globally, exerting tremendous physical, emotional and financial strain on individuals, families, communities and health systems.CRC patients undergoing chemotherapy frequently experience considerable depression. The objective of the study was to develop, implement, and evaluate the effectiveness of the developed module for pharmacists in reducing depression among CRC patients undergoing chemotherapy.

Materials and methods: A systematic, single-blinded study involving 98 patients receiving chemotherapy was carried out at the National Cancer Institute (NCI). The estimated sample size was 98 participants (49 in each group). A self-administered validated questionnaire was used to collect data on the sociodemographic characteristics of the respondents. The validated PHQ-9 (Patient Health Questionnaire-9) and the Multidimensional Scale of Perceived Social Support (MSPSS) were used to assess the depression level and social support of the patients. The intervention group received chemotherapy counselling using the newly developed module during their first, second, and third follow-up. The control group received the standard practice chemotherapy counselling upon their initial visit and during the first cycle. Data were analysed using the Statistical Package for Social Sciences (SPSS) version 26. Independent t-test and two-way repeated measures analysis of variance (ANOVA) were used to analyse the effectiveness of the intervention. A p-value <0.05 was considered significant, and partial eta squared was used to measure effect size.

Results: All participants completed the questionnaire at baseline and followed the first, second, and third chemotherapy counselling sessions, giving a response rate of 100%. No significant difference was detected between the intervention and control groups at the baseline concerning sociodemographic characteristics, depression and social support. The depression scores of the intervention group recorded significant decrements at the third follow-up (p= 0.043), indicating the effectiveness of repetitive counselling in addressing the psychological issues faced by CRC patients.

Conclusion: The newly developed counselling module was effective in reducing depression among colorectal cancer patients undergoing chemotherapy. This study provided evidence-based data on repetitive counselling in improving the psychological and social support of chemotherapy in CRC patients by pharmacists.

KEYWORDS:
Colorectal Cancer; Chemotherapy; Counselling; Depression

INTRODUCTION

Cancer was the second most frequent cause of mortality in 2018, with lung (2.09 million cases), breast (2.09 million cases), and colorectal (1.80 million cases) cancers being the top three.[1] World Health Organization (WHO) also reported stomach (783,000 deaths), colorectal (862,000 deaths), and lung (1.76 million deaths) cancers as the most frequent causes of mortality.[1]

Cancer represents several illnesses that can affect any body part. The disease also encompasses dangerous tumours and neoplasms. Cancer is characterised by the uncontrolled development of unusual cells beyond their boundaries. The cells might attack abutting body parts and spread to other organs, a phenomenon termed metastasis. Cancer mortalities are primarily due to metastases.[1]

Cancer patients frequently suffer from depression.[2] Colorectal cancer (CRC) patients are particularly susceptible to depression. Naser et al.(2021) reported that depression was commonly documented by CRC patients receiving chemotherapy.[3] Depressed cancer patients exhibit poor compliance towards medication, exacerbating their condition.[3]

CRC begins in the colon or rectum and is the second most common cancer in Malaysia, documenting 14.1% of the cancer cases in the nation.[4] In chemotherapy, medications are applied to kill cancer cells. Nevertheless, the medications have potential side effects, including physical (nausea, vomiting, anorexia, diarrhoea, constipation, anaemia, hair loss, and skin and nail changes) and psychological effects (depression).[5]

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Individuals suffering from depression exhibit sadness, inadequate interest or enjoyment of life, feeling guilty, low self-esteem, sleeplessness, trouble eating, fatigue, and difficulty concentrating. The disorder can persist or recur, considerably affecting the capacity of the day-to-day functions of patients. Depression is the most prevalent mental disorder linked to suicide which is related to cancer.6

MATERIALS AND METHODS

Study Design and Setting

The current study was a single-blind design involving cancer patients 18 years old or above, undergoing chemotherapy at NCI, who were able to communicate verbally. The participants were unaware of which treatment group they were in, but the researcher was aware of the treatment groups. Participants with language barriers and severe illnesses were excluded from this study. Sample size was calculated using a power of 90%, response rate of 80% and p of 0.05. Hence, the required sample size was 98.The 98 participants selected were systematically divided into the intervention and control groups. Participants in the intervention group were provided with chemotherapy counselling according to the newly developed module by the investigator. Meanwhile, the control group was provided with standard practice chemotherapy counselling to manage side effects. The intervention group received continuous chemotherapy counselling from their first through to their third follow-up, whereas the control group only received counselling upon their initial visit and during the first cycle.
In this study, the data obtained were analysed with SPSS version 26. Independent t-tests were also employed to compare the variables at baseline. The effectiveness of the intervention was determined with two-way repeated-measure ANOVA assessments. Accordingly, p-values under 0.05 were deemed notable, while partial eta squared represented the effect size.

Sampling Technique

The patients with chemotherapy appointments who met the pre-determined criteria were assigned numbers 1 to 98. The participants with odd numbers were included in the intervention group, while the control group had patients with even numbers. The participants of the intervention group underwent chemotherapy counselling from the investigator, followed by a specific module provided by pharmacists. Meanwhile, the patients in the control group maintained their regular treatment at NCI.

Intervention Module

The newly developed intervention module combines elements of Depression and Social Support. The final iteration of the module was finalized after a pilot study conducted with colorectal cancer patients undergoing chemotherapy, followed by an evaluation by a panel of experts. The module presents an overview of topics associated with colorectal cancer and its chemotherapy treatment. Chapter One introduces colorectal cancer, detailing its risk factors, stages, and treatment options, including chemotherapy. Chapter Two examines chemotherapy drugs and their possible side effects, as well as the preparations needed before, during, and after chemotherapy. Chapter Three addresses the management of physical side effects from chemotherapy, while Chapter Four explores coping strategies for dealing with emotions such as depression. The primary objective of this module is to reduce depression levels experienced by CRC patients. The intervention involved repetitive counselling by pharmacists after every chemotherapy cycle for those in the treatment group. Each counselling session lasted around 60 minutes per patient. These sessions were conducted face-to-face and in person by pharmacists. In contrast, patients in the control group were provided counselling through the hospital's standard counselling practices.

Questionnaire

The current study employed a pre-tested and validated questionnaire in English and Bahasa Malaysia. The survey consisted of three parts: sociodemographic profile, patient health questionnaires (PHQ-9) for depression, and social support multidimensional scaleaofaperceivedasocial support (MSPSS) for social support. In the sociodemographic section, the age, gender, race, marital status, education level, cancer profile (such as cancer stage, number of treatment cycles), and whether the patients were worried about the side effects of the chemotherapy were inquired.

Data Analysis

Descriptive and inferential statistical analyses were performed with SPSS version 26 (IBM SPSS Statistics 26, 2019). Subsequently, the sociodemographic characteristics of the participants were described according to the frequency, mean, standard deviation and percentage. The chi-square test was also adopted to determine the homogeneity of the sociodemographic variables of the patients in the intervention and control groups. Nevertheless, Fisher's exact test was applied when the number of expected counts of a category was under five for a 2 × 2 table.

The baseline data of the intervention and control patients were compared with an independent t-test. Meanwhile, non-normally distributed data were subjected to the Mann-Whitney U test. The effectiveness of the intervention implemented in this study was determined through the general linear model (GLM) with repeated-measure ANOVA. Subsequently, multiple pairwise comparisons were conducted within groups according to a pre-determined significance level of 0.05 alpha (α) value (Bonferroni correction). Furthermore, pairwise comparison effects between intervention and control groups over time were established by utilising independent t-tests. The level of significance, p-value, for the evaluations was set at 0.05.

Ethical Approval

This study procured ethical clearance from the National Medical Research Registry (NMRR) (NMRR ID-22-00402-1V0 (IIR) and NCI prior to data collection. The information forms provided to the participants communicated the objectives and data collection process. Written consent was procured from the patients before data collection.

RESULTS

Tables I summarise the baseline sociodemographic characteristics of the intervention and control groups evaluated in the current study. No significant variations were

Table I: The distribution of the patients' sociodemographic characteristics in the intervention and control groups

Characteristic	Frequency (n) and percentage (%)		Total ((N = 98)	p-value
	Control (n = 49)	Intervention (n = 49)		
1. Age				0.162
18–50	13(26.6)	12(24.5)	25	
51–70	30(61.2)	27(55.1)	57	
≥71	6(12.2)	10(20.4)	16	
2. Gender				
Male	35(71.4)	31(63.3)	66	0.389
Female	14(28.6)	18(36.7)	32	
3. Race				
Malay	21(42.9)	17(34.7)	38	0.863
Chinese	19(38.7)	23(46.9)	42	
Indian	7(14.3)	7(14.3)	14	
Others	2(4.1)	2(4.1)	4	
4. Marital status				
Single	1(2.0)	3(6.1)	4	0.552
Married	36(73.5)	37(75.5)	73	
Widowed	12(24.5)	9(18.4)	21	
5. Education level				
Primary	15(30.6)	10(20.4)	25	0.593
Secondary	13(26.5)	18(36.7)	31	
College/University	12(24.5)	11(22.4)	23	
No education	9(18.4)	10(20.4)	19	
6. Working				
Yes	23(46.9)	31(63.3)	54	0.072
No	18(36.7)	8(16.3)	26	
Retired	8(16.3)	10(20.4)	18	
7. Cancer stage				
One	1(2.0)	3(6.1)	4	0.497
Two	21(42.9)	17(34.7)	38	
Three	27(55.1)	29(59.2)	56	
8. Cancer cycle				
One	1(2.0)	1(2.0)	2	0.247
Two	5(10.2)	7(14.3)	12	
Three	22(44.9)	13(26.5)	35	
Four or more	21(42.9)	28(57.1)	49	
9. Pain chemotherapy				
Yes	33(67.3)	33(67.3)	66	1.000
No	16(32.7)	16(32.7)	32	
10. Fear of side effects				
Yes	40(81.6)	46(93.9)	86	0.121
No	9(18.4)	3(6.1)	12	
11. Cancer support group				
Yes	27(55.1)	23(46.9)	50	0.419
No	22(44.9)	26(53.1)	48	

Test used: Chi-square test

Table II: The comparison of depression mean score changes between the control and intervention groups across three follow-ups

Outcome measure	Mean ± SD		Mean difference (95%CI)	Independent t-test	p-value
	Control group (n = 49)	Intervention group (n = 49)			
Baseline	8.02 ± 5.039	8.55± 5.144	–0.531	–0.516	0.607
First follow-up	8.18 ± 4.969	7.94 ± 4.589 (–1.673, 2.163)	0.245	0.253	0.800
Second follow-up	8.29 ± 4.873	7.14 ± 4.765 (–0.790, 3.076)	1.143	1.174	0.243
Third follow-up	8.20 ± 5.046	6.27 ± 4.305 (0.058, 3.820)	1.939	2.046	0.043*

Note: *Significant at $p < 0.05$

Table III: The comparison of the effectiveness of the proposed module on depression between the control and intervention groups over time

Source	Type III sum of squares	Degree of freedom(df)	Mean square	F	p-value	Partial Ƞ2 (Effect size)
Group	47.880	1	47.880	0.533	0.467 (6.0%)	0.006
Time	61.620	1.465	42.068	14.880	< 0.001* (13.4%)	0.134
Group*Time	84.579	1.465	57.742	20.424	< 0.001* (17.5%)	0.175

Note: *Significant at p < 0.05

Table IV: The comparison of the effectiveness of the developed module on social support between the control and intervention groups over time

Source	Type III sum of squares	df	Mean square (Effect size)	F	p-value	Partial Ƞ2
Group	2.949	1	2.949	0.008	0.931	0.001 (0%)
Time	108.510	1.533	70.787	5.082	0.013*	0.050 (5.0%)
Group*Time	43.316	1.533	28.258	2.029	0.146	0.021 (2.1%)

Note: *Significant at p < 0.05

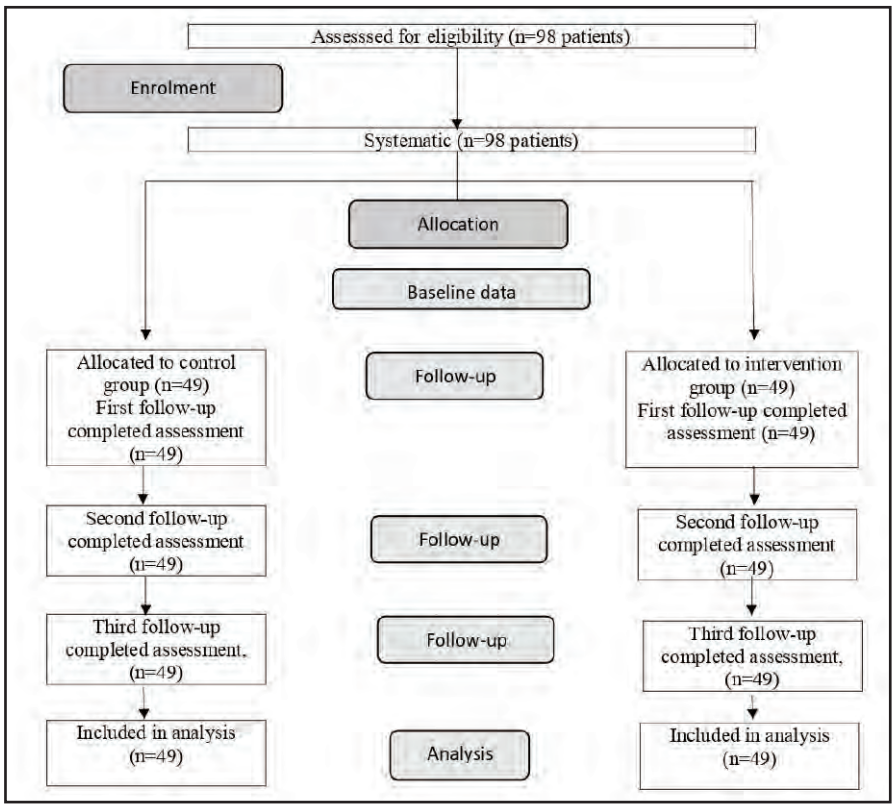

Fig. 1: CONSORT diagram of the study

observed, ensuring that both categories had similar outcome measures before the proposed intervention module was introduced.

Based on the age distribution results, most participants in the intervention and control groups were between 51 and 70 years old, recording 55.1% and 61.2%, respectively. The data also indicated that the highest percentage of participants were Chinese males. Most patients were also married, 75.5% and 73.5% of the participants in the intervention and control groups, respectively.

In the intervention group, 36.7% of patients in the intervention group attended secondary school, while 30.6% of the participants in the control group received primary education. A total of 63.3% of patients in the intervention group were employed, whereas 46.9% of their control counterparts were employed.

A majority of participants in both groups were in stage 3 of cancer and were receiving four or more cycles of chemotherapy. Moreover, numerous participants conveyed worries about chemotherapy pain and side effects. Nonetheless, a majority of patients in the intervention group did not participate in any cancer support groups.

The Effectiveness of the Intervention on Depression

The current study compared the depression mean score alterations between the control and intervention groups across three follow-ups (see Table II). At baseline, there were no significant differences in depression (p=0.607) between the intervention and control groups. Initially, no statistically significant differences in mean depression ratings were observed between the intervention and control groups at baseline (mean difference=-0.531, 95% CI=-2.573, 1.511. However, at the first follow-up (Mean=7.94, SD=4.589 in the intervention group, a significant decrease in mean score compared to the control group was observed in Depression. Positive significant changes were noted in the second follow-up (Mean=7.14, SD=4.765) and third follow-up (M=6.27, SD=4.305) follow-ups.

Table III summarises the effectiveness of the module implemented in this study on depression between the control and intervention groups over time. The results revealed that the assumption of sphericity was violated [Mauchly's test ($\chi 2$) =159.299 p<0.001]. Consequently, Greenhouse-Geiser corrected estimates were applied during the interpretation of the results.

For the group variable, no notable variation was observed regarding the primary effects (F=0.533, p=0.467, partial η^2=0.006). Nonetheless, significant differences were documented for the time variable (F=14.880, p<0.001, partial η^2=0.134) and the interaction between groups and time (F=20.424, p<0.001, partial η^2=0.175). The participants in the control group recorded increased depression, whereas the patients who received the intervention indicated improvement with each counselling session.

The Effectiveness of the Intervention on Social Support

The comparison of mean score changes in social support between the control and intervention groups across three follow-ups. At baseline, the social support mean scores between the groups were not considerably different (mean difference =–1.204, 95% CI =–5.467, 3.059, p=0.576). Similar findings were recorded for the first (mean difference =–0.041, 95% CI=–3.974, 3.892, p=0.984), second (mean difference=–0.102, 95% CI =–4.034, 3.830, p=0.959) and third (mean difference=0.653, 95% CI=–3.434, 4.740, p=0.752) follow-ups.

The effectiveness of the module on depression in the control and intervention groups over time is compared in Table IV. Greenhouse-Geiser corrected estimates were employed during result interpretation [Mauchly's test (χ^2)=161.184, p<0.001] as the assumption of sphericity was violated. No notable variations were observed for the primary effects regarding the group variable (F=0.008, p=0.931, partial η^2=0.001) and the interaction between group and time (F=2.029, p=0.146, partial η^2=0.021). Nonetheless, a significant difference was documented for time (F=5.082, =0.013, partial η^2=0.050). The patients in the intervention group demonstrated improved social support at baseline and first and second follow-ups, which declined during the third follow-up.

DISCUSSION

The Effectiveness of the Intervention on Depression

Psychiatric comorbidities, including depression, have been frequently observed in cancer patients. The illnesses can significantly impact the overall well-being and functioning of the patients.[7] A substantial number of CRC patients in the control and intervention groups of this study also documented notable depression scores, indicating their susceptibility to psychological disorders. Consequently, considering pharmacological and non-pharmacological approaches in targeting the obstacles faced by CRC patients undergoing chemotherapy is essential.

Education and counselling are vital to cancer patients, particularly in managing depression and stress.[8] Counselling offers the patients invaluable mental support and professional assistance, aiding in self-management and coping with overwhelming circumstances. Pharmacists also critically contribute to collaborations with healthcare professionals by educating and counselling CRC patients, promoting medication adherence and positive chemotherapy outcomes.[8]

Pharmacists are involved in cancer patient care to surpass its oncology focus. The strategy adopts a comprehensive management approach by identifying and addressing co-existing health conditions that might affect the patient.[9] Pharmacists possess the necessary knowledge to understand the interactions between all the medications a patient is prescribed, including for cancer treatment.[10]

In this study, the patients in the intervention group recorded considerably reduced depression from the baseline until the third follow-up. The results indicated that repetitive counselling was effective in addressing psychological issues in CRC patients. Moreover, the effect size for depression across time increased based on the pairwise comparisons [baseline versus (vs) the 1st, 2nd, and 3rd follow-ups, and the 1st vs the 2nd, the 1st vs the 3rd, and the 2nd vs the 3rd follow-ups]. The results revealed that repetitive counselling considerably diminishes depression scores. Conversely, no significant variation was demonstrated by the control group. The findings emphasised the vital role pharmacists play in improving depression among CRC patients undergoing chemotherapy through repetitive counselling sessions. Periasamy et al. (2017) reported similar results, where depression was significantly reduced following pharmacist counselling therapy for cancer patients undergoing chemotherapy.[8] In another study, Staynova et al.(2024)

noted that repetitive counselling by pharmacists enhances the mental state of cancer patients and improves their quality of life.[11]

Frequently spending time with CRC patients and engaging with them positively influences their views, perceptions, and self-management of the disease. Consequently, the patients exhibit better psychological health, as evidenced by the significant reduction in depression scores.[12]

The Effectiveness of the Intervention on Social Support
Patients diagnosed with CRC benefit from the social support their friends and family provide considerably. The support is crucial in assisting them navigate the various challenges that arise from the disease and its treatment. Tachi et al.(2015) noted that CRC patients may experience depression and anxiety at varying stages, such as while waiting for test results, upon receiving a diagnosis, during treatment, and when anticipating cancer recurrence.[13] The psychological disorders and physical effects are associated with a notable death risk, poor treatment adherence, inadequate pain management, and a desire for long-term care.

Social support from loved ones has positive effects on CRC patients. Tachi et al.(2015) indicated that such support is correlated to improved psychological wellness, overall quality of life, and physical health outcomes.[13] In this study, the baseline social support scores in the intervention group recorded a significant increase until the third follow-up, demonstrating the effectiveness of repetitive counselling in enhancing social support for patients suffering from CRC.

Based on the pairwise comparison results (between baseline and the 1st, 2nd, and 3rd follow-ups, and between the 1st and 2nd, between the 1st and 3rd, and between the 2nd and 3rd follow-ups), the effect size for social support scores consistently rose over time. The data suggested that the continual increment in social support scores throughout the study period was due to repetitive counselling. Conversely, no notable variation was recorded by the control group. The patients in the control group were not motivated to seek additional social support during the follow-up assessments.

Counselling interventions can improve the social support received by cancer patients. A cancer diagnosis can negatively affect patients' self-perception due to physical appearance alterations, the stigma associated with the disease, job loss, limitations in daily activities caused by treatment and the disease itself, and challenges of adapting to post-cancer therapy.[13] Nonetheless, consistent counselling throughout treatment might enhance social support, enabling CRC patients to address the issues.

The significant improvements in physical and psychological wellness documented by the participants in this study suggested potential awareness, self-esteem, and self-management improvement, contributing to their ability to receive social support and resume normal social activities. The findings also aligned with the previous investigations in Malaysia and China.[8] The articles documented enhanced cancer patients' self-esteem, social interaction, and overall quality of life with repetitive counselling.[12] Moreover, the intervention offers crucial mental support and guidance in understanding CRC, which is vital for motivating patients to adhere to chemotherapy.[14,15]

STRENGTHS AND LIMITATIONS

The results provided insights that might assist future studies to recognise the unique requirements of cancer patients receiving chemotherapy. This study were evaluated using self-questionnaire instruments that were self-administered. This approach is subjective and may make it difficult to differentiate symptoms from cancer or chemotherapy, as participants may report bias. Importantly, there was no intervention or educational program for the control group. Although this procedure was used to create a standard comparison group, we cannot exclude the possibility that patients in the control group were exposed to other sources of information. Moreover, pharmacists doing repetitive counselling have not been widely studied among CRC patients in Malaysia, and this study is the first attempt with CRC patients. Thus, this trial provides fundamental data and information and creates opportunities for further counselling research in CRC patients. Nevertheless, the findings significantly highlighted the importance of counselling for CRC patients receiving chemotherapy.

CONCLUSION

The participants in the intervention group reported a significant decrease in depression scores at the third follow-up and improved social support from the repetitive counselling sessions. Conversely, no positive outcomes were documented by the control group. The preferred effects of the counselling contents on aspects regarding medication adherence, treatment compliance, comprehension of the potential side effects of chemotherapy, and self-management care engagement might be the predominant force of the outcomes in the intervention group. The module developed in the present study can be considered in hospital settings under the Ministry of Health Malaysia and private hospitals with chemotherapy facilities. The framework empowers pharmacists to provide personalised care and address the physical challenges induced by chemotherapy. Furthermore, the module enables individual care while addressing depression and social support. Repetitive counselling sessions throughout treatment cycles also allow ongoing evaluation of the efficacy of the module in aiding patients with CRC.

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ORIGINAL ARTICLE

Perspectives on peer mentoring initiatives: Insights from first-year medical students

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ABSTRACT

Introduction :The transition into medical school represents a period of intense academic, social, and personal adjustment for students. Mentoring programmes have proven to be effective in enhancing students' academic, behavioural, emotional, and social well-being. Mentorship plays a crucial role in the success of a medical career, with growing evidence supporting the positive impacts of mentoring initiatives in undergraduate medical education. These initiatives significantly contribute to both professional and personal growth. Due to the limited research on peer mentoring programmes for new medical students, this study aimed to explore their perceptions of the Peer Mentoring Programme (PMP) at Universiti Tunku Abdul Rahman (UTAR).

Materials & Methods: A mixed-methods study was conducted, combining a cross-sectional survey with a qualitative focus group discussion among first-year medical students from the 2023/2024 academic year. Quantitative data were analysed using descriptive statistics in SPSS version 29, while qualitative data underwent thematic analysis according to Braun and Clarke's framework.

Results: A total of 37 students participated (90.24% response rate) in this study. The findings indicated a positive perception of the PMP with an overall mean score of M=3.63 (SD=0.74). Academic support was the primary reason for mentor meetings (83.8%). Also, thematic analysis revealed two major themes: 'Perceived Benefits of the Programme', which highlighted its role in academic guidance and social integration, and 'Suggestions for Improvement,' which called for better programme clarity, improvement in mentor matching, and increased peer interaction.

Conclusion: The findings indicated an overall positive perception of the peer mentoring programme among the students. While effective in providing academic and social support, its impact could be significantly increased by providing more structured enhancements, which can include formal mentor training, an improved matching process, and a continuous evaluation and monitoring system.

KEYWORDS:
Peer mentoring, perceptions, first-year medical students, academic and social development

INTRODUCTION

The transition into medical school represents a period of intense academic, social, and personal adjustment for students.[1,2] Various factors, such as a challenging and demanding curriculum, a highly competitive environment, and high expectations, can lead to significant stress, making strong support systems essential for student well-being and success.[1,3] Mentorship, in particular, has proven to be an integral component of undergraduate medical education, fostering both professional and personal growth.[4] Among various mentoring models, peer mentoring—where experienced senior students guide and support their juniors—has gained significant attention for its unique advantages.[5]

Peer mentoring is especially well-suited for medical students, who, as adult learners, can benefit from educational approaches that are self-directed and relevant to their immediate challenges.[6] This also aligns with the core principles of Adult Learning Theory, which posits that adults are most motivated to learn when they are actively involved in the learning process and can see the direct relevance of knowledge to solving real-world problems.[6,7] Peer mentoring programmes create a supportive environment that uses these principles. They offer a platform for learning that is built on shared experiences and solves social challenges in a way that faculty-student mentoring cannot always replicate.[3,8] This creates a comfortable, non-judgmental space for guidance on everything from study strategies to navigating campus life.[5,9]

The benefits of peer mentoring in medical education consistently show that these programmes enhance academic development, provide psychosocial support, improve communication skills, and help reduce student anxiety.[5,8,10] However, the effectiveness of such programmes is not guaranteed and often relies on practical experience rather than a strong evidence basis.[11] Many challenges exist, which include time management constraints, communication barriers, and mismatched mentor-mentee expectations.[2,8,12] This creates a significant gap in the literature: a need for formal, mixed-methods evaluations of established mentoring programmes to understand the perceptions of participants and identify specific factors contributing to success or failure, especially within unique institutional settings.

At UTAR, the Peer Mentoring Programme (PMP) is available for students who are interested in becoming mentors. Interested students may register at the Department of Student Affairs office and are required to attend an interview session. Selected participants must subsequently complete

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compulsory mentor training. This programme is one such initiative, designed to develop connections between senior and junior students and provide support for the transition into their demanding medical programme.

However, within the Faculty of Medicine, students generally do not participate in this PMP. Instead, mentoring for first-year medical students is informally organized by the class representative, with mentors randomly assigned from among Year 2 students. This informal arrangement lacks structured training, formal guidelines, and established meeting frequency.

Another motivation for this research is that, despite its long-standing implementation, the PMP at UTAR has not been formally evaluated to assess its impact and effectiveness from the students' perspective.[13] Therefore, this study aims to investigate the perceptions of first-year medical students participating in the PMP at UTAR. Using a mixed-methods approach, this research aims to provide a comprehensive understanding of student experiences, thus contributing to the evidence on peer mentoring and providing practical recommendations to enhance this support program.

MATERIALS AND METHODS

Study design

A concurrent mixed-methods study design was used, which combined a quantitative cross-sectional survey with qualitative focus group discussions. This approach helped collect perceptual data and deepen the exploration of students' experiences related to the PMP.

Settings and Participants

The study was conducted among first-year Bachelor of Medicine and Bachelor of Surgery (MBBS) students from the 2023/2024 academic year at Universiti Tunku Abdul Rahman (UTAR), Malaysia. All first-year medical students from the 2023/2024 academic year were invited to participate voluntarily.

The inclusion criterion was being a first-year medical student who provided informed consent to participate. Students who declined to participate or submitted incomplete questionnaires were excluded.

Sample size calculation

n = N / (1 + N e2)

N=41 (total number of year 1 students) , e=0.05

n= 37

We have sent out request all the students to participate in the study and response rate is 90.24%

Study Period and Data Collection

The study was conducted during the final two weeks of the second semester of the 2023/2024 academic year, from (June 20, 2024, to June 28, 2024). Data was collected at this time to ensure that first-year students had participated in the PMP for a full academic year, allowing them to provide informed and comprehensive feedback based on their complete experience.

Survey Instrument

A self-administered questionnaire was developed following a review of existing literature on peer mentoring assessment to explore the perceptions of mentoring programme on the academic performance and social well-being of medical students. A total of 37 students completed the survey. The questionnaire comprised two sections: (I) general demographic information and (II) a series of 10 items or statements assessing perceptions of the peer mentoring program, rated on a five-point Likert scale ranging from 'strongly agree' to 'strongly disagree.' Expert medical educationists assessed the content validity, and a pilot study was conducted with ten Year 2 medical students to assess the clarity and relevance of the items to ensure internal consistency, with the overall Cronbach's alpha coefficient meeting acceptable standards , Cronbach's alpha > 0.75.

Focus Group Discussion (FGD)

A purposive sample of eight volunteer students was recruited for one qualitative focus group discussion to explore their experiences in greater depth about the impact of mentorship programme on academic performance. The session was semi-structured, guided by an interview protocol questionnaire developed from the quantitative survey themes to facilitate a deeper exploration of student perceptions of peer mentoring programs. The discussion, conducted in English, the medium of instruction for the MBBS programme, lasted approximately 30 minutes and was recorded via Microsoft Teams with the participants' consent.

Data Analysis

Qualitative data from the FGD were analysed using thematic analysis, following the six-phase framework described by Braun and Clarke.[14] The process involved: (1) data familiarization through repeated listening to the recording and reading the verbatim transcript; (2) generation of initial codes from the data; (3) searching for potential themes by collating related codes; (4) reviewing the themes against the coded data and the entire dataset; (5) defining and naming the final themes; and (6) producing the final report with illustrative quotes. To ensure reflexibility, two researchers independently coded the transcript, and any discrepancies were resolved through consensus discussion, ensuring a rigorous and unbiased interpretation of the data.

Ethical Considerations

This study was approved by the Institute of Postgraduate Studies and Research (IPSR), UTAR. (UTAR FM-IPSR-R&D-056(A) response ID 413). Each questionnaire included a consent form that provided a brief overview of the study and its objectives. Participants were informed that their information would be used exclusively for this study and kept confidential. Participation was voluntary, and students were informed of their right to withdraw at any time without penalty.

RESULTS

Quantitative Findings

There were 41 medical students in the 2023/2024 cohort, of whom 37 participated in the study, resulting in a 90.24% response rate. All participants were first-year medical students aged between 16 and 20 years. The majority of

Table I: Sociodemographic characteristics of the participants

	N	Percentage%
Gender		
Male	16	43.2%
Female	21	56.8%
Ethnicity		
Chinese	33	89.2%
Indian	3	8.1%
Others	1	2.7%
Is there any opportunity for students to choose their peer mentor/mentee?		
No	32	86.5%
Yes	5	13.5%
What is the most common reason for meeting with your peer mentor?		
Academic purpose	31	83.8%
Social purpose	5	13.5%
All of the above	1	2.7%
Is it difficult to get an appointment with your peer mentor?		
No	33	89.2%
Yes	4	10.8%
Commonly Discussed Topics in Mentorship Meetings		
Education in general	18	48.6%
Life as a medical student	14	37.8%
Work-life balance related	4	10.8%
Future career	1	2.7%

N = number

Table II: Mean perception scores of the students

No	Items	Mean	SD
Item 1	I enjoy the peer mentoring programme because it benefits me.	3.68	0.92
Item 2	The peer mentoring programme provides me with psychosocial and emotional support.	3.35	1.11
Item 3	My peer mentor is very helpful/ cooperative	3.97	1.00
Item 4	My peer mentor guided me well to understand my studies better and improved my study skills.	3.68	0.92
Item 5	The peer mentoring programme boosts my overall confidence level.	3.51	0.93
Item 6	The peer mentoring program provides information-sharing resources for knowledge transfer and learning.	3.89	0.81
Item 7	The peer mentoring programme helped me improve my communication and collaboration skills.	3.31	1.09
Item 8	The peer mentoring programme able to increase my social network in UTAR	3.70	0.81
Item 9	The peer mentoring programme can shape attitudes and behaviours in learning and personal development.	3.49	0.93
Item 10	The peer mentoring programme enhances medical students' overall well-being and mental health.	3.65	.857
	Overall	3.63	0.74

Table III: Summary table on qualitative themes with representative quotes

	Theme	Quotes
Theme 1	Perceived Benefits of the Programme	"Very beneficial programme because it gives us chances to interact with medical students from different years so that we can learn from each other to improve ourselves and share learning skills and experience." "It was great. It helped me so far to cope with medical student life." "It is a good programme for first-year students, especially during the foundation where students might be lost at the start. Mentors can provide guidance and confidence, which helps the mentees to proceed." "The programme is useful as we get to communicate by looking into the problem faced and providing relevant solutions or advice."
Theme 2	Suggestions for Improvement	"A little bit not clear about the programme." "Some mentees are not happy with their mentors; perhaps every block, you can assign a new mentor to all the mentees." "Try to find a way that students won't feel like they are forced to join this programme. Mentors should be more friendly to their mentees so that they feel comfortable talking with them." "It should give chances for the mentee to choose a mentor because sometimes they feel uncomfortable with their mentor and are forced to talk to other seniors."

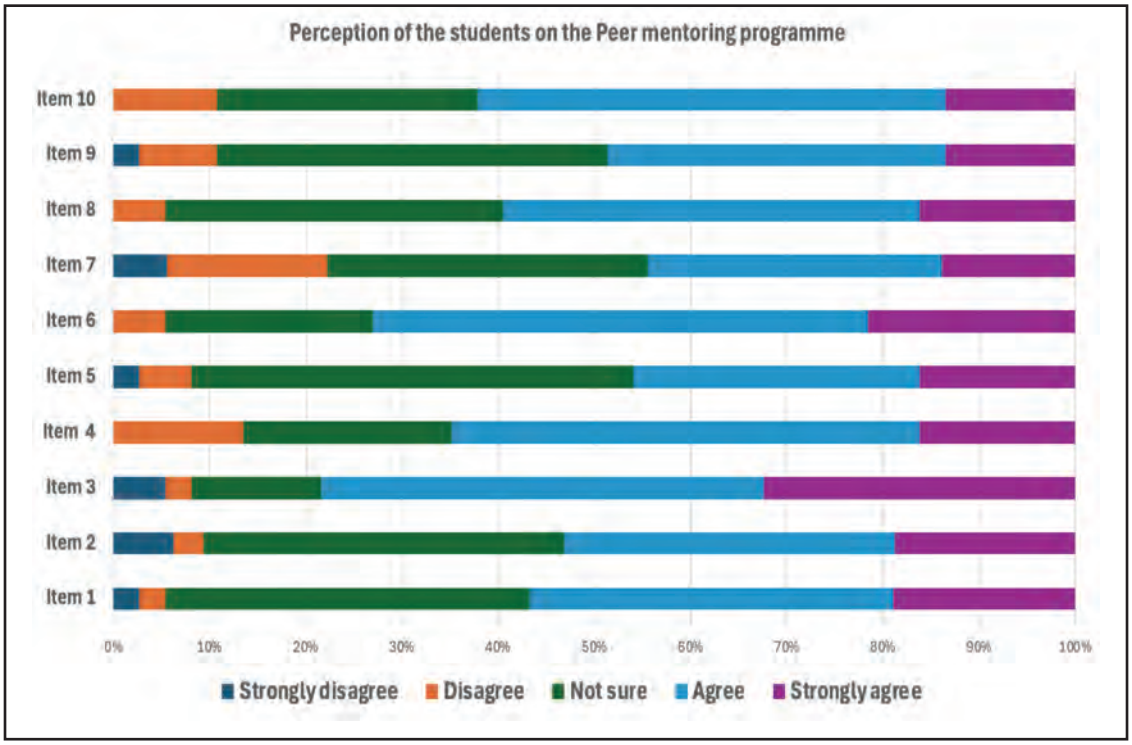

Fig. 1: Individual item perception scores

respondents were female (n=21, 56.8%) and of Chinese ethnicity (n=33, 89.2%).

The most common reason for meeting a peer mentor was academic purposes cited by 31 students (83.8%), followed by social purposes, 5 (n=5, 13.5%), with the remainder citing other reasons. Most students (n=33, 89.2%) reported no difficulty in arranging appointments with their mentors, though a minority (n=4, 10.8%) found the process complicated. Commonly discussed topics in mentorship meetings included general issues (n=18, 48.6%), life as a medical student (n=14, 37.8%), work-life balance-related matters (n=4, 10.8%), and future career discussions (n=1, 2.7%). The sociodemographic characteristics of the participants are shown in Table I.

The overall mean score for the 10 perception items was M=36.6 (SD=0.74), with individual item means ranging from 3.31 to 3.97, indicating a generally positive perception of the Peer Mentoring Programme (Table II).

