

REVIEW ARTICLE

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TABLE OF CONTENTS

EDITORIAL

- 3088 Mind the Gap in Translating Microcirculation Knowledge 1-3

EXPERT OPINION

- 2797 Disorders/Differences of Sex Development (DSD) and Gender Dysphoria: The Need of a 4-8

REVIEW ARTICLES

- 2849 Relationship Between Female Reproductive Factors and Osteoporosis among Postmenopausal Women in Malaysia: A Systematic Review and Meta-Analysis of Observational Studies 9-22
- 2889 The Practice of Primary Eye Care by Optometrists Worldwide - A Systematic Literature Review 23-30
- 2955 Scientific Evidence of Prophetic Medicine: Exploring Its Role in Integrative Medicine – A Review and Bibliometric Analysis 31-41

ORIGINAL ARTICLES

- 2895 Streptococcus Gallolyticus Infection and its Interrelation with Colorectal Cancer: Diagnostic Accuracy of Statistical and Machine Learning Models for Early Detection Algorithm 42-50
- 2783 The Avoidance Practice and Its Association with Self-Efficacy, Knowledge and Attitude among Mothers with Children under 6 Years Old on Environmental Tobacco Smoke Exposure to Their Children in Selangor 51-58
- 2717 Job Satisfaction among Medical Officers in a University Hospital: A Qualitative Study 59-68
- 2839 Study on the Effectiveness of Integrating Religious Approaches in Health Interventions for Transgender Individuals in Malaysia 69-77
- 2532 Effects of Sauropus Androgynus Extract on Cognitive Function Improvement and Neuron Enhancement in Trimethyltin Chloride-Induced Rats 78-86
- 2548 Spatial and Temporal Intensity of HFMD Cases in Pulau Pinang, Malaysia between 2017 and 87-93
- 2609 Development and Validation of Menstrual Disorder of Adolescent (MenDA) Questionnaire in the Malay Language 94-102
- 2714 Prevalence of Diabetes Mellitus and its Associated Factors among Adults in Malaysia: Findings from the National Health and Morbidity Survey 2019 103-113

ORIGINAL ARTICLES

- | | | |
|------|---|---------|
| 2852 | Effect of Antipsychotic on the Dimension of Auditory Hallucination Among Patients with Schizophrenia | 114-122 |
| 2834 | Predictors To Mental Well-Being at Workplace: A Quantitative Case Study Among Administrative Staff of a Public University in Malaysia | 123-131 |
| 2721 | Ameliorative Effects of <i>Olea europaea</i> Oil on Morphine Withdrawal: Behavioural, Biochemical and Histological Evidence in Rats | 132-139 |

CASE REPORT

- | | | |
|------|--|---------|
| 2596 | Locked Anterior Hip Dislocation with Ipsilateral Greater Trochanteric Fracture and Common Femoral Artery Compression: A Rare Case Report | 144-146 |
| 2564 | Scissor-Induced Penetrating Brain Injury in a Child: A Case Report | 147-150 |
| 2688 | Remission of Hypertension Through Lifestyle Modification: A Case Study | 148-152 |
| 2680 | Stroke Chameleon: Acute Bilateral Middle Cerebral Artery Infarct Complicated with Acute Pulmonary Oedema | 153-156 |
| 2690 | Cervical Intramedullary Cavernous Haemangioma: A Rare Cause of Acute Hemiparesis | 157-160 |
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Volume 24 Number 4, October 2025

Mind the Gap in Translating Microcirculation Knowledge and Clinical Impact

The paradox of haemodynamic coherence remains one of the most perplexing diagnostic challenges in modern critical care practice. Clinicians may achieve conventional targets of circulatory stability, such as a mean arterial pressure (MAP) above 70 mmHg, a normalised heart rate and adequate cardiac output indices. Nevertheless, a subset of critically ill patients continues to exhibit tissue hypoperfusion and progressive organ dysfunction. Cold extremities, mottled skin, prolonged capillary refill time (CRT) and oliguria exemplify this dissociation between reassuring macrocirculatory parameters and impaired microcirculatory flow. This phenomenon reveals a critical limitation of our current monitoring paradigm, which is the assumption that optimising systemic haemodynamic translate into adequate tissue perfusion. While macrocirculatory interventions can restore global variables, the true determinants of cellular oxygen delivery (DO_2) and tissue viability reside within the intricate microcirculatory network. This network cannot be directly captured by conventional monitoring; nevertheless, it plays a decisive role in determining patient outcomes.¹

The microcirculation, defined as the vascular network of vessels smaller than 100 μm , represents the functional interface between systemic circulation and cellular metabolism. This intricate system of arterioles, capillaries and venules relies on finely balanced interactions among haemodynamic forces, endothelial function and the protective glycocalyx. Dysfunction within this compartment explains the persistence of organ failure despite apparent macrocirculatory stability. Loss of haemodynamic coherence between macro- and microcirculation can be described by four mechanisms, each impairing tissue DO_2 through distinct pathways. Type 1 is heterogeneous perfusion, where obstructed and patent capillaries coexist, producing patchy hypoxia despite seemingly adequate flow and typifying sepsis. Type 2 arises from haemodilution, lowering capillary haematocrit and extending diffusion

distance, reducing oxygen-carrying capacity even with preserved plasma flow. Type 3 involves microcirculatory stasis from elevated arterial resistance or venous congestion, impeding red blood cell transit despite normal driving pressures. Type 4 results from tissue oedema caused by capillary leak, which increases the distance for oxygen diffusion despite adequate perfusion.²

Recognition of the four pathophysiological patterns of microcirculatory failure has driven the development of advanced monitoring techniques aimed at translating experimental insights into bedside practice. Among these, handheld videomicroscopy using sidestream dark-field and incident dark-field imaging has emerged as the current gold standard for real-time microvascular assessment. These devices allow quantitative analysis of sublingual microvascular parameters, including functional capillary density, microvascular flow index and perfused boundary region, all of which have demonstrated significant prognostic value in critically ill patients.³ Multicentre studies have confirmed that reduced capillary density correlates with higher mortality and organ dysfunction scores, independent of conventional haemodynamic variables.⁴ Despite this promise, routine clinical adoption remains limited. Image acquisition requires skilled operators, strict standardisation and advanced automated analysis, creating barriers to widespread use. Inter-observer variability, difficulty maintaining optimal probe positioning and challenges with image quality further reduce reproducibility across settings. Current analysis software also demands substantial computational resources and expert oversight, confining these tools largely to research environments. Consequently, only specialised centres can fully characterise sublingual microvascular function and glycocalyx integrity,⁵ while most ICUs continue to depend on indirect surrogates of microcirculatory status, reflecting the gap between technological capability and practical bedside accessibility.

Modern intensive care increasingly relies on simple, cost-effective tools to assess microcirculatory function at the bedside. CRT has regained prominence following the landmark ANDROMEDA-SHOCK trial, which demonstrated improved outcomes with CRT-guided rather than lactate-guided resuscitation in septic shock. CRT-targeted therapy accelerated organ recovery, limited fluid overload, and showed a favourable mortality trend. Its main advantages are speed, reproducibility, and sensitivity to changes in perfusion. Other complementary measures include the peripheral mottling score, which quantifies skin discolouration around the knee and reliably predicts mortality in septic and cardiogenic shock.⁴ The peripheral perfusion index, derived from routine pulse oximetry, offers real-time insight into peripheral microcirculatory status. Laboratory markers add value but have limitations. Serum lactate remains widely used; however, its delayed clearance and nonspecificity reduce its utility for real-time monitoring. More refined indices, such as the venous-to-arterial carbon dioxide gap and the Pv-aCO₂ to arteriovenous oxygen difference ratio, can reveal persistent flow-oxygen mismatch even when global haemodynamics appear normal.⁵ These modalities together create a pragmatic framework for perfusion assessment in diverse settings. No single surrogate fully reflects the complexity of microcirculatory failure. Repeated use of combined tools during early shock resuscitation improves diagnostic precision beyond macrocirculatory endpoints. Current protocols should integrate CRT, mottling scores, and perfusion indices alongside traditional haemodynamic targets.^{4,5}

Microcirculatory monitoring is evolving rapidly, with significant implications for critical care practice. Prospective studies in elderly intensive care populations have shown that admission sublingual microvascular dysfunction independently predicts 30-day mortality, confirming prognostic value beyond conventional haemodynamic variable.⁴ The integration of automated handheld videomicroscopy with artificial intelligence now allows standardised, operator-independent quantification of capillary density and flow, addressing long-standing concerns about reproducibility and interpretative consistency. Emerging biomarkers reflecting endothelial

glycocalyx integrity are also expanding diagnostic possibilities. Perfused boundary region analysis from sublingual imaging, combined with circulating glycocalyx degradation markers, shows early promise as an objective measure of microvascular barrier function.⁵ Near-infrared spectroscopy (NIRS) with vascular occlusion testing offers complementary insight into tissue oxygen use and microvascular reactivity, demonstrating prognostic value in cardiac surgery, trauma and septic shock.⁶ Despite these advances, robust validation in large-scale randomised controlled trials remains essential before such modalities can be adopted as resuscitation endpoints. An important development is phenotype-based resuscitation, which prioritises tissue perfusion over traditional macrocirculatory targets. The ongoing ANDROMEDA-SHOCK-2 trial illustrates this by testing whether perfusion-guided protocols improve outcomes compared with standard haemodynamic-based care.⁷ Positive findings could redefine intensive care, positioning microcirculatory assessment at the centre of evidence-based resuscitation.

The relevance of microcirculatory monitoring extends beyond systemic circulation, particularly in neurointensive care, where cerebral perfusion is far more complex than traditional pressure-based calculations suggest. Cerebral tissue oxygenation depends not only on the relationship between MAP and intracranial pressure (ICP) but also on microvascular flow patterns, autoregulatory capacity and endothelial barrier integrity. Secondary brain injury may persist despite apparently normal systemic haemodynamics because cerebral microcirculation often exhibits heterogeneous perfusion, impaired autoregulation and increased permeability following glycocalyx disruption. Current tools provide limited insight. Transcranial Doppler assesses large-vessel flow but cannot fully capture microvascular disturbances, while NIRS offers practical regional cerebral oxygenation monitoring and has shown utility after cardiac arrest and during cardiac surgery.^{6,8} Principles from systemic microcirculatory research, including dynamic assessment and phenotype-guided therapy, should guide cerebral perfusion management and shape the next generation of neuroprotective strategies beyond purely pressure-driven paradigms.