In the individual item analysis for 10 perception items, the individual item (Item 3), "My peer mentor is invaluable/ cooperative", scored the highest (M=3.97, SD=1.00). Also, Item 6, "Peer mentoring program provides information-sharing resources for knowledge transfer and learning," achieved the second highest score (M=3.89, SD=0.81). In contrast, Item 7, "The peer mentoring programme helped me improve my communication and collaboration skills," received the lowest score (M=3.31, SD=1.09) (Figure 1).

Qualitative Findings

The thematic analysis of the FGD data revealed two major themes: (1) Perceived Benefits of the Programme, and (2) Suggestions for Improvement, supported by direct quotes from participants.

Perceived Benefits of the Program

Participants overwhelmingly found the mentoring programme as beneficial, emphasizing its role in fostering peer learning, guidance, and confidence-building during their transition to medical school. The opportunity to interact with senior students was seen as a key advantage. One student remarked, "Very beneficial programme because it gives us chances to interact with medical students from different years so that we can learn from each other to improve ourselves and share learning skills and experience." Another participant highlighted its impact on adapting to medical school life, stating, "It was great. It helped me so far to cope with medical student life."

Additionally, the programme was praised for its supportive role in helping students during the transition phase, with one participant noted, "It is a good programme for first-year students, especially during the foundation where students might be lost at the start. Mentors can provide guidance and confidence, which helps the mentees to proceed." The programme's problem-solving aspect was also appreciated, as reflected in the statement, "The programme is useful as we get to communicate by looking into the problem faced and providing relevant solutions or advice."

Suggestions for Improvement

While the programme was well-received, participants offered constructive feedback to enhance its effectiveness. A recurring point was a lack of clarity regarding the programme's structure and objectives, with one stating, "A little bit not

clear about the programme." Others suggested reassigning mentors periodically to address mismatches, as one participant explained, "Some mentees are not happy with their mentors; perhaps every block, you can assign a new mentor to all the mentees." The need for a more welcoming and voluntary approach was also highlighted: "Try to find a way that students won't feel like they are forced to join this programme. Mentors should be more friendly to their mentees so that they feel comfortable talking with them." Participants also highlighted the critical importance of the mentor-mentee relationship and suggested changes to the matching process. Dissatisfaction with an assigned mentor led to the recommendation for periodic reassignment or allowing mentees to choose their mentors to foster greater comfort and autonomy. One student explained: "It should give chances for the mentee to choose a mentor because sometimes they feel uncomfortable with their mentor and are forced to talk to other seniors." Finally, there was a clear desire for a more welcoming environment and increased opportunities for interaction, with suggestions for mentors to be more proactive and friendly to facilitate open communication.

The findings suggest that the mentoring programme is highly valued for its role in facilitating peer learning, providing guidance, and easing the transition into medical school. However, improvements programme clarity, mentor-mentee matching, and fostering a voluntary and friendly environment are needed to enhance participant satisfaction and engagement. These insights can inform targeted refinements to maximise the programme's impact on first-year medical students.

DISCUSSION

In many medical universities, mentorship programmes help mentors and mentees begin a shared journey of learning and personal growth.[9] This study aimed to investigate the perceptions of first-year medical students participating in the PMP at UTAR. The findings reveal generally positive feedback, with students valuing the programme for its academic and social support. However, the results also highlight challenges and areas for a systematic and structured improvement. This discussion also helps interpret these findings within the context of Adult Learning Theory and the related literature and proposes suitable recommendations for programme improvement.

The study concept is based on Adult Learning Theory, which believes that adult learners are problem-centered and are motivated mainly by learning that is immediately relevant to their life tasks.[6] The intense focus on academic support in this study, with 83.8% of students meeting their mentors for this purpose only, aligns perfectly with this theory. First-year medical students, who have to confront a demanding new life and a new curriculum, actively try to seek practical and actionable advice from their seniors who have recently navigated the same challenges. The significance placed on mentors being "helpful/cooperative" (Item 3, M=3.97) and providing "information-sharing resources" (Item 4, M=3.89) further confirms this desire for relevant, problem-solving support. This academic focus is not only applicable to UTAR; it mirrors the same findings from another Malaysian institution where academic gain was the primary benefit and is consistent with studies from other parts of Asia as well.[11,15]

While academic support was primary, the programme's social integration is also important for a successful university orientation.[16] The qualitative findings showed the PMP helped students build relationships and expand their social network, as mentioned in recent literature.[8] However, the fact that only 13.5% of the first-year students met primarily for social purposes suggests a potential imbalance. Improving the social integration aspect could further help students' overall holistic well-being and resilience, which is a key result of effective mentoring.[10]

The challenges identified by students can also be interpreted through the Adult Learning Theory framework. The desire for mentees to "choose their mentor" and for mentors to be more "friendly" confirms the adult learners' needs for self-direction and a psychologically safe environment.[6,12] When mentees feel a lack of autonomy and psychological safety in the mentoring relationship, its effectiveness can also be reduced. Also, the challenges reported in this study, like scheduling difficulties (reported by 10.8% of students), mentor-mentee mismatch, and lack of programme clarity, are common across most of the peer mentoring programmes globally. A recent scoping review also identified logistical barriers and mentor workload as common issues, while other Asian studies indicated communication barriers and mismatched expectations.[8,12] The scheduling complications at UTAR are quite similar to the challenge of poor time management reported at another Malaysian University, UNIMAS, thus establishing a similar pattern and need for best practices.[9]

Strengths and limitations of the study

The study has some limitations. As survey-based research conducted at a single institution, a single cohort of a small sample size and Chinese ethnic predominance (89%) limits the generalizability of the study. This demographic profile may not be representative of the broader medical student population in Malaysia, thus limiting the generalizability of the results.

The specific context of UTAR—its curriculum, institutional and academic culture, and student demographics—significantly influences student perceptions.16 For example, the stress on academic support may be a direct reflection of a particularly demanding first-year curriculum. Also, as the student participation was voluntary, the study may have self-selection bias, where students with strong opinions most likely participated in the study.[17] The absence of subgroup or comparative analyses considered limitation of the study. For the qualitative part, one focus group discussion with 8 students may limit thematic saturation and transferability; minimal reflexivity and integration with quantitative data. However, a key strength of this study is the mixed-methods design, which includes quantitative survey data with rich qualitative insights, thus providing a deeper and better understanding of student experiences.

Based on our findings and previously established best practices, several recommendations can be made to improve

the UTAR's PMP in medical faculty. To address student feedback that the programme was "a little bit not clear," the PMP should establish clear goals and define a well-defined role for all participants.[8,13] The need for "more support from senior mentors" and the low rating for improving communication skills require enhanced mentor training that should ideally include communication, boundary setting, and providing constructive feedback.[8] The student's suggestion to allow mentees to choose their mentors should also be considered, as proper matching that is based on shared interests can improve rapport and effectiveness.[12,13]

To further enhance the academic and social aspects, the program could be designed to improve social integration by organising informal social activities as suggested by students.[16] Finally, the PMP should also implement a simple, ongoing evaluation process to guide continuous improvement.[8]

CONCLUSION

This mixed-methods study provides the information that the PMP at UTAR is an invaluable, albeit imperfect support system for first-year medical students facing the transition to higher education. This study also found that students perceive the programme positively, and that it provides essential, problem-focused academic support aligned with the principles of Adult Learning Theory. However, given the study's limitations, including its single institution focus and limited qualitative scope, these findings should be considered preliminary.

To improve this programme, it is extremely important to review the current mentoring system in the medical programme at UTAR and understand its ambiguities. Key recommendations that can help improve PMP include establishing a formal mentor training with clearer guidelines for participants, aligning the mentor-mentee matching process with student preferences, and increasing engagement through structured activities.[8,13] A system of continuous evaluation is also required to ensure the program continues to evolve to meet student needs. Ultimately, this research also describes the vital role of peer mentoring in creating essential academic and personal values, building confidence, and reducing stress for all stakeholders. While improvements are necessary, the study also provides evidence that even with its imperfections, the PMP provides a net benefit to students, affirming that some mentoring is indeed better than no mentoring at all.[17,18] This research helps with theory-driven evaluation and insights about a long-standing programme, while providing clear evidence that validates student experiences and suggests specific, actionable areas for improvement. Ultimately, investing in the evidence-based enhancement of such programme is a crucial commitment to promote the well-being, resilience, and professional identity of the next generation of physicians.

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ORIGINAL ARTICLE

Perceived usability of hospital information system and associated factors: Perspectives from healthcare providers in Hospital Al-Sultan Sbdullah, UiTM

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ABSTRACT

Introduction: The successful integration of Hospital Information Systems (HIS) in Malaysia is crucial for enhancing healthcare delivery, yet usability remains a significant concern among healthcare providers. This study aims to evaluate the perceived usability of the locally developed HIS (UniMEDS) and identify associated organisational and technological factors influencing usability among healthcare providers in Hospital Al-Sultan Abdullah (HASA), Universiti Teknologi MARA (UiTM).

Materials and Methods: A cross-sectional study was conducted from May 2025 to June 2025 at HASA, Puncak Alam. Data were collected using a structured online questionnaire incorporating the System Usability Scale (SUS) and items on organisational and technological factors. Incomplete questionnaires were excluded listwise. Descriptive and inferential analyses were performed using SPSS version 29, with $p < 0.05$ considered statistically significant. A SUS score of ≥68 was classified as "good" usability.

Results: The analysis involved a total of 164 respondents. UniMEDS was perceived as having good usability by 74.4% of respondents, with a mean SUS score of 68.02 (SD = 15.91). In multivariable analysis, good usability was significantly associated with perceived adequacy of data storage and privacy (AOR = 2.04; 95% CI: 1.15–3.64) and user-friendliness (AOR = 1.91; 95% CI: 1.15–3.16).

Conclusion: Overall, the UniMEDS at HASA achieved a borderline good usability among healthcare providers. Factors related to data storage, privacy, and user-friendliness were key determinants of perceived usability. Enhancing these aspects through user-centred design and secure system optimisation could improve HIS adoption and satisfaction among healthcare providers in Malaysia.

KEYWORDS:
Hospital Information System, Healthcare Providers, HASA, System Usability Scale, UniMEDS

INTRODUCTION

The successful integration and utilization of information and communication technology (ICT) in healthcare services is becoming increasingly important in the delivery of healthcare in a developing nation such as Malaysia. The Malaysian government has made substantial investments in initiatives and implemented a variety of innovations to integrate Health Information Systems into the local healthcare infrastructure since the Seventh Malaysian Plan (1996-2000).[1] Almost 85% of public hospitals in Malaysia have had trouble adopting and using HIS, which slows the country's progress toward its Vision 2020. Studies have reported that users often face challenges such as slow system response times, inadequate technical support, and lack of customization to local workflows, which undermine system satisfaction and usage.[2,3] System accessibility, especially in public hospitals, remains compromised due to inadequate infrastructure, including limited computers and unstable network connections.[4] These issues are made even worse by the absence of specific laws governing data security and digital health standards.[5] These systemic factors often cause slow adoption of workarounds that can undermine the integrity of the information system.[6,7] Further analysis of information system quality in Malaysian hospitals reveals that effective HIS implementations can yield substantial benefits, including reduced operational costs and improved service delivery through enhanced resource management.8 These findings collectively argue for the necessity of a holistic strategy that accounts for the multifaceted challenges of system complexity, compatibility, financial support, and the impact of government regulations.[9]

Hospital Information Systems are defined as integrated electronic systems that collect, store, retrieve, and display comprehensive patient data and information, including medical history, laboratory results, diagnoses, and billing, for use across various hospital departments.[10] Usability, in the context of this research, refers to the ability of the user to interact with the hospital information system and perform specific tasks effectively.[11] It reflects healthcare providers' perceptions of the system's efficacy in facilitating workflow, improving patient care, and meeting clinical requirements. Understanding the specific factors influencing HIS usability within the Malaysian context is essential to enhance both sustainability and efficiency in hospitals.[8]

Recent Malaysian studies have examined HIS user experience primarily in Ministry of Health hospitals[3,8] but none have comprehensively assessed usability metrics using validated

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tools such as the System Usability Scale (SUS) within a university hospital context. This gap is significant because teaching hospitals operate under more complex environments, involving concurrent clinical service, education, and research functions, which influence system interaction and adoption. This research aims to fill this gap by evaluating the perceived usability of UniMEDS in Hospital Al-Sultan Abdullah (HASA) and identifying factors influencing its usability. Findings from this study are expected to provide valuable insights for the refinement of HIS usability design and policy formulation for future digital health development in Malaysia.

MATERIALS AND METHODS

Study Design and Setting

This study used a cross-sectional study design to look at how healthcare practitioners thought the Hospital Information System (UniMEDS) worked and what factors affected that. The research took place at Hospital Al-Sultan Abdullah (HASA), Puncak Alam, Selangor, Malaysia. The study lasted from October 2024 to July 2025, and data gathering took place across two months, starting in May 2025.

Study Population and Participants

All registered healthcare workers at Hospital Al-Sultan Abdullah, UiTM using the UniMEDS system were part of the study population. Inclusion criteria include all the active UniMEDS users. Exclusion criteria include users with less than three months of experience with the system. The sample size was calculated using Cochran's formula, based on a total UniMEDS user population (N) of 2074. The calculated sample size was approximately 220. To account for a 20% non-response rate, an additional 55 participants were added, resulting in a final target sample size of 275 UniMEDS users. A stratified sampling method was used to ensure representation across various occupational roles within the hospital. Participants were stratified using the International Standard Classification of Occupations (ISCO).[12] From the total of 275 questionnaires distributed, 164 participants' responses (59.6%) were collected and analysed.

Data Collection Method

Data were collected using a self-administered questionnaire distributed via Google Forms. The questionnaire was provided in both Bahasa Malaysia and English to meet the preferences of the healthcare practitioners. Initially, the self-administered questionnaire was distributed to participants via email through Google Forms. After the initial distribution, reminders were sent via WhatsApp messages twice, at weekly interval, to encourage participation and facilitate follow-up with healthcare providers. The objective of this dual-channel strategy was to optimise engagement and reach among the target demographic. The questionnaire included sections on:

Background Information/Demography: Gender, age, education level, job role, working experience, experience in the healthcare sector, perceived experience using computer applications, experience with UniMEDS, frequency of UniMEDS use, and formal training received.

Organizational Factors: Assessed perceptions related to 4 items which are sufficient hardware, reliable internet connection, technical support, and data storage and privacy. These items were measured using a five-point Likert scale (1=Strongly disagree, 5=Strongly agree).

Technology Factors: Evaluated perceptions on 6 items including UniMEDS user-friendliness, ease of finding information, clarity of interface, accessibility, impact of version updates, and the system improvement request process. These items were also measured using a five-point Likert scale. Associated factors affecting usability of UniMEDS were examined using HOT-Fit framework[13] translated to Malay language and validated by Ahmad Shanniza et al. The framework categorizes evaluation factors and domains that fit and correspond to specific dimensions within the human (H), organisational (O), and technology (T) domains of HIS implementation success and the respective sub-domains (H: system development and system use; O: organisational structure; T: system quality, information quality, and service quality). The internal consistency by Cronbach's alpha (α) for each domain was 0.84 for technology, and 0.96 for organisational structure.[3]

System Usability Scale (SUS): This validated questionnaire comprised ten items to assess the overall perceived usability of UniMEDS.14 The SUS scores were calculated by converting responses for odd-numbered items (positive statements) to the scale position minus 1, and for even-numbered items (negative statements) to 5 minus the scale position. The sum of all item scores was then multiplied by 2.5 to yield a total score ranging from 0 to 100. A system or product with a score of ≥68 was considered to have good usability. The translated version of SUS into Malay language is called Skala Kebolehgunaan Aplikasi Mudah Alih (SKAMA).[15] The Cronbach alpha for the SKAMA questionnaire was determined to be 0.85 (95% CI 0.79-0.91) which is similar to the original English SUS questionnaire. Both authors have granted permission to use these questionnaires.

All responses were automatically recorded in Google Forms and exported to SPSS version 29 for analysis. Incomplete or partially answered questionnaires were excluded listwise, indicating that only fully completed responses were considered in the analysis. Specifically, questionnaires missing any of the ten SUS items, key demographic information, or main organisational and technological variables were excluded. The total number of responses received, exclusions due to incomplete data, and final sample retained are summarised in Figure 1 (Study Flowchart)

Data Analysis

Descriptive and inferential statistics were performed using the Statistical Package for the Social Sciences (SPSS) software version 29.0 (IBM SPSS Inc.). For the first objective, data was analysed using the System Usability Scale where a total score of ≥68 will indicate good usability. For the second objective, descriptive analysis of the associated factors will be presented using cross-tabulation (n, %). Factors measured using a 1–5 Likert scale are treated as continuous and reported using mean and SD (Median if data is not normally distributed). Analysis of technology and organization domains using Likert scoring was assessed for normality using the

Table I: Sociodemographic Factors of Healthcare Providers Using UniMEDS (n=164)

Sociodemographic factors	Total
Gender	
Male	52 (31.7)
Female	112 (68.3)
Age	
20-29 years old	29 (17.7)
30-39 years old	106 (64.6)
> 40 years old	29 (17.7)
Educational level	
Diploma	30 (18.3)
Degree	101 (61.6)
PhD/Specialist	33 (20.1)
Job Role	
ISCO Group 2	130 (79.3)
ISCO Group 3	18 (11.0)
ISCO others	16 (9.8)
Working experience	
≤10 years	139 (84.8)
>10 years	25 (15.2)
Working experience in healthcare sector	
<5 years	30 (18.3)
6-10 years	72 (43.9)
11-15 years	44 (26.8)
16-20 years	10 (6.1)
21-25 years	8 (4.9)
Perceived experience using computer application	
Low to moderate	101 (61.6)
High	63 (38.4)
Experience with UniMEDS	
< 1 year	78 (47.6)
1 - 3 years	64 (39.0)
>3 years	22 (13.4)
Frequency of using UniMEDS	
Occasionally	47 (28.7)
Daily	117 (71.3)
Have you undergone formal training on UniMEDS	
No	28 (17.1)
Yes	136 (82.9

Table II: Comparison of Median Scores for UniMEDS Usability with factors associated with the usability (n=164)

Associated Factors	Usability of UniMEDS		U	p-value
	Poor	Good		
Sufficient Hardware	64.49	88.70	1805.5	0.002*
Reliable connection	66.13	88.14	1874.5	0.006*
Technical	69.21	87.07	2004.0	0.023*
Data storage and privacy	61.30	89.80	1671.5	< 0.001*
User-friendly	55.92	91.65	1445.5	< 0.001*
Sufficient Information	64.15	88.82	1791.5	0.002*
Clean Interface	60.08	90.22	1620.5	< 0.001*
Accessibility	67.04	87.82	1912.5	0.012*
Version update	60.05	90.23	1619.0	< 0.001*
Improvement request (change request)	62.06	89.54	1703.5	< 0.001*

Statistical test used: Man Whitney U. Statistically significant at $p < 0.05$

Table III: Univariate Analysis for Factors Associated with Usability of UniMEDS

Variable	Category	B(S.E)	Walda (df)	OR (95% CI)
Gender	Male	Reference		
	Female	0.100 (0.381)	0.07 (1)	1.11 (0.52,2.33)
Age	20-29 years old	Reference		
	30-39 years old	-0.32 (0.51)	0.39 (1)	0.73 (0.27,1.97)
	40-49 years old	-0.19 (0.66)	0.09 (1)	0.83 (0.23,2.99)
	50-59 years old	-1.34 (1.10)	1.49 (1)	0.26 (0.03,2.25)*
Education level	Diploma	Reference		
	Degree	0.62 (0.47)	1.69 (1)	1.85 (0.73,4.67)*
	Master/PhD	-0.54 (0.53)	1.04 (1)	0.58 (0.21,1.65)
Job Role (ISCO)	ISCO Other	Reference		
	ISCO 2	0.69 (0.56)	1.56 (1)	2.0 (0.67,5.96)*
	ISCO 3	0.18 (0.72)	0.06 (1)	1.2 (0.29,4.91)
Working experience	less than 1 year	Reference		
	1 - 10 years	-0.46 (0.67)	0.48 (1)	0.63 (0.17,2.34)
	more than 10 years	-0.79 (0.77)	1.05 (1)	0.46 (0.10,2.05)
Experience in healthcare	< 5 years	Reference		
	6-10 years	0.163 (0.50)	0.11 (1)	1.18 (0.44,3.12)
	11-15 years	0.09 (0.54)	0.03 (1)	1.09 (0.38, 3.14)
	16-20 years	-0.16 (0.80)	0.04 (1)	0.85 (0.175, 4.10)
	>20 years	-0.50 (0.41)	0.36 (1)	0.61 (0.12, 3.13)
Experience using computer	Low and Moderate	Reference		
	High	0.12 (0.37)	0.10 (1)	1.12 (0.54,2.30)
Experience using UniMEDS	3 months - 1 year	Reference		
	1 year - 3 years	0.31 (0.39)	0.65 (1)	1.37 (0.64,2.90)
	more than 3 years	0.63 (0.60)	1.09 (1)	1.89 (0.57, 6.17)
Frequency using unimeds	Rarely	Reference		
	Monthly	-0.65 (1.28)	0.26 (1)	0.52 (0.04,6.36)
	Weekly	0.65 (0.79)	0.68 (1)	0.52 (0.11,2.46)
	Daily	0.82 (0.54)	1.98 (1)	0.44 (0.14,1.38)*
attended training	No	Reference		
	Yes	0.17 (0.21)	32.46 (1)	1.12 (0.38,3.25)
Organization	domain	0.46 (0.39)	1.36 (1)	1.58 (0.73,3.34)*
	sufficient hardware	0.68 (0.21)	9.94 (1)	1.94 (1.29,2.95)*
	reliable connection	0.65 (0.22)	8.9 (1)	1.91 (1.25,2.94)*
	technical support	0.53 (0.23)	5.24 (1)	1.70 (1.08,2.68)*
	data storage privacy	0.94 (0.25)	13.9 (1)	2.57 (1.56,4.21)*
Technology	domain	1.01 (0.38)	7.1 (1)	2.75 (1.31,5.76)*
	User-friendly	0.95 (0.23)	18.1 (1)	2.60 (1.67,4.03)*
	Sufficient Information	0.71 (0.23)	9.51 (1)	2.03 (1.30,3.19)*
	Clean Interface	0.89 (0.23)	14.58 (1)	2.43 (1.54,3.82)*
	Accessibility	0.36 (0.15)	5.78 (1)	1.43 (1.07,1.92)*
	Version update	0.82 (0.23)	13.13 (1)	2.27 (1.46,3.55)*
	Improvement request (change request)	0.79 (0.23)	11.33 (1)	2.19 (1.38,3.47)*

[a] Statistical test: Simple Logistic Regression. Statistically significant at α =0.25

Table IV: Multiple Logistic Regression of Factors Associated with UniMEDS Usability

Variable	B	SE	Wald (df)	p-value	aOR	95% CI
Education Level			6.089 (2)	0.048		
Diploma (ref)	–	–	–	–	–	–
Degree	0.871	0.513	2.890 (1)	0.089	2.39	0.88 – 6.53
Master/PhD	-0.238	0.589	0.163 (1)	0.686	0.79	0.25 – 2.50
Data Storage & Privacy	0.715	0.294	5.930 (1)	0.015	2.04	1.15 – 3.64
User Friendly	0.645	0.258	6.222 (1)	0.013	1.91	1.15 – 3.16
Constant	-4.648	1.276	13.270 (1)	<0.001	0.01	–

AOR: adjusted Odds Ratio, CI: Confidence Interval. The Cox & Snell R2 value is 0.175, indicating the proportion of variance explained by the model. The Hosmer and Lemeshow test yield a value of 0.216, suggesting good model fit. Area Under the Curve (AUC) is 73.9% (95% CI: 64.6-83.2). Test employed: Multiple Logistic Regression Analysis (Backward LR Method) Constant value: -4.648 and the model assumption is met. There is no interaction and multicollinearity.

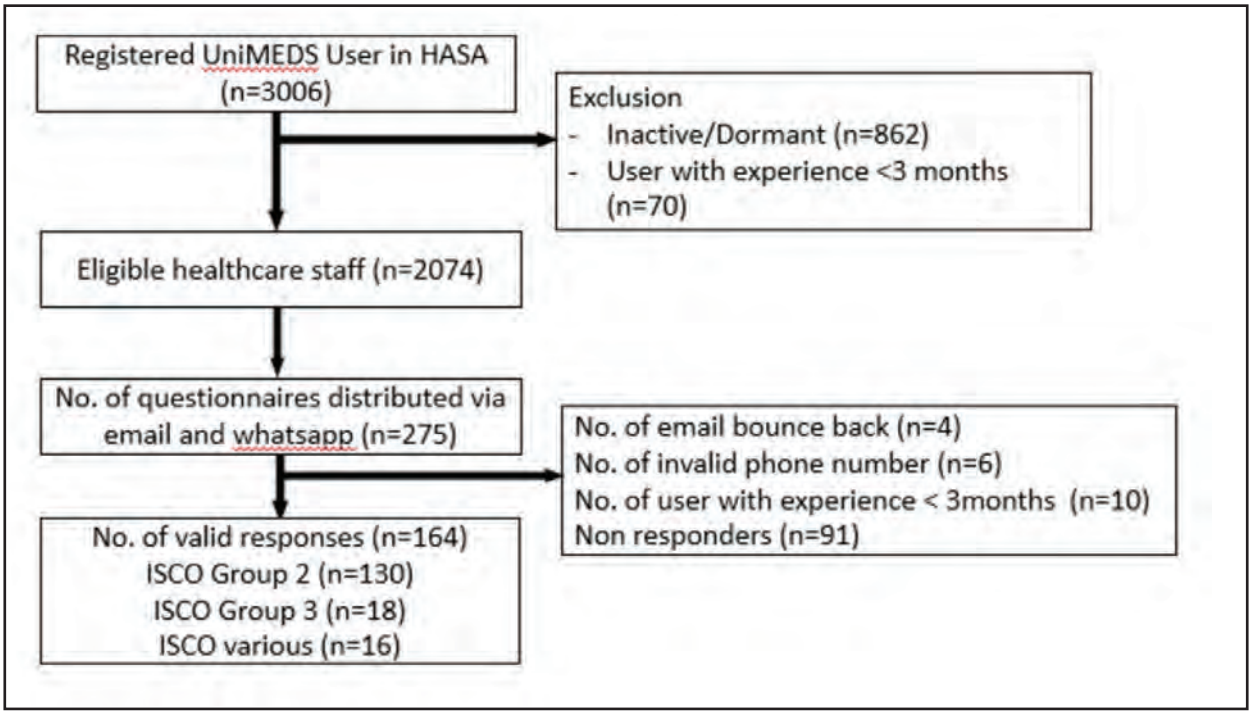

Fig. 1: Flowchart for questionnaire distribution and participant responses

Kolmogorov-Smirnov test. As the assumption of normality was not fulfilled, non-parametric tests were employed. The Mann-Whitney U test was used to compare the median domain scores between participants who reported poor and good usability of UniMEDS. Univariate analysis was conducted using simple logistic regression, followed by multiple logistic regression for multivariable analysis to identify independent predictors of the outcome.

Ethical Consideration

The National Medical Research Register (NMRR), Ministry of Health Malaysia approved this study with ID: NMRR ID-25-00474-7NH. This study has also been approved by the Faculty Ethics Review Committee, Faculty of Medicine, MARA University of Technology (UiTM) with reference number: 100 - FPR (PT.9/19) (FERC-1-25-04). Finally, an approval letter to conduct research was issued by PJI Hospital Al Sultan Abdullah (HASA) with reference number 500-HUiTM (PJI. 18/4/35).

RESULTS

The usability of UniMEDS is identified using SUS questionnaire with a score of 68 and more is considered good usability. The distribution of SUS scores is shown in Figure 2. The scores were normally distributed, with a mean of 68.02 (SD = 15.91).

From the total of 164 respondents, 122 (74.4%) reported good usability and the remaining 42 respondents (25.6%) reported poor usability. The mean (SD) for SUS score was 68.02 (15.91). As shown in Table I, the majority of the respondents are female (68.3%), aged between 30–39 years (64.6%), and holding a degree (61.6%). Most respondents belonged to ISCO Group 2 (79.3%) which comprises mostly by doctors, nurses, and pharmacists. Most of the respondents had less than 10 years of working experience (84.8%). About 47.6% had been using UniMEDS for less 1 year, and 71.3% reported daily usage. Most participants (82.9%) had undergone formal training on UniMEDS.

When respondents were categorised by usability outcome (poor vs. good usability), several differences emerged. As shown in Table II, respondents in the good usability group reported significantly higher median scores across all assessed factors, including sufficient hardware (median 88.70 vs. 64.49, $p=0.002$), user-friendliness (91.65 vs. 55.92, $p<0.001$), and system reliability (88.13 vs. 63.86, $p<0.001$). Similar trends were observed for clean interface, accessibility, and sufficiency of information, with all comparisons reaching statistical significance (Mann–Whitney U test, $p<0.05$).

On the other hand, usability results did not significantly correlate with sociodemographic traits as gender, age, or educational attainment. Similarly, there was no significant difference in training or years of UniMEDS experience between the poor and high usability groups ($p>0.05$) in the univariate logistic regression (Table III) It indicates that system design elements rather than user background traits were the main drivers of perceived usability. The multivariable logistic regression model included independent variables with p-values under 0.25. Given that some factors may become significant after controlling for confounders, this criteria was put in place to avoid the early exclusion of potentially important variables. According to Hosmer and Lemeshow,[16] using a broad cutoff during this stage can improve the robustness of multivariable model building.

In the multivariable logistic regression model (Table IV), data storage and privacy (AOR=2.04, 95% CI: 1.15–3.64) and user-friendly interface (AOR=1.91, 95% CI: 1.15–3.16) remained significantly associated with good usability of UniMEDS, after controlling for education level. Although education level showed an overall effect (p = 0.048), none of its categories reached statistical significance.

DISCUSSION

This study aimed to assess the perceived usability of UniMEDS from the perspective of healthcare providers and to identify factors associated with its usability. System Usability Scale (SUS) developed by John Brooke (1996) remains one of the most widely used and validated tools for assessing perceived usability across various technologies and user populations.[17,18] The Scale was then translated into the Malaysian language with the title Skala Kebolehgunaan Aplikasi Mudah Alih (SKAMA). The average SUS score of 68.02 for UniMEDS indicates that the system satisfies the established criteria for good usability, defined as a score of 68 or higher.[19] This conclusion is supported by a meta-analysis of digital health applications, which determined that a mean System Usability Scale (SUS) score of 68 is suitable for assessing the usability of digital health apps. The research indicated that certain applications, particularly those associated with physical activity, exhibited markedly elevated mean scores (83.28); however, when excluding these outliers, the average SUS score for the broader category of digital health applications was 68.05. This context is significant as it verifies that the UniMEDS score aligns with the established norm for numerous digital health technologies, and attaining a score of 68 is a legitimate indicator of good usability. Nonetheless, as indicated by the reviewer, this score is marginal. While most users find UniMEDS functional, a notable proportion experience difficulties or dissatisfaction during use. This borderline usability suggests a risk of mixed satisfaction levels among users, which can hinder consistent system adoption and long-term engagement. However, significant opportunities for enhancement exist to improve user satisfaction and efficiency, especially in contrast to systems that attain "excellent" ratings, exemplified by the 83.6 score documented in a separate research.[20]

The findings of this study provide clear, actionable insights for the redesign and iterative improvement of the UniMEDS. The statistically significant association of data storage & privacy (AOR=2.04, 95% CI: 1.15-3.64) and user-friendly interface (AOR=1.91, 95% CI: 1.15-3.16) with good usability suggests that these should be the primary focus of any system enhancement efforts. Users who perceive higher levels of data storage security and privacy are more than twice as likely to report good usability of UniMEDS. Healthcare workers are more inclined to trust and use systems that protect the confidentiality, integrity, and availability of patient information. Inadequate security not only creates legal and ethical concerns, but also reduces user confidence, which may compromise system utilization and care quality. Previous study[21] has also shown that data security has a direct impact on user satisfaction and the overall success of HIS acceptance. As a result, strengthening data security features such as secure login procedures, data encryption, and audit trail can boost system usability and user trust.[22]

Similarly, a user-friendly design is very consistent with recognized principles of Human-Computer Interaction (HCI) and usability engineering.[23] Non-intuitive interfaces, user-unfriendly designs, and inefficient performance factors will negatively impact the overall user experience.[24] Furthermore, a straightforward interface reduces cognitive burden and learning effort, allowing healthcare workers to execute activities more rapidly and focus on patient care rather than system complexities.

Even though many people (82.9%) had undergone formal training on UniMEDS, our results reveal that neither training nor experience with the system were statistically significant determinants of good usability. This indicates that the mere presence of training may be insufficient to affect perceived usability. Several possible explanations can be considered. First, training quality and relevance play an important role; if training sessions focus mainly on technical navigation rather than real-world clinical workflows, their impact on perceived usability may be limited. Second, usability problems rooted in interface design or system architecture cannot be fully mitigated through user training. Even experienced users may remain frustrated if the interface requires excessive steps or lacks intuitive navigation.[1]

Similarly, a user's extensive experience with a system that has fundamental flaws will not necessarily lead to a positive perception of its usability. The findings suggest that "user-friendliness" and "data storage & privacy" are more significant determinants of user impression than demographic factors such as training and experience. This aligns with other research emphasising the superior significance of user attitude and knowledge compared to demographic parameters for optimal system use.[11]

In conclusion, this research provides critical insights into the usability of UniMEDS from the viewpoint of healthcare providers. Although the overall usability was deemed marginally acceptable, there were substantial correlations between system design and reliability, rather than user characteristics or training. These results underscore the necessity of iterative, user-centred redesign to enhance system acceptability and ensure alignment with clinical workflows. This study emphasises the potential for UniMEDS to progress towards global usability standards while simultaneously addressing the distinctive challenges of healthcare delivery in Malaysia by situating the results within both local and international contexts.

The interpretation and generalisability of the research findings are influenced by several constraints. The cross-sectional design utilising self-reported data through an online Google Form just presents a snapshot of the current situation. This strategy facilitated participation for many individuals; nevertheless, it also introduces the potential for self-report and recall bias, particularly if respondents provided socially desirable answers or if non-respondents differed systematically from those who participated. Secondly, while System Usability Scale (SUS) ratings serve as

a widely utilised quantitative measure of perceived usability, they include inherent limitations. They provide a superficial, subjective summary instead of a thorough analysis of specific usability issues, failing to explain the reasons behind users' sentiments or propose viable solutions. Further qualitative research is necessary to obtain a comprehensive understanding of the factors influencing high or low SUS scores. Thirdly, the number of respondents directly influences the precision and statistical power of the results, thereby limiting the sample's representativeness and, thus, the generalisability of the findings. Finally, the study was conducted in a single teaching hospital, which limits the generalizability of the findings to other healthcare institutions in Malaysia. Hospitals vary considerably in their HIS design, implementation strategy, and user population. Therefore, caution should be exercised when extrapolating these results to other settings, especially non-teaching or private hospitals.

CONCLUSION

In conclusion, this study's evaluation of the UniMEDS system provides critical insights that extend beyond Hospital Al-Sultan Abdullah to the broader landscape of national Hospital Information System (HIS) deployment in Malaysia. Data storage and privacy, as well as an easy-to-use interface, play statistically important parts that draw attention to key areas that need strategic focus. In Malaysia, which has had trouble adopting and using these kinds of systems in the past, these things should be at the heart of any future HIS projects that are planned and carried out.

Beyond the local context of UniMEDS, the findings of this study hold broader implications for Malaysia's national digital health strategy. The country's ongoing transformation towards a fully digital healthcare ecosystem depends on the development of Hospital Information Systems (HIS) that are reliable, secure, and adaptable to diverse clinical settings. To achieve this, policymakers and system developers should prioritise strengthening data governance and security frameworks, integrating user-centred design principles during system development, and establishing national usability evaluation standards to guide HIS deployment and benchmarking across healthcare institutions.

Investing in these strategic areas would not only improve the usability and acceptance of HIS among healthcare providers but also promote long-term sustainability of digital health initiatives nationwide. Such efforts will ensure that HIS platforms are aligned with clinical workflows, enhance patient safety, and support data-driven decision-making within Malaysia's healthcare system. Future multi-centre and comparative studies are recommended to validate these findings and further inform the development of Malaysia's evolving digital health policy.

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ORIGINAL ARTICLE

Relationship between degree of central adiposity, inflammatory status and risk of sarcopenia in obese children

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ABSTRACT

Introduction: Childhood obesity is a most prevalent condition worldwide. The accumulation of adipose leads to its infiltration into various organs, including skeletal muscle, which called sarcopenia. Children with sarcopenic-obesity are at an increased risk of developing cardiovascular or metabolic diseases. This study aims to investigate the association between central adipose accumulation and the degree of chronic inflammation on muscle performance in obese children, a topic that has not been studied in Indonesia.

Materials and Methods: This study employed a cross-sectional design with consecutive sampling involving obese primary school children aged 7–13 years from Semarang and its surrounding areas who met the inclusion and exclusion criteria. Data collection included anthropometric measurements (waist and hip circumferences, waist-to-hip ratio, muscle mass assessed by bioelectrical impedance analysis/BIA), handgrip strength, three-day dietary recall, and blood biomarkers (CRP and IL-6). Muscle mass was classified as low when skeletal muscle mass adjusted for age and sex (SMMa z-score) was less than −2 SD. Reduced muscle strength was defined as handgrip strength below the 15th percentile (age/sex-specific). Central adiposity was defined as waist-to-height ratio (WHtR) ≥ 0.50 or waist-to-hip ratio (WHR) above the 90th percentile for age and sex. Elevated inflammatory markers were defined as CRP ≥ 3 mg/L and IL-6 > 5 pg/mL. Associations between variables were analyzed using chi-square or Fisher's exact tests, and logistic regression models were applied with a significance level set at α=0.05.

Results: Of the 86 children, 84.8% had low muscle mass, 38.4% had reduced muscle strength, and 69.8% demonstrated impaired physical performance. High waist-to-height ratio (WHtR) was significantly associated with low muscle mass (p = 0.016) and reduced muscle strength (p = 0.007). High C-reactive protein (CRP) levels were also associated with low muscle mass (p = 0.013). In addition, protein intake was significantly related to muscle mass (p = 0.016). In logistic regression analysis, WHtR was an independent predictor of both reduced strength (OR = 5.324, p = 0.021, 95% CI: 1.280–22.148) and low muscle mass (OR = 0.163, p = 0.011, 95% CI: 0.037–0.714). Although interleukin-6 (IL-6) was elevated in the majority of children, it did not show a significant association with sarcopenia outcomes.

Conclusion: Central adiposity, particularly as measured by WHtR, is a key predictor of sarcopenia in obese children, with significant associations observed with reduced muscle mass and strength. Elevated CRP levels further underscore the role of systemic inflammation in sarcopenia. These findings highlight the need for early identification and targeted interventions to mitigate the adverse effects of sarcopenic obesity in children.

KEYWORDS:
Central adiposity, children, obese, sarcopenia, WHtR

INTRODUCTION

Obesity is a clinical condition that arises from an imbalance between high energy intake and low energy expenditure, leading to high fat accumulation in body tissues. Obesity is a significant public health concern due to its increasing prevalence worldwide, particularly among children and adolescents.[1] In 2018, the prevalence of overweight and obesity in Indonesian children aged 5–12 years and adolescents aged 13–15 years was reported at 20% and 16%, respectively.[2] One of the critical aspects of obesity is the fat distribution pattern in the body, which can be generalized or central. Central obesity is characterized by fat accumulation in the abdominal region and is commonly assessed through anthropometric measurements such as waist circumference (WC), waist-to-hip ratio (WHR), or waist-to-height ratio (WHtR). Unlike generalized obesity, central obesity is strongly associated with a range of metabolic disorders, primarily due to the unique properties of visceral fat.[3,4] Adipose tissue, particularly visceral fat, is now recognized as a dynamic endocrine and metabolic organ that secretes various bioactive molecules, including adipokines and inflammatory mediators. These metabolic signals originating from adipose cells contribute to chronic low-grade inflammation, a hallmark of obesity, which plays a pivotal role in the pathogenesis of metabolic and cardiovascular complications. Central obesity has far-reaching health implications, significantly increasing the risk of chronic diseases such as type 2 diabetes mellitus, hypertension, dyslipidemia, and cardiovascular diseases. The inflammatory state induced by visceral fat not only affects metabolic homeostasis but also exacerbates insulin resistance, impairs vascular function, and promotes atherogenesis. Additionally, the interplay between adiposity and inflammation extends beyond metabolic complications, influencing musculoskeletal health.[4]

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Sarcopenia, a condition characterized by the progressive loss of skeletal muscle mass, strength, and function, is an emerging concern in the context of obesity. Sarcopenic obesity is a phenotype wherein individuals exhibit both high fat mass and low muscle mass, reflecting a complex interaction between excessive adiposity and muscle degeneration.[5] Although the precise mechanisms underlying sarcopenic obesity remain under investigation, it is hypothesized that chronic inflammation driven by visceral fat plays a central role. Inflammatory mediators such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), secreted by adipose tissue, contribute to insulin resistance and disrupt anabolic signaling pathways in skeletal muscle. These disruptions lead to impaired protein synthesis, increased protein degradation, and ultimately muscle atrophy and weakness.[6]

The implications of sarcopenic obesity are profound, particularly in children, as the combination of high fat mass and reduced muscle strength may compromise physical performance, increase the risk of falls, and contribute to a cycle of decreased physical activity and further adiposity.[7] Despite the growing recognition of sarcopenic obesity as a significant clinical concern, most research to date has focused on adult populations, leaving a critical knowledge gap regarding its prevalence, pathophysiology, and implications in pediatric populations.

In children, the interplay between central adiposity, inflammation, and sarcopenia is particularly complex and underexplored. Obese children with central adiposity may be at heightened risk of developing systemic inflammation, which could have detrimental effects on skeletal muscle growth and development during critical periods. Moreover, the long-term consequences of sarcopenic obesity in childhood, including the potential progression to chronic diseases and functional impairments in adulthood, remain poorly understood.[8] Given the limited research in this area, particularly in pediatric populations, it is crucial to elucidate the relationship between central adiposity, inflammatory markers, and the risk of sarcopenia in obese children.

This study aims to fill this knowledge gap by investigating the degree of central adiposity, markers of inflammatory status, and their association with the risk of sarcopenia in obese children. Understanding these relationships will not only advance the scientific understanding of sarcopenic obesity in pediatric populations but also inform the development of targeted interventions to mitigate its adverse health consequences.

MATERIALS AND METHODS

This cross-sectional study was conducted in public elementary schools within Semarang City and surrounding districts, with venous blood sample analyses performed at the GAKI Laboratory, Faculty of Medicine, Universitas Diponegoro, under internal quality-control procedures. Recruitment and data collection were coordinated with school administrations and carried out during school hours by a trained pediatric research team.

Consecutive sampling was applied to identify eligible participants. The study enrolled children aged 7–13 years, with both sexes eligible; girls were restricted to pre-menarcheal status to minimize maturational confounding. Obesity was defined as a BMI-for-age z-score greater than +2 SD based on WHO BMI-for-age reference standards for 5–19 years. Children classified as overweight only (z-score > +1 to ≤ +2 SD) were not included. Exclusion criteria were syndromic or genetic obesity diagnosed clinically, use of systemic corticosteroids, cytostatics, or other drugs affecting body weight within the past three months, participation in structured weight management programs, known chronic liver disease, or conditions that interfered with anthropometric or functional assessments. On the day of phlebotomy, children were screened for acute illness, including fever or signs of intercurrent infection; blood sampling was postponed when present. In total, 86 children met all eligibility criteria and completed the full protocol.

The study protocol was approved by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Diponegoro, and Dr. Kariadi General Hospital (No. 303/EC/KEPK/FK-UNDIP/VIII/2021). Parents/guardians received written study information sheets, and both parental informed consent and child assent were obtained before participation.

All measurements followed standardized procedures conducted by trained staff. Weight and body composition were measured with a Tanita BC 545N body composition analyzer. Height was measured to the nearest 0.1 cm using a stadiometer, with participants barefoot, heels together, and the head positioned in the Frankfort plane. Waist circumference was measured at the midpoint between the lowest rib and the iliac crest at end-expiration with a non-stretch tape. Hip circumference was measured at the maximal buttock protuberance with the tape horizontal and non-compressive.

Central adiposity was evaluated using two indices. Waist-to-height ratio (WHtR = waist [cm] / height [cm]) was classified as high when ≥0.50, an established cut-off that is age- and sex-independent in pediatric populations. Waist-to-hip ratio (WHR = waist [cm] / hip [cm]) was categorized as high when at or above the 90th percentile for age and sex. Since there is currently no universally accepted WHR cut-off for children, as noted in our reference studies, we applied a percentile-based approach consistent with the methodology used for waist circumference.[9]

Muscle mass was measured using a TANITA body composition scale at the same time as body weight assessment. The measurement was based on the bioelectrical impedance analysis (BIA) method. Muscle mass values were then categorized into low muscle mass and normal muscle mass according to sex- and age-specific Skeletal Muscle Mass (SMMa) reference curves. Low muscle mass was defined < –2 SD, while normal muscle mass was defined ≥–2 SD.[10]

Maximal isometric handgrip strength was assessed with a handheld dynamometer. Participants held the device in the dominant hand, elbow flexed at 90°, and squeezed maximally for 3–5 seconds. Three trials were performed with

Table I: Demographic, Clinical Characteristics, and Sarcopenia Prevalence in Obese Children

Variable	Category	Frequency (n)	Percentage (%)
Demography			
Age	7 years	18	20.9
	8 years	6	7.0
	9 years	9	10.5
	10 years	26	30.2
	11 years	14	16.3
	12 years	12	14.0
	13 years	1	1.2
Gender	Male	52	60.5
	Female	34	39.5
Central Adiposity			
WHR	Normal	55	64.0
	High	31	36.0
WHtR	Normal	12	14.0
	High	74	86.0
Inflammatory Marker			
IL-6	Normal	2	2.3
	High	84	97.7
CRP	Low	1	1.2
	Normal	69	80.2
	High	16	18.6
Sarcopenia Criteria			
Muscle Mass	Low Muscle Mass	73	84.8
	Normal Muscle Mass	12	15.2
Muscle Strength	Reduced Strength	33	38.4
	Normal Strength	53	61.6
Physical Performance	Low Performance	60	69.8
	Normal Performance	26	30.2
Confounding Variable			
Protein Intake	Insufficient	25	29.1
	Adequate	61	70.9
Carbohydrate Intake	Insufficient	68	79.1
	Adequate	18	20.9
Fat Intake	Insufficient	38	44.2
	Adequate	48	55.8
Physical Activity	Inactive	47	54.7
	Active	39	45.3

at least 30 seconds of rest; the highest value was used for analysis. Reduced muscle strength was defined as <15th percentile for age and sex based on normative pediatric curve of Relative Hand Grip Strength (RHGS).[11]

Physical performance was assessed at school with age-appropriate standardized field tests, which is 10-meter walking speed, results were categorized according to pediatric reference thresholds, with performance below cut-off (normal values as follows males: 1.07–1.45; females: 1.06–1.46 s was considered normal) defined as low.[12]

Dietary intake was assessed with a structured 3-day food recall conducted by trained interviewers with parental assistance. Household measures were converted into grams, and nutrient intakes were calculated using the Indonesian food composition database. Intakes ≥90% of national recommended ranges were considered adequate.[13]

Physical activity was measured using child/parent-assisted recall of the prior week, capturing time spent in moderate-to-vigorous physical activity (MVPA). Children were categorized as active if they achieved ≥60 minutes/day of MVPA on most days, in line with WHO guidelines.[14]

Fasting venous blood samples were collected in the morning when feasible. Prior to phlebotomy, children were screened for fever or intercurrent infection to avoid confounding of inflammatory markers. CRP was quantified with a validated immunoassay and reported in mg/L; low CRP was defined as <0.2 mg/L, normal CRP was defined as 0.2 – 3 mg/L; high CRP was defined as ≥3 mg/L according to pediatric standards. Interleukin-6 (IL-6) was measured with a quantitative immunoassay and reported in pg/mL. Because IL-6 levels are influenced by multiple biological and environmental factors, elevated IL-6 was defined as >5 pg/mL, based on the GAKI Laboratory reference cut-off and consistent with prior pediatric studies applying similar thresholds.[15]

Field teams were trained and standardized before data collection. Equipment was calibrated daily. Duplicate anthropometric measures were recorded; outliers were rechecked immediately. Data entry was double-checked and cross-validated. Statistical analyses were performed using SPSS (IBM Corp., Armonk, NY). Descriptive statistics summarized participant characteristics. Associations between categorical exposures (central adiposity indices, inflammatory markers, dietary adequacy, physical activity) and sarcopenia outcomes (low muscle mass, reduced

Table II: Relationships Between Variables and Outcomes

Variable	Category	Low Muscle Mass (n,%)	Normal Muscle Mass (n,%)	p	Low Muscle Strength (n,%)	Normal Muscle Strength (n,%)	p	Low Physical Performance (n,%)	Normal Physical Performance (n,%)	p
Central Adiposity										
WHR	Normal	44 (60.3)	11 (84.6)	0.122¥	23 (69.7)	32 (60.4)	0.519¥	38 (63.3)	17 (65.4)	1.000¥
	High	29 (39.7)	2 (15.4)		10 (30.3)	21 (39.6)		22 (36.7)	9 (34.6)	
WHtR	Normal	7 (9.6)	5 (38.5)	0.016£*	9 (27.3)	3 (5.7)	0.007£*	7 (11.7)	5 (19.2)	0.271£
	High	66 (90.4)	8 (61.5)		24 (72.7)	50 (94.3)		53 (88.3)	21 (80.8)	
Inflammatory Marker										
IL-6	Normal	2 (2.7)	0 (0)	1.000£	0 (0)	2 (3.8)	0.377£	1 (1.7)	1 (3.8)	0.516£
	High	71 (97.3)	13 (100)		33 (100)	51 (96.2)		59 (98.3)	25 (96.2)	
CRP	Low	0 (0)	1 (7.7)	0.013¶*	0 (0)	1 (1.9)	0.414¶	0 (0)	1 (3.8)	0.074¶
	Normal	57 (78.1)	12 (92.3)		26 (78.8)	43 (81.1)		46 (76.7)	23 (88.5)	
	High	16 (21.9)	0 (0)		7 (21.2)	9 (17)		14 (23.3)	2 (7.7)	
Confounding Variable										
Protein Intake	Insufficient	25 (34.2)	0 (0)	0.016£*	8 (24.2)	17 (32.1)	0.594¥	19 (31.7)	6 (23.1)	0.584¥
	Adequate	48 (65.8)	13 (100)		25 (75.8)	36 (67.9)		41 (68.3)	20 (76.9)	
Carbohydrate	Insufficient	58 (79.5)	10 (76.9)	1.000£	22 (66.7)	46 (86.8)	0.050¥	46 (76.7)		
Intake	Adequate	15 (20.5)	3 (23.1)		11 (33.3)	7 (13.2)		14 (23.3)	4 (15.4)	
Fat Intake	Insufficient	31 (42.5)	7 (53.8)	0.549¥	13 (39.4)	25 (47.2)	0.629¥	24 (40)	14 (53.8)	0.342¥
	Adequate	42 (57.5)	6 (46.2)		20 (60.6)	28 (52.8)		36 (60)	12 (46.2)	
Physical Activity	Inactive	42 (57.5)	5 (38.5)	0.238¥	21 (63.6)	26 (49.1)	0.272¥	36 (60)	11 (42.3)	0.201¥
	Active	31 (42.5)	8 (61.5)		12 (36.4)	27 (50.9)		24 (40)	15 (57.7)	

Note: * Significant ($p < 0.05$); ¥ Continuity Correction; £ Fisher's exact; ¶ Fisher's exact (alternative χ^2)

Table III: Logistic Regression Analysis for Physical Performance, Muscle Strength, and Muscle Mass

Outcome	Variable	p	OR	95% CI	Significant
Physical Performance	CRP	0.059	0.228	0.049 – 1.058	No
	Physical Activity	0.190	1.895	0.729 – 4.929	No
Muscle Strength	WHtR	0.021*	5.324	1.280 – 22.148	Yes
	Carbohydrate Intake	0.081	0.366	0.119 – 1.131	No
Muscle Mass	WHtR	0.011*	0.163	0.037 – 0.714	Yes
	CRP	0.998	0.000	–	No
	Protein Intake	0.252	3.574	0.408 – 31.308	No

Note: * Significant ($p < 0.05$); ¥ Continuity Correction; £ Fisher's exact; ¶ Fisher's exact (alternative χ^2)

strength, low physical performance) were examined using chi-square tests; Fisher's exact test or continuity correction was used when expected cell counts were <5. Variables with p <0.10 in bivariate analysis were entered into logistic regression to estimate adjusted odds ratios (OR) with 95% confidence intervals (CI). Statistical significance was set at p <0.05 (two-sided).

RESULTS

The study examined 86 obese children aged 7–13 years to assess the prevalence of sarcopenia and associated factors. Cutoffs for WHR, WHtR, CRP, IL-6, muscle mass, muscle strength, physical performance, nutrient intake, and physical activity were applied as described in the Methods section. Demographically, the majority were aged 10 years (30.2%), with a higher proportion of males (60.5%). Central adiposity was prevalent, with 36.0% having a high WHR and 86.0% a high WHtR. Inflammatory markers revealed elevated IL-6 in 97.7% and high CRP in 18.6% of participants. Sarcopenia criteria showed that 84.8% had low muscle mass, 38.4% had reduced muscle strength, and 69.8% exhibited low physical performance, highlighting a significant burden. Confounding variables included insufficient protein intake in 29.1%, inadequate carbohydrate intake in 79.1%, and low physical activity in 54.7%, underscoring the need for targeted nutritional and physical interventions to mitigate sarcopenia risk in this population.

The analysis reveals critical associations between central adiposity, inflammatory markers, dietary intake, and sarcopenia-related outcomes in obese children. Central adiposity, specifically a high WHtR, was significantly linked to low muscle mass (p=0.016) and reduced muscle strength (p=0.007), underscoring its role in sarcopenia development. While WHR showed no significant relationship with these outcomes, the overall CRP level demonstrated a significant association with low muscle mass (p=0.013), indicating that systemic inflammation may contribute to sarcopenia in obese children. Protein intake adequacy was strongly associated with normal muscle mass (p=0.016), highlighting the importance of sufficient protein consumption. Other factors, such as fat, carbohydrate intake and physical activity, did not exhibit significant relationships but remain critical considerations in comprehensive interventions.

The logistic regression analysis highlights key factors influencing physical performance, muscle strength, and muscle mass in obese children. WHtR was significantly associated with muscle strength (p=0.021, OR=5.324) and muscle mass (p=0.011, OR=0.163), underscoring its critical role in sarcopenia development. Although CRP and physical activity were not statistically significant for physical performance, CRP showed a notable trend toward association (p=0.059, OR=0.228), indicating inflammation as a potential contributor. Carbohydrate or protein intake, WHR, and physical activity were not significant predictors of muscle strength or mass, respectively, but remain relevant variables for further exploration.

DISCUSSION

This study examined 86 obese children aged 7–13 years to assess the prevalence of sarcopenia and its associated factors. The demographic data (Table I) provide valuable insights into the characteristics of the study population and highlight significant health concerns that merit detailed discussion.

Demographic Characteristics

The majority of participants were aged 10 years (30.2%), with the age distribution reflecting a critical period of growth and development. A higher proportion of males (60.5%) compared to females (39.5%) participated in the study. This gender difference aligns with some research suggesting that boys may have a higher prevalence of obesity due to differences in physical activity levels and dietary habits.[8] However, other studies have found varying gender distributions depending on cultural and socioeconomic factors.[16]

Central adiposity was highly prevalent, with 36.0% of the children having a high WHR and a striking 86.0% having a high WHtR. High WHtR, defined as ≥0.50, is widely recognized as a superior measure of abdominal fat distribution and cardiovascular risk in children, being age- and sex-independent.[9,17] By contrast, WHR thresholds for children are less established; hence, this study used the percentile 90th of the sample distribution, a limitation that should be noted. The significant associations of WHtR with both low muscle mass and reduced strength reinforce its utility over WHR for identifying sarcopenia risk in pediatric obesity.

Elevated inflammatory markers were observed, with 97.7% of participants showing high IL-6 levels and 18.6% exhibiting high CRP levels. Obesity, particularly central obesity, is associated with a chronic low-grade inflammatory state due to increased secretion of pro-inflammatory cytokines from adipose tissue. Elevated IL-6 and CRP levels have been linked to insulin resistance and endothelial dysfunction.[18] In comparison, a study by Dayal et al. (19) reported elevated CRP levels in obese children, which correlated with other cardiovascular risk factors.[19] The high prevalence of elevated IL-6 in this study underscores the potential for early development of inflammatory-related complications in obese children.

Sarcopenia criteria revealed that 84.8% of the children had low muscle mass, 38.4% had reduced muscle strength, and 69.8% exhibited low physical performance. These findings indicate a significant burden of sarcopenia among obese children, which is concerning given that sarcopenia is typically associated with aging populations.[20] The concept of sarcopenic obesity in children is emerging, with evidence suggesting that excess adiposity can coexist with diminished muscle mass and function. Park, et al (21) demonstrated that sarcopenic obesity in children was linked to increased metabolic risk factors than normal demographic.[21]

The study found that 29.1% of participants had insufficient protein intake, and a significant 79.1% had inadequate carbohydrate intake. Adequate protein intake is essential for muscle protein synthesis and growth, particularly during

childhood and adolescence.[22] Insufficient protein consumption may contribute to the high prevalence of low muscle mass observed. Inadequate carbohydrate intake can lead to decreased energy availability, potentially affecting growth, physical activity, and muscle function.[23] The high rate of insufficient carbohydrate intake suggests dietary patterns that may not support optimal muscle development and overall health.

Low physical activity levels were reported in 54.7% of the participants. Physical inactivity is a well-known risk factor for obesity and is associated with decreased muscle mass and strength.[24] Regular physical activity is crucial for developing and maintaining muscle mass, enhancing metabolic health, and preventing obesity-related complications. Physical inactivity among children is associated with higher adiposity and lower fitness levels. The combination of low physical activity and poor dietary intake may synergistically contribute to the development of sarcopenic obesity.[25]

The co-occurrence of high central adiposity, elevated inflammatory markers, low muscle mass, and poor dietary and physical activity behaviors in this study underscores the complex interplay between these factors in obese children. Other studies have similarly reported associations between central obesity, inflammation, and sarcopenia. For example, Axelrod et al. (26) discussed the concept of sarcopenic obesity and its implications for health outcomes. They emphasized that excess adiposity, particularly visceral fat, can promote inflammation and insulin resistance, leading to muscle catabolism.[26] Furthermore, Pena et al. (27) found that higher levels of IL-6 were associated with reduced muscle mass and strength in obese adolescents.[27] This supports the notion that chronic inflammation may contribute to muscle degradation in obese youth. The dietary findings align with research indicating that obese children often have diets high in energy-dense, nutrient-poor foods but low in essential nutrients like protein and complex carbohydrates.[28] Such dietary patterns may not provide sufficient nutrients for muscle growth and may contribute to adiposity and inflammation.

Central Adiposity and Sarcopenia Risk

Our results indicate that a high WHtR is significantly associated with low muscle mass (p=0.016) and reduced muscle strength (p=0.007) in obese children. This aligns with previous research suggesting that central adiposity adversely affects muscle health. For instance, Khaleghi et al. (29) reported that increased visceral fat is inversely related to muscle mass and strength in adolescents, potentially due to adipose tissue's endocrine function influencing muscle metabolism. Moreover, the lack of significant association between waist-to-hip ratio and sarcopenia risk in our study may reflect the limitations of WHR as a measure of central adiposity in children.[29] WHtR has been proposed as a more sensitive indicator of central fat distribution and associated metabolic risks in pediatric populations.[30] Therefore, WHtR may be a more appropriate anthropometric measure for assessing sarcopenia risk related to central adiposity in obese children.

Inflammation Status and Muscle Health

Overall CRP levels were significantly associated with low muscle mass (p=0.013), with high CRP values found exclusively in participants with low muscle mass, suggesting that systemic inflammation contributes to sarcopenia risk in obese children. Chronic low-grade inflammation is a known consequence of excess adiposity, particularly visceral fat, which secretes pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α).[30] These cytokines can promote muscle protein degradation and inhibit muscle synthesis, leading to muscle atrophy. While IL-6 levels were elevated in 97.7% of participants, no significant association was found with muscle outcomes, likely because IL-6 secretion from adipocytes occurs early and pervasively, reducing variability across the cohort. CRP, in contrast, is synthesized hepatically in response to sustained cytokine signaling and reflects a downstream inflammatory burden that more directly disrupts anabolic signaling pathways while enhancing proteolysis, thereby accelerating muscle loss. This difference also reflects a broader contrast between adults and children: in adults, both IL-6 and CRP are frequently elevated due to obesity, comorbidities, and age-related "inflammaging," making it harder to isolate their roles, whereas in children baseline levels are lower, so widespread IL-6 elevation marks early inflammation, while CRP identifies the subset in whom inflammation has advanced to produce measurable musculoskeletal consequences.[31]

Nutritional Intake and Sarcopenia Risk

Adequate protein intake was strongly associated with normal muscle mass (p=0.016), emphasizing the crucial role of dietary protein in muscle development and maintenance during childhood. Protein provides essential amino acids necessary for muscle protein synthesis, which is vital for growth and muscle repair.[32] Consistent with our findings, Arnesen et al. (33) found that higher protein intake was associated with better muscle mass indices in overweight and obese children.[33] Although carbohydrate intake showed a borderline significant relationship with reduced muscle strength (p=0.050), it remains an important energy source for physical activity and muscle function. Insufficient carbohydrate intake may impair glycogen stores, reducing energy availability for muscle contraction and potentially affecting muscle performance.[34] Fat intake did not exhibit a significant relationship with muscle health indicators in our study. However, dietary fats, particularly omega-3 fatty acids, have been shown to have anti-inflammatory properties and may support muscle protein synthesis.[35] Further research is needed to elucidate the role of specific types of dietary fats in pediatric muscle health.

Physical Activity and Muscle Function

Physical activity was assessed by recall and classified in binary terms: active (≥60 minutes/day moderate-to-vigorous activity, WHO standard) or inactive. In this study, physical activity did not show a significant association with muscle mass or strength in our sample. However, there was a trend indicating that physically active children had better muscle strength and physical performance. Regular physical activity, especially resistance training, is known to stimulate muscle protein synthesis and improve muscle mass and strength in

children and adolescents.[36] The lack of statistical significance may be attributed to the binary approach for screening, while practical, it may mask important gradations of activity (e.g., 15 vs. 45 minutes both classified as inactive), which could attenuate associations. Another possible reason was the self-reported physical activity measures, which can be prone to bias, or the cross-sectional nature of the study, which limits causal inference.

Our findings are consistent with prior studies that have identified central adiposity and inflammation as key factors in sarcopenia development among obese youth. For example, Shuster et al demonstrated that visceral adiposity is associated with metabolic complications and reduced muscle mass in children.[37] Additionally, Rolland et al. (38) highlighted the role of inflammation in muscle catabolism and sarcopenia in obese adolescents. However, some studies have reported differing results regarding the impact of physical activity and dietary factors on muscle health.[38] This variability may stem from differences in study design, population characteristics, and assessment methods. Longitudinal studies with objective measures of physical activity and comprehensive dietary assessments may provide more definitive insights.

A strength of this study is the comprehensive evaluation of factors related to sarcopenia risk, including anthropometric measures, inflammatory markers, dietary intake, and physical activity. However, several limitations should be acknowledged. The cross-sectional design precludes the establishment of causality. The relatively small sample size may limit the generalizability of the findings and reduce the power to detect significant associations for some variables. Additionally, reliance on self-reported dietary intake and physical activity may introduce reporting biases. Another limitation is that the cutoff for waist-to-hip ratio (WHR) was derived linearly from waist circumference, since no established pediatric-specific cutoff was available from previous studies.

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ORIGINAL ARTICLE

Association of oxytocin massage with oxytocin hormone levels and breast milk production in mothers with postpartum blues

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ABSTRACT

Introduction: Postpartum blues is a mild adaptation disorder in postpartum mothers that affects psychological and physiological conditions, including breast milk production. This condition significantly impacts maternal health and infant development. This study aimed to examine the association between oxytocin massage, oxytocin hormone levels, and breast milk production in mothers with postpartum blues.

Materials and Methods: A quasi-experimental pre-test and post-test design with treatment and control groups was used. The study was conducted at Siti Fatimah Special District Hospital for Maternal and Child Makassar and Pertiwi Mother and Child Hospital Makassar, from February to November 2024. A total of 68 postpartum mothers with postpartum blues were divided into two groups (34 participants per group). Screening was performed using the EPDS scale, oxytocin levels were measured using the ELISA method, and Breast milk production was assessed using a composite scoring system based on three main indicators: (1) infant weight gain, evaluated using the mean value (X) and standard deviation (SD); (2) breastfeeding frequency, recorded through maternal reports and structured observation; and (3) breastfeeding duration, assessed based on the average time per feeding session. Each indicator was assigned a score ranging from 1 to 3, corresponding to low (score 1), moderate (score 2), and high (score 3) levels. The total score from these three components was used to classify overall breast milk production into three categories: high production (total score 7–8), moderate production (total score 5–6), and low production (total score 3–4). Statistical analysis was conducted using SPSS.

Results: The baseline characteristics were evenly distributed across between the groups. The reduction in EPDS scores was greater in the treatment group (13.44 ± 2.765 to 12.12 ± 3.832) than in the control group (13.97 ± 3.196 to 13.26 ± 2.864), with a significant between-group difference (p = 0.000). Moreover, oxytocin levels increased significantly in the treatment group (47.57 ± 10.42 pg/mL to 52.62 ± 11.33, p = 0.001), whereas no significant change was observed in the control group, except for the comparison of the difference in oxytocin levels between the two groups confirming that this difference is statistically significant (p = 0.007).

Conclusion: This study suggests that oxytocin massage may serve as a complementary approach therapy for reducing postpartum blues symptoms and enhancing breast milk production. Its integration into clinical practice can support maternal postpartum care by promoting emotional well-being and improving lactation outcomes.

KEYWORDS:
Oxytocin Massage, postpartum blues, oxytocin hormone, breast milk production, postpartum depression

INTRODUCTION

Postpartum blues, also known as baby blues, is a postpartum adjustment disorder characterized by feelings of anxiety, panic attacks, fatigue, and guilt in caring for the newborn.[1] This condition is influenced by various factors, including education and employment.[2] Its effects include decreased maternal interest in the baby, an inability to provide proper care, and increased infant fussiness as a response to seeking attention.

Globally, the prevalence of postpartum blues in the general population ranges from 3% to 8%, with 50% of cases occurring among women of reproductive age (20–50 years).[3] The causes of postpartum blues are multifactorial, with hormonal fluctuations being one of the primary contributors. Changes in estrogen, progesterone, prolactin, and cortisol levels can lead to postpartum depressive symptoms.[4]

Breast milk production is one of the aspects affected in mothers experiencing postpartum blues. The hormones prolactin and oxytocin, which regulate milk production and ejection, are highly sensitive to maternal psychological

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conditions. Mothers experiencing stress, sadness, or anxiety tend to exhibit disruptions in breast milk production, potentially compromising the achievement of exclusive breastfeeding targets.[4]

According to the Central Bureau of Statistics (2024), the percentage of infants under six months receiving exclusive breastfeeding in South Sulawesi was 77.20% in 2023, which remains below the national target of 80%. Thus, effective interventions are needed to address this issue, one of which is oxytocin massage.[5]

Oxytocin massage has been reported to increase levels of oxytocin and prolactin, two hormones with antidepressant and anxiolytic effects. These hormones also contribute to strengthening the emotional bond between mother and baby while reducing stress in mothers with postpartum blues6–8. Additionally, oxytocin massage, through targeted stimulation of specific body points, has been shown to enhance oxytocin levels in the bloodstream, playing a crucial role in milk ejection during breastfeeding.[9,10]

Although several studies have demonstrated the effectiveness of oxytocin massage in postpartum mothers, its specific application in cases of postpartum blues remains underexplored. Therefore, this study aims to examine the association between oxytocin massage in reducing postpartum blues symptoms and its impact on increasing breast milk production. The findings of this study are expected to provide a scientific basis for developing broader intervention programs, supporting maternal and infant health in Indonesia, and contributing to national efforts to increase exclusive breastfeeding coverage.

MATERIALS AND METHODS

The materials used in this study included a Human Oxytocin ELISA Kit (BT LAB, Cat. No. E1046Hu, Shanghai, China), was purchased from CV. Abiramalab (Indonesia); Vacutainer EDTA; alcohol swabs (OneMed, Indonesia); olive oil (Herborist, Indonesia); and distilled water (Ikapharmindo, Indonesia). Additionally, blood samples from mothers with postpartum blues were collected.

Study Site and Timeline

This Study was conducted at Siti Fatimah Special District Hospital for Maternal and Child Makassar and Pertiwi Mother and Child Hospital Makassar, Indonesia, for screening and recruitment. Oxytocin massage and blood sample collection were performed at participants' homes, while sample analysis was conducted at Hasanuddin University Medical-Research Center (HUM-RC), Makassar. The research period lasted from February to November 2024.

Population and Sampling

The study included postpartum mothers receiving care at the study hospitals. A non-probability purposive sampling technique was used, selecting mothers with EPDS scores ≥10 (postpartum blues) who provided informed consent. Inclusion criteria: (1) postpartum mothers (cesarean or vaginal delivery) on the third day of hospitalization, (2) singleton birth, (3) residing in Makassar City, (4) willing to participate, (5) infants with normal birth weight (≥2500 g), (6) term birth, (7) no congenital abnormalities, (8) exclusively breastfed. Exclusion criteria: (1) history of peripartum depression, (2) maternal consumption of lactation-enhancing supplements. The sample size of 68 participants (34 per group) was determined using the Isaac and Michael formula. The first participant was randomly assigned using Excel, followed by alternate allocation until the target sample was reached.

Study Design

This study employed a quasi-experimental pre- and post-test design with treatment and control groups. Initial screening for postpartum blues was conducted using the Edinburgh Postnatal Depression Scale (EPDS) to identify eligible participants. The first participant meeting the inclusion criteria was randomly assigned using Excel randomization, followed by alternating allocation until the sample size reached 68 participants (34 in the treatment group and 34 in the control group). The treatment group received oxytocin massage for five consecutive days (20 minutes per session) starting from the third postpartum day, while the control group received no intervention. Oxytocin levels were measured before and after the intervention in the treatment group and at baseline and the end of the study in the control group. At the end of the study, EPDS scores were reassessed to evaluate changes in postpartum blues symptoms, while breast milk production was assessed in both groups.

Instrumentation

Postpartum blues was assessed using the Edinburgh Postnatal Depression Scale (EPDS), a validated 10-item questionnaire. Oxytocin levels were measured using the Human Oxytocin ELISA Kit (BT LAB, Cat. No. E1046Hu, Shanghai, China), with absorbance read using a Microplate Reader (450 ± 10 nm) and analyzed with Microplate Reader Software. Blood samples were stored in a laboratory-grade freezer (-20°C to -80°C) before analysis. Breast milk production was assessed using three parameters: infant weight gain, measured with the DIGIT-ONE BABY digital scale (Elitech Technology, Surabaya, Indonesia); breastfeeding frequency, recorded using a standardized observation forms; and Breastfeeding duration was recorded using a digital timer on participants' smartphones and documented in a structured logbook immediately after each session. Breast milk production was categorized as high, moderate, or low.

Oxytocin massage procedure

The procedure began with an explanation of its purpose and benefits to ensure maternal readiness. The mother was seated with her head resting on folded arms for optimal spinal access. Olive oil was applied to the therapist's palms before massaging along both sides of the spine using firm knuckle pressure and circular thumb motions, followed by downward strokes from the neck to the scapula. This sequence was repeated three times. To enhance relaxation, the session concluded with alternating warm and cool washcloths. The massage was administered once daily for 20 minutes per session and repeated for five consecutive days.[11–13]

Blood Sample Collection and Preparation

Blood samples were collected from the median cubital vein using a sterile 3-5 mL syringe, were collected twice in both groups: before the intervention and after the final session,

Table I: Characteristics of respondents based on treatment and control groups (n = 34 per group)

Variable	Intervention			Control		
	Initial	Final	p-value	Initial	Final	p-value
EPDS score	13.44 ± 2.765	12.12 ± 3.832	0,001*	13.97 ± 3.196	13.26 ± 2.864	0,055*
EPDS Score Difference	-1.32 ± 13.941				-0.71 ± 2.140	0.000**
Oxytocin levels (pg/mL)	47.57 ± 10.42	52.62 ± 11.33	0,001*	46.97 ± 11.77	48.30 ± 10.08	0.228*
Oxytocin level difference (pg/mL)		5.05 ± 2.97			1.33 ± 5.35	0.007**

Note: *Fisher's Exact Test, **Chi-Square Test, at a significance level of $p < 0.05$. SC = Cesarean Section

Table II: Comparison of EPDS scores, oxytocin levels (pg/mL) between treatment and control groups, as well as the score differences between the two groups (n = 34 per group)

Characteristics	intervention n (%)	Control n (%)	Total (%)	p-value
Age (years)				
20 - 35	27 (79.4)	22 (64.7)	49 (72.06)	0.378*
< 20 dan > 35	7 (20.6)	12 (35.3)	19 (27.94)	
Education (years)				
≤ 9	13 (38. 24)	10 (29.41)	23 (33.82)	0.057*
≥ 9	21 (61.76)	24 (70.59)	45 (66.18)	
Occupation				
Employed	1 (2.9)	2 (5.9)	3 (4.41)	1.000*
Not employed	33 (97.1)	32 (94)	65 (95.59)	
Parity				
Primiparous	9 (26.5)	12 (35.3)	21 (30.88)	1.000*
Multiparous	25 (73.5)	22 (64.7)	47 (69.12)	
Delivery Type				
Normal	18 (52.9)	19 (55.9)	37 (54.41)	0.515**
SC	16 (47.1)	15 (44.1)	31 (45.59)	

Note: *Wilcoxon Signed-Rank Test, **Mann-Whitney U Test, at a significance level of $p < 0.05$.