Malaysian intensive care encounters both challenges and opportunities in adopting microcirculatory assessment strategies. While sophisticated videomicroscopy remains largely inaccessible, pragmatic bedside tools can be introduced immediately. Systematic training of medical and nursing staff in CRT assessment, mottling score documentation, peripheral perfusion index measurement, and lactate clearance monitoring could elevate care standards without major infrastructure costs. These parameters should be reassessed dynamically during resuscitation, guiding fluid therapy, vasopressor selection, and inotropic support based on microcirculatory response rather than macrocirculatory targets alone. Simultaneously, academic centres should establish dedicated microcirculation laboratories, standardise imaging techniques, and build patient registries. Such initiatives will enable international collaboration, prepare for emerging technologies, and drive a truly tissue-focused, outcome-driven approach to resuscitation in Malaysian ICUs.

Therefore, clinicians, researchers, and trainees must sustain a strong commitment to advancing the science of microcirculation. We should integrate simple bedside markers into daily practice, invest in the expertise needed to adopt emerging imaging technologies and contribute to multicentre studies.¹⁷ Our patients deserve more than reassuring numbers on a monitor; they deserve organs that recover and lives that can be saved. Microcirculation now plays a decisive role in critical illness rather than being just a niche research area. By making microcirculation visible, measurable, and actionable, we can move beyond pressure-driven targets toward a new era of tissue-focused, outcome-driven intensive care.

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Disorders/Differences of Sex Development (DSD) and Gender Dysphoria: The Need of a National Guideline for Malaysia

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ABSTRACT

Disorders/Differences of Sex Development (DSD) are congenital conditions characterized by atypical chromosomal, gonadal, or anatomical sex, affecting approximately 0.1–2% of the global population. A subset of individuals with DSD also experiences gender dysphoria (GD), a psychological distress arising from incongruence between assigned sex at birth and experienced gender. Misdiagnosis between GD and DSD remains a major concern, particularly in Muslim-majority contexts such as Malaysia, where socio-cultural, religious, and medical perspectives intersect. Many individuals with unrecognized DSD are mistakenly categorized as transgender, resulting in stigmatization, marginalization, and limited access to healthcare, education, and religious participation. Islamic jurisprudence introduces the concept of *khuntha* to describe sex ambiguity, which overlaps with some DSD cases but requires nuanced differentiation from *mutasyabbih* (gender imitation) and transgenderism. While classical scholars distinguished between *khuntha wadhah* (discernible) and *khuntha mushkil* (intractable), contemporary management demands multidisciplinary collaboration. Integrating medical expertise with Shariah rulings is essential to determine appropriate pathways, including gender assignment, surgical interventions, and psychosocial support. The absence of structured guidelines in Malaysia exacerbates clinical, ethical, and religious dilemmas in managing these complex cases. This paper argues for the urgent development of a national guideline that combines evidence-based medical protocols with Islamic jurisprudence, ensuring culturally competent and patient-centered care. Such a framework would harmonize the roles of endocrinologists, psychiatrists, psychologists, religious scholars, and community stakeholders, providing comprehensive management that upholds both health outcomes and spiritual well-being. Establishing this synergy positions Malaysia to pioneer an integrated model for DSD and GD management in Muslim societies.

Keywords

Gender Dysphoria, Differences of Sex Development, *Khuntha*, Transgender, Islamic jurisprudence

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INTRODUCTION

The 2024 Paris Olympic Games triggered a worldwide interest in gender-related issues when Imane Khelif, the Algerian female boxer faced protest that she should not be allowed to compete in the woman's category. The International Olympic Committee (IOC) defended the right of the boxer to participate in the women's category against the claims by another sports body, *viz* International Boxing Association (IBA), stating that

Imane Khelif had failed the gender test based on chromosomal and testosterone level tests. The IBA was later stripped of its world governing body status by the IOC over integrity and governance issues.

Nevertheless, Imane Khelif is a Muslim who comes from Algeria, a Muslim country with strict regulations regarding *tasyabbuh* (pretending to be the opposite sex) which

created public interest over how this delicate issue was handled from both health and religious perspectives.

How do we approach cases of Gender Dysphoria (GD), of those suspected of having Differences/Disorder of Sex Development (DSD) issues professionally? How do we delicately manage affected Muslim individuals, who fit into the category of *khuntha* (sex ambiguity) from the Shariah perspectives amidst the stigma and lack of awareness? This paper explores these questions and attempts to illustrate the need of a national guideline for Malaysia drawn from multidisciplinary approaches for health experts and other authorities.

The confusion on gender identity

In any society, there are individuals who are confused with their gender identity; however, they are not transgenders. With the increase in transgender issues worldwide, including Malaysia, such individuals face various challenges in their daily lives due to gender dysphoria (GD). These individuals, may be classified as undiagnosed Disorders/Differences of Sex Development (DSD) based on clinical examination by a trained medical professional.

As these individuals experience gender incongruence, and yet to be identified as DSD, they most likely live in families and societies where they are discriminated and stigmatized. This condition can lead to significant psychological distress and burden, known as GD. Approximately 0.1%-2.0% of the global population is affected by DSD, from which, 15% are affected with GD.¹ DSD individuals also suffer from other mental health problems such as depression and anxiety which negatively impact their daily lives.

Individuals who experience gender incongruence when examined by trained physicians in the management of DSD, is more likely to be categorized as DSD or *khuntha*, rather than transgender. The *khuntha* status however, should be confirmed by Shariah experts. When both DSD and *khuntha* are confirmed, affected individuals can legally change their gender status, and receive appropriate medical and surgical treatment in Malaysia. The medical

attention received, can change their lives positively, alleviate their mental health problems and allow them to live as Muslims, whether as men or women to the best of their ability.

Disorders/Differences of Sex Development (DSD)

Disorders/Differences of sex development (DSD) is defined as '*congenital conditions in which development of chromosomal, gonadal, or anatomical sex is atypical*'.² This new nomenclature indicates that there is a mismatch between chromosomes, gonads, internal reproductive organs, and external genitalia of an individual. DSD embraces almost all conditions of congenital sexual anomalies, with or without ambiguous genitalia.

The incidence of a child with DSD is approximately 1:1000-4500 live births. The most frequent condition is congenital adrenal hyperplasia (CAH), followed by androgen insensitivity (AIS) and mixed gonadal dysgenesis, and Swyer syndrome.^{3,4}

Individuals with DSD may present with a wide range of phenotypes from ambiguous genitalia, absence of secondary sexual characteristics development (delayed puberty), primary amenorrhea, hypospadias, clitoromegaly, virilization of a woman, to complex congenital defects.⁵ All these varied phenotypic existences are influenced by various pathophysiological conditions such as gonadal developmental; genetic, chromosomal, hormonal function abnormalities; and others.

Gender Dysphoria (GD)

Gender dysphoria (GD) refers to '*psychological distress arising from a marked incongruence between an individual's assigned gender at birth and their experienced or expressed gender*'. According to the Diagnostic and Statistical Mental Disorder, Fifth Edition (DSM-5-TR), GD is defined as '*lasting at least six months and being accompanied by a strong desire for a different gender, physical characteristics of another gender, or significant distress or impairment in social, occupational, or other areas of functioning*'.⁶ It may create a significant psychological burden or problems functioning to those with GD.⁷

The DSM-5-TR includes DSD as a specifier for GD, recognizing the overlap between the two conditions. However, this categorization raises concerns about potential misdiagnosis and stigma, especially in cases where individuals with DSD are erroneously labelled as having GD. This misclassification can be problematic because for many individuals, gender identity issues may arise due to the complexities of their medical condition rather than from dysphoria itself. Therefore, accurate diagnosis requires a multidisciplinary approach which combines genetic, hormonal, and psychosocial evaluations. Establishing clear guidelines to differentiate GD from DSD is essential to ensure appropriate care and minimize the risk of stigmatization.

In Malaysia, many individuals with GD are yet to be properly investigated for possible underlying conditions like DSD or *khuntha*, and may be misidentified as part of the LGBT community. This misidentification further contributes to their marginalization, with limited access to religious activities, community participation, employment opportunities, and public services. In some cases, these social barriers drive affected individuals to sex industry for survival. These challenges can exacerbate their mental health problems, leading to feelings of isolation, depression, and anxiety.

Khuntha

Islamic scholars have highlighted the issues regarding gender incongruence and confusion among individuals which is known as *khuntha*. In the classical definition, one of the Islamic lexicographers, Muhammad Ibn Manẓur, stated that *khuntha* refers to 'a person who cannot be recognised as male or female; and/or the person has both criteria/ characteristics of a male and female'.⁸

*Khuntha*⁹ is illustrated when individual possesses any one of the followings; i) both male and female genitalia; ii) neither male nor female genitalia, but has an orifice that functions for urination purposes; or iii) ambiguous genitalia which does not look like male or female genitalia. This latter type is connected closely to some DSD cases.

However, in contemporary discussion, *khuntha* is referred to as 'a congenital condition which may include the presence of ambiguous genitalia along with atypical development of chromosomal and/or gonadal and anatomy sex'.¹⁰ In exploring the relationship between DSD and *khuntha*, studies by Anisatul Qalbi and Taqwa Zabidi reported that not all DSD are *khuntha* but all *khuntha* are DSD.¹¹ For example, Turner syndrome is one of DSD diagnoses but is not categorised as *khuntha* because these affected individuals are without male characteristics, but have deficiencies in female characteristics. In contrast to congenital adrenal hyperplasia (CAH) *viz* someone with both male and female characteristics, the affected individual has female karyotype ie 46 XX, but produces excessive male hormones resulting in the formation of ambiguous genitalia and gender dysphoria (GD), is referred to as *khuntha*.

Islamic scholars have divided *khuntha* into two types, namely *khuntha wadhib* (discernible *khuntha*) and *khunthā mushkīl* (intractable *khuntha*). This division is based on the level of complexity to ascertain the correct gender, which was initially to identify to what extent the juridical rulings of *khuntha* is applied to them. It is easy to ascertain the gender of a *khuntha wadhib* as the sex characteristics of one gender is more dominant compared to the other whilst in the case of *khuntha mushkīl*, it is difficult to ascertain the correct gender as there is no dominant sex characteristics of a gender. The difference between the two types is that *khuntha wadhib* will follow any juridical rulings of the ascertained gender and if required may undergo gender reassignment surgery,¹² whilst *khunthā mushkīl* however, will follow the specific juridical rulings of *Khuntha* to perform their obligations, and any gender reassignment surgery is prohibited for as long as the correct gender is uncertain.¹³

The determination of *khuntha wadhib* and *khuntha mushkīl* cannot solely rely on external observation. The determination should involve both the medical experts and Islamic scholars to address and solve this issue.

Mutasyabbih and Transgender

Khuntha is different from another group of individuals who are broadly categorized as *mutasyabbih*, in which the latter mainly ‘occurs due to psychological factors without having ambiguity of his/her genitalia, or chromosomal abnormalities, gonads or sexual anatomies’.

Mustasyabbih refers to ‘the person who resembles the other gender, including conversation, way of walking, dressing and behaviour’. On the other hand, *Tasyabbuh* is ‘an expression of the efforts or actions of a man who resembles a woman, or a woman who resembles a man in terms of conversation, way of walking, dressing manner and behaviour’.

Mutasyabbih can be divided into two, i) *mukhannath* and ii) *mutarajilat*. *Mukhannath* is defined as ‘a man exhibiting characteristics resembling those of a woman’, while *mutarajilat* refers to ‘a woman exhibiting the characteristics of a man’.¹⁴ Some of them born with such characters, but many others deliberately act and personify the other gender. Thus, transgender individuals align with the latter concept by typically having male biological attributes while presenting physical traits similar to that of a woman and vice versa.¹⁵

The 119th Muzakarah Committee of the National Council for Malaysian Islamic Religious Affairs which convened from 7-9 April 2021, echoed classical scholars on *mukhannath khalqi* (inherent) and *mukhannath ghayr khalqi* (unnatural) and differentiated between *khuntha* and *mukhannath* on the basis of biological condition for the former and psychological attributes for the latter.¹⁶ Accordingly, transgenders/transwomen in the Malaysian context known locally as ‘*mak nyah*’ are categorized in the *mukhannath ghayr khalqi* and not *khuntha* because they are not naturally feminine and have no medical issues in terms of physiology and gender development. The clear understanding of these conditions is vital prior to proposing any medical interventions according to Islamic perspectives. Figure 1 summarizes the classification of GD into possible conditions.

CONCLUSION

For affected Muslim individuals in Muslim-majority population, concepts such as *khuntha* and religious fatwas

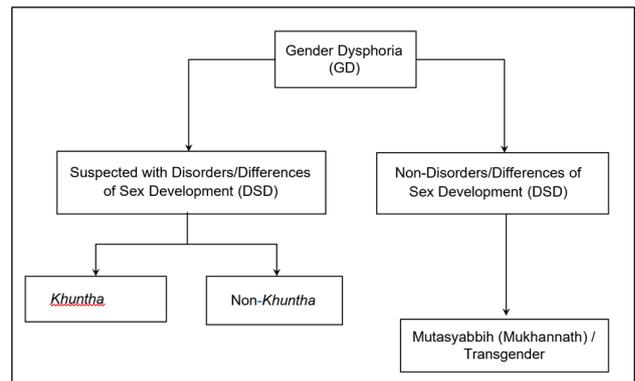


Figure 1. Gender dysphoria (GD) relation to Disorders/Differences of Sex Development (DSD)

regarding gender reassignment, require greater integration into clinical and social practices to ensure culturally competent and inclusive care.¹⁷ Islamic scholars have debated the permissibility of gender reassignment, with some Malaysian fatwas acknowledging it in cases of confirmed medical necessity, particularly for individuals with DSD. These religious perspectives should be integrated into clinical management frameworks to ensure that care aligns with both medical needs and Islamic principles. In the case of transgenders, socioreligious and cultural knowledge-enhancement methods through the voluntary participations may reduce risk of HIV transmission.¹⁸

In the face of fast evolving Shariah and medical knowledge, it is imperative that these bodies of experts discuss and share their expertise to make a comprehensive decision on the case in-hand. There is an urgent need for culturally sensitive guidelines which combine the expertise of health professionals, religious scholars, and community stakeholders. A well designed flow of referrals should be established incorporating comprehensive psychosocial support, religious counselling, and individualized care provided by multidisciplinary teams, including psychiatrists, endocrinologists, psychologists, and social workers.

The synergy between fiqh and medical knowledge forms a robust foundation to determine the juridical rulings as well as a comprehensive approach to addressing the complex issues concerning DSD, GD, and transgenderism. The authors strongly propose the establishment and implementation of a guideline for Malaysia combining

both medical and Shariah aspects in managing DSD. This will be the first of its kind in the Muslim world.

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Relationship Between Female Reproductive Factors and Osteoporosis among Postmenopausal Women in Malaysia: A Systematic Review and Meta-Analysis of Observational Studies

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ABSTRACT

Numerous studies in Malaysia have investigated the potential link between female reproductive factors and osteoporosis in postmenopausal women; however, a comprehensive synthesis of these findings is lacking. This systematic review seeks to elucidate the association between female reproductive factors and bone health indices in postmenopausal Malaysian women. A comprehensive search of PubMed, Scopus, and the Cochrane Library databases was conducted up to October 2024. Inclusion criteria comprised case-control and cross-sectional studies that reported comparisons, correlations, or regression analyses involving years-since-menopause, parity, or lactation with osteoporosis. Qualitative analysis was conducted on eight cross-sectional studies and one case-control study. Five out of the nine studies indicated a relationship between years-since-menopause and osteoporosis. Additionally, two out of four studies found a relationship between parity and osteoporosis, while two out of three studies demonstrated a relationship between lactation and osteoporosis. Quantitatively, a meta-analysis was performed for five studies, with a pooled sample size of 1134 postmenopausal women. A significant negative correlation emerged between years-since-menopause and osteoporosis indices (Fisher's correlation coefficient: -2.51 [95% CI-0.305-0.195], $p < 0.001$, fixed-effect model, I^2 97%). Unfortunately, the available data on parity and lactation history were insufficient for meta-analysis of correlation. Limitations in the regression data did not allow for meta-analysis. The findings underscore the potential importance of years-since-menopause as a reproductive factor associated with osteoporosis in postmenopausal Malaysian women. Additional research is imperative to substantiate this association and contribute to the development of a robust risk assessment tool.

Keywords

bone health, fragility fracture, osteoporosis, post menopause, reproductive factors

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INTRODUCTION

Osteoporosis is a prevalent global health concern, commonly diagnosed through assessment of bone mineral density (BMD).¹ A study conducted in Klang Valley, a densely populated region in Malaysia's capital, approximately 9.9% of Malaysian men and 20.1% of Malaysian women over the age of 50 were found to have osteoporosis.² These figures align with another study conducted in Selangor, another populous state in Malaysia, which reported that the prevalence of osteoporosis among men aged over 40 ranged from 7.5%

to 15.8%, while for women in the same age group, the prevalence was between 17.6% and 27.0%.³

Dual-energy X-ray absorptiometry (DXA) is the gold standard, employing T-scores to evaluate BMD at the lumbar spine or proximal femur. According to World Health Organization (WHO) guidelines, osteoporosis is identified when BMD falls 2.5 standard deviations or more below the mean for young adults (T-score ≤ -2.5), while osteopenia is diagnosed when the T-score falls

between -1 and -2.5.⁴ While DXA is integral in clinical settings, its cost limits widespread accessibility. In contrast, quantitative ultrasonography (QUS) offers a portable, radiation-free, and cost-effective alternative for bone health screening, using methods like broadband ultrasound attenuation (BUA) and speed of sound (SOS).⁵ However, the T-scores generated by QUS may differ from DXA.⁶ Another valuable tool for detecting bone loss is the measurement of bone resorption markers, such as N- and C-telopeptides of type I collagen (NTX and CTX), which reflect the enzymatic breakdown of the bone matrix.^{7,8}

Oestrogen is essential for maintaining BMD as it inhibits bone resorption. A decline in oestrogen levels accelerates bone loss and increases the risk of fractures.⁹ Recent research from Korea has highlighted the independent fracture risk associated with shorter lifetime exposure to endogenous oestrogen.¹⁰ During the postpartum period, particularly while breastfeeding, oestrogen levels are temporarily suppressed, and they consistently decline after menopause.¹¹ Some studies suggest that earlier menopause increases the risk of osteoporotic fractures.¹²⁻¹⁶ Additionally, pregnancy and lactation impact maternal bone health;¹⁷ however, the long-term relationship between these factors and postmenopausal osteoporosis remains debated.^{9,13,18-21} Consequently, reproductive factors such as menopausal age, parity, and lactation are frequently studied in osteoporosis research, as they significantly influence cumulative oestrogen exposure.^{11,22-24}

Despite substantial racial and ethnic differences in BMD and fracture incidence,²⁵ limited epidemiologic data exist on osteoporotic fractures in Asian women, particularly in Malaysia. While previous studies have examined reproductive factors in Malaysian postmenopausal women, their findings have been inconsistent.^{11,22-24} This study is the first to systematically review and meta-analyse the available evidence regarding the relationship between female reproductive risk factors and osteoporosis within the Malaysian population.

Our primary goal is to develop an effective Malaysian-specific osteoporosis screening tool that relies less on

DXA scans and more on strong predictors. Effective risk assessment models begin by identifying the strength of these risk factors. This systematic review aims to establish the relationship between female reproductive factors and bone health indices in postmenopausal Malaysian women. The objective is to pool data qualitatively and quantitatively on the relationship between reproductive factors (years-since-menopause (YSM), parity, and lactation) and osteoporosis in this population.

MATERIALS AND METHODS

Data source and search strategy

A systematic search was conducted across three prominent databases (PubMed, Scopus, and the Cochrane Library) using a curated set of keywords: Postmenopause* OR Post-menopause* OR Menopause* AND Malaysia OR Malaysian* AND osteoporosis OR "fragility fracture" OR "bone loss" OR osteoporotic OR "osteoporotic fracture" OR fracture (Table I). Studies published between 1975, and October 2024 were considered, with eligibility restricted to articles in English or Malay, and studies affiliated with Malaysia. The search followed the PICO framework, where Population (P) referred to postmenopausal women in Malaysia, and Outcome (O) included bone health indices, osteoporosis, fragility fracture, or bone loss. These criteria formed the basis for the search strings employed in this study.