Table III: Comparison of breast milk production in postpartum blues mothers who received oxytocin massage and those who did not receive oxytocin massage

Oxytocin Massage	Low n (%)	Moderate n (%)	High n (%)	Total n (%)	p-value
Intervention	2 (5.9%)	6 (17.6%)	26(76.5%)	34 (100%)	0.001*
Control	11 (32.4%)	18 (52.9%)	5(14.7%)	34 (100%)	
Total	13 (19.1%)	24(35.3%)	31(45.6%)	68 (100%)	

*Chi-Square Test, at a significance level of $p < 0.05$.

between 07:00 and 09:00 AM to minimize circadian variation. In the intervention group, the post-intervention blood draw was performed 15 minutes after the last massage session to capture the immediate hormonal response. The collected blood was immediately transferred into a vacutainer EDTA and stored in a cool bag at 4°C during transport to the laboratory. The blood samples were then centrifuged at 3000 rpm for 15 minutes to separate plasma from other blood components. The obtained plasma was pipetted into microtubes and stored at -20°C to -80°C until analysis

Oxytocin Level Measurement in Human Plasma

Oxytocin levels were measured using the Human Oxytocin ELISA Kit according to the manufacturer's protocol. The assay involved sample incubation, washing, substrate reaction, and absorbance measurement at 450 ± 10 nm using a microplate reader.[14,15]

Breast Milk Production Measurement

Breast milk production was assessed using a composite scoring system based on three main indicators: (1) infant weight gain, evaluated using the mean value ($\bar{X}$) and standard deviation (SD); (2) breastfeeding frequency, recorded through maternal reports and structured observation; and (3) breastfeeding duration, assessed based on the average time per feeding session. Each indicator was assigned a score ranging from 1 to 3, corresponding to low (score 1), moderate (score 2), and high (score 3) levels. The total score from these three components was used to classify overall breast milk production into three categories: high production (total score 7–8), moderate production (total score 5–6), and low production (total score 3–4).Infant weight gain was assessed at the beginning and end of the study using a calibrated digital scale. Breastfeeding frequency was documented in a structured logbook, recording the number of feeding sessions per day. Breastfeeding duration per session

was measured using a digital timer on the participants' smartphones, with instructions to start and stop the timer at the beginning and end of each breastfeeding session and record the duration in the logbook. Participants received training on data recording before the study began to enhance accuracy and minimize bias. Researchers monitored adherence to data recording during each visit, which coincided with the administration of oxytocin massage and blood sample collection.[14,15]

Data and Statistical Analysis

Oxytocin levels were analyzed using Microplate Reader Software (ELISA), with data were presented as mean ± SD. Wilcoxon signed-rank and Mann-Whitney U tests assessed intra- and inter-group EPDS and oxytocin levels, while the Chi-square test evaluated breast milk production. Statistical significance was set at $p < 0.05$.[14,15]

Ethical Approval

This study was approved by the Research Ethics Committee of Hasanuddin University, Makassar, Indonesia, with the ethical approval reference number: 52/UN4.6.4.5.31/PP36/2024. All participants provided written informed consent prior to participation.

RESULTS

This study evaluated association between oxytocin massage, oxytocin hormone levels, and breast milk production in mothers with postpartum blues. As shown in Table I, the baseline characteristics of the treatment and control groups were statistically comparable ($p>0.05$), confirming group homogeneity prior to the intervention. This ensures an unbiased evaluation by eliminating the influence of external factors, such as demographic differences, on the results. With comparable baselines, the study guarantees valid comparisons and focuses on the primary variables. Normality tests on EPDS scores and oxytocin showed non-normal distribution ($p\leq0.05$) for most of the data. Therefore, non-parametric tests, including the Wilcoxon Signed-Rank and Mann-Whitney U tests, were used for intra- and inter-group comparisons.

Following the intervention (Table II), the treatment group exhibited a significant reduction in EPDS scores and a corresponding increase in oxytocin levels ($p=0.01$), whereas no significant changes were observed in the control group, except for the comparison of the difference in oxytocin levels between the two groups using the Mann-Whitney test, which yielded a p-value of 0.007, confirming that this difference is statistically significant. In addition, breast milk production outcomes (Table III) showed a significant improvement in the treatment group, with a higher proportion of mothers achieving high production compared to the control group ($p=0.01$), where 76.5% of mothers achieved high milk production campared to 14.7% in the control group.

DISCUSSION

The greater reduction in EPDS scores in the treatment group compared to the control group indicates the positive impact of oxytocin massage in alleviating postpartum blues symptoms. The very small p-value ($p=0.001$) (Table II) confirms the statistical significance of this change, directly resulting from the oxytocin massage intervention. These results are consistent with previous studies showing that oxytocin massage reduces EPDS scores by increasing oxytocin levels, a neuropeptide hormone known for its antidepressant and anxiolytic effects, which in turn reduces depression symptoms and strengthens the mother-baby bond, particularly in postpartum blues.[7] Increased oxytocin levels through this intervention also elevate endorphins, reduce cortisol, decrease anxiety, and improve maternal emotional well-being [16,17], whereas low oxytocin levels are often associated with higher EPDS scores and increased risk of postpartum depression (Kim et al., 2014), suggesting that oxytocin massage can help reduce depression symptoms.[18]

The greater increase in oxytocin levels in the treatment group compared to the control group (5.05 pg/mL vs. 1.33 pg/mL) further supports the effectiveness of the intervention. Without oxytocin massage, hormone levels in the control group remained stable, indicating no significant natural increase during the observation period.[19] These findings align with studies suggesting that physical stimulation, such as massage, can trigger oxytocin release, enhance milk production, and provide relaxation effects for postpartum.[8,11]

A significant difference in milk production distribution between the treatment and control groups demonstrates the positive effect of oxytocin massage on milk production in postpartum blues.[20] Oxytocin stimulation through massage enhances hormone levels and affects the physiological mechanisms related to lactation, including stimulating the let-down reflex, which impacts the efficiency and volume of milk production.[13] These results align with previous studies that have shown that oxytocin massage not only increases oxytocin, a hormone crucial for milk ejection, but also supports overall breastfeeding success.[10,17,21,22] Moreover, oxytocin massage also improves breastfeeding frequency and duration, which ultimately contributes to the increase in infant weight gain.[23]

This study demonstrates that oxytocin massage is associated with increases oxytocin levels, reduces postpartum blues symptoms, and enhances milk production in postpartum. While this therapy has been widely applied to mothers without emotional disturbances, its focus on postpartum blues remains limited. This study introduces oxytocin massage as a complementary intervention to support breastfeeding success and improve the psychological condition of mothers.

Based on these findings, oxytocin massage can be recommended as a safe and effective nonpharmacological intervention to support breastfeeding, particularly for postpartum blues. Increased oxytocin levels promote milk production and maternal emotional well-being, which strengthens the mother-baby bond. As a practical intervention, oxytocin massage can be integrated into maternal and child health services.

The study has limitations, such as not measuring other hormones related to postpartum blues and other factors that

could influence the outcomes, such as maternal psychological conditions and social support. Larger sample studies are needed to confirm these findings and broaden the generalizability of the results.

CONCLUSION

This study confirms that oxytocin massage significantly increases oxytocin levels, alleviates postpartum blues symptoms, and enhances breast milk production in postpartum. Based on these findings, oxytocin massage is a promising non-pharmacological intervention to be integrated into postpartum care, particularly for mothers experiencing breastfeeding difficulties or early signs of postpartum depression. This technique is simple, non-invasive, and cost-effective, making it suitable for application by healthcare providers, midwives, or even family members in both home and community settings. The practical implications suggest that oxytocin massage could be incorporated into a holistic maternal care approach to enhance breast milk production and maternal emotional well-being. Future research with larger sample sizes, direct milk volume measurement over a longer period, and additional biochemical markers is needed to further validate its effectiveness and expand its clinical application.

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Thoracic vent versus conventional intercostal tube drainage in management of pneumothorax in a tertiary referral centre

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ABSTRACT

Introduction: Strategies in managing primary spontaneous pneumothoraces are shifting toward simple aspiration and ambulatory follow-up rather than the traditional chest tube and hospital admission. This study is to determine the differences in outcome between the treatment of pneumothorax using a Thoracic Vent (TV) versus conventional intercostal chest tube drainage (CITD) in terms of pain (Visual Analogue Score, 0-10 cm), complications, rate of expansion, and length of stay (LOS).

Materials and Methods: Randomized single-center prospective interventional study of inpatient pneumothorax patients. Subjects were randomized to treatment with True-Close Thoracic Vent with Heimlich valve or conventional chest tube. Both arms received standard medical care and analgesia. Pain score was assessed at baseline (2 hours post insertion), 24 hours after, and before removal.

Results: Twenty subjects were recruited and randomly assigned to treatment with TV (n=10) and CITD (n=10). The mean pain score at baseline (2 hours post insertion) for TV was 1.36. The mean time to chest expansion in those treated with TV is 1.9±0.56 days and 4.9±2.23 days for the CITD group. The mean time of removal in TV was about 3 days, while CITD was almost 8 days. Mean LOS in those treated with TV and CITD was 4.8±3.6 days and 13.1±4.7 days, respectively. We recorded 3 cases of recurrences within 14 days from both groups.

Conclusion: Pain scores were significantly lower in the TV group, and the lung expansion and LOS rate were substantially shorter than CITD. There were fewer complications in the TV group, and no difference in pneumothorax recurrence on follow-up between the two groups.

KEYWORDS:
Pneumothorax, Thoracic Vent, Tru-close

INTRODUCTION

Pneumothorax means air in the pleural cavity (i.e., interspersed between the lung and the chest wall). Back then, most pneumothorax was secondary to tuberculosis, although some were recognised as occurring in otherwise healthy patients ('pneumothorax simple').[1] This classification has persisted since then, with the first modern description of pneumothorax occurring in healthy people (primary spontaneous pneumothorax, PSP) as was defined by Kjærgaard in 1932.[1]

Secondary pneumothorax (SSP) is associated with underlying lung disease, distinguishing it from PSP. The sequelae of pneumothorax in patients with pre-existing lung disease are higher, making it more challenging. Both PSP and SSP are considered spontaneous pneumothorax. Another known cause of pneumothorax is non-spontaneous or iatrogenic pneumothorax. As the name implies, it is caused by trauma and procedure-related, i.e., most commonly from subclavian vein catheterisation and transthoracic biopsies.[2]

Treatment of pneumothorax aims to eliminate intrapleural air and re-expand the collapsed lung simultaneously, while the long-term goal is to prevent a recurrence. To achieve these, various non-operative initial treatments have been used in the clinical setting: from the non-invasive method of observation with/without supplemental oxygen to invasive procedures such as intercostal chest catheter (ICC), e.g, Seldinger chest drain, pleural catheter, pigtail catheter, or conventional intercostal tube drainage (CITD). They can be connected to a suction system, an underwater closed system, or a one-way valve suction system (Heimlich valve).[3]

Pneumothorax management is shrouded in controversy despite being a known disease. Evidently, attempts at standardizing its management have been made by guidelines published by the American College of Chest Physicians (ACCP) in 2001, the Belgian Society of Pulmonology in 2005, and the British Thoracic Society (BTS) in 2023.[4-6]

Treatment for PSP can be personalized according to patient preference, symptoms, and the size of the pneumothorax. There is an option for a conservative method (non-intervention) in selected patients and treatment with simple aspiration or small-bore ICC.[4-6]

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However, in secondary pneumothorax, ACCP recommends ICC for pneumothorax size >3 cm (apex to cupola) while the latest BTS guideline states that pneumothorax size no longer dictates the need for invasive management, but still informs procedural safety, with chest drain use now driven mainly by high-risk clinical features.[4-6] The Belgian Society of Pulmonology guidelines recommend a small-bore ICC connected to a Heimlich valve.[5]

According to a systematic review by Brims et al., using the Heimlich valve can improve patients' comfort and mobility and prevent hospital admission with a comparable outcome to current practice.[7] The rate of complications with the Heimlich valve was reported to be <1%.[7]

Alternatively, the Thoracic Vent (TV) is another tool allowing ambulatory pneumothorax treatment. A study in Korea, in which TV was inserted under fluoroscopic guidance for the treatment of pneumothorax, achieved a 100% success rate without complications (18/18 patients). They have concluded that TV is a safe and effective method for immediately treating pneumothorax. As this was a 3-year prospective study, they also reported a high recurrence-free overall success rate (72.2%, 13/18 patients).[8]

Thus, in summary, TV is a relatively new device for treating primary, secondary, and iatrogenic pneumothorax and has the potential to change the paradigm of inpatient management of pneumothorax and open the horizon of outpatient care for pneumothorax. This is a new concept, especially in the Malaysian scenario, as the mainstay of treatment is inpatient CITD, and the plausibility of outpatient care has yet to be explored. The rationale for this study was to compare the TV with the CITD, as large-bore drainage remains the standard practice for pneumothorax management in our centre. Small-bore ICCs would have introduced variability; hence, they were not selected for this pilot comparison. TV was chosen as it not only represents a small-bore device but also offers the advantage of facilitating early ambulation, with the potential for future use in outpatient management within our local healthcare setting. Hence, we aim to determine the differences in outcome between the treatment of pneumothorax using a TV versus CITD. Our primary objective was to determine differences in outcome between TV and CITD regarding pain, complication rate, rate of lung expansion, and length of stay (LOS). Our secondary objective was to assess the recurrence of pneumothorax 10-14 days after discharge.

MATERIALS AND METHODS

Study design

A randomized single-center prospective interventional study of pneumothorax patients in the National University of Malaysia was conducted between December 2020 and March 2024. The study was approved by the Research Ethics Committee, National University of Malaysia, FF-2021-016. The sample size was based on Julious' calculation method; for a pilot study, the recommendation is a sample size of 12 per group. Considering the 10% dropout rate, 14 per group was obtained.[9]

Patients diagnosed with pneumothorax were recruited prospectively from the emergency department (ED), general wards, and Interventional Radiology (IR) department. We included the following patients: those older than 18 years, those with spontaneous primary pneumothorax, or secondary pneumothorax with a size of more than 20%, based on Collin's method.[10]

Collin's method of calculation of pneumothorax size (%) = 4.2 + (4.7 x [A + B + C]) in cm, where A is the maximal apical interpleural distance, B is the midpoint of the upper half of the collapsed lung. C is the midpoint of the bottom half of the collapsed lung.[10]

Subjects were excluded if they had bilateral pneumothorax, tension pneumothorax, or hydropneumothorax. Subjects who are ventilated, pregnant, have a body mass index (BMI) of more than 35 kg/m2, thrombocytopenia (platelets < 50,000 x 10^9/L), and coagulopathy, INR >1.5, were also excluded from this study. Following enrolment, baseline demographic data, including age, gender, race, BMI, smoking history, and comorbidities, were recorded.

Procedure

Eligible subjects who consented to the study were then randomized using block randomization. They are randomized with a block of 4 with random permutations of 2 groups: group A, Thoracic Vent (TV), and group B, conventional intercostal tube drainage (CITD).

A TV size 13 Fr with a length of 10 cm was used in this study for subjects recruited in this group. Based on imaging, it was inserted either in the second intercostal space in the midclavicular line or in the most suitable location. The procedure was done by a trained doctor (a registrar or respiratory fellows with supervised training in pleural procedures) or an interventional radiologist, under standard local anesthesia with lignocaine 2%.

A red signal diaphragm indicates when the trocar has initially entered the pleural space during insertion and reflects pressure changes in the pleural space. The movement of the red signal diaphragm during breathing will indicate drainage of a pneumothorax (Figure 1A). This movement will eventually stop once the lung is fully expanded. A specialized plug (provided in the TV insertion kit) was used to occlude the TV to confirm the resolution of the pneumothorax. A repeat chest radiograph following 4 hours of occlusion that showed no recurrence of pneumothorax will confirm no air leaks. The TV can then be safely removed after confirmation that any air leaks have resolved by evidence of the absence of movement of the signal diaphragm, and the patient remains asymptomatic.[8-11] Figure 1B shows the image of the thoracic vent and how it looks on a chest radiograph (Figure 1C). Figure 1D shows a double-valve aspiration cannula connected to a self-sealing port, which attaches to a syringe to allow manual air aspiration from the pleural cavity.

For those who underwent CITD management, a chest tube, size 24 Fr, was inserted through the fifth intercostal space in the safety triangle under local anaesthesia (lignocaine 2%) and connected to closed underwater seal drainage. Daily

Table I: Baseline characteristics and outcome of pneumothorax patients

Demographics	Pneumothorax patient		p-value
	TV (n=10)	CITD (n=10)	
Age (in years)			
Mean	49.8±19	56.20±22	0.496a
Sex, n (%)			
Male	8(80)	9(90)	0.53b
Female	2(20)	1(10)	
Ethnicity, n (%)			
Malay	7(70)	8(80)	0.61b
Chinese	3(30)	2(20)	
Indian	0	0	
Others	0	0	
Smoking status, n (%)			
Non-smoker	3(30)	5(50)	0.361b
Active smoker	7(70)	5(50)	
BMI (kg/m^2)			
Mean	20.8±2.7	22.4±5.5	0.43a
Co-morbidities n			
Diabetes Mellitus	1	3	0.264b
Hypertension	1	4	0.120b
Ischemic Heart Disease	0	1	0.310b
Chronic Obstructive Pulmonary Disease	2	0	0.136b
Dyslipidemia	2	0	1.00b
Lung Cancer	2	2	1.00b
Retroviral Disease	1	1	
Types of pneumothoraces:			
Spontaneous primary	1	3	n/a
Spontaneous secondary	7	6	
Iatrogenic	2	1	
Lung involvement n,:			
Right	4	8	n/a
Left	6	2	
Size of Pneumothorax			
Mean	59.5% ±24.9	62.4% ±23.0	0.788b

The data are described using mean + SD or n (%)
a Paired t-test;
b Pearson Chi-square;
p-value < 0.05 is significant
n/a -not applicable

Table II: Comparison of Pain score within TV and CITD groups (n=20) difference

Variables Pain score	TV (n= 10)			CITD (n=10)		
	Baseline Mean (SD)	Prior to removal Mean (SD)	p-value	Baseline Mean (SD)	Prior to removal Mean (SD)	p-value
Sleeping	1.3±0.51	1.2 ±0.42	0.591[a]	3.0±0.67	2.9±0.99	0.509[a]
Shower	1.3 ±0.51	1.1±0.32	0.343[a]	3.0±0.67	3.0±0.82	1.00[a]
Toilet	1.4 ±0.52	1.1±0.32	0.193[a]	3.1±0.74	2.9±0.74	0.343[a]
Deep Breathing	1.5±0.52	1.1±0.32	0.104[a]	3.0±0.67	3.1±0.88	0.726[a]
Ambulation	1.3±0.53	1.1±0.32	0.343[a]	3.2±0.62	2.9±0.74	0.279[a]

[a] Paired T-test; p-value < 0.05 is significant

Table III: Pain reduction during daily life activities and pain change from before removal compared to baseline (2 hours post insertion) between TV and CITD

Variables	TV	CITD	p-value
Sleeping	-0.1(+0.57)	-0.2(+0.92)	0.773a
Shower	-0.2(+0.63)	0(+0.94)	0.580a
Toilet	-0.3(+0.68)	-0.3(+0.95)	1.00a
Deep breathing	-0.4(+0.69)	0.1(+0.88)	0.175a
Ambulation	-0.2(+0.20)	-0.3(+0.26)	0.764a
Pain change from prior to removal compared to baseline, n(%)			
Reduction /no change in pain	9 (90%)	8 (80%)	0.531
Increase pain	1 (10%)	2 (20%)	

The data are described using mean + SD.
[a] Independent t-test; p value <0 .05 is significant

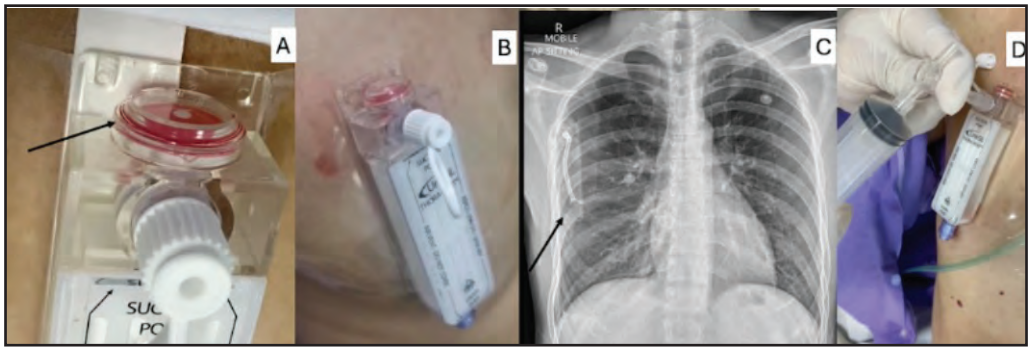

Fig. 1: The red signal diaphragm (A) on the thoravent. Image of the thoracic vent (B) on the chest wall and a chest radiograph (C). The double-valve aspiration cannula is connected to a self-sealing port, which attaches to a syringe to allow manual air aspiration from the pleural cavity. (D)

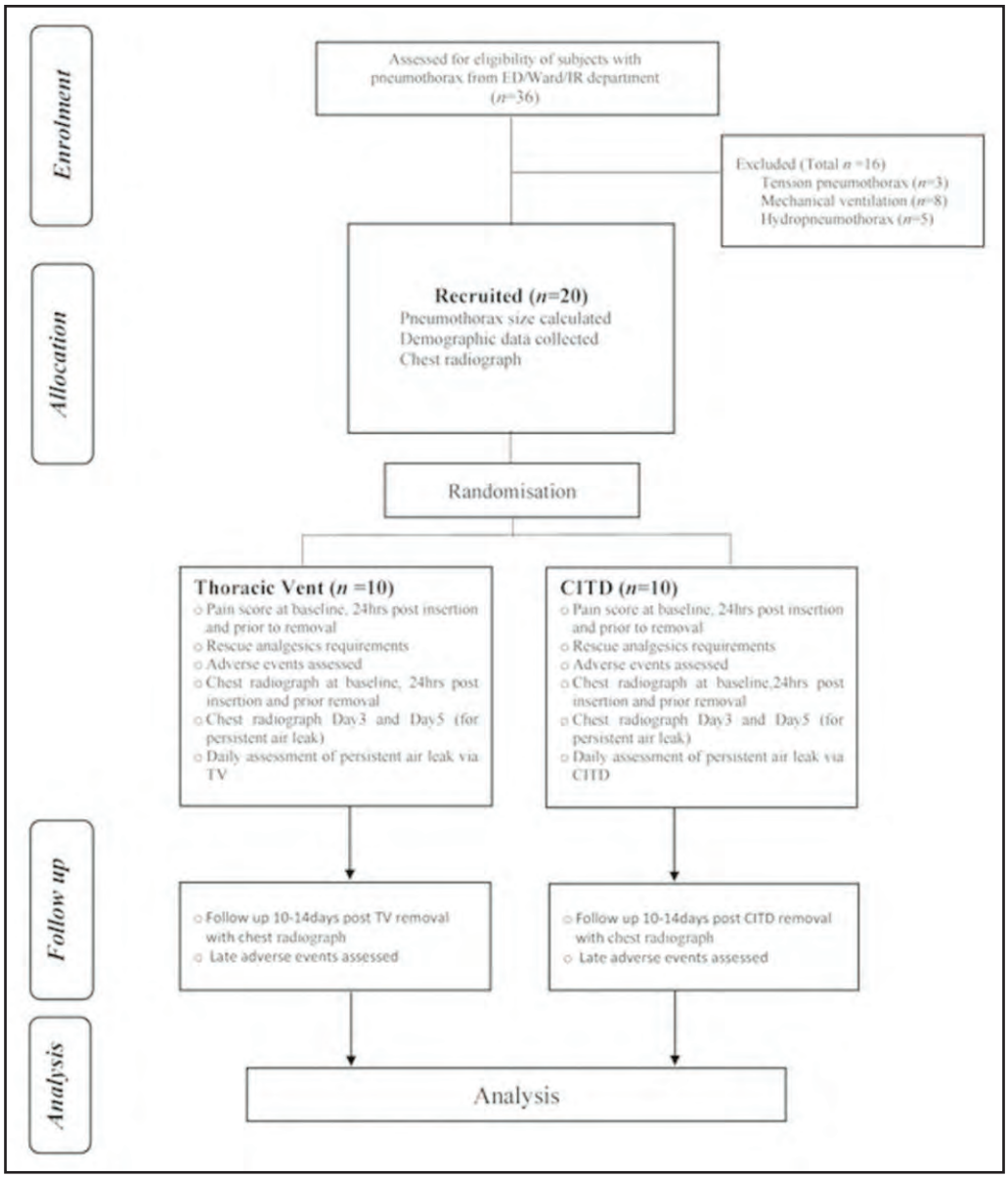

Fig. 1: Consort flow chart

assessment of the CITD was done to ensure the system is intact, such as inspection of fluid oscillation with respiration within the tube. We also ensured the tube was not accidentally clamped and flushed with saline when necessary.

Pain score was assessed at three intervals: at baseline (2 hours post insertion of TV/CITD), 24 hours post insertion, and 1-2 hours before removal.

Two hours following insertion of either TV / CITD, a baseline pain score was recorded to allow the local anesthetic to subside and before prescribing systemic analgesics. Pain scores were recorded upon interviews at the given intervals for different activity levels of daily life (i.e., sleep, showering, deep breathing, going to the toilet, ambulation), depending on the patient's ability, according to the Visual Analogue Scale (VAS) for pain (0-10cm). The pain score assessment during various activities was adapted from a study by Kim et al.[8]

Standard analgesics were given to both arms: oral tramadol 50 mg 8 hourly post-procedure, with intravenous morphine permitted as rescue analgesia in accordance with the TIME 1.[12] While paracetamol and NSAIDs can be considered as adjuncts, they were not adopted in this study as we aimed for a standardized analgesic protocol across both groups.

Subjects were then followed up daily till discharge/removal of TV/CITD to assess persistent air leak. Serial chest radiographs were also done, similar to the assessment of pain scores, i.e, at 2 hours post insertion, after 24 hours, and before removal, to assess for chest expansion. Repeated chest radiographs were done on days 3 and 5 for those with persistent air leaks. Patients in the TV group with persistent air leaks on day 3 and significant pneumothorax were converted to CITD. On Day 5, a referral to cardiothoracic surgery was made for those with persistent air leaks.

Follow-up was done 10-14 days post removal of TV/CITD to assess symptoms, and a chest radiograph was repeated to determine recurrence of pneumothorax.

Technical success was defined as successful placement of the TV/CITD within the pleural cavity without procedure-related complications. After TV/CITD insertion, clinical success was described as a complete resolution of baseline clinical symptoms and/or pneumothorax-related signs.

Statistical analysis

All data were analyzed using Statistical Package for Social Sciences (SPSS) version 27 according to 'intention to treat' analysis. The continuous variables were tested with the Student t-test for normal distribution and the Mann-Whitney U test for non-normal distribution to compare the TV and the CITD group. The categorical data were tested using the Pearson Chi-square and Fisher's exact tests. The data results between the two groups were analyzed using an independent-sample t-test or its equivalent non-parametric Mann-Whitney U test for parameter non-normal distribution. Paired t-tests were used to analyze data in each group. Statistical significance was declared when $p<0.05$.

RESULTS

A total of 36 patients were screened. Twenty patients fulfilled the inclusion criteria and were successfully recruited for this pilot study: the study design and CONSORT flow diagram are shown in Figure 2.

Patients' baseline characteristics and outcomes are summarized in Table I. The mean age, in years (+ SD), for the TV arm and CITD was 49.8 ± (19) and 56.2 ± (22), respectively. In both arms, males were predominant, with 80% in TV and 90% in CITD. There were 70% of active smokers in patients treated with TV, while those treated with CITD were only half. Most (70%) of the pneumothoraces treated with TV were secondary and involved the left lung. In comparison, those treated with CITD were mainly engaged in the right lung. The size of pneumothoraces was similar in both arms: TV (59.5% + 24.9) and CITD (62.5% + 23).

TV had an 80 percent clinical success while those in the CITD arm had a 70 percent clinical success rate. Three patients (30%) were referred for surgical intervention as inpatients. An Interventional Radiologist inserted sixty percent of the cases treated with TV. There was one conversion to chest tube from TV due to a ruptured bulla due to vigorous coughing after complete resolution of pneumothorax at day 3, which then resolved with CITD. One referral to cardiothoracic was done under the TV arm due to failure to achieve clinical success. Patient underwent video-assisted thoracoscopy, which converted to open thoracotomy for bullectomy and adhesiolysis. This patient was followed up according to the intention-to-treat analysis in the TV arm to which he was initially assigned.

Both TV and CITD had one patient who developed subcutaneous emphysema as a procedure-related complication. We recorded 2 cases of dislodged chest tubes and 1 case of procedure-related infection in the CITD arm.

The mean time to chest expansion in those treated with TV is 1.9±0.56 days, while the mean time to chest expansion in those treated with CITD was 4.9±2.23 days. The mean time of removal in TV was 3.2+2.93 days, while CITD was 7.8+3.91 days. Mean LOS in those treated with TV was 4.8±3.6 days, and in those treated with CITD was 13.1±4.7 days.

Ten to 14 days after removal of TV/CITD, there was one recurrence of pneumothorax in the TV arm and 2 in the CITD arm. The mean pain score at baseline (2 hours post insertion) in TV.

Mean pain scores at different activity levels and mean reduction of pain scores are shown in Tables II and III, respectively. Ninety percent of cases treated with TV had a decrease in mean pain score from before removal compared to baseline, while CITD noted a sum of 80 percent as per Table III.

DISCUSSION

There has been a paradigm shift in the strategies for managing primary spontaneous pneumothoraces from the traditional chest tube and hospital admissions to simple aspiration and ambulatory follow-up.[7] Some hospitals in Japan have been treating pneumothorax using a minimally

invasive strategy via the thoracic vent. It was deemed advantageous for patients as they are not required to be admitted.[11,13,14] A previous study showed a reduction in the percentage of hospitalized patients in those with simple aspirations compared to those with intercostal tube drainage.[15]

A TV is a 13 Fr thoracic tube containing a one-way valve with a small extracorporeal box (9×2.5×2 cm). It is beneficial for draining air but not fluids because the capacity of the extracorporeal box is only 30 mL. Therefore, a TV is not indicated for a pneumothorax with a significant pleural effusion. In a study by Martin et al., a TV is indicated for spontaneous and iatrogenic pneumothoraces without pleural effusion.[16]

As with many medical devices, there is always some degree of pain related to the insertion of the device. TV is not excluded from this known fact. However, few studies assess the pain associated with the insertion of TV; hence, not much data is available. A Korean pilot intended to evaluate TV's technical feasibility and procedural safety in the outpatient management of pneumothorax also included the mean pain score in daily activities while the patient is on TV.[8]

Fysh et al. have highlighted that small-bore catheters are generally associated with less pain than large-bore tubes, with comparable efficacy, although robust randomized data remain limited.[17] Our findings support this observation, as patients in the TV group (small bore) reported significantly lower pain scores than those managed with CITD.

In our study, the mean baseline pain score at rest after insertion of TV is 1.36(0.5), while in the CITD group, it was 3.06(0.6). This result corresponds to the mean pain score from the Korean pilot trial, with a mean of 2.4.[8]

In our study, even though patients in the TV arm have less pain score reduction during various activities, as in Table III, there is no statistical difference compared to patients in the CITD arm. This could be explained by the fact that patients in the TV arm already had a lower baseline pain score than those in the CITD arm, as shown in Table II.

However, pain is often regarded as a scaled variable when it is not. Using the mean pain score (VAS, cm) alone may not be accurate, as subjects have different baseline pain scores. In our trial, we have included the degree of mean pain reduction, from before removal of TV/CITD to baseline pain score, as stated in Table IV. Most (90%) of patients in the TV group and 80% of CITD patients had a reduction of pain scores of at least 2 points (Table IV).

The minimal clinically important difference (MCID) for pain on the VAS has been reported to range between 8–40 mm (0.8–4.0 cm) on a 100 mm scale in acute pain studies, depending on baseline severity and methodology.[18] Tashjian et al. specifically reported an MCID of approximately 1.4 cm in VAS for pain in surgical patients.[19] Based on these data, we considered a ≥ 1.0–1.5 cm reduction on the 10 cm VAS to represent a clinically meaningful difference in our study population.

Pain is not the only factor that should be considered. Patients' preference, especially in elderly patients, where the pain threshold might be higher, but the ability to be mobilized would have a better impact on avoiding complications like orthostatic pneumonia from prolonged immobilization. Hence, TV would have a better advantage over CITD in this aspect.

With regards to complication, in a systemic review by Brims et al. in 2013 on ambulatory treatment in the management of pneumothorax, they have managed to identify from the total reported cases (n= 1235) there were four hemothorax, one local cellulitis, two blocked tubes due to exudate, eight dislodged catheters, four subcutaneous emphysema and one tension pneumothorax due to incorrect connection.[7] In our study, 10 percent of the TV patients had subcutaneous emphysema. While in the CITD arm, there were noticeably more complications, such as two dislodged catheters, one tube-related infection, and one subcutaneous emphysema. This could be due to several factors: TV allows earlier tube removal. This, in turn, reduces the time the tube dwells in the pleural cavity and lessens the chance of causing infection. Our findings were similar to the Danish study that showed more drainage-related complications in patients treated with CITD than TV.[20]

The mean time for chest expansion for TV was 1.9(0.56) days and 4.9(2.23) days for the CITD. We postulate that the delay in lung expansion observed in the CITD group compared to the TV group may be due to the larger bore tube causing greater pleural irritation and patient discomfort, which limited early mobilization and contributed to slower expansion.

Meanwhile, the mean time for removal for TV was 3.2 days (2.93), and for CITD, it was 7.8(3.91). This corresponds to the results in the Danish retrospective trial, which showed a mean of 4.9 days in the small-bore/TV, and CITD had a mean of 8.3 days. We showed 80 percent clinical success in patients treated with TV, with an 80 percent technical success. CITD showed 70 percent clinical success and about 40 percent technical success. Martin et al. studied thoracic vent mainly in iatrogenic pneumothorax, which showed a similar drainage time of 3.3 days and a success rate of 85%.[16] Samelson and Anbalayanan et al. studied thoracic vent in primary spontaneous pneumothoraces and showed similar drainage time, which was 5.5 days and 3.2 days, with a success rate of 82.4% and 100%, respectively.[21-22]

Patients' stay in the TV group was 4.8 days (3.6), while the CITD was 13.1 (4.7) days. Comparing these results with the retrospective trial in Denmark, they recorded a mean length of stay of 6.9 days (TV and Portex/pigtail chest tube), while the large-bore chest tube was 11.8 days.[19] Outpatient management of pneumothorax using TV has been successful in the Korean pilot study and Japan.[8,11,13,14] Massongo et al. found that hospital-stay costs can be reduced by applying simple aspiration as the first step in an outpatient management algorithm. Furthermore, if the simple aspiration fails, a portable small-bore chest tube connected to a Heimlich valve is inserted, and the patient is sent back home.[23]

This could offer a safe first step in the outpatient management of pneumothorax. Furthermore, this would support the findings of TV to reduce medical expenses as it reduces hospital stay and has been proven efficacious as an outpatient management.[11] This, in turn, is associated with significant economic benefits.[11]

Our study differs from the Korean pilot trial in both setting and design.[8] The Korean study evaluated 18 patients with spontaneous and iatrogenic pneumothoraces managed with Thoracic Vent under fluoroscopic guidance in an outpatient setting, reporting high technical success and a recurrence-free rate of 72.2% over three years.[8] In contrast, our randomized pilot study involved 20 inpatients. It directly compared Thoracic Vent with conventional large-bore intercostal tube drainage, demonstrating lower pain scores, faster lung expansion, and shorter hospital stay in the TV group.

These differences underscore the relevance of our study in highlighting TV as a viable alternative to large-bore drainage within the local inpatient context, while also paving the way for future outpatient applications. Both studies support the broader role of TV across different clinical settings.

Our study possesses some limitations. This trial was a prospective pilot study done in Malaysia with a few participants, partly due to the COVID-19 pandemic, as our institution was a centre for managing COVID-19 patients. Future multi-centre randomized controlled trials with longer study durations are required to assess the effect of TV further compared to CITD. They may also compare non-intervention, minimal intervention/ambulatory management, and conventional ICD regarding hospital stay, pain score, recurrence rates, and cost-benefit analysis.

We concluded that pain associated with TV was significantly less compared to CITD and had fewer procedure-related complications. We also noted that expansion and hospital stay rates were shorter in TV than in CITD. Our findings support the idea that TV can be used to manage pneumothorax outpatients.

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ORIGINAL ARTICLE

Prevalence and factors associated with seizures in tuberculous meningitis

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ABSTRACT

Introduction: Tuberculous meningitis (TBM) is a severe manifestation of extrapulmonary tuberculosis that can lead to debilitating neurological complications. Seizures in TBM pose diagnostic and therapeutic challenges and are associated with adverse outcomes and prolonged hospitalisation. This study aims to determine the prevalence, risk factors, and outcomes associated with seizures in patients with TBM patients.