Table I: The curated set of keywords for the systematic search conducted on 27th October 2024

Database	Keywords string
Pubmed	("postmenopaus*" [All Fields] OR "post menopaus*" [All Fields] OR "menopaus*" [All Fields]) AND ("malaysia" [MeSH Terms] OR "malaysia" [All Fields] OR "malaysia s" [All Fields] OR "malaysian*" [All Fields]) AND ("osteoporosis" [MeSH Terms] OR "osteoporosis" [All Fields] OR "osteoporoses" [All Fields] OR "osteoporosis, postmenopausal" [MeSH Terms] OR "osteoporosis" [All Fields] AND "postmenopausal" [All Fields]) OR "postmenopausal osteoporosis" [All Fields] OR "fragility fracture" [All Fields] OR "bone loss" [All Fields] OR ("osteoporotic" [All Fields] OR "osteoporotics" [All Fields]) OR "osteoporotic fracture" [All Fields] OR ("fractur" [All Fields] OR "fractural" [All Fields] OR "fracture s" [All Fields] OR "fractures, bone" [MeSH Terms] OR "fractures" [All Fields] AND "bone" [All Fields]) OR "bone fractures" [All Fields] OR "fracture" [All Fields] OR "fractured" [All Fields] OR "fractures" [All Fields] OR "fracturing" [All Fields])
Scopus	((postmenopaus*) OR (post-menopaus*) OR (menopaus*)) AND ((osteoporosis) OR ("fragility fracture") OR ("osteoporotic fracture") OR (osteoporotic) OR (fracture) OR ("bone loss")) AND ((malaysia) OR (malaysian*)) AND (LIMIT-TO (AFFILCOUNTRY , "malaysia")) AND (LIMIT-TO (DOCTYPE , "ar"))
Cochrane Library	Postmenopaus* OR Post-menopaus* OR Menopaus* (Title/ Abstract/Keyword) AND osteoporosis OR 'fragility fracture' OR 'bone loss' OR osteoporotic OR 'osteoporotic fracture' OR fracture (Title/ Abstract/Keyword) AND Malaysia OR Malaysian* (Title/ Abstract/Keyword)

STUDY SELECTION

The selection process followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.²⁶ Nine studies were included in the qualitative analysis, all exploring the relationship between reproductive factors (YSM, parity, lactation) and osteoporosis, specifically those discussing correlation and/or regression among postmenopausal women in Malaysia. Only studies with full texts available were considered. Exclusion criteria included studies that did not assess these associations, focused on injectable contraception, examined unrelated reproductive risk factors, lacked bone health measurements, or were interventional or case reports. Studies in languages other than English or Malay were also excluded.

Specifically, inclusion criteria were studies examining the relationship between YSM, parity, lactation, and osteoporosis in postmenopausal women in Malaysia, using observational designs (cross-sectional, case-control, cohort). Excluded were duplicates, unrelated studies, unclear methodologies, interventional studies, and those not in English or Malay.

QUALITY ASSESSMENT

The quality of the included studies underwent evaluation using the Newcastle-Ottawa Scale (NOS) tailored for cross-sectional and case-control studies.²⁷ The NOS includes eight items across three domains: subject selection (four items), comparability (one or two items), and outcome (two or three items). Total NOS scores were calculated by dividing the achieved score by the maximum attainable score (14 points). Studies scoring >75% (11-14 points) were deemed "high quality," 50-75% (7-10 points) as "moderate quality," and ≤50% (0-6 points) as "low quality".²⁸

RISK OF BIAS ASSESSMENT

The risk of bias in the studies was assessed using the Joanna Briggs Institute (JBI) tool.²⁹ For cross-sectional studies, the checklist included eight questions covering criteria such as subject selection, exposure and outcome measurement, confounding factors, and statistical analysis. For case-control studies, the checklist included

ten questions focusing on the comparability of groups, exposure measurement, confounding factors, and outcome assessment, with responses similarly categorized. Responses were categorized as 'Yes/low risk,' 'No/high risk,' or 'Cannot tell/unclear risk'.

DATA EXTRACTION

Data were extracted from the selected studies on the following: (1) study type, (2) total population size, (3) population source, (4) bone-related parameters, (5) population categorization, (6) findings from comparison/regression/correlation analyses, and (7) conclusions regarding the relationship between risk factors (YSM, parity, and lactation) and bone health. Two independent reviewers (S.Z.M. and S.H.N.) assessed all articles, with disagreements resolved through discussion with the second and third authors (M.N.A.T. and M.A.S.).

META-ANALYSIS

Fisher's *z* transformation was applied to convert correlation coefficients to Fisher's *z* scores for meta-analysis.³⁰ These scores were pooled to estimate the overall correlation using MedCalc® Statistical Software version 22.014 (MedCalc Software Ltd, Ostend, Belgium). A significance level of $p < 0.05$ was considered significant. For data comparing osteoporotic versus non-osteoporotic groups, continuous data were pooled as mean values with standard deviations (SDs) using Review Manager 5 (RevMan 5) version 5.4 analytical software for an overall estimate of the effect size. The pooled mean difference (MD) with 95% confidence intervals (CIs) was used as the effect measure. A random effects model was applied to account for heterogeneity, denoting the extent of variation in effect sizes within the meta-analysis, and was quantified using the I^2 index (ranging between 0 and 100%), with a *p*-value of < 0.05 indicating significant heterogeneity. Funnel plots were created to assess publication bias, with asymmetry suggesting potential bias.

ETHICAL APPROVAL

As this systematic review and meta-analysis involve a secondary analysis of published data, ethical approval was not required.

RESULTS

ARTICLE IDENTIFICATION AND SELECTION

The initial search identified 814 articles, of which 646 were excluded during title screening for irrelevance. After removing duplicates using EndNote®, 216 articles were retained for abstract and title screening. Following this, 21 full-text articles were retrieved for eligibility assessment based on the inclusion and exclusion criteria. Twelve articles were excluded, leaving nine articles (eight cross-sectional studies and one case-control study) that met all criteria (Figure 1).

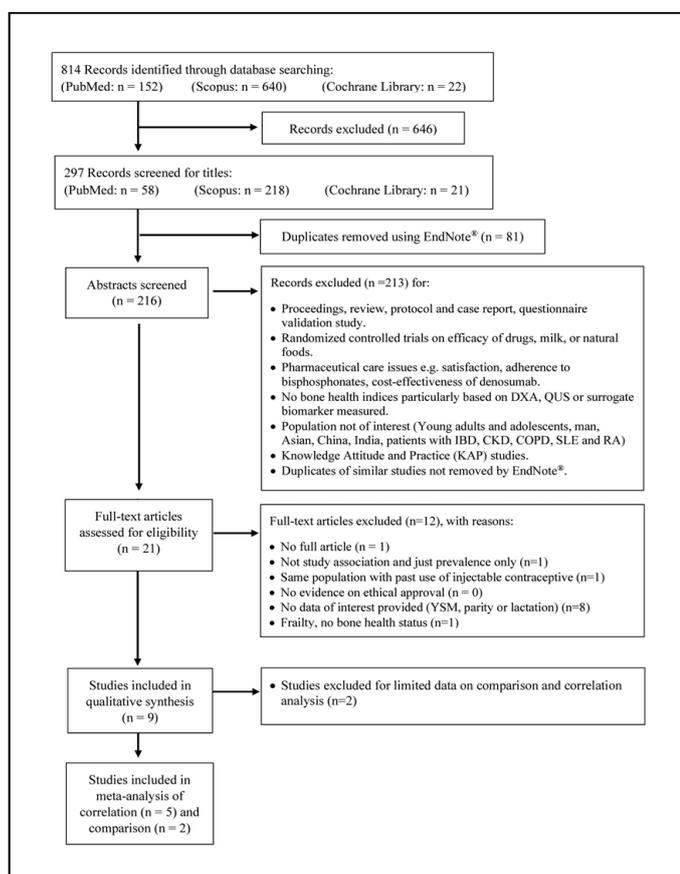


Figure 1: PRISMA flow chart.

All nine included studies are summarized in the evidence tables under the respective sections. One case-control study compared continuous data on YSM and parity between osteoporosis (case) and non-osteoporosis (control) postmenopausal women.³¹ Another cross-sectional study categorized populations into osteoporotic and non-osteoporotic groups before comparison.²² Two studies did not clearly define osteoporosis status or conduct

correlation analyses, leading to their exclusion from the meta-analysis.^{24,32} Data from these studies were qualitatively synthesized. Five of the included cross-sectional studies provided complete correlation data and were included in the meta-analysis for the correlation of YSM.^{8,11,22,33,34}

QUALITY ASSESSMENT

One cross-sectional study and the case-control study received scores of 11 and 13 points, respectively, categorizing them as high-quality studies. The eight cross-sectional studies scored between 9 and 10 points, classifying them as moderate quality. Several cross-sectional studies that used purposive or convenience (non-random) sampling from a single centre received a score of 0 for the representativeness of the target population. One study used random sampling from a single ethnicity and centre,⁸ earning a score of 1, while others used purposive sampling from multiple centres,^{22,35} earning a score of 1 for representativeness.

Most studies met the target sample inclusion rate, but none provided data on non-respondents after exclusion criteria were applied. Studies that used either gold-standard or validated non-gold-standard tools for outcome assessment received an additional point. Similarly, controlling for confounders resulted in a one-point difference in scores.

RISK OF BIAS ASSESSMENT

All included studies achieved at least 75% "Yes/low risk" responses in the risk of bias assessment, with each study scoring ≥ 6 "Yes/low risk" in total. Studies that did not control for potential risk factors were categorized as "Cannot tell/unclear risk" for identifying confounders,^{11,33,34} as these factors have not been confirmed as true confounders. The remaining studies controlled for confounders using multiple linear regression. Additionally, studies employing non-gold standard but validated tools for

measuring osteoporosis, such as QUS and bone resorption biomarkers, were also categorized as "Cannot tell/unclear risk" for using objective, standard criteria for measuring the condition.

RELATIONSHIP BETWEEN YEARS-SINCE-MENOPAUSE (YSM) AND STEOPOROSIS

Table II presents the results from nine studies examining the relationship between YSM and osteoporosis in postmenopausal women in Malaysia. One study reported that osteoporotic women (n=20) had a longer YSM (9.5±6.08 years) than non-osteoporotic women (n=20) (6.10±4.32 years, p=0.048).³¹ In contrast, another study found no significant difference in YSM between osteoporotic (n=144) and normal women (n=57) (p=0.06), with values of 4.63±3.08 years and 3.74±3.22 years,

respectively.²² Another study also reported no significant difference in bone resorption markers (CTx and NTx) between postmenopausal women with <10 years or >10 YSM.³² The continuous data from two studies were pooled in a meta-analysis (77 osteoporotic women versus 164 controls). Seven studies with unavailable YSM data were excluded.^{8,11,24,32-35} The forest plot in Figure 2(A) shows a trend favouring longer YSM in osteoporotic women, but this was not statistically significant (Overall Mean Difference=1.64; 95% CI:-0.61 to 3.89; P=0.15). Heterogeneity was moderate (I²=52%, p>0.05), and the symmetrical funnel plot indicated no publication bias (Figure 2 (B)).

Table II: Evidence table - Years-since-menopause (YSM)

First author	Type of study and population (sample size and source)	Bone-related parameters	Categorization of population	Comparison/ correlation/ regression analysis	Relationship/ Association (Presence or absence)
Lim et al. ⁸	Cross-sectional study conducted in 217 healthy postmenopausal Chinese women that were recruited from the (NACSCOM) in Kuala Lumpur Malaysia.	CTX1: serum collagen type 1 cross-linked CTx	NA	Comparison analysis: NA Bivariate Pearson correlation: <ul style="list-style-type: none"> YSM was not significantly correlated with serum CTX1 (r= -0.109; p>0.05). Hierarchical regression analysis: <ul style="list-style-type: none"> YSM is not a predictor of bone loss (CTX1); B=NA; β= -0.053; p=0.624). 	Absent
Md Isa et al. ¹¹	Cross-sectional study. In total, 116 post-menopausal women were selected; All subjects were recruited from the Orthopaedic and menopause clinic at Hospital Tengku Ampuan Afzan, Kuantan, Pahang, Malaysia.	BMD using DXA scan.	BMD status: Osteopenia (n=61) Osteoporosis (n=55)	Comparison analysis: NA Pearson correlation: <ul style="list-style-type: none"> YSM was significantly negatively correlated with BMD (r = -0.284, P=0.001). Regression analysis: NA	Present but weak relationship.
Mohammadi et al. ²²	Cross-sectional study. 201 postmenopausal women aged ranged from 45 to 71 years, with a mean age of 53.6 ± 3.6 years; All subjects were recruited from menopause clinics at Hospital Kuala Lumpur and the National Population and Family Development Board (NPFDB).	Calcaneal QUS The mean BMD defined as BUA and T-score ≤ 1.8 at calcaneus was the threshold to determine osteoporosis and normal density.	Non-osteoporotic (n=144) Osteoporotic (n=57)	Comparison using Student's t-test: <ul style="list-style-type: none"> Osteoporotic subjects had longer YSM (4.63±3.08) than the normal subjects (3.74±3.22) (p=0.06). Pearson's correlation: <ul style="list-style-type: none"> YSM negatively correlated with BUA (r = -0.176, p<0.005). Correlation analysis: NA Stepwise regression: <ul style="list-style-type: none"> YSM was not a predictor of BUA (Result not shown). 	Present.

Cont'd

First author	Type of study and population (sample size and source)	Bone-related parameters	Categorization of population	Comparison/ correlation/ regression analysis	Relationship/ Association (Presence or absence)
Chin et al. ²⁴	Cross-sectional study. 344 women (mean age 61.8 ± 7.6) were recruited from a tertiary medical centre in Kuala Lumpur, Malaysia.	Bone health was determined using calcaneal QUS device. ● SOS (m/s) ● BUA (dB/MHz) ● T-score ● Stiffness index (SI)	● BUA (n=320) ● SI (n=319) ● T-score (n=318)	Comparison analysis: NA Correlation analysis: NA Stepwise multiple linear regression between QUS indices and variables of interest: ● YSM was a negative predictor of BUA (B=-0.018, SEB= 0.003; β= -0.306; p<0.001), SI (B= -0.562, SEB= 0.081; β= -0.358; p< 0.001) T-score (B=-0.054, SEB=0.008; p<0.001). YSM is not a significant predictor of SOS (data not shown in table).	May be present.
Chan et al. ³¹	Case-control; Postmenopausal women with (n=20) or without osteoporosis (n=20); Subjects were randomly drawn postmenopausal women with or without osteoporosis from a bone health study in Klang Valley, Malaysia.	Lumbar spine (average of L1-L4) and hip BMD were computed automatically by the DXA scan. ● T-score ≤ -2.5 indicates osteoporosis, between -2.5 and -1 indicates osteopenia, and more than >-1 indicates normal bone health.	● Normal group (n=20): T-score >-1 ● Osteoporosis group (n=20): T score ≤ -2.5	Comparison using univariate (t-test): Osteoporotic group had longer YSM (9.50 ± 6.08 year) than normal group (6.10 ± 4.32 year) than (p = 0.048). Correlation analysis: NA Regression analysis: NA	Present
Hapidin et al. ³²	Cross-sectional study. A total of 51 healthy premenopausal women and 99 healthy postmenopausal women were recruited. Mean age for all subjects was 55.8 ± 7.11 years; All subjects were recruited from lower income family, based on Pendapatan Garis Kemiskinan (PGK) 2009 by Economic Planning Unit, Prime Minister's Department Malaysia.	Biochemical markers of bone resorption can be used clinically to predict future bone loss. ● CTx and NTx of type 1 collagen	● Healthy pre-menopausal group (n=51). ● Postmeno-pausal A group (n=65) who had been in menopausal state for less than 10 years. ● Postmeno-pausal B groups (n= 34) who had been in menopausal state for more than 10 years.	Comparison using ANOVA: The mean for CTx level was significantly different (p<0.05) between pre-menopausal group and both post-menopausal A and B. However, there was no difference between post-menopausal A and B. The mean serum CTx of the subjects were: Pre-menopausal (0.2833 ± 0.1769 ng/mL) ● Post-menopausal A (0.423 ± 0.2529 ng/mL) ● Post-menopausal B (0.510 ± 0.241 ng/mL) The mean for NTx level was significantly different (p<0.05) between pre-menopausal group and both post-menopausal A and B. However, there were no difference between post-menopausal A and B. The mean serum NTx of the subjects were: ● Pre-menopausal (15.203 ± 15.2025 nM BCE) ● Post-menopausal A (17.900 ± 7.7959 nM BCE) ● Post-menopausal B (19.351 ± 7.3775 nM BCE) Correlation analysis: NA Multiple linear regression using simultaneous multiple regression analysis: ● Duration of menopause was a significant positive predictor influencing CTx (B= 0.007; SEB=0.002; β= - 0.265 (p<0.05) and NTx (B= 0.013; SEB=0.005; β= 0.211) bone resorption marker (n=150; p<0.05)	Maybe absent since there is no difference in bone resorption markers between post-menopausal A and post-menopausal B.

Cont'd

First author	Type of study and population (sample size and source)	Bone-related parameters	Categorization of population	Comparison/ correlation/ regression analysis	Relationship/ Association (Presence or absence)
Mohd Hatta et al.³³	Cross-sectional study. 87 post-menopausal women; All subjects were recruited from the orthopaedic and menopause clinics of Hospital Tengku Ampuan Afzan Kuantan, Pahang, Malaysia	FRAX® was used to calculate the risk for major and hip fracture probability in 10 years. ● BMD result of the osteopenic range (T-score of less than -1 and greater than -2.5 SD).	FRAX 10-year risk score: ● Major osteoporotic fracture (9.7%) ● Hip fracture (3.5%)	Comparison analysis: NA The Pearson correlation coefficient showed a significant positive but weak correlation between year of menopause and FRAX major osteoporotic ($r=0.581$, $p < 0.001$) and hip fracture probability ($r=0.495$, $p < 0.001$). Regression analysis: NA	Present
Lim et al.³⁴	Cross-sectional study. A total of 514 disease-free, uterus-intact, non-HRT-using women aged 45 years and older were recruited into the study; Subjects were recruited from residential areas around a tertiary referral hospital, but subjects from other areas responded as well after being informed by friends.	BMD using DXA. ● Bone mass at the spine and hip (g/cm^2) ● Hip and spine T-score.	● Pre-menopausal (year 0) $n=308$ ● Post-menopausal ($n=205$) Overall, 42.1% postmenopausal women and 11.1% premenopausal women were osteoporotic.	Comparison analysis: NA Pearson's correlation: YSM negatively correlated with BMD: ● Spine T-score ($r= -0.439$, $p < 0.001$). ● Spine Z-score ($r= -0.289$, $p < 0.001$), ● hip T-score ($r= -0.441$, $p < 0.001$), ● hip Z-score ($r= -0.186$, $p < 0.001$). Regression analysis: NA	Present
Mohammadi et al.³⁵	Cross-sectional study. A total of 201 postmenopausal, disease-free women. Their ages ranged from 45-71 years, with a mean age of 53.6 ± 3.6 years; All subjects were recruited from menopause clinics at Hospital Kuala Lumpur and the National Population and Family Development Board (NPFDB).	Calcaneal BMD was measured by QUS and was expressed in BUA as well as T-score.	● Non-osteoporotic ($n=144$) ● Osteoporotic ($n=57$)	Comparison analysis: NA Correlation analysis: NA Hierarchical regression analysis: ● YSM was not a predictor of BUA. ● Step 1: ($B=1.116$; $SEB 0.735$; $\beta=0.227$; $p>0.05$) ● Step 2: ($B= 0.935$; $SEB 0.654$; $\beta=0.190$; $p>0.05$)	Absent

Abbreviations: ANOVA (Analysis of variance), Bone mineral density (BMD), Broadband ultrasound attenuation (BUA), C-telopeptide (CTx), Not applicable (NA), N-telopeptide (NTx), Quantitative ultra-sonography (QUS), Speed of Sound (SOS), years-since-menopause (YSM).