Materials and Methods: A retrospective observational study was conducted on 96 adult patients diagnosed with TBM at a tertiary hospital in Malaysia. Patients with the diagnosis of tuberculous meningitis were included and classified into the seizures and non-seizures groups. Clinical, laboratory, radiological, and treatment-related variables were analysed. Antiseizure medication use and neurological outcomes were also assessed.

Results: Seizures occurred in 30.2% (n=29) of patients; generalized seizures were the predominant type. Patients with seizures were more likely to present with altered behaviour (48.3% vs 31.3%) and focal neurological deficits (24.1% vs 14.9%). Patients with seizures were more likely to be on antiseizure medications, particularly phenytoin, valproate and levetiracetam (p<0.05). Lower Glasgow Coma Scale scores on admission were more common among seizure patients (17.2%) compared to non seizure group (7.5%). Patients with seizures had higher rates of mortality (27.6% vs. 13.4%) and poor functional outcomes compared to those without seizures.

Conclusion: Seizures are common in TBM and are associated with worse clinical outcomes. Early clinical signs such as altered behaviour and focal deficits may help identify high-risk TBM patients with seizures. Seizures in TBM are associated with worse neurological outcomes. The common antiseizure therapy initiated for treatment include phenytoin, valproate and levetiracetam. Further prospective studies are needed to refine risk stratification and optimize management.

KEYWORDS:
tuberculosis, tuberculous meningitis, seizures, associated factors

INTRODUCTION

Tuberculosis (TB) remains a leading cause of infectious death worldwide, with an estimated 10.8 million people affected by TB and an estimated 1.09 million deaths among HIV-negative people in 2023, according to the World Health Organization (WHO).[1] TBM accounts for approximately 1% of all TB cases[2] but contributes disproportionately to TB-related neurological complications and deaths.[3,4] The burden of TB in Asia countries is high, contributing more than 50% of global cases.[5] In Southeast Asia (SEA), TB continues to be a major public health threat, compounded by challenges in early diagnosis, limited access to healthcare, and overlapping burdens of HIV.[6]

Tuberculous meningitis (TBM) often results in significant neurological impairment and long-term consequences.[7] Seizures results from meningeal inflammation, cerebral infarction, tuberculomas, and hydrocephalus.[8] Prevalence rates of seizures in TBM range from 17% to 93%, with differences attributed to patient demographics and study methodologies.[9] Misra et al. identified seizures in 34% of TBM patients[8], while Song et al. observed an incidence of 20%.[10] The presence of seizures was associated with poorer neurological outcomes.[8,11] TBM patients with seizures were reported to have poorer functional outcomes at 12-months follow-up.[10]

The risk factors associated with seizures have been documented in patients with tuberculous meningitis (TBM). Dharmana et al. identified cerebral vasculitic infarcts as an independent predictor of seizures in TBM.[11] Cortical involvement and epileptiform discharges were significant independent risk factors for recurrent seizures.[10,12] The associated factors for the development of epilepsy in central nervous system TB include young age, early onset of seizures, refractory seizures, tuberculomas, cortical involvement, epileptiform discharges, and residual brain lesions.[13] Abdulaziz et al. observed early-onset seizures in TBM were associated with meningeal irritation and cerebral oedema, while late-onset seizures were linked to cerebral infarction, hydrocephalus, tuberculomas, and paradoxical inflammatory responses.[9]

Given the significant potential for seizures to arise from TBM-related comorbidities and to adversely affect treatment and recovery, a focused investigation into their frequency, risk

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Table I: Demographic of the study participants

Variables	All N=96 (%)	Seizure N=29 (%) N=67 (%)	No Seizure N=67 (%)
Age, years			
18-40	29 (30.2)	11 (37.9)	18 (26.9)
41-60	29 (30.2)	8 (27.6)	21 (31.3)
>60	38 (39.6)	10 (34.5)	28 (41.8)
Sex			
Male	52 (54.0)	12 (41.0)	40 (60.0)
Female	44 (46.0)	17 (59.0)	27 (40.0)
Race			
Malay	54 (56.3)	15 (51.7)	39 (58.2)
Chinese	27 (28.1)	10 (34.5)	17 (25.4)
Others	9 (9.4)	2 (6.9)	7 (10.4)
Indian	6 (6.3)	2 (6.9)	4 (6.0)
Smoking			
Yes	11 (11.5)	4 (13.8)	7 (10.4)
No	85 (88.5)	25 (86.2)	60 (89.6)
Diabetes mellitus			
Yes	22 (22.9)	7 (24.1)	15 (22.4)
No	74 (77.1)	22 (75.9)	52 (77.6)
Cancer			
Yes	7 (7.3)	2 (6.9)	5 (7.5)
No	89 (92.7)	27 (93.1)	62 (92.5)
Chronic kidney disease			
Yes	6 (6.3)	1 (3.4)	5 (7.5)
No	90 (93.8)	28 (96.6)	62 (92.5)
Hematological disorders			
Yes	3 (3.1)	0 (0.0)	3 (4.5)
No	93 (96.9)	29 (100)	64 (95.5)
Human immunodeficiency virus disease			
Yes	6 (6.3)	2 (6.9)	4 (6.0)
No	90 (93.8)	27 (93.1)	63 (94.0)
Autoimmune disorder			
Yes	4 (4.2)	1 (3.4)	3 (4.5)
No	92 (95.8)	28 (96.6)	64 (95.5)
Clinical			
Duration of seizure (days)			
0-5	38 (39.6)	16 (55.2)	22 (32.8)
6-9	32 (33.3)	8 (27.6)	24 (35.8)
>9	26 (27.1)	5 (17.2)	21 (31.3)
Seizure type			
Generalised	20 (20.8)	19 (65.5)	1 (1.5)
Focal	10 (10.4)	10 (34.5)	0 (0.0)
No seizure	66 (68.8)	0 (0.0)	66 (98.5)
Frequency of seizure (months)			
0	76 (79.2)	10 (34.5)	66 (98.5)
1	12 (12.5)	12 (41.4)	0 (0.0)
2	4 (4.2)	3 (10.3)	1 (1.5)
>2	4 (4.2)	4 (13.8)	0 (0.0)
Focal deficit			
Yes	17 (17.7)	7 (24.1)	10 (14.9)
No	79 (82.3)	22 (75.9)	57(85.1)
Cranial nerve palsy			
Yes	6 (6.3)	3 (10.3)	3 (4.5)
No	90 (93.8)	26 (89.7)	64 (95.5)
Fever			
Yes	54 (56.3)	14 (48.3)	40 (59.7)
No	42 (43.8)	15 (51.7)	27 (40.3)
Headache			
Yes	46 (47.9)	15 (51.7)	31 (46.3)
No	50 (52.1)	14 (48.3)	36 (53.7)
Vomiting			
Yes	28 (29.2)	7 (24.1)	21 (31.3)
No	68 (70.8)	22 (75.9)	46 (68.7)
Altered behaviour			
Yes	35 (36.5)	14 (48.3)	21 (31.3)
No	61 (63.5)	15 (51.7)	46 (68.7)
GCS			
13-15	46 (47.9)	12 (41.4)	34 (50.7)
9-12	40 (41.7)	12 (41.4)	28 (41.8)
3-8	10 (10.4)	5 (17.2)	5 (7.5)

Table II: Laboratory Parameters

Variables	All N=96 (%)	Seizure N=29 (%)	No Seizure N=67 (%)
Laboratory			
Hb (g/dL)			
Hb <13	59 (61.5)	19 (65.5)	40 (59.7)
Hb 13-17	36 (37.5)	9 (31.0)	27 (40.3)
Hb >17	1 (1.0)	1 (3.4)	0 (0.0)
Total white cell ($x10^9$)			
TWC 0-3	2 (2.1)	0 (0.0)	2 (3.0)
TWC 4-10	59 (61.5)	18 (62.1)	41 (61.2)
TWC >10	31 (32.3)	11 (37.9)	20 (29.9)
Platelet ($x10^9$)			
Platelet 0-149	8 (8.3)	3 (10.3)	5 (7.5)
Platelet 150-410	73 (76.0)	21 (72.4)	52 (77.6)
Platelet >410	15 (15.6)	5 (17.2)	10 (14.9)
Sodium (mmol/L)			
Sodium 0-135	48 (50.0)	12 (41.4)	36 (53.7)
Sodium 135-145	39 (40.6)	14 (48.3)	25 (37.3)
Sodium >145	9 (9.4)	3 (10.3)	6 (9.0)
Creatinine (µmol/l)			
Creatinine 0-63	42 (43.8)	15 (51.7)	27 (40.3)
Creatinine 64-104	37 (38.5)	7 (24.1)	30 (44.8)
Creatinine >104	17 (17.7)	7 (24.1)	10 (14.9)
Total Protein (g/l)			
Total protein 0-63	32 (33.3)	10 (34.5)	22 (32.8)
Total protein 64-83	54 (56.3)	15 (51.7)	39 (58.2)
Total protein >83	10 (10.4)	4 (13.8)	6 (9.0)
Alkaline phosphatase (ALP) U/L			
ALP 0-39	5 (5.2)	3 (10.3)	2 (3.0)
ALP 40-150	77 (80.2)	20 (69.0)	57 (85.1)
ALP >150	14 (14.6)	6 (20.7)	8 (11.9)
Alanine transaminase (ALT) U/L			
ALT 0-55	77 (80.2)	23 (79.3)	54 (80.6)
ALT >55	19 (19.8)	6 (20.7)	13 (19.4)
CSF culture			
Yes	3 (3.1)	1 (3.4)	2 (3.0)
No	92 (95.8)	28 (96.9)	64 (95.5)
NA	1 (1.0)	0 (0.0)	1 (1.5)
CSF cell count			
High	22 (22.9)	7 (24.1)	15 (22.4)
Low	73 (76.0)	22 (75.9)	51 (76.1)
NA	1 (1.0)	0 (0.0)	1 (1.5)
CSF TB PCR			
positive	17 (17.7)	8 (27.6)	9 (12.4)
negative	79 (82.3)	21 (72.4)	58 (86.6)
CSF geneXpert			
positive	5 (5.2)	3 (10.3)	2 (3.0)
negative	31 (32.3)	13 (44.8)	18 (26.9)
NA	60 (62.5)	13 (44.8)	47 (70.1)
AFB identified from other sources			
Yes	12 (12.5)	5 (17.2)	7 (10.4)
No	84 (87.5)	24 (82.8)	60 (89.6)
EEG findings			
Generalised	19 (20.7)	12 (42.9)	7 (10.9)
Focal	4 (4.3)	3 (10.7)	1 (1.6)
NA	69 (75)	13 (46.4)	56 (87.5)

CSF cerebrospinal fluid, AFB acid fast bacilli, EEG electroencephalogram, TB PCR tuberculous polymerase chain reaction, FEME full examination microscopic examination, NA not available

Table III: Types of medications

	All N=96 (%)	Seizure N=29 (%)	No Seizure N=67 (%)
AntiTB			
Ethambutol			
Yes	95 (99)	29 (100)	66 (98.5)
No	1 (1)	0 (0)	1 (1.5)
Rifampicin			
Yes	94 (97.9)	28 (96.6)	66 (98.5)
No	2 (2.1)	1 (3.4)	1 (1.5)
Isoniazid			
Yes	94 (97.9)	28 (96.6)	66 (98.5)
No	2 (2.1)	1 (3.4)	1 (1.5)
Pyrazinamide			
Yes	94 (97.9)	29 (100)	65 (97)
No	2 (2.1)	0 (0)	2 (3)
Moxifloxacin			
Yes	5 (5.2)	2 (6.9)	3 (4.5)
No	91 (94.8)	27 (93.1)	64 (95.5)
Streptomycin			
Yes	7 (7.3)	2 (6.9)	5 (7.5)
No	89 (92.7)	27 (93.1)	62 (92.5)
Carbamazepine			
Yes	1 (1)	0 (0)	1 (1.5)
No	95 (99)	29 (100)	66 (98.5)
Levetiracetam			
Yes	15 (15.6)	13 (44.8)	2 (3)
No	81 (84.4)	16 (55.2)	65 (97)
Phenytoin			
Yes	15(15.6)	14 (48.3)	1 (1.5)
No	81 (84.4)	15 (51.7)	66 (98.5)
Sodium valproate			
Yes	5 (5.2)	4 (13.8)	1 (1.5)
No	91 (94.8)	25 (86.2)	66 (98.5)
Side effects			
Rash			
Yes	7 (7.3)	1 (3.4)	6 (9)
No	89 (92.7)	28 (96.6)	61 (91)
Hepatitis			
Yes	25 (26)	7 (24.1)	18 (26.9)
No	71 (74)	22 (75.9)	49 (73.1)
Neuropathy			
Yes	1 (1)	0 (0)	1 (1.5)
No	95 (99)	29 (100)	66 (98.5)
Optic neuritis			
Yes	1 (1)	0 (0)	1 (1.5)
No	95 (99)	29 (100)	66 (98.5)
Sequelae			
Deceased	17 (17.7)	8 (27.6)	9 (13.4)
Vegetative state	3 (3.1)	2 (6.9)	1 (1.5)
Severe disability	3 (3.1)	1 (3.4)	2 (3)
Moderate disability	12 (12.5)	1 (3.4)	11 (16.4)
Recovery	61 (63.5)	17 (58.6)	44 (65.7)
Intervention			
Yes	25 (26)	9 (31)	16 (23.9)
No	71 (74)	20 (69)	51 (76.1)

Table IV: Association between sociodemographic, clinical factors, laboratory and anti-tuberculosis medication

Mann-Whitney U test						
Variables	**Seizure**	**Mean Rank**	**U**	**Z**	**p-value**	**Effect size**
Gender						
	Yes	54.64	793.5	-1.646	0.05	0.01
	No	45.84				
Smoking	Yes	47.38	939.0	-0.470	0.32	
	No	48.99				
Focal neurological	Yes	45.41	882.0	-1.080	0.14	
	No	49.84				
Cranial nerve palsy	Yes	46.53	914.5	-1.085	0.14	
	No	49.35				
Fever	Yes	52.33	860.5	-1.031	0.15	
	No	46.84				
Headache	Yes	46.67	918.5	-0.489	0.31	
	No	49.29				
Vomiting	Yes	50.91	901.5	-0.709	0.24	
	No	47.46				
Altered behaviour	Yes	42.83	807.0	-1.574	0.06	
	No	50.96				
Alanine transaminase	Yes	48.93	959.0	-0.145	0.44	
	No	48.31				
CSF culture	Yes	48.66	967.0	-0.119	0.45	
	No	48.43				
CSF cell count	Yes	49.09	954.5	-0.186	0.43	
	No	48.25				
AFB from other sources	Yes	50.78	905.5	-0.919	0.18	
	No	47.51				
AntiTB						
Ethambutol	Yes	48	957.0	-0.658	0.26	
	No	48.72				
Rifampicin	Yes	49.16	952.5	-0.613	0.27	
	No	48.22				
Isoniazid	Yes	49.16	952.5	-0.613	0.27	
	No	48.22				
Pyrazinamide	Yes	47.50	942.5	-0.935	0.17	
	No	48.93				
Moxifloxacin	Yes	47.69	948.0	-0.487	0.31	
	No	48.85				
Streptomycin	Yes	48.69	966.0	-0.097	0.46	
	No	48.42				
Clonazepam	Yes	48.28	971.5	0.000	0.50	
	No	48.50				
Carbamazepine	Yes	49	957.0	-0.658	0.26	
	No	48.28				
Lamotrigine	Yes	48.50	971.5	0.000	0.50	
	No	48.50				
Levetiracetam	Yes	34.48	565.0	-5.157	< 0.01	0.02
	No	54.57				
Phenytoin	Yes	32.83	517.0	-5.766	< 0.01	0.03
	No	55.28				
Topiramate	Yes	48.50	971.5	0.000	0.50	
	No	48.50				
Valproate	Yes	44.38	852.0	-2.478	< 0.01	0.02
	No	50.28				
Side effect						
Rashes	Yes	50.34	918.0	-0.948	0.17	
	No	47.70				
Hepatitis	Yes	49.41	945.0	-0.278	0.39	
	No	48.10				
Neuropathy	Yes	49	957.0	-0.658	0.26	
	No	48.28				
Optic neuritis	Yes	49	957.0	-0.658	0.26	
	No	48.28				
Surgery	Yes	46.10	902.0	-0.730	0.23	
	No	49.54				
Independent t -test						
		t-value	df	p value	CI	
Age		0.826	94	0.411	-5.034 – 12.204	
CSF glucose		-0.364	94	0.717	-0.995 – 0.687	
CSF cerebrospinal fluid						

p significant at <0.05. U: Mann-Whitney test; Z: Z value; t: t statistics; df: degree of freedom

Table V: Relationship between medications and seizures

	Seizure	Sex	Levetiracetam	Phenytoin
1. Seizure				
2. Sex	0.169*			
3. Levetiracetam	-0.529**	-0.295**		
4. Phenytoin	-0.592**	-0.065	0.289**	
5. Valproate	-0.254*	0.027	0.157	0.028

*Correlation is significant at the 0.05 level (2-tailed)
**Correlation is significant at the 0.01 level (2-tailed)

factors and clinical impact is essential. Notably, there is a conspicuous lack of comprehensive data on seizure-related complications among TBM patients within the Malaysian context. Seizures in TBM can complicate therapeutic management, prolong hospitalization, increase healthcare utilisation and ultimately worsen patient prognosis. This research aims to determine the prevalence of seizures in TBM to guide early interventions and improve neurological outcomes in patients.

MATERIALS AND METHODS

This retrospective study was conducted at Hospital Canselor Tuanku Muhriz (HCTM), Universiti Kebangsaan Malaysia from 1st January 2018 to 30th June 2025, and approved by the Ethics and Research Committee (JEP-2023-530). Patients aged 18 years and above were included, excluding those with neurodegenerative disorders and other central nervous system infections. An epileptic seizure is defined conceptually as a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity.[14] A diagnosis of TB meningitis was made following the consensus case definition of definite, probable and possible tuberculous meningitis.[15]

The demographic and clinical data were documented. Radiological findings were categorized based on computed tomogram (CT) or magnetic resonance imaging (MRI) reports into the presence or absence of hydrocephalus, infarcts, basal meningitis, or tuberculomas. The Glasgow outcome scale was used to assess the patients' recovery after brain injury. 16 It can be categorised into 1 -good recovery, 2- moderate disability, 3- severe disability , 4- persistent vegetative state, and 5- death.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics for Windows, Version 30. Categorical variables were presented as frequencies and percentages, while continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR) for nonnormally distributed data. The Mann-Whitney U test was applied to compare qualitative variables. Spearman's correlation was used to analyze the relationship between individual risk factors and the occurrence of seizures. Statistical significance was established at a p-value <0.05.

RESULTS

We screened 152 patients with a total of 96 TBM patients. 29 patients (30.2%) experienced seizures during illness. Most patients were aged over 60 years (39.6%), and 54.2% were male. Comorbidities were evenly distributed between groups, with no statistically significant associations observed ($p > 0.05$) (Table I).

Patients with seizures were more likely to present with altered behaviour (48.3% vs. 31.3%, p=0.06) and focal neurological deficits (24.1% vs. 14.9%, p=0.14), although not significant Generalized seizures were the predominant type in 65.5%.
Lower GCS scores on admission were more common among seizure patients, with 17.2% having a GCS of 3–8 compared to 7.5% in the non-seizure group. (Table I).
No significant differences were found between seizure and non-seizure patients in laboratory, CSF parameters and radiological abnormalities (Table II). Levetiracetam (44.8%) and phenytoin (48.3%) were the most prescribed antiseizure drugs. (Table III)

Mortality was higher in the seizure group compared to the non-seizure group. Additionally, the proportion of patients with severe disability or vegetative state was also higher in the seizure group (10.3% vs. 4.5%). Full recovery was achieved in 58.6% of seizure patients compared to non-seizure patients. Adverse drug reactions did not significantly differ between groups (Table III).

Statistical Associations

Univariate analysis identified several variables associated with seizures (Table IV). Gender showed a significant association with seizures (p=0.05). The patients with seizures in TBM are more likely to be on antiseizure medications such as levetiracetam (p<0.001), phenytoin (p<0.001), and valproate (p=0.007).

Missing Data

Missing values for CSF cell count were imputed using mode values as data were not normally distributed, provided it does not exceed 10%. Missing categorical data for CSF culture and EEG were imputed using the most frequent category to minimise bias and preserve data structure.

Correlation Between Seizure and Medications

Spearman's correlation analysis revealed moderate negative correlation between seizure history and the use of levetiracetam (r=–0.529, p<0.001), phenytoin (r=–0.592, p<0.001) as shown in Table V. Sex demonstrated a very weak positive correlation (r=0.169, p=0.05).

DISCUSSION

Tuberculosis is a challenging problem in a developing country such as Malaysia, where the estimated incidence rate was 234 per 100, 000 population.[17] This study investigated the prevalence, risk factors, and outcomes associated with seizures in patients with TBM in a local tertiary hospital. Seizures occurred in approximately 31.2% , which aligns with seizure rates globally, ranging from 17% to 93% depending on study setting and population.[9] Our findings are consistent with those of Misra et al., with an incidence of 34% among TBM.[8]

Seizure occurrence in TBM patients was associated with altered behaviour, focal neurological deficits, and lower GCS scores on admission. These findings support prior studies indicating that seizures are often markers of more severe central nervous system involvement.[10,11] Seizures following central nervous system infection are related to brain inflammation and subsequent neuronal injury and reactivation of glial cells.[18] Acute symptomatic seizures that occur in the first 2 weeks may be associated with meningeal irritation and cerebral edema. Late seizures are usually due to infarct, hydrocephalus, tuberculoma and paradoxical response.[19]

TBM demonstrate CSF lymphocytosis, raised protein and reduced glucose ratio. This current study found positivity for CSF PCR and CSF GeneXpert was 17.7% and 5.4% respectively. A previous study reported 9.8% with positive CSF tuberculous PCR 20. Studies reported that CSF PCR had a high specificity of 87%-98% and sensitivity between 56% -75%.[21, 22] Advanced diagnostics include urine lipoarabinomannan (LAM), which is a phosphorylated lipopolysaccharide in the Mycobacterial cell wall. Alere TB- LAM in people living with HIV have a sensitivity of 33% (95% CI 9.9- 65.1%) and a specificity of 96% (95% CI: 85.5-99.5%).[23] Using a cut point of > 5.5 mmol/L, CSF lactate was able to diagnose definite/probable TBM with a sensitivity of 67.7% and specificity of 80.3%.[24] The diagnosis of TBM is largely clinical and aided by various investigations. Despite advances in the technological methods in TBM diagnosis, clinical vigilance is of utmost importance in suspected patients presenting with altered behaviour or focal deficits.

A recent study on risk factors for seizures in TB meningitis reported that vasculitic infarcts were strongly associated with seizure recurrence.[11] Seizures were also significantly associated with advanced disease, cortical involvement and epileptiform pattern. In addition, focal to bilateral seizures, status epilepticus and rifampicin resistance were significantly associated with poor outcome at 6 months.[25] Additional factors contributing to increased risk of epilepsy following TB meningitis include a younger age, recurrent seizures and status epilepticus, tuberculoma, infarction, hippocampal sclerosis and persistent epileptic activity in EEG.[19]

Our correlation analysis demonstrated more frequent use of phenytoin and levetiracetam, particularly in patients with more severe or recurrent seizures. These parenteral antiseizure medications are available in the emergency department setting, where patients are initially treated in the acute setting.

Phenytoin and levetiracetam were the most prescribed medications, which may reflect clinician familiarity, availability, and local treatment protocols. Valproate, though less commonly used, was also an important therapeutic medication. These patterns are aligned with the findings of Song et al. and Ramos et al., who noted a higher likelihood of antiseizure treatment in patients with cortical involvement, refractory seizures, or epileptiform EEG discharges.[10,13]

Seizures were associated with worse neurological outcomes, including higher rates of death, disability, and vegetative state. Our centre reported mortality rates of 18% in TBM patients in a previous study. Dharmana et al., did not find seizures to be an independent predictor of mortality.[11] Our results suggest that seizures are at least a surrogate marker of more severe disease and are linked to poorer functional recovery. This finding supports the need for early identification and aggressive management of seizures in TBM to improve long-term outcomes.

These findings highlight several important clinical implications. First, early recognition of seizure risk based on clinical signs, is critical for timely intervention. Second, the absence of significant associations with routine cerebrospinal fluid or radiological markers suggests that these investigations alone are insufficient for predicting seizure risk, reinforcing the importance of clinical judgment in patient assessment. Finally, the observed pattern of antiseizure medication use in seizure management must be individualised rather than prophylactic. While this supports rational prescribing practices, further research should be carried out to determine if high-risk patients could benefit from earlier initiation of seizure prophylaxis.

This study has several limitations. First, the retrospective design may limit data completeness and introduce selection bias. Second, EEG availability was limited, which may have led to underdiagnosis of subclinical seizures. Third, the sample size may not have been sufficient to detect weaker associations. Finally, the exclusion of GCS from multivariate analysis, while methodologically justified limits the ability to formally model consciousness level as a predictive factor.

Future studies should incorporate prospective designs, larger sample sizes, and standardized EEG monitoring to better elucidate seizure subtypes, temporal patterns, and long-term outcomes. There is also a need to evaluate the role of seizure prophylaxis in high-risk TBM patients and the comparative effectiveness of different antiseizure medications in this population.

CONCLUSION

Seizures are a clinically significant complication of tuberculous meningitis, affecting nearly one-third of patients in this cohort. Clinical features such as altered mental behaviour and focal neurological deficits were more prominent among seizure patients . Seizures were associated with poorer neurological outcomes, including higher rates of death and disability. These findings underscore the importance of early clinical recognition and individualized

management strategies to mitigate seizure-related morbidity in TBM. Future prospective studies are warranted to explore the role of prophylactic anticonvulsants in high-risk patients and to further refine risk stratification tools.

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ORIGINAL ARTICLE

Evaluation of analytical performance of Sebia Capillarys 3 Octa electrophoresis method for serum protein electrophoresis

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ABSTRACT

Introduction: Protein electrophoresis is a crucial test in clinical diagnostic laboratory, aimed for evaluation of plasma protein distribution. With its capability for high-resolution protein separation, rapid analysis and automated features, capillary electrophoresis (CE) has emerged as a valuable alternative to the traditional gel-based methods that are widely used in our country. This study aimed to evaluate the analytical performance of Sebia Capillary 3 Octa CE system in our laboratory setting.

Materials and Methods: The study was conducted at the Protein Diagnostic Laboratory, Hospital Pakar Universiti Sains Malaysia. Within-run and between run precision was assessed using Sebia Capillarys 3 Octa CE system with commercially available normal and pathological control sera. Accuracy was evaluated by comparing results from the Sebia Capillarys 3 Octa with those from the Sebia Hydrasys 2 Scan gel electrophoresis analyzer using both healthy and patient serum samples. Reference interval verification involved testing serum from healthy volunteers. Statistical analyses included mean, standard deviation, coefficient of variation (CV), linear regression, and Bland-Altman analysis.

Results: Sebia Capillarys 3 Octa demonstrated good precision across all serum protein fractions, with within-run CVs for normal serum ranging from 0.97% (albumin) to 7.04% (alpha-1), and between-run CVs below 7.22%. Pathological serum showed CVs from 0.60% (gamma) to 5.09% (alpha-1), and from 0.89% (albumin) to 10.32% (alpha-2) for within-run and between run CV, respectively. CE correlated strongly with gel electrophoresis for albumin and gamma globulin (r > 0.95), with alpha 1, alpha2 and beta showed good correlation (r >0.80) between the two methods. There was minimal bias (–1.1 to +2.1) noted. Reference interval verification confirmed compatibility with manufacturer-provided ranges.

Conclusion: Sebia Capillarys 3 Octa provides reliable, automated analysis for serum protein fractions, offering performance comparable to the conventional agarose gel electrophoresis analyzer with enhanced operational benefits for routine laboratory use.

KEYWORDS:
Capillary electrophoresis, Sebia Capillarys 3 Octa, protein electrophoresis, analytical evaluation, method verification

INTRODUCTION

Capillary electrophoresis (CE) is an analytical technique that separates charged molecules in solution based on their electrophoretic mobility under an electric field.[1] Its efficiency, sensitivity and high resolution have led to its significant impacts in recent years for analyzing complex biological mixtures, especially in healthcare diagnostics.[2] In particular, CE has been increasingly applied in protein electrophoresis for the separation of major serum protein fractions i.e. albumin, alpha-1, alpha-2, beta, and gamma globulins.[3] Protein electrophoresis plays a crucial role in the diagnosis and monitoring of plasma cell dyscrasias through the detection of monoclonal immunoglobulins and related electrophoretic abnormalities indicative of conditions such as amyloidosis.[4-6]

The foundational principles of CE date back to the 1950s, with significant technical advances made in the 1980s by Jorgenson and Lukacs[7], who pioneered the concept of high-efficiency separations in capillary formats. Modern CE systems offer enhanced analytical performance, shorter turnaround times, and automation capabilities compared to traditional gel-based methods.

In compliance with ISO 15189:2022, clinical laboratories are mandated to verify a method's analytical performance prior to clinical implementation. This includes precision studies encompassing within-run and between-run variability according to CLSI EP15-A3 guidelines for method verification and error management.[8] Precision verification is essential, as analytical imprecision may result in misleading results that can impact patient management.[9-11] Accuracy, defined as the closeness of a measurement to the true value, is assessed via method comparison with a validated reference method using patient specimens, as outlined in CLSI EP09.[12] Such evaluations help identify potential biases and assess the clinical suitability of a new method. In addition, CLSI EP28-A3c provides guidance for verifying reference intervals, ensuring that the laboratory reference ranges are appropriate for the local patient population.[13]

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The SEBIA Capillarys 3 Octa system is a fully automated CE platform optimized for routine clinical serum protein electrophoresis, offering high-resolution profiles with over 95% concordance with gel electrophoresis results.[14,15] Nevertheless, gel electrophoresis remains widely practiced in Malaysian laboratories due to its cost-effectiveness, operational familiarity, and visual interpretability.[16] Despite its analytical performance that has been validated in other countries, the utility of CE in Malaysia remains limited. The study on Sebia Capillarys 3 Octa system in Malaysia is important as it provides valuable data for the implementation of this method in the country. The analytical performance verification using our population sample strongly supports its applicability, to suit our local laboratory workflow and healthcare system. Hence, our study aims to evaluate this by performing precision, accuracy studies, and reference interval verification of the system in our centre.

MATERIALS AND METHODS

The experimental study was conducted in the Specialized Diagnostic Protein Laboratory, Department of Chemical Pathology, Hospital Pakar Universiti Sains Malaysia (HPUSM), Kubang Kerian, Kelantan.

Sample collection

The determination of sample size followed international standards, specifically the Clinical and Laboratory Standards Institute (CLSI) guidelines and ISO 15189:2022 Medical Laboratory Accreditation requirements for method verification.[11-13] These standards were used to guide the minimum number of replicates and samples needed for evaluating analytical performance, including precision, accuracy, and reference interval verification. For the precision study, commercially available quality control materials i.e. normal and hypergamma controls were utilized. The accuracy study involved 40 fresh serum samples of healthy and diseased subjects, ensuring a representative range of electrophoretic protein patterns. For the reference interval verification study, at least 20 serum samples were collected from healthy adult subjects. For both accuracy study and reference interval verification studies, individual sample from every study subject were analysed.

For experiments which required serum sample collection, study subject recruitment was done according to specific inclusion and exclusion criteria. For healthy subjects, volunteers were recruited through advertisement posters displayed in hospital areas accessible to the general public, including patients' family members and hospital staff. For diseased group, data was retrieved from existing laboratory records. The study was approved by the Human Research Ethics Committee USM (HREC), and written informed consent was obtained from all subjects.

Laboratory measurement

Laboratory analysis involved total protein measurement using the biuret method on the Roche Cobas E701 analyzer. Serum protein electrophoresis was conducted using Sebia Capillarys 3 Octa. For method comparison, Sebia Hydrasys 2 protein electrophoresis analyzer were used.

Statistical analysis

Data was analysed using MedCalc version 23.2.0 software. The mean, standard deviation (SD), and coefficient of variation (CV) were calculated to assess within-run imprecision (repeatability) and between-run imprecision (reproducibility). The CVs obtained were compared with the manufacturer's claims and, if necessary, against the upper verification limits to evaluate acceptability. Linear regression and Bland-Altman plots were used to evaluate both the correlation coefficient (r-value) and the degree of bias between methods. A correlation value closer to +1 indicates a stronger positive correlation, while values approaching -1 indicates a strong negative correlation; a value of 0 indicates no correlation. For reference interval verification, the number of outliers was assessed according to CLSI EP28-A3 guidelines, with two or fewer outliers among 20 samples considered acceptable for verification of the manufacturer's reference interval.

RESULTS

Precision study

Table I and II display the precision study for both normal serum and pathological serum in 8 capillaries, including within-run and between-run CV. For the normal serum, all coefficients of variation (CV) values for the six protein fractions were within acceptable ranges, as determined by either the manufacturer's claim or the upper verification limit. The within-run precision was highest for albumin, which had the lowest CV 0.97%, while Alpha-1 had the highest within-run CV 7.04%. Similarly, between-run precision remained within acceptable limits, with albumin averaging 0.88%, while Alpha-1 ranged from 4.59% to 7.22%.

In the pathological serum, all CV values were also within acceptable limits. The within-run CV was lowest for Gamma of 0.6%, indicating excellent precision, while alpha-2 showed the highest within-run variability 10.32%. Between-run CV values for albumin ranged from 0.89% to 2.07%, whereas Alpha-2 varied between 4.91% and 10.32%. This analysis demonstrates the reliability of capillary electrophoresis in measuring serum protein fractions, with all fractions falling within acceptable CV limits.

Accuracy study

Table III represent the comparison between the Sebia Capillarys 3 Octa and Sebia Hydrasys 2 Scan gel electrophoresis systems. The correlation coefficient (r) indicates excellent correlation for albumin and gamma globulin ($r>0.95$), while other fractions showed good correlation ($r>0.80$). The slope and intercept values for albumin, alpha 2 and gamma supported the strong linear relationship between the two systems for the analytes. However, minor discrepancies were observed for alpha-1 and beta regions.

Bland-Altman analysis showed biases ranging from -1.1 to 2.1 for all protein fractions, with 95% differences within ±1.96 standard deviations. These findings demonstrate high agreement between the two methods. The small observed biases are within the clinically acceptable limit, thus unlikely to affect the test interpretation and medical decision.

Table I: Precision study for normal serum using 8 capillaries for each protein fraction

Fraction	Run	Mean (%)		Standard Deviation (%)		Coefficient of variation (%)		Manufacturer's claim CV (%)
		Lowest	Highest	Lowest	Highest	Lowest	Highest	
Albumin	Within run	60.80	61.69	0.02	0.11	0.97	1.33	2.00
	Between run			0.61	1.12	0.99	1.85	
Alpha-1	Within run	4.09	4.33	0.14	0.31	3.24	7.04*	7.00
	Between run			0.19	0.31	4.59	7.22*	
Alpha-2	Within run	8.74	9.09	0.29	0.47	3.19	5.34	7.00
	Between run			0.31	0.46	3.58	5.10	
Beta-1	Within run	6.39	6.62	0.14	0.34	2.16	5.29	7.00
	Between run			0.25	0.35	3.78	5.51	
Beta-2	Within run	4.73	4.90	0.14	0.26	2.96	5.38	7.00
	Between run			0.14	0.26	2.89	5.26	
Gamma	Within run	14.05	14.41	0.18	0.24	1.27	1.73	4.00
	Between run			0.22	0.30	1.54	2.08	

*Upper verification limit was applied

Table II: Precision study for pathological serum using 8 capillaries for each protein fraction

Fraction	Run	Mean (%)		Standard Deviation (%)		Coefficient of Variation (%)		Manufacturer's claim CV
		Lowest	Highest	Lowest	Highest	Lowest	Highest	
Albumin	Within run	48.81	49.70	0.40	0.79	0.81	1.62	2.00
	Between run			0.44	1.01	0.89	2.07*	
Alpha-1	Within run	3.32	3.58	0.02	0.30	5.09	8.28*	7.00
	Between run			0.21	0.35	6.29	9.93*	
Alpha-2	Within run	6.86	7.34	0.23	0.58	3.50	7.84*	7.00
	Between run			0.36	0.74	4.91	10.32*	
Beta-1	Within run	4.97	5.34	0.14	0.24	2.68	4.80	7.00
	Between run			0.18	0.36	3.61	7.26*	
Beta-2	Within run	3.42	4.82	0.10	0.19	2.90	4.92	7.00
	Between run			0.18	0.30	4.20	7.57*	
Gamma	Within run	31.49	31.76	0.19	0.70	0.6	2.49	4.00
	Between run			0.45	0.72	1.36	2.27	

*Upper verification limit was applied

Table III: Comparison between Sebia Octa 3 Capillary and Sebia Hydrasys 2 Scan Gel electrophoresis for each protein fraction

Protein fraction	Correlation coefficient (r value)	Slope	Intercept	Mean bias
Albumin	0.99	0.873	3.071	2.10
Alpha-1	0.80	0.840	1.215	0.93
Alpha-2	0.94	0.721	1.194	0.78
Beta	0.81	1.136	-0.375	-0.7
Gamma	0.99	0.973	1.45	-1.1

Correlation coefficient (r), slope, intercept, and mean bias comparing protein fraction measurements between two electrophoresis methods

Table IV: Comparison of observed serum protein fraction with manufacturer's reference interval

	Observed Mean (%)	Observed Upper limit (%)	Observed Lower limit (%)	Manufacturer's reference interval n=246 (%)
Albumin	58.9	55.1	65.1	55.8 - 66.1
Alpha-1	3.5	2.9	4.2	2.9 - 4.9
Alpha-2	8.4	7.2	9.9	7.1 - 11.8
Beta-1	5.9	5.3	6.5	4.7 - 7.2
Beta-2	5.2	3.9	5.7	3.2 - 6.5
Gamma	18.2	12.0	18.8	11.1 - 18.8

Observed mean, lower, and upper limits were calculated based on the study population. Verification was considered acceptable if ≥95% of observed values fell within the manufacturer's reference intervals

Reference interval study
Table IV presents the reference interval verification study. The observed data, expressed as percentages, fall within the manufacturer's reference intervals for all protein fractions. Albumin met the criteria with 18 out of 20 data points within the range, while other fractions were fully verified. This demonstrates the reliability of the reference intervals for the local population studied.

DISCUSSION

Our study aimed to evaluate the analytical performance of serum protein electrophoresis (SPE) using the Capillarys 3 Octa system by Sebia. Our findings collectively support the reliability and clinical applicability of capillary electrophoresis (CE) as an effective methodology for routine protein fractionation in a clinical laboratory setting.

Precision study
The within-run and between-run demonstrated excellent reproducibility for albumin and gamma globulins, with coefficients of variation (CVs) ranging from 0.81% to 2.29%. The finding was aligned with previous research finding by Bossuyt et al.[17] who reported CVs between 0.3% and 3.5% for the Capillarys system, affirming the high reproducibility of CE-based SPE systems across various laboratory settings. However, imprecision was notably higher in the alpha-1 and alpha-2 globulin regions, with CVs ranging from 5.34% to 10.32%. This is consistent with previous findings by Lebricon et al., who observed lower precision in these zones, with CVs reaching 10–25%, attributed to protein heterogeneity and challenges in automated integration.[18] Capillarys, in particular, showed higher inter-day CVs in the alpha-2 globulin region (>6%) compared to intra-day CVs (<4%).[17]

RICOS biological variation data provides desirable specifications for imprecision, bias, and total allowable error, derived from intra- and inter-individual biological variation.[19] For albumin, the desirable CV for imprecision is set at 1.6%, aligning closely with the manufacturer's specifications. However, for α1- and α2-globulin fractions, the biological variation data suggests higher acceptable CVs, reflecting the inherent challenges in resolving these fractions due to overlapping peaks and lower signal intensity.[19] Nonetheless, all observed CVs were within acceptable thresholds, particularly when compared against the upper verification limit (UVL). The usage of UVL for CVs exceeding the manufacturer's specification is critical in ensuring analytical reliability, especially in pathological samples where variability may exceed expected thresholds. To limit false rejection due to chance, the UVL for repeatability was calculated and compared against imprecision estimates. This approach reduces the likelihood of erroneous result rejection and strengthens the robustness of the precision verification process.[20]

The good precision observed may be attributed to the high level of automation and standardized separation environment offered by the Capillarys 3 Octa platform. Unlike gel electrophoresis, which involves manual sample loading, staining, and densitometry, the capillary system minimizes human handling and environmental variation. Furthermore, the use of internal temperature control, buffer stability, and real-time quality monitoring within the Capillarys system may enhance analytical consistency. The system's standardized separation environment, including temperature-controlled buffers and RFID-tracked reagents, ensures consistent performance in high-throughput laboratories.[21]

Accuracy study
The study findings demonstrated high agreement between CE and gel electrophoresis system, supporting their reliability for protein fraction analysis. However, for the slope and intercept, minor discrepancies were observed for alpha-1 and beta regions, which may be attributed to differences in dye-binding affinities or algorithmic peak recognition. These findings are consistent with previous study which reported similar correlation coefficients using the Capillarys 2 Flex Piercing system.[22] Likewise, Berth et al.[23] demonstrated comparable accuracy between CE and AGE, highlighting the improved automation and reproducibility in CE systems. The inherent strengths of CE features such as automation, precise sample injection, and consistent temperature control contribute to enhanced reproducibility and reliability. Favresse et al. supported these advantages in their evaluation of the Helena V8 system, where albumin and gamma globulin showed minimal bias and strong correlation.[24] Bossuyt et al. also emphasized the high comparability of CE with gel-based methods but noted increased bias in more complex protein fractions like alpha and beta globulins.[25] These findings suggest that while CE systems like Capillarys 3 Octa offer strong overall agreement and practical advantages, certain fractions particularly alpha-1 and beta may still present limitations in inter-method comparability. Further refinement in peak integration algorithms and improved zone discrimination may enhance performance in these regions.

Reference Interval
It is known that manufacturer's RI may not be representative of all populations. This could be due factors such as demography or methodology used for the establishment of the RI. Thus, it is important to carry out RI verification procedure based on the established guideline to ensure that it is applicable for our population. Our findings demonstrated that all observed values for major serum protein fractions albumin, alpha-1, alpha-2, beta-1, beta-2, and gamma globulins were within the manufacturer's specified reference ranges, affirming the analytical consistency and suitability of of the Sebia Capillarys 3 Octa system for routine clinical application in the studied population. These findings are consistent with prior literature supporting the reliability of capillary electrophoresis in protein fraction analysis. Favresse et al. (2021) showed that capillary electrophoresis yields reproducible and robust results across varied populations, reinforcing its utility in RI establishment and clinical interpretation.[24] It is known that population-specific considerations are important. Bossuyt et al. (2001) provided age-specific RIs for Caucasian paediatric subjects across four developmental age groups, highlighting significant age-dependent shifts in serum protein patterns that warrant dedicated RI evaluation for children.[25,26] Gender-based differences in serum protein fractions have also been

documented. Lichtinghagen et al. (2010), using the Sebia Capillarys II system, analyzed serum from 428 healthy donors and found significantly higher albumin levels in males, while females exhibited elevated levels of alpha-2 and gamma globulins. These findings emphasize the value of gender-specific RIs to enhance diagnostic accuracy.[27] Furthermore, RIs are known to vary across electrophoresis platforms. Chartier et al. (2011) compared the Sebia Capillarys 2 and Helena V8 systems and found statistically significant differences in most protein fraction RIs, except for beta globulins.[28] Similarly, Howard et al. (2021) identified notable discrepancies in protein fraction patterns between the Hydragel 30 gel system and the Capillarys III Tera, underlining the necessity of analyzer-specific validation before adopting RIs in clinical settings.[29]

National initiatives have also recognized the importance of standardization in capillary electrophoresis. Albert et al. (2010) described a quality control program in France that emphasized harmonizing protein quantification and SPE interpretation using the Sebia Capillarys 2 system. Their efforts underscored the value of local RI verification and method harmonization to enhance inter-laboratory consistency and result comparability.[30]

CONCLUSION

In conclusion, the findings from this study support the Sebia Capillarys 3 Octa capillary electrophoresis system as a reliable, precise, and clinically valid method for serum protein fractionation. The automation, throughput capacity, and reproducibility offered by CE support its adoption in high-volume clinical laboratories.

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CONFLICT OF INTEREST

The sponsor involved in the technical support for the study. However, the sample collection, data analysis and interpretation were done independently by the researchers. The authors declared no other conflict of interest.

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ORIGINAL ARTICLE

MUC5AC gene expression in COVID-19 nasal discharge with rhinorrhea symptoms

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ABSTRACT

Introduction: Coronavirus Disease 2019 (COVID-19) is an acute respiratory infection caused by SARS-CoV-2. On May 1, 2021, there were 153 million confirmed positive cases worldwide with a total of 3.2 million deaths. The number of Indonesian cases on November 10, 2021, was recorded at 4,249,323 confirmed positive cases with 143,592 deaths. In COVID-19, rhinorrhea symptoms were found in 4% of cases, while in influenza and the common cold, 91% of cases experienced rhinorrhea. COVID-19 causes epithelial destruction and stimulates local immune response and the release of macrophages, monocytes, inflammatory cytokines, B cells, and T cells. The nasal epithelium is a physical barrier that protects the nasal mucosa from inflammatory agents by producing glycoproteins such as mucin, cytokines, and chemokines.

Materials and Methods: The study aimed to analyze the relationship between MUC5AC expression in nasal secretions and COVID-19 infection. This research was analytical research with a cross-sectional design. We used stored nasal swab samples at a laboratory designated for COVID-19 detection from 2021 until 2022, the pandemic. Selection of the sample using a simple random sampling technique. The population in this study were patients with a positive (n=40) and negative (n=40) diagnosis of COVID-19 confirmed by RT-qPCR and according to the inclusion and exclusion criteria. The data were analyzed using an independent Student's t-test.

Results: The sample characteristics in this study showed that 58% of females and 42% of males were confirmed positive for COVID-19. About 22% of COVID-19 positive cases had runny nose symptoms. The relative expression of MUC5AC increased 9.77 times.

Conclusion: MUC5AC expression is increased in the nasal secretions of COVID-19 patients, but this study found that only 22% of cases experienced symptoms of a runny nose.

KEYWORDS:
MUC5AC, runny nose, rhinorrhea, COVID-19

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is an acute respiratory infection caused by SARS-CoV-2. In December 2019 in Wuhan, China, there was an outbreak of pneumonia of unknown cause. Based on epidemiological data, WHO stated that until November 7, 2021, there were 294 million positive confirmed cases and more than 5 million deaths worldwide. In the United States, there were 510,968 cases, and in the United Kingdom, 252,104 cases. The Russian Federation reported a 3% increase in cases at 281,305 new cases. Turkey reported an 8% increase in new cases and Germany 29%. On May 1, 2021, there were 153 million confirmed positive cases worldwide with a total of 3.2 million deaths. (WHO. The number of Indonesian cases on November 10, 2021, was recorded at 4,249,323 confirmed positive cases with 143,592 deaths.[1]

COVID-19 causes epithelial destruction and stimulates local immune response and the release of macrophages, monocytes, inflammatory cytokines, B cells, and T cells. SARS-CoV-2 is a cytopathic virus, which causes cell damage and death. Viral infection and replication occur in the epithelium of the respiratory tract, causing pyroptosis followed by vascular leakage. Pyroptosis is an inflammatory process that is a cell death program often found in cytopathic viruses. The result of pyroptosis will stimulate the release of inflammatory cytokines.[2]

COVID-19 stimulates type 1 immune responses and the release of pro-inflammatory cytokines. Several studies have mentioned that in COVID-19 there is an increase in IL-1ß, which induces the production of MUC5AC mucin in the respiratory tract. IL-1ß induces MUC5AC production through regulation of cAMP response element-binding protein (CREB)-dependent NF-kB transcription. The COVID-19 inflammatory response causes mast cell dysfunction. Mast cells stimulate the synthesis of TNF-α, which can be released rapidly. The release of COVID-19 histamine causes inflammation, platelet aggregation, bronchial constriction, vasodilation, edema, and mucus secretion.[3]

There are 22 types of mucin genes expressed in the human airway epithelium. MUC5AC and MUC5B are mucins that function to maintain nasal epithelial hemostasis. The main components that make up mucin are glycoproteins encoded by several mucin genes. The MUC5AC gene is produced by epithelial goblet cells, while MUC5B is produced by submucosal glandulars in the lower airway.[4–6] The MUC5B genes are predominantly found in normal conditions, which function to keep the epithelium in a normal state by

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controlling bacterial infection and preventing further inflammation. In normal conditions, MUC5AC levels are found to be low. When a viral infection occurs, MUC5AC secretion will increase. MUC5AC acts as a decoy for viral receptors and is essential for the inflammatory response.[7]

Inflammation stimulates the release of inflammatory mediators such as TNFα, IL-9, IL-4, acrolein, neutrophilelastase, oxidative stress, and Epidermal Growth Factor Receptor (EGFR), which will induce an increase in MUC5AC production.[8,9] Ali et al. found 75% MUC5AC increased in nasal polyps.[10]

Mucin functions as a protective barrier and intercellular signal transducer that has a role in maintaining homeostasis and survival in epithelial cells. In advanced infections, mucin expression can become pathological. Mucin hypersecretion is the main clinical symptom seen in COVID-19, and it has severe symptoms. The accumulation of mucus in the respiratory tract causes airflow obstruction, making it difficult for patients to breathe and worsening the course of the disease.[11] COVID-19 stimulates the release and activation of an inflammatory cascade of cytokines and inflammatory chemokines that influence the inflammatory response and increase mucus secretion in the respiratory tract.[12]

In COVID-19, rhinorrhea symptoms were found in 4% of cases, while in influenza and the common cold, 91% of cases experienced rhinorrhea.[13] In other studies, rhinorrhea was found in only 4% of cases, and cough was still a common symptom.[14] Lovato, in his study, found symptoms of nasal congestion in COVID-19 in 3.7% of cases, while rhinorrhea was rarely found.[15]

MATERIALS AND METHODS

Experimental Design

This study protocol was approved by the Ethical Review Committee Faculty of Medicine, Universitas Andalas, Indonesia (613/UN.16.2/KEP-FK/2023). This research is analytical research using a cross-sectional design.

Sample Isolation

The research was conducted at the Laboratory of the Center for Diagnostics and Research of Infectious Diseases (PDRPI), Faculty of Medicine, Andalas University during 2021 until 2022, the pandemic. The samples in this study are biological materials stored in the Laboratory of the Center for Diagnostics and Research of Infectious Diseases (PDRPI), Faculty of Medicine, Andalas University. The sample population of this study was patients aged 20 to 40 years who were confirmed positive and negative for COVID-19 through RT-qPCR examination (using the Kaira-2019 nCov Detection KitTM). Control samples consisted of patients presenting with symptoms of viral rhinitis who underwent COVID-19 screening due to a history of contact with confirmed COVID-19 cases. All control subjects tested negative by RT-PCR.

RT-PCR analysis

RNA isolation from nasal discharge was conducted using the Kaira-2019 nCov Detection KitTM reagent. The IL-4, IFN-γ, and MUC5AC levels were measured by RT-PCR using specific primers and probes for the IL-4, IFN-γ, and MUC5AC genes. For relative quantification of the expression of the IL-4, IFN-γ, and MUC5AC mRNA, we used beta-actin primers.

The IL-4 *was used with primer sequences as follows:* 5'TTGGCTTAATTCTCTCGG'3, and the reverse primer sequence was used 5'TTTACATATGGGTCCTGG3'. The IFN-γ *was used with primer sequences as follows: 5'* TGGGTTTTACTTAGCTTTGG'3 and the reverse primer sequence was used, *5'* GGCGATACCTTTTCTGTT'3. The MUC5AC γ *was used with primer sequences as follows: 5'* CTCCTACCAATGCTCTGTA'3 and the reverse primer sequence was used 5' GTTGCAGAAGCAGGTTTG'3. The *beta-actin primer was used as a control with the primer sequences as follows: 5'*CATGTACGTTGCTATCCA'3, and the reverse primer sequence was used 5' TTCATGAGGTAGTCAGTC'3.

Data analysis

Data were analyzed by SPS. The normality of IL-4, IFN-γ, and MUC5AC gene expression data in nasal discharge, runny nose, and anosmia in COVID-19 patients was tested. The data was analyzed by means of an independent T-test.

RESULTS

Characteristic of sample

Based on Table I, the demographic distribution of the sample based on gender in the control population is 60% female and 40% male. In the case population, 58% of the samples were female and 42% male. There were clinical symptoms of COVID-19 found in the case population, namely runny nose in 22% of cases, anosmia in 18% of cases, and nasal congestion in 25%. There were no symptoms of anosmia in patients with confirmed negative COVID-19.

Based on the symptoms of a runny nose with the expression of IL-4, IFN-γ, and MUC5AC in the nasal secretions of COVID-19 patients, the largest standard deviation value is obtained in IFN-γ with runny nose symptoms, namely 2.08 with an average value of 19.8, a minimum value of 16.54, and a maximum value of 22.64. The smallest standard deviation was obtained in the MUC5AC group with non-runny nose complaints, namely 0.86 with an average of 9.78, a minimum value of 8.28, and a maximum value of 11.42. Expression of IL-4, IFN-γ, and MUC5AC Expression with Runny Nose

The relative increase in IL-4 expression in COVID-19 with runny nose symptoms (Figure 2) is 4.75 times higher than in COVID-19 without a non-runny nose. IFN-γ expression in COVID-19 with runny nose symptoms also increased 1.58 times higher than in COVID-19 without runny nose. MUC5AC gene expression in COVID-19 with a runny nose has increased 9.77 times higher compared to COVID-19 without a runny nose.

DISCUSSION

Rhinorrhea, or runny nose, is a symptom that often occurs in COVID-19. In this study, 22% of patients had a runny nose, 18% had anosmia, and 75% had nasal congestion. El Anwar, Esa M et al. found as many as 20% of patients experienced a

runny nose.[16] Khongsiri et al. found that in the Omicron variant, 40.2% of cases had a runny nose. Omicron variants have a tendency to infect the upper airway. So that in the wave of omicron variants, the dominant symptom that appears is a runny nose or nasal congestion.[17]

A runny nose and sneezing are the body's protective mechanisms when infected by a virus. Mucus produced by the epithelial mucosa functions as a mucoprotector. T. Klopfenstein et al. found that 57% of runny nose symptoms were followed by nasal obstruction. More than 85% of anosmia cases are followed by dysgeusia.[18] Lechien et al. found that 66.2% had anosmia and 13.5% had hyposmia.[19] The physiology of smell involves a complex process of interaction of olfactory compounds with chemoreceptors involving olfactory neurons and airflow conduction. Olfactory disorders can be caused by sensorineural damage or damage to airflow conduction.

COVID-19 is a new viral infection. Researchers assume that perhaps at the beginning of infection, the body's immunity has difficulty recognizing this virus, so this virus tends not to be detected at the beginning of infection. In the first mechanism, SARS-CoV-2 on the ciliary surface will bind to ACE2 through the receptor binding domain (RBD) and then activate through proteolysis. oleh TMPRSS2, which will activate protein S, and then fusion occurs on the ciliary membrane. In the second mechanism, the SARS-CoV-2-ACE2 complex will be transported from the tip of the cilia to the cell body to the cell membrane, and then fusion occurs through the process of endocytosis. This mechanism causes COVID-19 infection to go unrecognized at first. Ahn et al. found SARS-CoV-2 damaged the mucociliary system in the nose. Ahn found that there was an increase in ACE2 receptor levels in the apical cells of the nasal epithelium, the expression of ACE2, TMPRSS2, and FURIN protein on goblet cells in the nasal epithelium, while the MUC5AC gene was rarely found or found in low expression; this is in accordance with the findings of the low percentage of rhinorrhea symptoms in COVID-19 patients.[20]

To prevent pathogen infection, the epithelium increases mucus expression. MUC5AC is the dominant mucus secreted to fight pathogens. Morison et al. found that the rapid spread of SARS-CoV-2 infection caused goblet cells to fail to secrete mucus. Intracellular MUC5AC is depleted.[21] Lu et al. reported an increase in MUC5AC levels in COVID-19. The retention of mucus in the respiratory tract causes hypoxia, and patients require bronchoscopic aspiration.[22] Kumar et al. reported an increase in MUC2, MUC5AC, and MUC5B in COVID-19. In this study, it was found COVID-19 stimulates IFN-γ and IFN-β to activate aryl hydrocarbon receptor signaling (Ahr) and stimulate the formation of mucin genes.[23]

This study found that the expression of MUC5AC in COVID-19 increased by 9.77 times. The resulting reactive oxygen species and inflammatory mediators cause mucus gene expression to increase. Mucus works to reduce viral load. Lee et al., in nasal mucosal epithelial cultures, found that MUC5AC expression increased due to the spike protein RBD SARS-CoV-2.[24] In this research, there is a significant relationship between the expression of IL-4 and IFN-γ in COVID-19 with a runny nose. The IL-4 expression and COVID-19 with a runny nose increased 4.75 times. Wang et al. cultured MUC5AC goblet cells and transient secretory cells. Wang found that goblet cells and transient secretory cells are vulnerable to COVID-19.[25]

The pro-inflammatory cascade not only disrupts mucus secretion but also impairs cilia function. Therefore, this condition can trigger recurrent infections and lead to airway obstruction. Damage to the mucociliary system leads to obstruction or congestion of the nose. Excessive mucus production causes nasal congestion. COVID-19 disrupts respiratory epithelial cell homeostasis by increasing excess mucus production, resulting in respiratory obstruction.21 The inflammatory response releases a pro-inflammatory cascade that not only disrupts mucus secretion but also disrupts cilia function. Therefore, this condition can trigger recurrent infections in the airway and cause more obstruction. [12]

The IL-4 expression in COVID-19 with runny nose symptoms was found to be 4.75 times higher. Yin et al. found MUC5AC increased in COVID-19 infection. There was hyperplasia of goblet cells, hypoplasia of club cells, and also multiciliated cells. COVID-19 disrupts respiratory epithelial cell homeostasis by increasing mucus production, which can lead to obstruction.[21] The inflammatory response in the form of the release of pro-inflammatory cascades not only disrupts mucus secretion but also disrupts cilia function. Therefore, this condition can trigger recurrent infections in the airway and cause more obstruction.[12]

Proinflammatory and anti-inflammatory processes occur together in the body. This balance is important for maintaining homeostasis and responding to various invasions. When an infection occurs, immune cells trigger a proinflammatory response to fight the pathogen. Simultaneously, anti-inflammatory mechanisms work to suppress the inflammatory process and prevent excessive damage to healthy tissues. This interaction ensures a controlled and effective immune response. Viral or toxin infections cause an inflammatory response in the form of immune cell infiltration and cytokine production. Inflammation induces olfactory-sensitive neuron degeneration and apoptosis as a protective mechanism.[26]

The infection process due to coronavirus will be responded to by the immune system, producing several cytokines, including IL-4 and IFN-γ. The IL-4 plays a role in the activation of B cells in antibody production and the production of several types of cytokines. The IFN-γ, as a type 1 interferon, plays a role in proinflammation by helping activate macrophages to become M1 and increasing antigen presentation, thus triggering an immune response against infected cells. IFN-γ can also play an anti-inflammatory role. The IFN-γ activation contributes to the activation of macrophages to M2, helping the resolution of the infection process and promoting tissue repair, indirectly affecting the anti-inflammatory process. Low IFN-γ response at the beginning of infection will lead to increased viral load and progressive inflammation due to local immune dysfunction.[26] The involvement of IL-4 and MUC5AC in the infection process due to COVID-19 is through a complex

immunological process. Excessive immune response can result in inflammation and mucin production that contributes to respiratory symptoms.[27]

This study has several limitations. First, to find out the patient's symptoms, one must be on the phone, so there is a time interval between the examination and the symptoms felt so that we cannot know directly the condition of the patient. Second, this study does not differentiate between COVID-19 virus variants. Researchers did not distinguish between acute and recovery phases when sampling.

CONCLUSION

There was an increase in the relative expression of MUC5AC in COVID-19 with runny nose symptoms.

ETHICS APPROVAL

This study protocol was approved by the Universitas Andalas Ethics Committee (Ethical Code: 613/UN.16.2/KEP-FK/2023) on December 13th, 2023.

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ORIGINAL ARTICLE

Incidence and clinical patterns, severity and preventability of cutaneous adverse drug reactions among hospitalized patients in a tertiary centre

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ABSTRACT

Introduction: Cutaneous adverse drug reactions (cADRs) are among the most common manifestations of adverse drug reactions, ranging from mild eruptions to severe, life-threatening conditions such as Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS). Despite increasing reports from Malaysia's National Pharmaceutical Regulatory Agency, local epidemiological data at the state level remain scarce. This study aimed to determine the incidence, clinical patterns, severity, and preventability of cADRs among hospitalized patients in Hospital Tuanku Ja'afar Seremban (HTJS), and to identify the drugs most frequently implicated and predictors of severe disease.

Materials and Methods: We conducted a prospective, observational cross-sectional study over six months (February–July 2024) at HTJS. Patients admitted with, or developed cADRs during hospitalization secondary to systemic medications were included. Exclusion criteria were allergic/irritant contact dermatitis, chemotherapy-induced alopecia, allergic reactions to radiographic contrast or blood products, and outpatient cases. Data on demographics, clinical features, implicated drugs, severity (modified Hartwig and Siegel scale), preventability (Schumock and Thornton scale), and causality (Naranjo's Algorithm) were collected. Multiple logistic regression identified predictors of severe cADRs.

Results: Among 30,667 admissions, 70 patients met inclusion criteria (incidence: 0.228%). The mean age was 46.2 ± 21.4 years; 55.7% were female and 71.4% Malay. Most cases occurred in medical departments (60%). The commonest reaction patterns were maculopapular eruption (37.1%) and urticaria (35.7%). Antibiotics accounted for 50% of cases, with penicillin being the leading culprit (37.1%), followed by NSAIDs, analgesics, anti-platelet and anti-tuberculosis drugs. Most reactions were of moderate severity (80.0%); one SJS/TEN case was classified as severe according to Hartwig scale. Preventability assessment found 14.3% definitely preventable events, primarily due to re-exposure to known allergens. Multiple logistic regression identified raised eosinophil count (AOR 21.83, p=0.001), mucosal involvement (AOR 29.82, p=0.016), and impaired renal function (AOR 7.98, p=0.024) as independent predictors of severe reactions.

Conclusion: Our study highlights a cADR incidence of 0.228% among hospitalized patients, with antibiotics, especially penicillin group, being the most frequent culprit drug. While most reactions were moderate and not preventable, significant predictors of severity included raised eosinophils, mucosal involvement, and renal impairment. Enhanced vigilance, careful drug selection, and early recognition of high-risk clinical features are crucial to reducing the burden of cADRs in hospital settings.

INTRODUCTION

WHO defines adverse drug reaction as a "response to a drug which is noxious and unintended and occurs at doses normally used in man in any substance or product that is used or intended to be used to modify or explore physiological systems or pathological states for the benefit of the recipient".[1] Adverse drug reactions (ADRs) are a significant cause of morbidity and mortality worldwide, contributing to increased hospital admissions, prolonged hospital stays, and elevated healthcare costs.[2] Cutaneous adverse drug reactions are the most common form of ADRs, with incidence ranging from 1% to 3% in hospitalized patients.[3,4] These reactions are variable and can range from mild forms such as maculopapular eruptions and urticaria to severe and potentially life-threatening conditions including Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). Cutaneous adverse drug reactions can have significant impact on the management of patients and have implications/complications for patient health and can affect the healthcare economy.[2]

In Malaysia, the National Pharmaceutical Regulatory Agency (NPRA) has documented an increasing number of ADR reports over the years, with cADRs constituting a considerable proportion.[5] Despite the rising trend, local data at the state or institutional level, remain limited. Negeri Sembilan, a state in Peninsular Malaysia, is home to several healthcare institutions, including Hospital Tuanku Ja'afar Seremban (HTJS), the primary tertiary referral center in the state. However, no recent comprehensive study has been conducted to evaluate the incidence and clinical spectrum of cADRs in this setting. This gap in knowledge limits efforts to develop local clinical guidelines and pharmacovigilance strategies to reduce the burden of these adverse events.

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This study aimed to determine the incidence, clinical patterns, severity, and preventability of cutaneous adverse drug reactions (cADRs) among hospitalized patients at Hospital Tuanku Ja'afar Seremban (HTJS). The study also determined the drugs most commonly implicated in cADRs and their corresponding reaction patterns. Additionally, it examined the distribution of cADR cases across various clinical departments within HTJS, evaluated the demographic profiles of affected patients, and factors affecting severity.

MATERIALS AND METHODS

This was a prospective, observational cross-sectional study with purposive sampling. Data was collected for 6 months from February 2024 to July 2024, involving patients admitted for cADR or developed cADR during hospitalization in HTJS secondary to systemic medication. An official notification letter was disseminated to the relevant hospital departments and pharmacy department, informing them of the study and the procedures for case reporting. All suspected cADR cases were promptly notified to the dermatology team for evaluation. All the patients satisfying the inclusion criteria were enrolled in the study. The exclusion criteria were allergic or irritant contact dermatitis, chemotherapy induced alopecia, allergic type reaction to radiographic contrast media and blood products. Outpatients and patients in the emergency department who were not admitted were also excluded.

A written informed consent was obtained from either the patient or guardian. All the relevant information regarding the patient including present complaints, past history, laboratory data results, clinical details, treatment received, and final outcome were recorded in data collection form. Data on cADRs like type and pattern, severity, dates on which reaction started and stopped were recorded. Details of suspected medication like generic and brand names, dosages, route, frequency, indication, date of starting, and stopping drug, concomitant drugs with doses and frequency, were also recorded. The patients were followed up till their discharge from hospital to determine outcome.

The collected data were analysed for demographic details, drug details, causality, preventability, and severity of adverse effects. Causality was assessed by using Naranjo's Algorithm, preventability by Schumock and Thornton scale and severity by modified Hartwig and Siegel scale. The Hartwig and Siegel Severity Assessment Scale categorizes adverse drug reactions into mild (levels 1–2), moderate (levels 3–4), and severe (levels 5–7) based on clinical impact and intensive management requirements.

The data were sorted, coded, and entered into Statistical Package for the Social Science (SPSS) for Windows Version 29.0 (SPSS Inc., Chicago, USA) and subsequently analysed. Descriptive statistics were used to calculate the prevalence of cADRs during the study period. Prevalence rate was determined by dividing the number of identified cADR cases by the total number of hospital admissions during the same period. Quantitative variables were expressed as means and standard deviations. Qualitative variables were expressed as frequency and percentage. Multiple logistic regression analysis was conducted to examine the association between risk factors and the likelihood of developing severe disease outcomes. The overall model was statistically significant, χ^2 (4)=31.170, $p<0.001$, indicating that the set of systemic complications meaningfully contributed to predicting severity. The model explained 35.9 of the variance in disease severity according to the Cox & Snell R^2 and 53.6 according to the Nagelkerke R^2, and it correctly classified 82.9 of cases. The Hosmer-Lemeshow goodness-of-fit test yielded a non-significant result, χ^2 (4) = 6.124, p = 0.190, suggesting that the model fits the data well.

RESULTS

A total of 70 patients were identified with suspected cADRs during the 6-month study period. With a total of 30,667 hospital admissions during the same period, the estimated incidence of cADRs was 2.28 per 1,000 admissions, equivalent to 0.228% of all admissions. The prevalence rate was higher in patients hospitalized in medical departments (60.0%) followed by dermatology (15.7%) and paediatric (10.0%). The rest of the department report sparse cases that count for less than 10.0%.

Among the 70 cADR patients, females made up a slightly higher proportion [39 (55.7%)] than males [31 (44.3%)].The ethnicity distribution of patients was predominantly Malay [50(71.4%)], with Indians [10 (14.3%)], Chinese [8(11.4%)], and other ethnicities [2(2.9%)]. This reflects the hospital admission rates: Malays had overall 19,787(64.5%) admissions, followed by Indians with 4,901(15.9%), Chinese with 3,551(11.57%). This distribution reflects the general patient demographic pattern observed in the hospital's catchment area. The mean age of patients was 46.2 ± 21.4 years. The majority of patients were adults aged 19 to 60 years [41(58.6%)], followed by elderly patients above 60 years [21(30.0%)] and paediatric patients aged 0 to 18 years[8 (11.4%)].

The majority of patients did not have pre-existing skin conditions, with only 3 patients (4.3%) reporting an underlying skin disease. A history of prior cADRs was documented in 13 patients (18.6%), while 4 patients (5.7%) had a history of atopy, such as asthma, allergic rhinitis, or eczema. Chronic comorbid conditions were present in a subset of patients. Autoimmune diseases and malignancies were each reported in 6 patients (8.6%), as was chronic kidney disease (CKD). A single patient (1.4%) was found to have an RVD (retroviral disease) infection. Only 9 patients (12.9%) did not have any co-morbids (no known medical illness). The majority of patients, 41 (58.6%) were hospitalized for 7 days or less. The mean length of hospital stay was 10.31 ± 9.96 days. The number of concurrent medications ranged from 0 to 12. The number of concurrent medications among patients had a mean of 3.69 ± 2.91. The median number of concurrent medications was 3.0, with an interquartile range (IQR) of 3.0. (Table I)

Moderate severity reactions accounted for 56 (80.0%) cases. This typically required medical intervention or hospitalization but were not life-threatening. Mild reactions

Table I: Demographic and clinical characteristics of patients with cADR

Characteristics	n (%)
Gender	
Male	31 (44.3)
Female	39 (55.7)
Ethnicity	
Malay	50 (71.4)
Indian	10 (14.3)
Chinese	8 (11.4)
Other	2 (2.9)
Age group	
Paediatric (0-18)	8 (11.4)
Adult (19-60)	41 (58.6)
Elderly (>60)	21 (30.0)
Comorbidities	
Underlying skin disease	3 (4.3)
History of cADR	13 (18.6)
History of Atopy	4 (5.7)
RVD infection	1 (1.4)
Autoimmune disease	6 (8.6)
Malignancy	6 (8.6)
CKD	6 (8.6)
No comorbids	9 (12.9)
Concurrent medications	
0-4	48 (68.6)
5-9	19 (27.1)
>10	3 (4.3)
Number of cADRs reported by department	
Dermatology	11 (15.7)
Medical	42 (60.0)
O & G	5 (7.1)
Paediatric	7 (10.0)
Rehab	1 (1.4)
Surgical	4 (5.7)
Length of hospital stay	
≤7 days	41 (58.6)
7–14 days	13 (18.6)
>14 days	16 (22.9)

Table II: Causality, preventability and severity of cADR among the study population

Parameters	n (%)
Severity of cADR (Hartwig Scale)	
Mild (1-2)	13 (18.6)
Moderate (3-4)	56 (80.0)
Severe (5-7)	1 (1.4)
Causality (Naranjo Adverse Drug Reaction Probability Scale)	
Possible (1-4)	11 (15.7)
Probable (5-8)	51 (72.9)
Definite (>8)	8 (11.4)
Preventability (Schumock and Thornton scale)	
Definitely preventable	10 (14.3)
Not preventable	60 (85.7)

were reported in 13 (18.6%) patients, involving self-limiting cutaneous eruptions that resolved with drug discontinuation and minimal supportive care. Only one (1.4%) patient with SJS fell in the severe category. The modified Schumock and Thornton criteria classified 10 reactions (14.3%) as definitely preventable, and 60 reactions (85.7%) were considered not preventable. 51(72.86%) patients had a probable causality score (5–8), 11 (15.7%) patients were assessed as possible (score 1–4), and 8 (11.43%) patients were classified as definite (>8) according to the Naranjo Adverse Drug Reaction Probability Scale. (Table II)

The onset of cADRs varied across clinical patterns. Urticaria had the earliest onset, typically occurring within less than 1 to 6 days (mean 0.40 ± 1.32 days), reflecting its nature as an immediate hypersensitivity reaction. AGEP and cutaneous vasculitis also presented early, within 2 to 7 days and 2 days, respectively. In contrast, maculopapular eruptions (MPE) showed a broader onset window ranging from 2 to 21 days (mean 7.62 ± 4.89), while TEN/SJS developed between 2 and 17 days (mean 8.67 ± 7.64), indicating their delayed hypersensitivity mechanisms. Fixed drug eruption, erythroderma, and DRESS had longer latency periods in this

Table III: Characteristics of cADR among the study population

Duration to cADR onset	**range and mean(SD) in days**	
MPE	2 -21	7.62 (4.89)
Urticaria	< 1 – 6	0.40 (1.32)
Fixed drug eruption	4	4.00 (0.00)
Cutaneous vasculitis	2	2.00 (0.00)
Erythroderma	14	14.00 (0.00)
AGEP	2-7	3.00 (1.77)
DRESS	21-56	33.60 (15.18)
TEN/SJS	2-17	8.67 (7.64)
Clinical manifestations of cADR	**n (%)**	
MPE	26 (37.1)	
Urticaria	25 (35.7)	
Fixed drug eruption	1 (1.4)	
Cutaneous vasculitis	1 (1.4)	
Erythroderma	1 (1.4)	
AGEP	8 (11.4)	
DRESS	5 (7.1)	
TEN/SJS	3 (4.3)	
Drug implicated in various cADR		
Antibiotics, total	35 (50.0)	
Bactrim	3 (4.3)	
Cephalosporin	4 (5.7)	
Meropenem	1 (1.4)	
Penicillin	26 (37.1)	
Vancomycin	1 (1.4)	
Anti-TB, total	5 (7.1)	
Akurit-4	5 (7.1)	
Anticonvulsant, total	3 (4.3)	
Lamotrigine	2 (2.9)	
Sodium valproate	1 (1.4)	
Urate-lowering, total	3 (4.3)	
Allopurinol	3 (4.3)	
NSAIDS, total	7 (10)	
Diclofenac	2 (2.9)	
Etoricoxib	1 (1.4)	
Ibuprofen	1 (1.4)	
Mefenamic acid	1 (1.4)	
Naproxen	2 (2.9)	
Other analgesics, total	7 (10)	
Fentanyl	1 (1.4)	
Paracetamol	3 (4.3)	
Paracetamol/Ibuprofen	1 (1.4)	
Tramadol	2 (2.9)	
Antiviral, total	1 (1.4)	
Acyclovir	1 (1.4)	
Antifungal, total	1 (1.4)	
Fluconazole	1 (1.4)	
Immunosuppressant, total	1 (1.4)	
Methotrexate	1 (1.4)	
Anticoagulant, total	1 (1.4)	
Rivaroxaban	1 (1.4)	
Anti-platelet, total	6 (8.6)	
Aspirin	6 (8.6)	

study. DRESS, in particular, had the most delayed onset, occurring between 21 and 56 days (mean 33.60 ± 15.18).