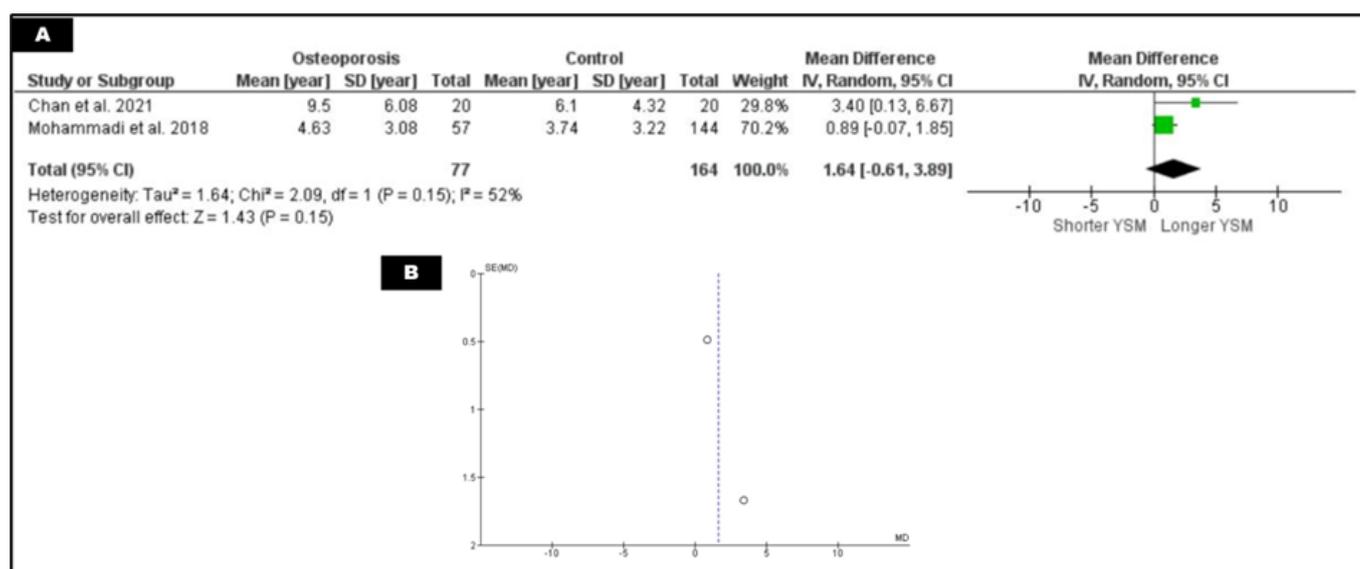


Figure 2: Comparison of YSM between postmenopausal women with and without osteoporosis. (A) Forest plot illustrating the mean difference in YSM, and (B) funnel plot assessing publication bias.

Several studies consistently found a significant negative correlation between YSM and BMD (measured by BUA or DXA), although the correlation strength was weak ($r=-0.284$, $r=-0.176$, $r=-0.439$, respectively; $p<0.01$).^{11,22,34} In contrast, another study reported a positive correlation between YSM and the Fracture Risk Assessment Tool (FRAX®) major osteoporotic fracture risk score ($r=0.581$; $p < 0.001$) and FRAX® hip fracture probability ($r=0.495$; $p<0.001$).³³ One study found no significant correlation between YSM and serum CTx ($r=0.109$; $p > 0.05$).⁸ The forest plot in Figure 3(A) summarizes the correlation results, with each study's bone indices indicated. Five studies were included in the meta-analysis, pooling data from 1134 postmenopausal women. The fixed effect model yielded a pooled effect size of -0.251 ($p<0.001$), while the random effect model resulted in -0.0677 ($p=0.712$). The heterogeneity I^2 was 96.99%, and the symmetrical funnel plot suggested no publication bias (Figure 3(B)).

Two studies indicate that YSM can predict osteoporosis. Based on multiple linear regression, one study found that YSM was not a predictor of BUA ($B=0.935$; $\beta=0.190$; $p>0.05$),³⁵ while another reported that YSM predicted

BUA ($B=-0.018$), SI (-0.562), and T score ($B=-0.054$) ($p<0.001$), but not SOS.²⁴ Another study found YSM to be a significant positive predictor of CTx ($B=0.007$; $\beta=-0.265$; $p<0.05$) and NTx ($B=0.013$; $\beta=0.211$) bone resorption markers ($n=150$; $p<0.05$).³² Conversely, one study reported that YSM was not a predictor of CTx ($B=NA$; $\beta 0.053$; $p=0.624$).⁸

Relationship between parity and osteoporosis

Table III summarizes five studies on the association between parity and osteoporosis in postmenopausal women in Malaysia. Only one study examined the relationship, and two studies measured the association between parity and osteoporosis. One study found no significant difference in the number of pregnancies between osteoporotic (2.85 ± 2.06) and non-osteoporotic women (3.10 ± 2.27).³¹ However, another study reported that osteoporotic women had significantly more pregnancies (5.43 ± 1.89) than non-osteoporotic women (4.77 ± 2.05 , $p=0.027$).²² Another study found that middle-aged and elderly women with more than three pregnancies had lower BUA than those with fewer pregnancies or nulliparous women ($p=0.010$).²⁴

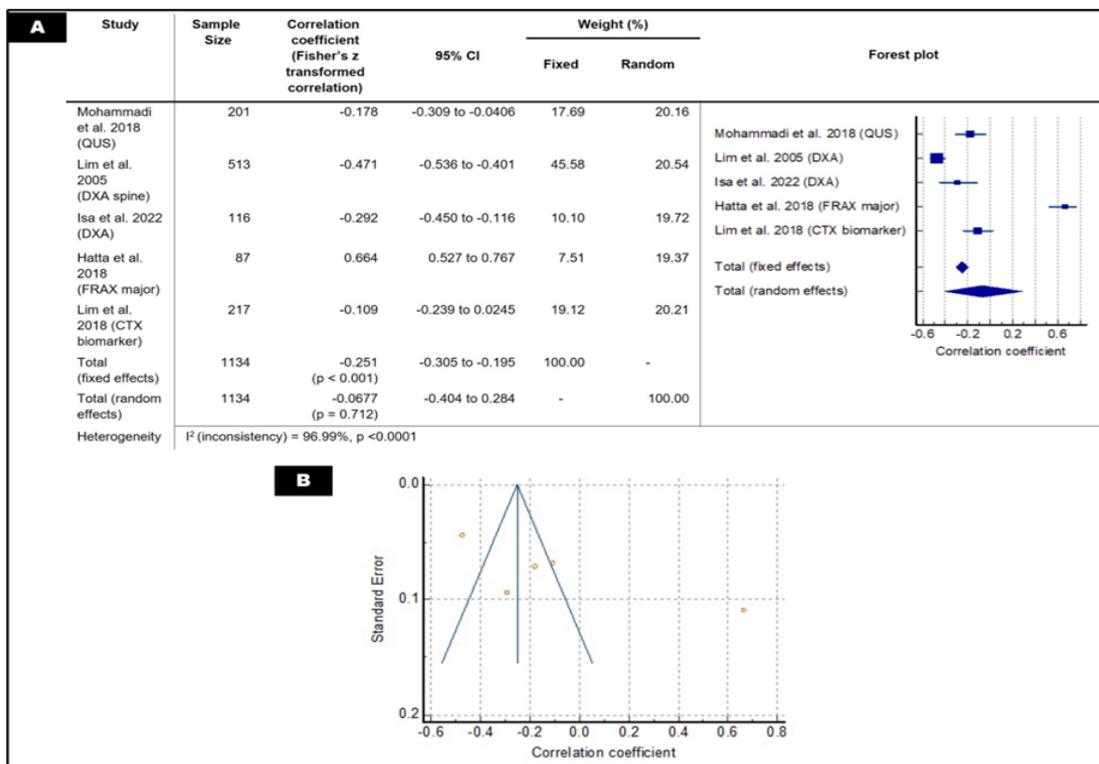


Figure 3: Correlation between YSM and osteoporosis indices. (A) Forest plot depicting the correlation coefficients, with bone health assessment methods indicated for each study, and (B) funnel plot evaluating publication bias.

The pooled results for parity in postmenopausal women with and without osteoporosis are shown in Figure 4(A). The meta-analysis included data from 77 postmenopausal women with osteoporosis and 164 controls from two studies,^{22,31} excluding other studies with unavailable parity data.^{24,32,35} Notably, one study divided groups based on menopausal years without specifying osteoporosis status, so it was not included in the meta-analysis of comparison.³² The overall result did not significantly favour osteoporosis in either direction, with no clear association between parity and osteoporosis (Overall Mean Difference=0.41; 95% CI: -0.38 to 1.21; P=0.31). The heterogeneity test ($p=0.22$, $I^2=32\%$) showed acceptable variability, and the symmetrical funnel plot indicated no publication bias (Figure 4(B)).

In terms of the strength of this relationship, only one study measured the correlation between parity and bone status. One study found that parity was negatively correlated with BUA ($r=-0.162$; $p<0.005$).²² However, based on multiple linear regression, another study found that parity was not a predictor of BUA ($B=-0.152$ $\beta=-0.020$; $p>0.05$),³⁵ which contrasts with findings from another study that reported parity as a predictor of BMD measured using BUA ($B=-0.040$; $\beta=-0.133$; $p=0.011$) and stiffness index ($B=-0.888$; $\beta=-0.112$; $p=0.033$).²⁴ Other studies did not perform multiple linear regression, making it difficult to definitively confirm the relationship or predictive value of parity in osteoporosis.

Relationship between lactation and osteoporosis

Table IV presents three studies on lactation and osteoporosis in postmenopausal women in Malaysia. Of these, two studies measured the relationship or association. One study found that osteoporotic women had a significantly longer lactation period (46.30 ± 19.75 months) than non-osteoporotic women (39.07 ± 23.16 months).²² In the same study, lactation was inversely correlated with BUA ($r=-0.159$; $p<0.05$). However, the relationship between lactation and BUA remains unclear. Stepwise multiple regression showed lactation as a positive predictor of BUA ($B=0.036$; $p=0.015$),²² while hierarchical multiple regression indicated it as a negative predictor ($B=-0.111$; $\beta=-0.158$; $p<0.01$) for the same population.³⁵ This inconsistency highlights the need for further studies to confirm whether lactation can reliably predict osteoporosis.