Antibiotics were the most frequently implicated drug class, accounting for a total of 35(50%) cases, with penicillins being the most common culprit (26 cases, 37.1%). Other antibiotics included cephalosporins (5.7%), bactrim (4.3%), vancomycin (1.4%), and meropenem (1.4%).

NSAIDs and analgesics were the second most frequently implicated drug classes. Diclofenac and naproxen each accounted for 2 cases (2.9%), while etoricoxib, ibuprofen, and mefenamic acid were each implicated in 1 case (1.4%). For other analgesics, paracetamol was the most common, contributing 3 cases (4.3%), followed by tramadol with 2 cases (2.9%), and fentanyl and the combination of paracetamol/ibuprofen with 1 case each (1.4%).

Antiplatelet agents, namely aspirin, were implicated in 8.6% of all cases. Anti-tuberculosis drugs, specifically Akurit-4, contributed to 7.1% of cases. Among anticonvulsants, lamotrigine (2.9%) and sodium valproate (1.4%) were implicated. Allopurinol used for gout management, was responsible for 4.3% of cADRs. Less frequently implicated

Table IV: Reaction patterns, drug groups, and specific culprit drugs in cADR patients

Reaction Pattern (n)	Drug Group – n (%)	Specific Drugs (n)
MPE (26)	Antibiotics – 17 (65.4)	Penicillin (10), Bactrim (3), Cephalosporin (2), Vancomycin (1), Meropenem (1)
	Anti-TB – 1 (3.8)	Akurit-4 (1)
	Anticonvulsants – 2 (7.7)	Lamotrigine (2)
	Antigout – 1 (3.8)	Allopurinol (1)
	Analgesics – 1 (3.8)	Tramadol (1)
	Antifungal – 1 (3.8)	Fluconazole (1)
	Immunosuppressant – 1 (3.8)	Methotrexate (1)
	Anticoagulant – 1 (3.8)	Rivaroxaban (1)
	Antiplatelet – 1 (3.8)	Aspirin (1)
Urticaria (25)	Antibiotics – 10 (40.0)	Penicillin (9), Cephalosporin (1)
	NSAIDs – 5 (20.0)	Aspirin (5), Diclofenac (2), Ibuprofen (1), Mefenamic acid (1), Naproxen (1)
	Analgesics – 4 (16.0)	Paracetamol (2), Tramadol (1), Fentanyl (1)
	Antiviral – 1 (4.0)	Acyclovir (1)
	Antiplatelet – 5 (20.0)	Aspirin (5)
Fixed drug eruption (1)	NSAIDs – 1 (100)	Etoricoxib (1)
Cutaneous vasculitis (1)	Antibiotics – 1 (100)	Penicillin (1)
Erythroderma (1)	Anti-TB – 1 (100)	Akurit-4 (1)
AGEP (8)	Antibiotics – 6 (75.0)	Penicillin (5), Cephalosporin (1)
	Anti-TB – 1 (12.5)	Akurit-4 (1)
	Analgesics – 1 (12.5)	Paracetamol (1)
DRESS (5)	Anti-TB – 2 (40.0)	Akurit-4 (2)
	Anticonvulsant – 1 (20.0)	Sodium valproate (1)
	Antigout – 1 (20.0)	Allopurinol (1)
	NSAIDs – 1 (20.0)	Naproxen (1)
TEN/SJS (3)	Antibiotics – 1 (33.3)	Penicillin (1)
	Antigout – 1 (33.3)	Allopurinol (1)
	Analgesics – 1 (33.3)	Paracetamol/Ibuprofen (1)

drugs included antivirals (acyclovir), antifungals (fluconazole), immunosuppressants (methotrexate), and anticoagulants (rivaroxaban), each contributing a small proportion of cases at 1.4% respectively. (Table III)

The analysis of drug-specific associations with various cADR revealed that maculopapular eruptions (MPE) and urticaria were the most frequently observed manifestations, involving 26 (37.1%) and 25 (35.7%) patients respectively. MPE was most linked to penicillin, which accounted for 10 out of 26 cases (38.5%). Other drugs implicated in MPE were Bactrim (3 cases), cephalosporins (2 cases), lamotrigine (2 cases), and several single-drug cases such as Akurit-4, allopurinol, aspirin, fluconazole, meropenem, methotrexate, rivaroxaban, tramadol, and vancomycin (each with 1 case). In urticaria, penicillin was again the leading cause (9 cases, 36%), followed by aspirin (5 cases, 20%). Other drugs included diclofenac (2 cases), paracetamol (2 cases), and one case each involving acyclovir, cephalosporin, fentanyl, ibuprofen, mefenamic acid, naproxen, and tramadol.

Fixed drug eruption (FDE) and cutaneous vasculitis were each observed in a single case, linked to etoricoxib and penicillin, respectively. Erythroderma was reported in one patient and was attributed to Akurit-4. Acute generalized exanthematous pustulosis (AGEP) was associated with penicillin (5 out of 8 cases, 62.5%), Akurit-4, cephalosporin, and paracetamol (1 case each). DRESS syndrome was predominantly caused by Akurit-4 (2 cases), followed by allopurinol, naproxen, and sodium valproate (1 case each). Toxic epidermal necrolysis/Stevens-Johnson syndrome (TEN/SJS) was reported in 3 patients and was associated with allopurinol, a paracetamol/ibuprofen combination, and penicillin. (Table IV)

Three risk factors were found to significantly predict severe cADRs after adjusting for other variables. The odds of severe disease were approximately 22 times higher among patients with raised eosinophils (AOR=21.832, 95 CI: 3.637 to 131.050, p=0.001), while those with mucosal involvement had nearly 30 times higher odds of severity (AOR = 29.815, 95 CI: 1.888 to 470.810, p=0.016). Additionally, patients with impaired renal function had almost 8 times higher odds of developing severe disease (AOR=7.977, 95 CI: 1.320 to 48.207, p). Although fever was associated with increased odds of severity (AOR=5.385, 95 CI: 0.956 to 30.328), the result did not reach statistical significance (p=0.056). (Table V)

DISCUSSION

Cutaneous adverse drug reactions remain a major challenge in hospital practice due to their frequency, varied presentations, and potential severity. The incidence in our study was lower than that reported in local retrospective studies (~1%) [6,7] likely due to our study design and exclusion criteria. Some other studies have included broader definitions of cADRs such as those caused by topical agents, radiocontrast media, blood products and outpatients which were excluded from our cohort. Our inclusion of all hospitalized patients across various departments, including lower risk groups, may have diluted incidence compared to studies focused on high-risk populations such as internal medicine inpatients (0.4%).[8] Nevertheless, higher cADR rates

Table V: Multiple Logistic Regression for severe cADRs

Risk factors		Non -severe caDR (%) (n=53)	Severe caDR %() (n=17)	Univariate analysis		p-value	Multivariate analysis p-value
				Crude OR	95 CI		
Sex	Male#	23 (43.4)	8 (47.1)	1	-	-	-
	Female	30 (56.6)	9 (52.9)	-0.863	0.288, 2.582	0.791	
Race	Malay#	39 (73.6)	11 (64.7)	1	-	0.655	-
	Chinese	5 (9.4)	3 (17.6)	2.127	0.438,10.328	0.349	
	Indian	8 (15.1)	2 (11.8)	0.886	0.164,4.793	0.889	
	Other	1 (1.9)	1 (5.9)	3.545	0.205,61.381	0.384	
Underlying Skin Disease	No#	3 (5.7)	17 (100.0)	1	-	-	-
	Yes	50 (94.3)	0 (0)	0.000	0.000	0.999	
History of CADR	No#	44 (83.0)	13 (76.5)	1	-	-	-
	Yes	9 (17.0)	4 (23.5)	1.504	0.398,5.690	0.547	
History of Atopy	No#	47 (88.7)	17 (100.0)	1	-	-	-
	Yes	6 (11.3)	0 (0)	1.042	0.101,10.729	0.973	
RVD Infection	No#	51 (96.2)	14 (82.4)	1	-	-	-
	Yes	2 (3.8)	3 (17.6)	0.000	0.000	1.000	
Autoimmune Disease	No#	50 (94.3)	16 (94.1)	1	-	-	-
	Yes	3 (5.7)	1 (5.9)	0.600	0.065,5.526	0.652	
Malignancy	No#	52 (98.1)	17 (100.0)	1	-	-	-
	Yes	1 (1.9)	0 (0)	0.000	0.000	0.999	
CKD	No#	48 (90.6)	16 (94.1)	1	-	-	-
	Yes	5 (9.4)	1 (5.9)	1.633	0.272,9.814	0.592	
Systemic Complications: Fever	No#	47 (88.7)	10 (58.8)	1	-	-	0.056
	Yes	6 (11.3)	7 (41.2)	5.483	1.515,19.849	0.010	
Systemic Complications: lymphadenopathy	No#	51 (96.2)	14 (82.4)	1	-	-	-
	Yes	2 (3.8)	3 (17.6)	5.464	0.830,35.968	0.077	
Liver Dysfunction	No#	48 (90.6)	11 (64.7)	1	-	-	-
	Yes	5 (9.4)	6 (35.3)	5.236	1.350,20.313	0.017	
Renal Dysfunction	No#	47 (88.7)	10 (58.8)	1	-	-	0.024*
	Yes	6 (11.3)	7 (41.2)	5.483	1.515,19.849	0.010	
Raised Eosinophils	No#	49 (92.5)	9 (52.9)	1	-	-	0.001**
	Yes	4 (7.5)	8 (47.1)	10.889	2.699,43.932	0.001	
Mucosal Involvement	No#	52 (98.1)	13 (76.5)	1	-	-	0.016*
	Yes	1 (1.9)	4 (23.5)	16.000	1.646,155.495	0.017	
Causative Drug Category	Antibiotics #	28 (52.8)	7 (41.2)	1	-	-	-
	Anti-TB	1 (1.9)	4 (23.5)	16.00	1.537,166.533	0.020	
	Anticonvulsant	2 (3.8)	1 (5.9)	2.000	0.158,25.342	0.593	
	Antigout	1 (1.9)	2 (11.8)	8.000	0.631,101.369	0.108	
	NSAIDs	6 (11.3)	1 (5.9)	0.667	0.069,6.474	0.727	
	Analgesics	5 (9.4)	2 (11.8)	1.600	0.255,10.045	0.616	
	Others (combined)	10 (18.9)	0 (0)	0.000	0.000	1.000	
Age Group	Paed#	5 (9.4)	3 (17.6)	1	-	-	-
	Adult	35 (66.0)	6 (35.3)	0.286	0.054,1.522	0.142	
	Elderly	13 (24.5)	8 (47.1)	1.026	0.191,5.507	0.976	
Concurrent Medications	0–4#	37 (69.8)	11 (64.7)	1	-	-	-
	5–9	13 (24.5)	6 (35.3)	1.552	0.478,5.045	0.464	
	>10	3 (5.7)	0 (0)	0.000	0.000	0.999	

#Reference **p-value< 0.001*p-value<0.05

were noted in medical-based departments (internal medicine, dermatology, paediatrics), consistent with findings from France and Singapore[3,9] likely reflecting better awareness and reporting among clinicians.

Demographic patterns in our cohort were consistent with both local and international studies.[6,7,9,10] A slight female predominance was observed, consistent with studies from Singapore and India[9,10] which has been linked to differences in pharmacokinetics, hormonal and immunological factors.[11] Adults aged 19–60 formed the majority of affected patients, a finding mirrored in Malaysian studies and international cohorts,[6,7,10] likely due to higher rates of drug exposure, polypharmacy, healthcare utilization and the dominant age group requiring inpatient treatment.

Latency periods in this study reflected expected immunological mechanisms and are key to identifying the culprit drug through temporal relationship. Urticaria showed rapid onset, while DRESS exhibited delayed presentation. Most reactions were deemed not preventable (85.7%) The presence of preventable cases reinforces the need for meticulous allergy enquiry and safer prescribing practices.

Maculopapular eruptions (MPE) and urticaria were the most common patterns, similar to trends reported globally.[3,6,7,9,10,12] The relative frequency of MPE and urticaria may also reflect their shorter latency, and greater likelihood of detection and reporting compared to other cADRs. Often it was challenging to differentiate from viral exanthems, particularly in febrile patients receiving antimicrobials. Infection-related immune

alteration may contribute to drug hypersensitivity [13,14] often driven by skin-resident memory T cells that have been primed either by prior sensitization or cross-reactivity with viral antigens. [15]

Penicillin were the most frequently implicated drugs, causing diverse reaction types from mild maculopapular eruptions and urticaria to life-threatening SCARs such as AGEP and SJS/TEN. This aligns with their widespread use and strong immunogenic potential. This may be explained by how penicillin-haptenated peptides can form intracellularly and extracellularly, activating multiple T-cell pathways that result in various clinical phenotypes.[15] Nonsteroidal anti-inflammatory drugs (NSAIDs) and other analgesics were the second and third most commonly implicated drug classes after antibiotics, reflecting their widespread inpatient use and established link to both immunologic and non-immunologic cADRs.[16] Urticaria was the most frequent clinical presentation for NSAIDs among our patients. Urticaria and angioedema are well recognized presentations of NSAIDs induced cutaneous reaction consistent with previous studies.[6,7,9,10] Nonallergic hypersensitivity reactions, particularly NSAID-induced urticaria/angioedema (NIUA), accounted for most NSAID-related cases in Southeast Asia, with diclofenac, mefenamic acid, and paracetamol commonly implicated.[17] These trends may reflect both prescribing practices and genetic susceptibility, as suggested by pharmacogenomic research.[17]

Although paracetamol is generally regarded as low risk, emerging data has link it to severe reactions such as SJS/TEN.[18] While no association was found in France, up to a ninefold increased risk was reported in Germany, Italy, and Portugal, where paracetamol is more frequently used as an antipyretic. [19] This may reflect confounding by indication, as infections themselves can predispose to SCARs[20] Paracetamol was implicated in one SJS/TEN case in our study, underscoring the importance of careful assessment even for widely used over-the-counter medications.

Allopurinol was responsible for several SCARs, particularly SJS/TEN and DRESS, reaffirming its status as a high-risk agent in this country.[21–23] A 15-year Malaysian study reported a SCAR incidence of 2.5 per 1000 new users, with SJS being most common (46.8%).[24] Genetic predisposition plays a key role, with HLA-B*58:01 allele increasing susceptibility. The highest prevalence is seen among Chinese, followed by Malays, consistent with our cohort's ethnic distribution.[25] Current local guidelines do not recommend routine genetic screening due to cost-effectiveness concerns, but caution is warranted when prescribing allopurinol.[26] The lower frequency of allopurinol-induced SCARs in our study compared to earlier Malaysian reports [6–8] may reflect improved clinical awareness and risk reduction strategies.

Anticonvulsants were less frequently implicated but still caused both mild and severe reactions. Lamotrigine and sodium valproate were involved in 2.9% and 1.4% of cADRs, respectively. Aromatic anticonvulsants like phenytoin and carbamazepine have been linked to SCARs in previous studies.[8–10] A Malaysian study noted a decline in carbamazepine-induced SCARs after 2016, likely due to the implementation of HLA-B15:02 screening and a shift in prescribing practices.[27] This decline in carbamazepine use was accompanied by an increased use of sodium valproate and lamotrigine, which may explain the continued presence of cADRs and SCARs associated with these agents.

We also identified five cADR cases related to anti-TB therapy, all involving Akurit-4. Reaction types included MPE, AGEP, erythroderma, and DRESS. These findings are consistent with earlier Malaysian and Indian data[28,29] Notably, recent NPRA safety alerts highlighted the risk of ethambutol-induced DRESS[30], underscoring the need for continued vigilance in TB pharmacovigilance as Malaysia has one of the higher TB incidence rates in Southeast Asia, particularly among high-risk populations such as the elderly, immunocompromised, and migrant communities.[31,32]

Most cADRs in our study were of moderate severity, consistent with Malaysian and international data [8,10] The Hartwig scale did not always align with SCAR classifications, as many SCAR cases (about one-quarter) were rated moderate due to the absence of ICU need, only one SJS/TEN case required intensive care. Penicillin was the most frequently implicated drug in SCARs, including AGEP and one SJS/TEN case. Other culprits included allopurinol, Akurit-4, NSAIDs, and paracetamol.

We identified raised eosinophil count, mucosal involvement, and renal impairment as significant predictors of severe cADRs, with mucosal involvement being the strongest predictor. Other risk factors that have been identified in the literature included age over 60 years [8] concomitant drug use, delayed onset and generalized skin involvement.[10] Our findings highlight the added value of integrating laboratory parameters, such as eosinophil count and renal function for a more precise risk stratification and early identification of patients at higher risk, trigger prompt escalation of care, and potentially improve outcomes by enabling earlier interventions.

This study was conducted at a single tertiary center over a 6-month period, which may limit the generalizability of findings as it may not fully represent the broader population particularly in other settings with different drug formularies or prescribing practices. Underreporting and under-recognition of cADRs are possible, especially for milder cases that may have been missed. Patients with short hospital stays (e.g., for elective procedures or deliveries) may have developed cADRs only after discharge and were not captured. The causality assessment in cases involving polypharmacy remains a challenge, particularly in the absence of drug rechallenge.

CONCLUSION

Our data underscore the continued dominance of antibiotics, NSAIDs, analgesic and anti-tuberculosis drugs as key culprits, and highlight the role of systemic complications in driving disease severity. The reduced incidence of anti-gout and anticonvulsant-related reactions observed in this study is likely attributable to increased prescriber awareness and greater caution exercised during the initiation of these high-risk medications.

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SYSTEMATIC / NARRATIVE REVIEW ARTICLE

Unlocking the potential of augmented reality in education: Insights from a systematic review of AR-enhanced instructional approaches

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ABSTRACT

Introduction: This review explores instructional approaches for AR-enhanced learning to improve student motivation, engagement, and learning outcomes. With AR technology gaining momentum, educators aim to implement best practices that leverage its benefits in diverse subject areas.
Materials and Methods: Using a systematic review approach and following PRISMA guidelines, this study analyzed 26 peer-reviewed articles published from 2014 to 2024.

Results: Findings were grouped around three central themes: AR's impact on learning and motivation, instructional approaches that support AR integration, and barriers to AR adoption in educational contexts. The analysis suggests that inquiry-based and collaborative approaches with AR improve student engagement, understanding, and academic performance. These results underscore the need for thoughtfully designed AR activities that provide a balance between student autonomy and guided instruction to avoid cognitive overload. However, challenges like accessibility, inclusivity, and limited resources remain obstacles to broader implementation, especially in under-resourced areas.

Conclusion: Future research should concentrate on developing standardized frameworks for AR in education, improving inclusivity, and assessing AR's long-term impact on learning outcomes across various educational settings.

KEYWORDS:
Instructional strategies, augmented reality, educational approaches, education

INTRODUCTION

Augmented reality (AR) has the potential to enhance learning by adding interactive and immersive elements that extend beyond traditional classroom methods. By enabling learners to visualise abstract ideas, manipulate three-dimensional models, and engage in hands-on digital experiences, AR is particularly useful in disciplines such as science, medicine, and engineering where spatial understanding is critical.[1,2] As technology-enhanced learning grows, interest has increased in how AR can be used effectively to strengthen comprehension and engagement.

Research indicates that AR can improve learning outcomes by enhancing engagement, supporting spatial reasoning, and helping learners understand complex information through real-time interaction with digital objects. 3 Studies also report increased motivation, particularly in areas requiring visualisation of abstract or dynamic content. However, AR's impact depends heavily on how it is integrated into instructional design. Comparisons between self-directed and guided AR activities show inconsistent results, with no clear agreement on which approach yields stronger learning benefits.[4]

Uncertainties remain regarding the best practices for AR implementation across educational contexts. Key questions involve selecting suitable AR tools, balancing learner autonomy with guidance, and preventing cognitive overload when activities are poorly aligned with learning goals. 5 This review addresses these gaps by examining instructional strategies used in AR-enhanced learning and synthesising evidence to identify approaches that most effectively support learning performance, engagement, and understanding.

MATERIALS AND METHODS

Identification

This study followed systematic review procedures to identify relevant research on AR in education. After selecting key terms and their synonyms, search strings were developed for Scopus, Web of Science, and ERIC (see Table I). These databases were chosen for their strong coverage of interdisciplinary and education-related studies, ensuring a robust evidence base.[6] The search yielded 776 records across the three databases. Titles and abstracts were screened to determine relevance to the research question.

Screening

During the screening phase, studies were examined to ensure they addressed the research questions on instructional strategies for AR in education. After removing duplicates, 203 records remained for full-text assessment (Table II). Only peer-reviewed journal articles published in English between 2014 and 2024 were included to maintain methodological consistency. Conference papers, book chapters, and dissertations were excluded. All references were managed in Mendeley to organise citations and eliminate 59 duplicate records.

This article was accepted:
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Eligibility
In the eligibility phase, 144 articles were screened by title and abstract to determine their relevance to the research objectives. A total of 118 were excluded for being outside the scope, unrelated to the topic, or lacking full access. Ultimately, 26 articles met all criteria and were included in the final review.

Quality Appraisal
Three independent reviewers evaluated all 26 studies using the eight-item CASP checklist (Table III). The quality appraisal was conducted by experts with over 10 years of experience in educational technology, providing a consistent evaluation of studies from varied evidence sources.[7] The appraisal examined clarity of aims, methodological alignment, and the appropriateness of data collection and analysis. Any differences in scoring were resolved through discussion, with a fourth reviewer consulted when necessary. All studies met acceptable quality standards and were retained for synthesis, as summarised in Table III.

Data Abstraction and Analysis
An integrative approach was used to synthesise findings across varied study designs. Key information was extracted and reviewed collectively, then organised into preliminary themes. Coding differences were resolved through discussion. Three experts in educational technology and instructional design reviewed the refined themes to ensure clarity and alignment with the study objectives.

The questions are as follows below:
1. How does the use of augmented reality (AR) technology influence learning outcomes and motivation among health professional students compared to traditional learning methods?
2. What are the most effective instructional approaches for implementing augmented reality (AR) to enhance students' comprehension and engagement in anatomy education?
3. What are the primary challenges and limitations of using augmented reality (AR) in higher education, and how do these factors affect its effectiveness in enhancing learning outcomes?

RESULTS

Table IV outlines how the authors thoroughly analyzed 26 publications to extract assertions or information pertinent to the study's focus and Figure 1 shows a PRISMA flowchart detailing the search and selection processes.

This review synthesized evidence from 26 studies on the use of augmented reality (AR) in educational. The results were organized into three main themes: (i) the impact of AR on learning outcomes and motivation, (ii) instructional approaches for effective AR implementation, and (iii) challenges and limitations influencing AR adoption.

Impact of AR on Learning Outcomes and Motivation
Across the reviewed studies, augmented reality (AR) consistently improved academic performance, conceptual understanding, and learner engagement. Many investigations reported higher post-test scores and better retention among students using AR compared with traditional instruction.[8,9,13,18,19,23,26,30] These benefits were especially evident in science, medical, and engineering subjects that rely on spatial reasoning, where interactive 3D models helped learners understand abstract or dynamic concepts more effectively than static resources.

AR also enhanced motivation, with studies noting increased curiosity, emotional involvement, and overall satisfaction.[9,11,13,18,20,25] Its immersive qualities promoted intrinsic motivation by increasing enjoyment and reducing boredom. Overall, the evidence indicates that AR enhances both cognitive and affective learning when aligned with clear learning objectives.

Instructional Approaches for Effective AR Implementation
Most studies highlighted that the effectiveness of augmented reality (AR) depends on the instructional framework used to support it. Inquiry-based learning was the most common approach, with several studies reporting improvements in scientific inquiry, problem-solving, and higher-order thinking when AR was embedded within structured investigations.[9,16,17,21,24,32] These designs encouraged exploration, hypothesis testing, and linking virtual observations to real-world concepts.

Collaborative and game-based approaches were also widely used. AR activities involving teamwork or gamification enhanced communication, participation, and shared problem-solving, supporting social learning and deeper conceptual understanding.[14,19,27,29]

Several studies implemented systematic instructional design models such as ADDIE or design-based learning (DBL).[15,17,22,28,30] These frameworks ensured alignment with learning goals and reduced unnecessary cognitive load, leading to better comprehension and application of concepts.

Overall, AR produced stronger outcomes when integrated within inquiry-based, collaborative, or design-model pedagogies rather than used in isolation.

Challenges and Limitations of AR in Education
Despite its benefits, several challenges limit AR implementation. Technical constraints—including limited devices, unstable connectivity, and insufficient support—reduce accessibility, especially in under-resourced settings.[15,21,26,31] These issues reduced accessibility, particularly in under-resourced settings. Pedagogical issues also arise when AR content is overly complex or misaligned with learning goals, leading to cognitive overload and reduced instructional value.[15,18,23,27] Poor alignment with curriculum objectives further limited instructional value. Social and contextual barriers further restrict use, as many educators lack adequate training, and accessibility concerns affect students with disabilities or those in rural areas.[21,24,30] Addressing technological gaps, instructional misalignment, and educator readiness is essential. AR can enhance learning when supported by strong design and sufficient resources.

Table I: The Search String

Scopus	TITLE-ABS-KEY (("learn* approach*" OR "learn* technique*" OR "instructional technique*" OR "teach* strategie*" OR "instructional strategie*") AND ("augmented reality") AND ("education")) AND (LIMIT-TO (PUBYEAR , 2014) OR LIMIT-TO (PUBYEAR , 2015) OR LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2017) OR LIMIT-TO (PUBYEAR , 2018) OR LIMIT-TO (PUBYEAR , 2019) OR LIMIT-TO (PUBYEAR , 2020) OR LIMIT-TO (PUBYEAR , 2021) OR LIMIT-TO (PUBYEAR , 2022) OR LIMIT-TO (PUBYEAR , 2023) OR LIMIT-TO (PUBYEAR , 2024)) AND (LIMIT-TO (DOCTYPE , "ar")) AND (LIMIT-TO (LANGUAGE , "English"))
Wos	("learn* approach*" OR "learn* technique*" OR "instructional technique*" OR "teach* strategie*" OR "instructional strategie*") AND ("augmented reality") AND ("education") (Topic) and 2024 or 2023 or 2022 or 2021 or 2020 or 2019 or 2018 or 2017 or 2016 or 2015 or 2014 (Final Publication Year) and Article (Document Types) and English (Languages)
ERIC	augmented reality AND ("learning approaches" OR "instructional techniques" OR "learning techniques" OR "teaching strategies" OR "instructional strategies") AND education

Table II: The Selection Criterion is Searching

Criterion	Inclusion	Exclusion
Language	English	Non-English
Timeline	2014–2024	< 2014
Literature type	Journal (Article)	Conference, Book, Review

Table III: The Quality Appraisal

		Yes Expert 1	Yes Expert 2	Yes Expert 3	No Expert 1	No Expert 2	No Expert 3	Total agreement (%)	Comments
Section A: Are the results valid?	1. Was there a clear statement of the aims of the research?	/	/	/				100	Excellent
	2. Is a qualitative, quantitative and mixed-method research approach appropriate?	/	/	/				100	Excellent
	3. Was the research design appropriate to address the aims of the research?	/	/	/				100	Excellent
	4. Was the recruitment strategy appropriate to the aims of the research?	/	/	/				100	Excellent
	5. Was the data collected in a way that addressed the research issue?	/	/	/				100	Excellent
Section B: What are the results	6. Was the data analysis sufficiently rigorous?	/	/	/				100	Excellent
	7. Is there a clear statement of findings?	/	/	/				100	Excellent
Section C: How valuable is the research?	8. How valuable is the research?	/	/	/				100	Excellent

DISCUSSION

This review of 26 studies shows that augmented reality (AR), when embedded within instructional frameworks, generally improves learning outcomes, engagement, and motivation. The effects are strongest in science and health-related disciplines that require visual–spatial and procedural understanding. Common pedagogical approaches include inquiry-based, collaborative, and design-model strategies, though variations in study quality and learner groups warrant cautious interpretation.[35,36]

In medical and health-science education, AR has been effective for teaching anatomy, clinical skills, and radiology by helping learners visualise complex structures and procedures. Tools such as AEducaAR, which combine AR with 3D printing, have improved anatomical understanding, confidence, and motivation.[18] AR-based nursing and radiology modules similarly enhance procedural performance and reduce reliance on static 2D materials.[37] By overlaying dynamic 3D structures onto real-world views, AR supports both cognitive and psychomotor learning.[38]

When implemented through structured instructional models, AR promotes deeper and more sustained learning. Inquiry-based designs encourage exploration and concept construction, while collaborative and game-based approaches support active participation and teamwork. Systematic models such as ADDIE help ensure alignment with learning goals and reduce cognitive overload.[39,40] Through this structured use, AR can bridge theoretical knowledge with practical application, strengthening students' clinical preparedness.[41]

Despite these benefits, challenges persist. Hardware costs, connectivity issues, and limited technical support restrict use in low-resource settings.[39] Misaligned or overly complex AR content can overwhelm learners, while many educators lack sufficient training. Social and accessibility barriers, particularly for students with disabilities, further limit adoption.[42,43] Addressing these issues requires improved infrastructure, stronger instructional design, and continuous professional development, alongside research on AR's long-term learning impact.

Table IV: Summary of Selected Article

No	Authors	Title	Journal	Findings
1	Huang et al. [8]	Animating eco-education: To see, feel, and discover in an augmented reality-based experiential learning environment	Computers & Education (2016)	- Improved engagement, curiosity, and learning effectiveness.
2	Chiang et al. [9]	An Augmented Reality-based Mobile Learning System to Improve Students' Learning Achievements and Motivations in Natural Science Inquiry Activities	Educational Technology & Society (2014)	- Better achievement and motivation; reduced cognitive load.
3	Cai et al.[10]	Tablet-based AR technology: Impacts on students' conceptions and approaches to learning mathematics according to their self-efficacy	British Journal of Educational Technology (2019)	- Enhanced understanding and learning approach, especially among high self-efficacy learners.
4	Hsieh [11]	Development and Application of an Augmented Reality Oyster Learning System for Primary Marine Education	Electronics (2021)	- Improved learning achievement, interest, and interactivity.
5	Hsu [12]	Learning English with Augmented Reality: Do learning styles matter?	Computers & Education (2017)	- Self-directed and task-based AR yielded similarly high learning effectiveness.
6	Czok et al. [13]	Learning Effects of Augmented Reality and Game-Based Learning for Science Teaching in Higher Education in the Context of Education for Sustainable Development	Sustainability (2023)	- Increased motivation and engagement; comparable achievement to traditional learning.
7	Kamal and Junaini [14]	The Effects of Design-Based Learning in Teaching Augmented Reality for Pre-University Students in The ICT Competency Course	International Journal of Scientific & Technology Research (2019)	- DBL approach improved academic performance and both LOTS and HOTS.
8	Nasir and Fakhruddin [15]	Design and Analysis of Multimedia Mobile Learning Based on Augmented Reality to Improve Achievement in Physics Learning	International Journal of Information and Education Technology (2023)	- AR-based mobile learning improved physics achievement.
9	Chiang et al. [16]	Students' online interactive patterns in augmented reality-based inquiry activities	Computers & Education (2014)	- AR inquiry learning increased interaction, concentration, and higher-order thinking.
10	Wen et al. [17]	Integrating augmented reality into inquiry-based learning approach in primary science classrooms	Education Tech Research Dev (2023)	- AR-supported inquiry enhanced autonomy and creative thinking.
11	Cercenelli et al. [18]	AEducaAR, Anatomical Education in Augmented Reality: A Pilot Experience of an Innovative Educational Tool Combining AR Technology and 3D Printing	International Journal of Environmental Research and Public Health (2022)	- Improved motivation, confidence, and anatomical understanding.
12	Rodríguez-Abad et al.[19]	Online (versus face-to-face) augmented reality experience on nursing students' leg ulcer competency: Two quasi-experimental studies	Nurse Education in Practice (2023)	- AR improved performance, motivation, satisfaction, and learning outcomes.
13	Li et al. [20]	From motivational experience to creative writing: A motivational AR-based learning approach to promoting Chinese writing performance and positive writing behaviours	Computers & Education (2023)	- Motivational AR approach improved writing performance and immersion.
14	Lin et al. [21]	Mitigating the Urban-rural Digital Divide: A Dual Scaffolding-embedded Mobile Augmented Reality Learning Approach in the Post-COVID-19 Pandemic	Educational Technology & Society (2023)	- Dual-scaffolding AR improved achievement, cognition, and self-efficacy.
15	Lee and Hsu [22]	Sustainable Education Using Augmented Reality in Vocational Certification Courses	Sustainability (2021) Anatomical Sciences Education (2016)	- AR improved learning effectiveness and reduced cognitive load.
16	Küçük et al. [23]	Learning Anatomy via Mobile Augmented Reality: Effects on Achievement and Cognitive Load	Journal of Pedagogical Research (2024)	- Mobile AR enhanced anatomy achievement and lowered cognitive effort.
17	Rizki et al. [24]	Cooperative model, digital game, and augmented reality-based learning to enhance students' critical thinking skills and learning motivation	Int. J. Innovation and Learning (2018)	- AR + cooperative digital learning improved critical thinking and motivation.
18	Harncharnchai and Saeheaw [25]	Context-aware learning using augmented reality and WebQuest to improve students' learning outcomes in history	Education and Information Technologies (2024)	- Improved outcomes and engagement; high learner satisfaction.
19	Weng et al. [26]	Can an augmented reality-integrated gamification approach enhance vocational high school students' learning outcomes and motivation in an electronics course?		- AR gamification improved outcomes across cognitive, affective, and psychomotor domains.

Table IV: Summary of Selected Article

No	Authors	Title	Journal	Findings
20	Cascales-Martínez et al. [27]	Using an Augmented Reality Enhanced Tabletop System to Promote Learning of Mathematics: A Case Study with Students with Special Educational Needs	EURASIA Journal of Mathematics Science and Technology Education (2017)	- Improved knowledge, motivation, and collaboration among special-needs learners.
21	Hsu [28]	Effects of gender and different augmented reality learning systems on English vocabulary learning of elementary school students	Univ Access Inf Soc (2019)	- Two AR gaming systems produced high vocabulary learning effectiveness.
22	Cheng et al. [29]	An in-depth analysis of the interaction transitions in a collaborative Augmented Reality-based mathematic game	Interactive Learning Environments (2019)	- AR-based collaborative game showed dynamic, non-linear interaction patterns.
23	Ruiz-Ariza et al. [30]	Effect of augmented reality game Pokemon GO on cognitive performance and emotional intelligence in adolescent young	Computers & Education (2018)	- Improved attention, concentration, and sociability; no effect on memory or maths.
24	Bos et al. [31]	Educational Technology and Its Contributions in Students' Focus and Attention Regarding Augmented Reality Environments and the Use of Sensors	Journal of Educational Computing Research (2019)	- AR increased focus and attention compared to other digital platforms.
25	Giancaspro et al. [32]	An active learning approach to teach distributed forces using augmented reality with guided inquiry	Computer Applications in Engineering Education (2024)	- Guided-inquiry AR improved understanding and corrected misconceptions.
26	Chen et al. [33]	Supporting informal science learning with metacognitive scaffolding and augmented reality: effects on science knowledge, intrinsic motivation, and cognitive load	Research in Science & Technological Education (2023)	- Metacognitive scaffolding + AR improved science knowledge and intrinsic motivation.

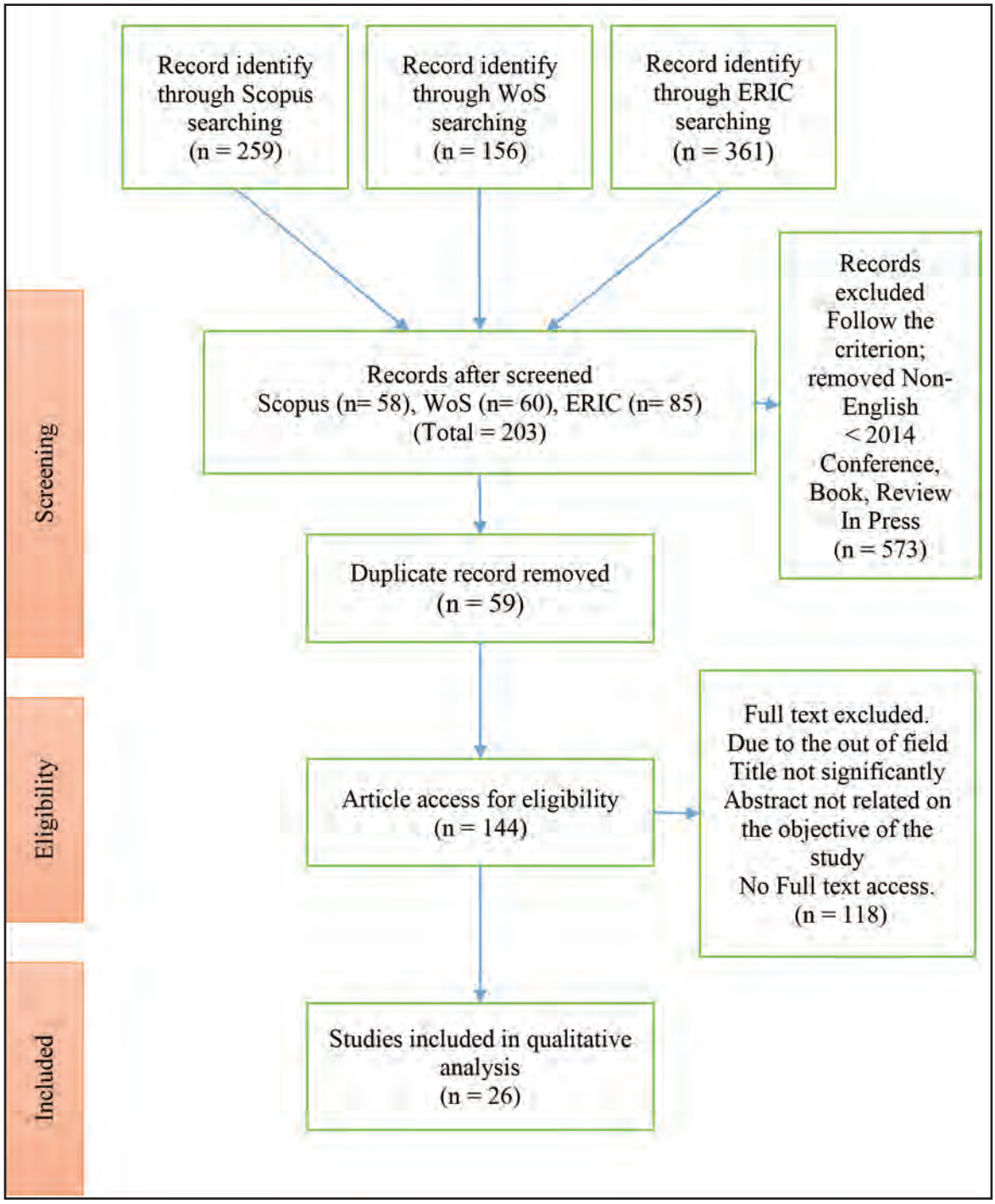

Fig. 1: Flow Diagram of the Proposed Searching Study[34]

Review Strengths and Weaknesses

A key strength of this review is its rigorous methodology and broad coverage of educational contexts. The systematic search identified 26 peer-reviewed studies across multiple databases, providing a credible evidence base on AR use in health sciences and STEM education. However, limiting the review to English-language, peer-reviewed publications excluded grey literature and may introduce reporting bias. Considerable variation in AR applications and instructional models also prevented meta-analysis due to data heterogeneity.

CONCLUSION

Augmented reality has strong potential to improve learning when paired with structured instructional approaches such as inquiry-based and collaborative designs. Its success, however, depends on effective design, educator support, and adequate

infrastructure. Addressing technical, pedagogical, and social barriers through coordinated institutional efforts is essential. Developing clear implementation frameworks, ensuring inclusive access, and evaluating long-term outcomes will further strengthen its use. With these supports, AR can become a sustainable tool that promotes engagement and deep learning.

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Getting to outcomes (GTO) approach towards stewardship of patient blood management for the Malaysian health care system

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ABSTRACT

Introduction: The Patient Blood Management (PBM) program provides optimal stewardship of limited blood resources using evidence-based practice. PBM applies evidence-based strategies for reducing costs and improving patient outcomes while conserving scarce blood bank resources. However, implementing a PBM program requires multidisciplinary collaboration, organizational support, organizational change, and motivating a wide range of stakeholders. The COVID pandemic has abridged blood donations globally to the point that there is a chronic critical shortage in many locations.

Materials and Methods: This paper explored the application of the Getting To Outcomes® (GTO) implementation science framework to support effective PBM implementation. GTO integrates Readiness Assessment and Empowerment Evaluation techniques to assess local needs, build capacity, and ensure stakeholder alignment. These methods are particularly useful for adapting programs to dynamic healthcare environments.

Results: Evidence from the literature indicates that GTO enhances organizational readiness, engages diverse stakeholders, and promotes sustainable implementation. The structured 10-step process of GTO enables PBM programs to be tailored to local settings. A hub-and-spoke peer-mentoring model is also proposed to support wider adoption.

Conclusion: Systematic execution and sustainability of PBM Programs is facilitated by structural approach of the implementation of science in adapting PBM programs to local needs, using framework such as the Readiness Assessment and Empowerment Evaluation from the Getting to Outcomes model. Successful implementation guided by this framework could support the development of hub-and-spoke networks of peer mentorship and help fulfill the World Health Organization's call to strengthen patient blood management worldwide.

KEYWORDS:
Implementation Science strategies, Patient Blood Management, Getting to Outcomes

INTRODUCTION

Patient blood management (PBM) is a patient-centered, systematic, evidence-based approach to improve patient outcomes by managing and preserving the patient's own blood while promoting patient safety and empowerment.[1] Major topics addressed in the PBM framework include iron deficiency, anemia, blood loss, and coagulopathy.[2-4] Blood transfusion is reserved for situations where all alternative strategies have been evaluated and deemed insufficient, with shared decision-making (SDM) ensuring that patients are actively involved in determining their own care.[5-6] PBM was first introduced in Western Australia in 2008, and since then it expanded worldwide. PBM was endorsed by World Health Assembly Resolution WHA63.12 in 2010.[7] Policy briefs on the urgent need for PBM implementation have been introduced by World Health Organization (WHO) since 2010.[4,8-9]

Iron Deficiency Anemia (IDA) affects 1.24 billion people globally and is a leading cause of long-term disability, especially among women.[10] Preoperative anemia is common, affecting 30–60% of patients undergoing major surgeries.[11] In Malaysia, one in five individuals is anemic, with higher prevalence among women, rural populations, retirees, and low-income groups.[12] Transfusions, while necessary, are linked to increased complications and prolonged hospital stays.[13] A study showed that implementing PBM can reduce transfusion needs and lower costs by approximately RM3,690 per patient annually.[14] Despite its benefits, PBM remains champion-driven rather than standard practice. A key milestone of advancing PBM practice was the launch of Malaysia's National Document Consensus Statement on PBM by the Health Minister on May 16, 2024 which marked a step toward broader implementation and potential cost savings.[15]

While this national initiative is a significant milestone, the sustained implementation of PBM requires a systematic, evidence-based approach. The Getting to Outcomes (GTO) framework provides a structured model for planning, executing, and evaluating PBM strategies to ensure effectiveness and long-term sustainability.

A well-implemented PBM program reduces transfusion risks, adverse events, morbidity, mortality, hospital stays, and medical costs.[1,6,16-18] However, despite strong evidence, resources, and policy support, its adoption remains

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limited.[5,19-20] Global gaps persist due to barriers at multiple levels such as policy, organizational, and multidisciplinary which are further influenced by interpersonal and intrapersonal factors.[19,21-22] Internal barriers, such as healthcare providers' knowledge and attitudes, impact awareness, willingness to change, and adherence to best practices. Meanwhile, external barriers including education, infrastructure, financial constraints, and regulatory policies further hinder implementation.[23-24] Addressing these challenges requires a comprehensive approach that strengthens policy adherence, enhances organizational support, and fosters multidisciplinary collaboration.

Therefore, the formation and effective implementation of a wide-ranging PBM program require evidence-based interventions, multidisciplinary collaboration, organizational readiness, and change to adopt and sustain the program.[19,25-26] The successful execution of an enhanced recovery pathway involves coordinated efforts and education across multiple departments and members of the health care team, also known as "stakeholders." PBM decisions must involve all levels of stakeholders through multidisciplinary, multi-professional, multimodal, and individualized approaches involving general practitioners, care physicians, surgeons, anesthesiologists, hematologists, pharmacists, transfusion medicine specialists, nurses, administrators, and ultimately the patient.[5,19,23] Not coordinating the motivations of these stakeholders can emasculate a PBM program. According to the "Knowledge-Attitude-Behavior Framework", all stakeholders have to be aware and conversant of the policy and guidelines aligned, afterward knowledge will influence attitudes, and attitudes affect the practice behavior.[24,27] The intertwining between these three is dynamic and sometimes reciprocal.[27]

Implementation

In general, the PBM framework emphases on the risks of iron deficiency, anemia, blood loss, and coagulopathy.[17,18,26] PBM implementation approaches may vary among subspecialties, surgical routes, institutions, and organizational settings. The creation and effective implementation of a comprehensive PBM program require evidence-based interventions and there are communal barriers experienced. However, there is currently no conclusive evidence to suggest which implementation strategies are most effective.[19,22]

GTO is a Prevention Support System intervention, which is conceptualized by the Interactive Systems Framework and provides the necessary guidance and tools, tailored to individual capacity and program performance. The Readiness Assessment, and Empowerment Evaluation techniques developed by GTO align stakeholders in planning, demonstrate local needs, and identify when an organization is ready for policy change or policy sustainability developed by RAND corporation and the University of South Carolina.[25,28-34]

For the implementation of a complex, multidisciplinary initiative like PBM within the MOH hospital system, the GTO framework is recommended as the core operational model due to its pragmatic and structured approach.[29,30] In contrast to frameworks like PRECEDE-PROCEED, which require an exhaustive and potentially resource-prohibitive diagnostic process, GTO offers a well-balanced, 10-step guide that is adequate for the task without being overwhelming for clinical teams operating under resource constraints.[30,35] This flexible structure provides an accessible "roadmap" for frontline staff, fostering a common language essential for aligning diverse stakeholders. Furthermore, its integrated focus on capacity building, planning, and continuous quality improvement directly addresses the primary challenges of standardizing clinical practice and embedding sustained organizational change within a hospital setting.[29,30]

Despite its operational advantages, it is important to recognize the scope of the GTO framework. GTO does not invariably translate to improved final health outcomes. The framework's diagnostic steps are intentionally more streamlined than the deep analysis found in models like PRECEDE-PROCEED which provide just enough structure to guide clinical teams without the burden of an overly complex investigation.[30,35] Similarly, its evaluation components are focused on program-level improvement, which empowers the implementation team through an actionable and manageable process, rather than assessing the broader public health impact detailed in frameworks like RE-AIM (Reach, Effectiveness, Adoption, Implementation, Maintenance) or CFIR (Consolidated Framework for Implementation Research).[36] Therefore, GTO serves as a highly effective and motivating engine for implementation, and its efficacy is optimized when its focused, practical steps are understood as a tool to empower the multidisciplinary clinical team through a clear and achievable process. GTO embeds stakeholder engagement and empowerment evaluation throughout the implementation process, enabling diverse teams to co-design strategies, adapt interventions to local contexts, make data-informed adjustments, and build long term capacity for sustainability.[29,30]

GTO 10-step systematic methods bridge the gap between ideal program design and real-world implementation. This validated comprehensive planning approach (manual, training, technical assistance) place the logic and tools of evaluation into the hands of stakeholders, equipping them to address challenges related to program planning, implementation, and success evaluation (See Table II). Empowerment evaluation engages stakeholders in every step of implementation to be accountable in their own specific settings, and to use program data to make mid-course corrections.30 This powerful approach to broadening participation has not been used in PBM. Introduction of this GTO as evidence base intervention into PBM implementation theory is a way forward to advance understanding and the impact.

The planning phase (steps 1-6) focuses on identifying needs, setting goals, assessing resources, and developing strategies to ensure readiness for execution. An advisory team will tailor the GTO framework for PBM, addressing implementation barriers and stakeholder roles. To drive culture change, it is crucial to identify PBM's key barriers, drivers, and stakeholder roles.[37] The advisory team, with members from key partner organizations, ensures collaboration and adaptability to evolving challenges like

Table I: Stakeholders, accelerators, and challenges/barriers for patient blood management

Stakeholders	Accelerator	Challenges/Barrier
Government Ministry of health	Support from hospital administration and committed PBM committee	No uniform approach- stakeholders- guidance-implementation and monitoring Limited PBM experience
Healthcare provider level	Patient safety	No legal framework, standards, accreditation and quality certification Limited infrastructure and support
Hospital Administrator	National policy and organizational guidelines	Segmentation and fragmentation of health system Number of stakeholders
Primary care physician	Extensive PBM engagement: promotion, education, awareness, publication and certification.	Lack of awareness, promotion and education Lack of knowledge on current transfusion practice
Surgeon including surgical scheduler, advanced practice providers and trainees	Motivation towards evidence-based practices for better care and practices	Scared or resistant for practice change Attitude of strong belief in transfusion
Obstetrics gynecology	Interdisciplinary alignment and collaboration	Lack of interdisciplinary commitment and communication Change in work practice
Anesthesiologist and anesthesia team, including nurse anesthetists	Quality assurance metric and obligation: Audit, benchmarking and improvement strategies	No quality and metric planning, guide and monitoring Collaboration
Hematologist	Health economic analyses, cost saving and cost transparency	Perceived high cost and too slow progress Communication
Transfusion Medicine Specialist and blood bank	Blood shortage. reduced complication and transfusion adverse events	No resources or selective information dissemination Cost for alternative implementation
Others: Nurses, Pharmacist, information technologist (IT) personnel, laboratory personnel	Patient demand	No involving patient/patient request immediate surgery/litigation fear Quality matric
Patients and patient advocate	Blood scarcity	Assume blood is always available Sustainability
Public health/health research	Opportunities for improvement, competition for implementation and evidence base medicine publication	No motivation and demotivation Resources and cost No funding and resources. Medication not available
Pharmaceutical industries and insurance company	Funding, resources, available equipment, incentive PBM engagement, clear agreement provider and insurance	with outdated equipment and point of care testing (POCT) Resources and cost

Table II: The 10 steps of GTO

No.	GTO Step	Purpose
1	Needs and resources assessment	This step helps you identify and document the need for a program and related existing community resources.
2	Goals and desired outcomes	This step prompts you to develop a goal, specific desired outcomes, relevant program activities to reach the goal, and a logic model that displays all these elements.
3	Best or promising practices	This step guides you to review existing best/promising practices for achieving the established goals/objectives and selecting the best approach.
4	Assess fit	This step provides a structure to determine whether the program you identified during GTO Step 3 is appropriate for your target, community, and organization.
5	Address capacities issue	This step provides a structure to determine whether the program(s) you identified during GTO Step 3 (e.g. human, financial, technical, intellectual) can be carried out effectively with the knowledge, skills, and resources of your organization and its partners. Also, to address any capacity gaps.
6	Develop a plan Implementation plan and conduct process evaluation	This step helps you make a detailed work plan for delivering and evaluating the program you identified in Step 2 and 3 and selected at the end of Steps 4 and 5.
7	Outcome evaluation	This step provides guidance on what to include in, and how to gather data for, a process evaluation, which tells you how well you delivered the program (monitoring implementation)
8	Continuous Quality	This step helps with planning an outcome evaluation and using the results from it. An outcome evaluation reveals how well you met the goals and desired outcomes you set for the program in Step 2. Assess the effectiveness of the innovation.
9	Improvement	This step provides a framework for using process and outcome evaluation data to make program improvements. Short-term (mid-course) and long-term (strategic) corrections across the stages of the program.
10	Sustainability	This step guides you through some questions to consider when making decisions about whether your organization should continue a program.

Table III: The Getting to Outcome (GTO) Framework For the Patient Blood Management Program

GTO Step	Core Objective	Key Activities & Responsibilities with Healthcare Examples	Key Stakeholders
1. Needs & Resources Assessment	To understand the current situation and establish a foundation for the PBM program.	• Form a multidisciplinary steering committee with champions from key departments. • Assess current practices: Audit transfusion triggers (e.g., pre-transfusion hemoglobin levels), calculate the crossmatch-to-transfusion (C/T) ratio, and review blood ordering patterns. • Assess resources: Map the availability of point-of-care testing (POCT), IV iron infusion services, and cell salvage technology. • Identify gaps: Pinpoint issues like the lack of a standardized preoperative anemia screening protocol or inconsistent use of blood conservation agents. • Gather patient perspectives: Conduct surveys or focus groups to understand patient awareness of transfusion risks and alternatives.	Hospital Leadership, Clinical Department Heads (Surgery, Anesthesia, Hematology), Transfusion Medicine, Nursing, Pharmacy, Patients/Patient Advocates.
2. Goals & Objectives	To set clear, specific, and measurable goals for the PBM program.	• Define target population: Initially focus on high-volume elective surgeries (e.g., orthopedic or general surgery). • Establish specific KPIs: For example, "Reduce red blood cell units transfused per 1,000 patient days by 20% within two years" or "Ensure 70% of anemic elective surgery patients are identified and treated preoperatively." • Develop a logic model: Visually map how PBM activities (e.g., establishing an anemia clinic) will lead to short-term outcomes (e.g., increased preoperative hemoglobin) and long-term goals (e.g., reduced mortality, complications, and costs). • Run safe and inexpensive care awareness on transfusion alternatives.	Steering Committee, All Clinical Staff, Hospital Administration, Patients.
3. Best Practices	To select evidence-based PBM strategies that align with the program's goals.	• Review evidence: Systematically review national and international PBM guidelines (e.g., WHO, AABB). • Develop local protocols: Achieve consensus on and formalize core clinical protocols, such as implementing a restrictive transfusion threshold, standardizing the use of tranexamic acid in major surgeries, and creating a clear pathway for preoperative anemia management. • Run engagement awareness on transfusion alternatives.	Steering Committee, Clinical Champions, All Clinical Staff, Patients.

COVID-19.[5,23] (See Table III). The implementation phase puts planned interventions into action while the formative evaluation phase (7-10) uses the GTO empowerment evaluation procedure in monitoring progress, refining strategies, and ensuring sustainability. This evidence-based, systematic approach enhances program effectiveness, accountability, and long-term impact. Stakeholder capacity to make adjustments will be tracked, with local conditions balanced against program fidelity. The fidelity of PBM will be assessed by the local advisory committee and central evaluation teams. Observational data will guide adjustments to training or support, and adherence to longitudinal data collection on outcomes will serve as a key performance measure.[29,31] This structured, evidence-based approach strengthens accountability and supports sustainable culture change in patient blood management. Table III therefore serves not only as a consolidated overview of the GTO framework, but also as a practical, context-adaptable guide that Malaysian hospitals can use to plan, implement, and evaluate PBM initiatives within their own settings.

Implementation matrix in PBM

Successful PBM implementations are the result of careful planning, constant collaboration, and customized strategies that balance critical priorities for the plan with specific needs and expectations from stakeholders. Recognizing effective measures for Patient Blood Management implementation depends on the aim, measures, and expected outcome based on the economic and healthcare context in the organization or country (See Table IV).[18,37]

Malaysia faces unique systemic barriers that hinder widespread adoption. These barriers are largely shaped by funding limitations, hierarchical decision-making processes, and demographic pressures on the blood supply. Overcoming these challenges requires a structured, context-specific implementation strategy anchored in the GTO framework.[29,30]

Funding Limitations

Malaysia's predominantly tax-based public healthcare system allocates finite resources to high volume service delivery, leaving limited funding for quality improvement initiatives like PBM.[4] Costs associated with PBM include training, anemia screening programs, intraoperative blood conservation technology, and point-of-care diagnostics. To address this barrier, evidence demonstrating PBM's cost-effectiveness in reducing transfusions, complications, and length of hospital stay should be generated and presented to policymakers. Pilot PBM programs in major tertiary hospitals could showcase measurable financial benefits, supporting the case for dedicated funding.[19,22] Additionally, public-private partnerships, including collaborations with private hospitals and NGOs, could further provide seed funding for initial implementation.[16]

Institutional Hierarchies

Decision making in public hospitals often follows a centralized, top-down structure, requiring approvals from hospital directors, state health authorities, and the Ministry of Health. This hierarchy can slow innovation and limit flexibility for departmental level PBM pilots. Overcoming this

Table IV: Patient Blood Management Implementation Matrix

Implementation matrix in PBM	Purpose
Coordination of PBM implementation practices	Accreditation and certification Awareness survey Extension of promotion: local, state and national level
Implementation best practice	Identifying hospital champion Identifying PBM coordinators Incentive and rewards IT expansion and impact outcome
Measurable outcome	Metrics, data, and benchmarking Number of PBM-related presentations and publications published Research Expanding PBM knowledge
Transfusion practices	Blood request Blood utilization Group Screen and Hold (GSH) vs Group Cross-matched (GXM) CT ratio Adherence to MSBOS
Anemia management	Pre anesthesia anemia referral Infusion or anemia clinic data collection Impact on early pre anemia referral and intervention
Patient-centered practices	Shared decision Informed consent Morbidity and mortality Patient safety impact
Transfusion associated adverse events	Transfusion transmitted infection (TTI) Transfusion associated Adverse events
Cost	Saving of PBM vs. transfusion Blood cost transparency Length of stay Established funding options and incentives Funding impact analysis towards the betterment of PBM implementation e.g. POCT, thromboelastogram (TEG)
Multidisciplinary engagement	PBM implementation survey involving multidisciplinary and multi-professional level
Education and Awareness	Number of continuous medical education (CME) across departments, public Change in guidelines, protocol, and curriculum Social media engagement and education

barrier requires early engagement of hospital leadership to integrate PBM into institutional policies and strategic plans.[24] Establishing formal multidisciplinary implementation teams which include surgeons, anesthetists, transfusion medicine specialists, nurses, and administrators. Mission is to foster horizontal collaboration, streamline decision-making, and ensure shared ownership of PBM initiatives.[38] At the national level, Malaysia's 2024 MOH Consensus Statement on PBM marks a key policy milestone. Greater awareness, dissemination, and enforcement of this statement alongside its integration into national clinical guidelines, similar to antibiotic stewardship programs would strengthen institutional commitment and accelerate PBM adoption.

Patient Demographics and Blood Supply Constraints

Malaysia faces rising demand for blood transfusions due to its aging population, high surgical volumes, and increasing prevalence of chronic diseases such as diabetes, cancer, and chronic kidney disease.[12] Simultaneously, voluntary blood donation rates remain low, compounded by misconceptions about blood donation and logistical barriers for donors.[39] To mitigate, PBM programs should prioritize preoperative anemia screening and treatment pathways, including intravenous iron supplementation and erythropoiesis-stimulating agents.[40] Parallel public health campaigns aimed at culturally tailored donor recruitment and patient education on PBM benefits can reduce transfusion dependence and improve patient acceptance of alternatives.

Scale-up strategies: PBM Hubs and peer support

Hubs that have developed expertise in PBM can serve as peer support for new PBM sites, by building communication between individuals with similar roles. These can be informal (38) or formalized networks with a Project ECHO model for ongoing support via a monthly teleconference structure.[34] The program director of a successful Hub can advise a new site's program director on policies and implementation strategies accordingly. In addition, the program director would be able to connect with specific stakeholders who have been involved in a particular setting e.g. surgical leadership, and surgical nurses can reach out to their peers in a PBM Hub for advice and examples.

Most of these interactions can be conducted by teleconference, thus leveraging the reach of a Hub over a large region. The PBM program can provide some funding for the Hub to compensate them for these efforts.

LIMITATIONS

This paper reviews the authors' experiences collated from documented international literature and reviews

supplemented by conversation and discussion with members of PBM and bloodless medicine society, organization, and implementers. As the methods did not include formal quantitative or qualitative evaluation, the information presented is descriptive and reflects the individual and cumulative perspectives of the authors.

CONCLUSION

The implementation of Patient Blood Management (PBM) in Malaysia has recently gained national recognition, but its long-term success depends on structured planning, ongoing evaluation, and strong stakeholder engagement. PBM is practically and evidently manageable within healthcare systems, and the use of implementation science can help generalize lessons learned, leading to faster scale-up and better sustainability. The Getting to Outcomes framework provides a strategic multidisciplinary roadmap to ensure PBM is effectively integrated, continuously improved, and sustained across Malaysia's healthcare system. By incorporating readiness assessments and empowerment evaluation of outcomes, GTO can enhance patient safety, optimize blood resources, and strengthen the overall healthcare infrastructure. This structured approach will facilitate long-term adoption and ensure PBM becomes a standard practice in clinical care nationwide.

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Immunotherapy for non-oncogene driven resectable non-small cell lung cancer: A true gamechanger but for whom and when?

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Curative-intent surgery remains the definitive treatment for resectable non-small cell lung cancer (rNSCLC) in medically operable patients, offering a realistic cure, superior disease-free survival (DFS) and overall survival (OS). For several decades, adjuvant platinum-based chemotherapy (PBC) was the standard-of-care however despite R0 resections, recurrence rates remain unacceptably high with correspondingly poor survival and a modest 5.4% OS benefit over surgery alone.[1] Relapse is often due to occult micro metastasis present at initial therapy hence alternative agents and strategies are required to improve long-term prognosis. In recent years, the treatment paradigm for rNSCLC has evolved considerably. In non-oncogene driven rNSCLC, immune checkpoint pathway blockade with programmed cell death-1 (PD1) or programmed cell death ligand-1 (PDL-1) inhibitors have emerged true gamechangers for patients who achieve a major pathological response (MPR) or complete pathological response (pCR). Several phase 3 neoadjuvant/peri-operative chemo-immunotherapy trials (CM816, KN671, AEGEAN, Neotorch and CM77T) demonstrated impressive pCR rates that correlate with excellent event-free survival (EFS) and OS.[2-6] pCR is emerging as a good surrogate for EFS and OS. CM 816 (3 cycles of neoadjuvant nivolumab plus chemotherapy (CT) versus CT-only) reported excellent outcomes; median OS not reached (NR) (nivolumab arm) vs 73.7 months (CT-only) [HR 0.72 CI (0.523-0.998) (p=0.04)] and 5-year OS 65% vs 53% [HR 0.70 CI (0.47-1.05)] favouring nivolumab in patients with stage IIIA disease. Similarly, in KN671 (4 cycles of neoadjuvant pembrolizumab and CT followed by adjuvant pembrolizumab vs. CT-only) reported median OS was NR (pembrolizumab arm) vs 52.4 months (CT-only) and 4-year OS benefit: 67.1% vs 51.5% [HR 0.72 CI (0.56-0.93) p=0.005).

The relative benefit of any immunotherapy must be viewed in the context of an individual patient's baseline risk and weighed against financial cost, immune-related adverse events, and increased technical complexity and morbidity of surgery, compared to operating on a treatment-naive patient. Cancer physicians must be aware of potential delays in initiation of definitive treatment and crucially, missing the window for upfront curative surgery. Treatment failure, with resulting disease progression precluding resection contributes towards the reported surgical attrition rate (16.8-22%).[2-6]

Judicious patient selection for the optimal combination and sequence of therapies must be determined by tumour stage and biology, clinician experience, patient preference and affordability. A multi disciplinary approach with shared patient decision-making is required. Real-world care extends beyond clinical trials findings, and must be pragmatic and personalized. In Malaysia, approximately half of patients with rNSCLC will harbour an actionable sensitizing genomic mutation (EGFR, ALK), best treated with adjuvant TKI therapy after curative surgery. In patients without a driver mutation, up to 1 in 4 (17-25%) will achieve a pCR and 1 in 3 (30-37%) a MPR following neoadjuvant chemoimmunotherapy.

Several key clinical considerations merit discussion. First, which patients will accrue maximal benefit from immunotherapy needs evaluation. The magnitude of DFS, EFS and OS benefit appears greatest in EGFR and ALK- wild type patients with stage III disease and for tumours with higher PDL-1 expression, preferably > 1% and ideally > 50%.[2-6] However, PDL-1 expression is variable with considerable discordance even in matched samples due to intra-tumoural heterogeneity or temporal changes. Though useful for patient selection and treatment reimbursement, PDL-1 levels may not always predict therapy efficacy. Second, the optimal strategy for stage II non-oncogene driven rNSCLC remains contentious. No randomized trials compare a surgery-first approach (+/- adjuvant therapy) versus a neoadjuvant approach. Upfront surgery seems reasonable if an R0 curative resection is feasible, with adjuvant immunotherapy reserved for tumours which exhibit high-risk microscopic features or nodal disease. Most patients can commence therapy swiftly following contemporary minimally invasive surgery. Adjuvant pembrolizumab (KN091) and atezolizumab (IM010) provide good DFS benefit translating to meaningful OS benefit over best supportive care or adjuvant PBC-only, whilst interim results from the NADIM Adjuvant trial report promising cancer-specific DFS at 3 years with adjuvant nivolumab.[7-9] Conversely, a neoadjuvant approach may evoke a stronger immune response, is possibly better tolerated and less costly, and can address early on, occult microscopic disease, the culprit for relapse. Additionally, a potential downsizing effect may enhance resectability in borderline cases, although no trials were designed to convert patients with unresectable disease into surgical candidates.

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Third, in patients who are likely to benefit from neoadjuvant therapy, it is difficult to ascertain in whom a neoadjuvant-only protocol would suffice, rendering adjuvant treatment superfluous. Again, no head-to head randomized data exists comparing a neoadjuvant-only versus a peri-operative approach. It is difficult to tease out the relative additive EFS benefit of the adjuvant component from various peri-operative studies. An indirect propensity matched cross trial weighted analysis (CM816) (3 cycles of nivolumab) versus (CM77T) (4 cycles of neoadjuvant nivolumab and one or more adjuvant cycles) concluded adjuvant therapy enhanced EFS but only for non-pCR patients and low PDL-1 expressers (TPS < 1%).[10]

Circulating tumour deoxyribonucleic acid (ctDNA) holds promise as a predictive and prognostic biomarker for minimal residual disease (MRD). Patients who achieve ctDNA clearance pre-surgery are more likely to achieve a pCR and vastly superior EFS, DFS and OS.[2-4] Worse outcomes were observed in patients who remained ctDNA positive, pre and post surgery despite neoadjuvant therapy. In AEGEAN, all patients with pCR and > 93% who achieved MPR, had ctDNA clearance pre-surgery, illustrating the high negative predictive value (NPV) for pCR.[3] Patients with detectable ctDNA post surgery had significantly inferior DFS. In CM77T, ctDNA clearance was a strong predictor for EFS whilst CM816 reported excellent survival for patients with pCR and ctDNA clearance (5-year OS 95% vs 56% HR 0.11 CI [0.04-0.36]), tempting adjuvant therapy de-escalation, sparing financial and pharmacological toxicity.[2,4] However, presently, concerns persist regarding the NPV and sensitivity of ctDNA assays to facilitate a personalized MRD-based adaptive approach. Whilst pCR may indicate a molecular 'cure' at the primary tumour site, it cannot exclude possible occult micrometastases. Furthermore, it remains challenging for pathologists to accurately sample the entire tumour bed and concerns of inter-observer variability remain.

Finally, safety remains paramount. A recent meta-analysis of 8 contemporary neoadjuvant and peri-operative trials (CM816, TD-FOREKNOW, AEGEAN, CM77T, KN671, Neotorch, NADIM II and RATIONALE-315) concluded that EFS was similar for patients with a PDL-1 < 1% or 1-49%, with either a neoadjuvant-only or peri-operative approach however patients with PDL-1 > 50% derived a greater EFS benefit with neoadjuvant-only therapy and lower incidence of treatment related adverse events (TRAEs) [relative risk (RR 0.96) 95% CI (0.87—1.12)] over a peri-operative approach.[11]

The evolving treatment paradigm reflects recent advances in the diagnostic and treatment landscape for rNSCLC. Surgery, as part of a multi modality, still offers the best outcomes. Tumour biology plays a critical role alongside disease stage to select the optimal combination and sequence of therapy. For non-oncogene rNSCLC, immunotherapy beit neoadjuvant-only or peri-operative, offers excellent outcomes for patients who achieve pCR. A neoadjuvant-only approach may be sufficient for high PDL-1 expressers who achieve a pCR and ctDNA clearance suggesting no MRD and possibly a cure. Adjuvant therapy following upfront surgery remains a reasonable strategy particularly for stage II disease. Serial ctDNA monitoring facilitates a nuanced personalized adaptive MRD approach with appropriate therapy step-up or de-escalation. The challenge remains in selecting the right treatment, for the right patient, at the right time, taking into consideration real-world considerations of affordability, toxicity and patient preference and fitness.

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The need to consider oral hygiene in preventing the onset of oral bacteria-related systemic diseases: Commentary

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A relationship between oral bacteria and systemic diseases,[1] such as Alzheimer's disease (AzD), type 2 diabetes mellitus, rheumatoid arthritis, and cardiovascular diseases, has been suggested. These systemic diseases pose major public health challenges in most countries. Thus, the importance of oral bacteria has been even gaining more attention in regard to the interrelationships with these systemic diseases. However, hundreds of species of bacteria live in the oral cavity, making it difficult to identify and eradicate the causative bacteria. So far, preventive measures should be required to treat these systemic diseases. We discuss oral hygiene approaches to prevent the onset of these systemic diseases caused by oral bacteria, as an unavoidable immediate issue.

Alzheimer's disease

AzD[2] is the most common form of dementia, a general term for the loss of memory and other intellectual abilities that is serious enough to interfere with daily life, affecting most people aged 65 years and older.[1] The number of AzD patients is said to be on the rise.[3] AzD is associated with many aetiologies and pathophysiological processes, such as amyloid beta (Aβ) plaques and neurofibrillary tangles in the brain.[2] Recently, it has been confirmed that AzD is caused by *Porphyromonas gingivalis (P. gingivalis)*,[1] probably via the accumulation of immune complexes with the fimbriate oral bacterium *P. gingivalis* and its immune reactor in the brain.[1] It has been pointed out that components of *P.gingivalis* can cross the blood brain barrier and may accelerate AzD-specific neuropathology by increasing neuroinflammation,[1] due to plaque/tangle formation and dysregulation of iron homoeostasis.[4]

Type 2 diabetes mellitus

Type 2 diabetes mellitus[5] also known as adult-onset diabetes, is characterised by high blood sugar, insulin resistance, due to insufficient insulin production in the beta cells. Obesity is common, and serious systemic complications associated with the setting of insulin resistance are concerned.[6] Considering the number of patients with type 2 diabetes worldwide,[7] the bacterial aetiology hypothesis,[1] that oral bacteria may also be a cause, is supported.

Systemic diseases and ozonated water

The author has recently reported that leukocyte-mediated inflammatory skin disease, palmoplantar pustulosis (PPP),[8] a peculiar skin disease that forms pustules on the palms and soles, was cured by oral rinsing with ozonated water, indicating a novel oral bacteria-related disease.[8] This new sterilising agent has shown mechanical antibacterial effects, which disrupts the bacterial cell wall through its strong oxidation power. However, it is also necessary to consider the existence of bacteria that are resistant to oxidation.[9] The Alzheimer's causative agent *P. gingivalis* is also oxidation-resistant,[9] due to extracytoplasmic components that protect the cell from oxidative stress and antioxidant enzymes that neutralise these oxidants. Antibacterial agents alone cannot deal with them, although the strength against ozone oxidation, mechanical and not chemical, of this bacterial wall structure in the anti-oxidant mechanism has not been sufficiently investigated. So far, periodontal care, including plaque removal from the periodontal pockets, may be necessary to manage these systemic diseases. This is especially important for patients with a family history of the disease.[2]

However, from the onset mechanism of these systemic diseases, we have pointed out that even if the cause is oral bacteria, there is a large difference in the symptom improvement of the disease, when using ozone water.[10] PPP, an inflammatory disease mediated by neutrophils,[8] can be cured by rinsing the mouth with ozone water,[8] but not AzD,[10] which may be caused by the accumulation of causative substances in the brain, and type 2 diabetes, which should also be considered to be a dysfunction of the pancreatic islet cells.[5] In recent clinical studies, it has become clear that oral care for AzD patients has been debated,[11] with it being said that only a certain degree of effectiveness can be expected in early-stage cases. The same could be said about type 2 diabetes. In a study examining the effect of periodontal treatment on HbA1c, blood glycaemic control in diabetic patients was not improved.[12] In the case of rheumatoid arthritis,[1] even if the cause is oral bacteria, arthritis accompanied by joint deformation cannot be expected to improve even if the causative bacteria are removed. While the susceptibility to UV (ultraviolet) rays of these oral bacteria is currently being investigated,[13] it is necessary to further consider the effects of UV rays to be utilised.

Bacterial transmission

Moreover, it has been shown previously that bacteria that cause tooth decay is often passed from mother to child,[14] because baby food may be tasted or pre-chewed by the mother. It is not difficult to imagine thus the mother's oral flora is passed on to the child. In support of this, both AzD[2] and type 2 diabetes[15] have been reported to occur in families, and familial AzD has been pointed out to be conspicuous in young-onset cases.[2] The way in which the oral flora is inherited from mother to child, and the onset of the disease, along with the genetic predisposition, may be inherited within the family similar to a hereditary disease.

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CONCLUSION

As previously shown, a cure, let alone improvement, in a patient with AzD and a patient with type 2 diabetes, cannot be expected, even if the bacteria is eradicated.[10] Based on these evidences, in cases where the familial onset of these systemic diseases is expected, it is important to take appropriate measure, such as periodontal cleaning, before the onset of symptoms, because the disease can be prevented. While the development of new drugs is being actively carried out, it is also important to prevent the onset of systemic diseases caused by these oral bacteria, and shouldn't the WHO also be working on this issue?

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