DISCUSSION

This systematic review highlights that most studies on osteoporosis in Malaysia are cross-sectional. While cross-sectional studies are adept at determining prevalence and identifying potential associations, they are often preliminary and require further investigation through cohort or randomized controlled studies. Case-control studies on osteoporosis risk factors in Malaysian postmenopausal women are limited, often with small sample sizes.³¹ There is also a dearth of cohort studies

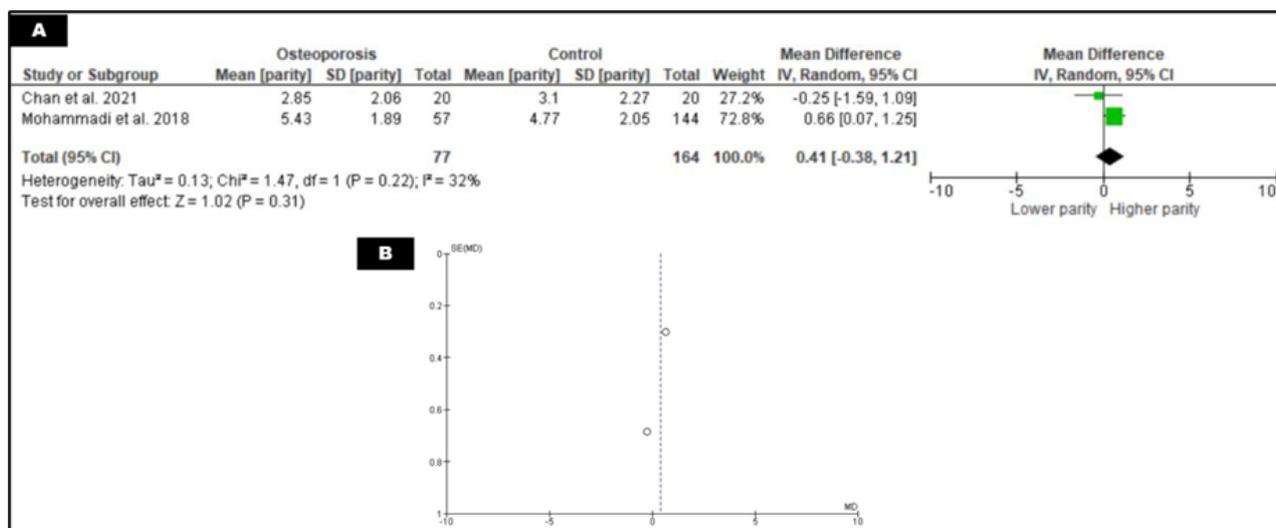


Figure 4: Comparison of parity between postmenopausal women with and without osteoporosis. (A) Forest plot illustrating the meta-analysis results, and (B) funnel plot assessing publication bias.

specifically focused on this population.³⁶ A group of researchers conducted a cohort study on osteoporosis risk factors for osteoporosis in the Malaysian population, but it included participants of mixed gender.³⁷ While randomized controlled trials are the gold standard for establishing causality, practical and ethical constraints often preclude their implementation. In these cases, observational research, such as case-control studies, provides valuable insights and is cost-effective.³⁸ More studies in this direction were anticipated.^{31,39} This review offers an overview of the research trends in Malaysia, highlighting a pronounced bias towards cross-sectional studies. It emphasizes the heavy reliance on cross-sectional designs and underscores the scarcity of case-control, cohort, and randomized controlled trials. This indicates a pressing need for more robust research

methodologies to enhance the quality and depth of findings in the field.

A significant portion of the cross-sectional studies in this review used purposive sampling, which, although lacking statistical representativeness,⁴⁰ allows for the selection of participants expected to provide valuable insights.⁴¹ In contrast, convenient sampling, as used in some studies,^{24,32} is less representative but was still included in this systematic review due to its overall moderate quality score. Given Malaysia's ethnically diverse population, studies focused on a single ethnicity may not adequately represent the entire population. Therefore, factors beyond sampling methods, such as ethnicity and whether the study was conducted at single or multiple centres, must also be considered.

Table IV: Evidence table - Lactation

First author	Type of study and population (sample size and source)	Bone-related parameters	Categorization of population	Comparison/ correlation/ regression analysis	Relationship/ Association (Presence or absence)
Mohammadi et al.²²	Cross-sectional study. 201 post-menopausal women, aged ranged from 45 to 71 years, with a mean age of 53.6 ± 3.6 years; All subjects were recruited from menopause clinics at Hospital Kuala Lumpur and the National Population and Family Development Board (NPFDB).	Calcaneal QUS The mean BMD defined as BUA and T-score ≤ 1.8 at calcaneus was the threshold to determine osteoporosis and normal density.	<ul style="list-style-type: none"> Non-osteoporotic (n=144) Osteoporotic (n=57) 	Comparison using Student's t-test: <ul style="list-style-type: none"> Osteoporotic subjects had longer lactation period (46.30±19.75 months) than the normal subjects (39.07±23.16 months) (p=0.028). Pearson's correlation: <ul style="list-style-type: none"> Total lactation period negatively correlated with BUA (r= -0.15, p<0.005). Stepwise regression: <ul style="list-style-type: none"> Lactation period was a predictor of BMD (B=0.036, SEB=-0.126; p=0.015). 	Present
Hapidin et al.³²	Cross-sectional study. A total of 51 healthy premenopausal women and 99 healthy postmenopausal women were recruited. Mean age for all subjects was 55.8 ± 7.11 years; All subjects were recruited from lower income family, based on Pendapatan Garis Kemiskinan (PGK) 2009 by Economic Planning Unit, Prime Minister's Department Malaysia.	Biochemical markers of bone resorption can be used clinically to predict future bone loss. CTX and NTx of type 1 collagen	<ul style="list-style-type: none"> Healthy pre-menopausal group (n=51). Postmeno-pausal A group (n=65) who had been in menopausal state for less than 10 years. Postmeno-pausal B groups (n=34) who had been in menopausal state for more than 10 years. 	Comparison: There was no significant difference in duration of breastfeeding among the groups: Data presented in percentage, no standard deviation or mean. ANOVA: NA Correlation analysis: NA Regression: NA	Maybe absent
Mohammadi et al.³⁵	Cross-sectional study. A total of 201 postmenopausal, disease-free women. Their ages ranged from 45-71 years, with a mean age of 53.6 ± 3.6 years. All subjects were recruited from menopause clinics at Hospital Kuala Lumpur and the National Population and Family Development Board (NPFDB).	Calcaneal BMD was measured by QUS and was expressed in BUA as well as T-score.	<ul style="list-style-type: none"> Non-osteoporotic (n=144) Osteoporotic (n=57) 	Hierarchical regression analysis: Lactation negative predictor of BUA (N=201) Step 1: (B= -0.082; SEB 0.050; β = -0.116; p<0.001) Step 2: (B= -0.111; SEB 0.045; β = -0.158; p<0.01)	Present

Abbreviations: ANOVA (Analysis of variance), Bone mineral density (BMD), Broadband ultrasound attenuation (BUA), C-telopeptide (CTX), Not applicable (NA), N-telopeptide (NTx), Quantitative ultra-sonography (QUS).

Epidemiological evidence indicates that reduced lifetime oestrogen exposure, such as that resulting from early menopause and late menarche, is linked to lower BMD and a higher incidence of fractures.^{12,13,42} Research involving women from other ASEAN countries has demonstrated that early menopause reduces oestrogen exposure and is consistently associated with an increased risk of osteoporosis.^{12,13} While lactation induces a temporary hypoestrogenic state that can lead to transient bone loss, the long-term effects of this phenomenon remain a subject of debate.^{19,21} Furthermore, parity introduces repeated hormonal fluctuations, with high parity showing mixed associations with BMD.^{43,44} The differences in oestrogen decline, transient during pregnancy and lactation versus continuous after menopause, may explain why our findings revealed a relationship between young maternal age and osteoporosis, while parity and lactation did not show the same connection.

The meta-analysis on the impact of YSM on bone health indicates a tendency towards osteoporosis or compromised bone health with increased menopausal age, though this effect was not statistically significant due to the limited number of studies and the use of cross-sectional study designs. The meta-analysis of the correlation between YSM and bone health indices suggests a negative relationship, indicating lower bone density with an extended duration of postmenopausal state. However, the correlation was weak, regardless of whether a fixed or random effects model was used. Due to significant heterogeneity among studies, the random effects model was deemed more appropriate.⁴⁵ Variations in methods for assessing bone health, such as DXA, QUS, FRAX®, and biomarkers, likely contributed to this heterogeneity. While DXA is the gold standard, its limited availability must be considered.⁴⁶ Additionally, confounding factors like age may influence results, highlighting the need to consider both menopausal and age-related factors when assessing osteoporosis risk and deciding on hormone treatments for prevention.⁴⁷ Studies in this review that found YSM as a non-significant predictor of bone indices reflect the complexities associated with the temporal sequence of osteoporotic fractures,^{8,35} which are influenced by bone type and age.

The association between parity and osteoporosis remains inconclusive, as only one study measured the relationship, and two studies assessed the association with contradictory findings. Similarly, there is a lack of studies to confirm the relationship between lactation and osteoporosis among postmenopausal women.

This systematic review highlights the heterogeneity in assessing bone health, with varying methods such as DXA, QUS, and biomarkers. Beyond summarizing current evidence and suggesting avenues for future research, this review emphasizes the challenges in using reproductive factors as reliable risk assessment measures for osteoporosis screening. Key issues include the lack of standardization in bone health assessments, with varying methods such as DXA, QUS, and biomarkers, as well as potential recall bias in the studies reviewed. A significant limitation of our review is the small number of studies and their observational design. Therefore, further research is essential to validate the association between reproductive factors, particularly young maternal age, before integrating them into a robust risk assessment tool for Malaysia. Identifying women needing DXA and implementing preventive measures necessitates a comprehensive understanding of these factors. This initiative aims to enhance screening and prevention efforts, particularly in primary care and community health settings.

CONCLUSION

Years-since-menopause (YSM) is a key reproductive factor associated with osteoporosis in postmenopausal women in Malaysia, though the relationship remains weak and warrants further study. Qualitative analysis revealed that five out of nine studies indicated a relationship between YSM and osteoporosis, while two out of four studies showed a connection between parity and osteoporosis, and two out of three studies indicated a link between lactation and osteoporosis. Quantitatively, a significant negative correlation was found between YSM and osteoporosis indices; however, the available data on parity and lactation were insufficient for a thorough quantitative analysis. These findings suggest that future research should prioritize YSM when developing risk assessment models to enhance osteoporosis screening and prevention in this population.

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The Practice of Primary Eye Care by Optometrists Worldwide - A Systematic Literature Review

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ABSTRACT

Primary eye care involves detecting and managing conditions that cause preventable blindness, as well as diagnosing and treating eye diseases. Optometrists play a central role in primary eye care, yet their scope of practice and challenges vary globally. This systematic review was conducted to examine the roles, scope and challenges faced by optometrists in their practices. The systematic search was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines using a registered review protocol. An electronic search of PUBMED, PubMed Central (PMC), Scopus, EBSCO, OVID, and Web of Science (WoS) was conducted between February and September 2022. Two reviewers independently screened and extracted eligible studies. Eleven publications met the inclusion criteria; 10 cross-sectional studies and one retrospective study. Extracted data focused on structural aspects of care delivery, including instrumentation, procedures, services, management, referral pathways, and training. The scope of practice varied widely, ranging from refraction to advanced clinical management, including therapeutic interventions. Standards of optometric practice in several settings extended well beyond refraction and dispensing, incorporating disease management and collaborative care. Optometrists are capable of delivering comprehensive primary eye care that extends beyond basic refractive services. Harmonising educational standards and implementing enabling policies can empower optometrists to work to the full extent of their training, thereby improving access to eye care services and reducing strain on general healthcare systems.

Keywords

Optometrist, scope, practice, primary eye care, vision, systematic review

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INTRODUCTION

The World report on Vision 2020 by World Health Organization (WHO) estimated that 2.2 billion worldwide have a vision impairment or blindness.¹ Of these, approximately one billion people have preventable vision impairment, with uncorrected refractive error and unaddressed presbyopia being the leading cause.¹ This reflects a growing demand for eye care services, compounded by the increasing prevalence of eye disorders such as cataracts, age-related macular degeneration, and presbyopia. A rise in referrals for minor eye conditions can strain tertiary care facilities, reducing the quality and timeliness of specialised services.^{2,10} This underscores the need for robust primary eye care services.^{2,10}

Primary eye care involves detecting and managing preventable causes of blindness, diagnosing and managing eye diseases, and referring patients when appropriate.^{3,4} These services should be capable of managing conditions at the primary level and making timely referrals to secondary or tertiary care.⁴ Primary eye care also provides initial access to refractions and optical correction (glasses or contact lenses), screening for asymptomatic disorders, diagnosis and treatment of common eye conditions, referral to specialists, and coordination with other healthcare services.^{1,5}

Optometrists key primary eye care providers, delivering comprehensive eye and vision care.⁵ An optometrists'

scope of practice includes refraction and dispensing, detection, diagnosis, management of eye diseases, and rehabilitation of visual system disorders.⁵ However, this scope varies widely across countries due to differences in legislation, licensing regulations, therapeutic privileges, and governance by regulatory bodies. Despite their high accuracy in detecting eye conditions, optometrists' skills remain underutilised.⁶

Despite the growing need for primary eye care practising optometrists, the limited integration of optometrists into primary healthcare systems can hinder early detection, disrupt referral pathways, and restrict resources for service delivery. Therefore, this systematic review aimed to explore and compare the optometrists' scope of practice worldwide.

MATERIALS AND METHODS

Study Design

This study used the systematic review of literature (SLR), which synthesizes existing evidence to provide a comprehensive overview of current knowledge in the field.⁷ The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed, and the review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42022321326).

A systematic search was conducted in the following databases: PUBMED, PubMed Central (PMC), Scopus, Elton B. Stephens Company (EBSCO), OVID and Web of Science (WoS). These databases were selected for their relevance to public health and optometry. Additional searches were performed using Google Scholar and Google Search to capture grey literature, reducing publication bias. The PROSPERO register and Cochrane library were also reviewed to identify existing systematic reviews and prevent duplication. The search terms used for this review were as follows:

1. Profession-specific terms: "Optometr*", "Optician*", "Ophthalmic practitioner*".
2. Condition-specific terms: primary eye care, scope of practice
3. 1 AND 2

Inclusion Criteria

The search included only full-text studies published in English. Additional abstracts identified through google scholar were excluded if the full articles were not available in English. The search was limited to a 20-year period, from year 2002 till year 2022, to ensure that the synthesised evidence was current and reflective of contemporary practices, trends, and advancements in the field. This timeframe was chosen to focus the review on recent findings most likely to influence current practice and policy decision-making.

Exclusion Criteria

Articles published in languages other than English were excluded. The review also excluded literature reviews, technical reports, doctoral theses, and conference proceedings. Studies unrelated to the research topic, as well as duplicate publications, were also excluded.

Selection Criteria

The review included publications that explored optometrists' scope of practice using the Population, Interest, and Context (PICo) framework.

Population

The review focused on publications involving optometrists, whether or not they practising primary eye care. Publications primarily addressing patients' perceptions or ophthalmologists were excluded, as the primary focus of the publications was on optometrists' practices.

Interest

The core focus of this review was the scope of practices of optometrists in primary eye care. Studies assessing effectiveness of primary eye care were excluded, as the objective was to explore scope rather than outcomes.

Context

The context was the provision of primary eye care by optometrists, with emphasis on structural aspects of care delivery, including instrumentation, procedures, services, management, referral, and training. Publications centred

on the prevalence of eye conditions, patients' satisfactions, policy and regulations were excluded from this review.

Data Selection

The review included any primary research article from both the quantitative and qualitative study design. The selection process began with the screening of titles and abstracts by Reviewer 1. Publications meeting the inclusion criteria were classified as potentially eligible and were retrieved in full text. Reviewer 1 and Reviewer 2 independently assessed the full text to determine their relevance to the review question and compliance with the inclusion criteria. A preliminary list of potentially relevant publications was compiled, after which both reviewers discussed each publication until consensus was reached on the final list of included articles.

Data Extraction

Titles and abstracts of studies were retrieved using the search strategy. Publications from additional sources were also screened for eligibility. Full texts of potentially eligible studies were retrieved and assessed against the inclusion criteria. A data extraction table was created to summarise key study details, including author(s), year of publication, publication type/study design, country, survey methodology, study condition(s), and study population (if applicable). Extracted data were organised chronologically from the earliest to the most recent publication.

Data Analysis

Given the descriptive nature of this review, a narrative synthesis was conducted. Following data extraction, each reviewer independently examined the scope of practice reported in the studies to identify potential subthemes. Reviewer 1 and Reviewer 2 then met to refine these subthemes and determine overarching themes common across the studies. The reviewers continuously discussed until a consensus on the themes and sub-themes for the scope of eye practice on primary eye care by optometrists were reached.

RESULTS

The search identified a total of 43 articles across the databases. Of these, 29 articles were excluded due to duplication, two articles were excluded as they were article review, and one article was excluded as because only an abstract was available despite attempts to obtain the full text from the author. Consequently, 11 studies met the inclusion criteria and were included in the review. The literature selection process is summarised in Figure 1.

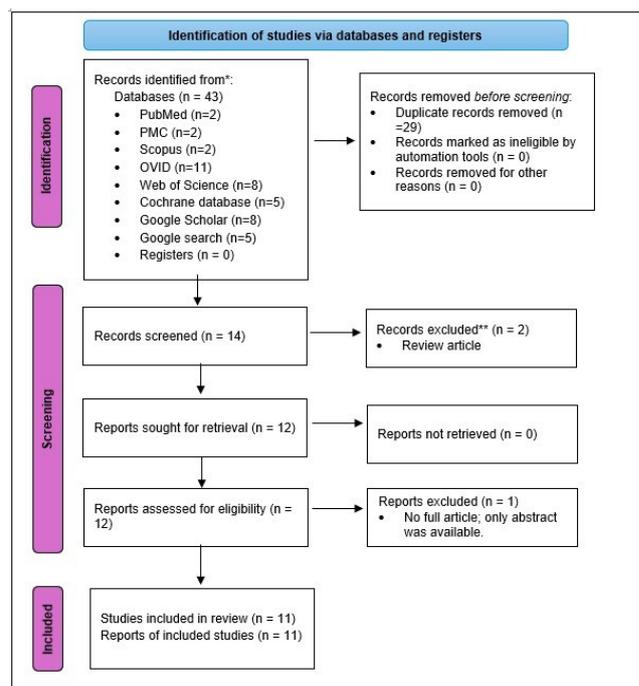


Figure 1. Overview of Literature Selection Process

Overview of Included Studies

The review identified 11 primary research publications, of which 10 employed a cross-sectional study design and one utilised a retrospective design involving analytical review of patients' record. The studies were conducted between 2008 and 2021, with the exception of one undated study. The geographic distribution of the studies was classified according to the World Economic Situation and Prospects (WESP) by the United Nations; developed, developing and under developed.²³ Six studies originated from developed countries (United Kingdom, Australia, Ireland, Scotland, Portugal), four from developing countries (Ghana, Saudi Arabia, Sudan, Singapore), and one from an underdeveloped country (Kenya).

Study Population and Tools

All studies targeted optometrists, with approximately 90% of respondents being community-based practitioners.^{8,9} In the remaining publications, the specific practice setting was not reported. One retrospective study conducted in the Middle East reviewed patient records maintained by optometrists, whereas all other studies collected data using online self-administered questionnaires.¹⁰ The preference for this method was attributed to its ease of administration and cost-effectiveness, particularly for studies involving larger cohorts.

Response Rate

Reported response rates for the self-administered questionnaires ranged from 23% to 100%. Six of the 10 cross-sectional studies reported response rates below 50%. Lower participation was observed when questionnaires were distributed via email, whereas rates of 80% or higher were achieved when questionnaires were disseminated through professional associations or targeted optometrist networks. An overview of the selected studies is presented in Table 1.

The analysis revealed notable regional disparities in the scope of primary eye care practice. In countries such as the United Kingdom, Australia, and Scotland, optometrists practise at an advanced scope, which includes the management of ocular diseases, prescribing therapeutic medications, and performing minor surgical procedures. In contrast, in countries with more restrictive

regulatory frameworks, particularly parts of Asia and Africa, optometrists' roles are limited to vision testing and prescribing corrective lenses. Across all 11 studies, optometry practices were identified based on the procedures performed. Fundamental procedures, such as history taking and refraction, were consistently undertaken by optometrists. The overall scope of practice for each study is summarised in Table 2.

WCO Classification of Optometric Services Categories

The World Council of Optometry (WCO) have classified optometric services into four categories. Category 1: dispensing only, Category 2: dispensing and refraction, Category 3 is sub-divided into two sections; Category 3(a): services in Category 2 plus screening for eye diseases, and Category 3(b): services in Category 3(a) plus diagnosis of eye conditions using diagnostic agents, Category 4: provision of ocular therapeutic services. Using this framework, all reviewed studies were classified at Category 3(a) or higher, indicating that worldwide, optometrists engage in primary eye care that includes screening for ocular conditions in addition to refraction and dispensing. The highest levels of service (Category 4) were reported in Ireland and Australia, where optometrists provide comprehensive ocular therapeutic care.¹¹ In contrast, some developing countries continue to operate at the minimal threshold of primary eye care relative to the WCO model.^{9,13,14,15} The categorisation of the reviewed studies according to WCO standards is presented in Table 3.

Table 1. Description of Study Population and Responses.

No.	Author/ Year	Study Design	Country	Population	Sample Size	Response Rate	Tools Used
1	Needle et al. ⁹ ,2008	Cross-sectional	United Kingdom	Optometrist	n=1288	24%	Online survey
2	Boadi-Kusi et al. ¹⁹ ,2015	Cross-sectional	Ghana	Optometrist	n=146	62%	Survey
3	Harper et al. ¹¹ ,2016	Cross-sectional,	United Kingdom	Optometrist	n=76	89%	Survey
4	Kiely et al. ¹³ ,2017	Cross-sectional	Australia	Optometrist	n=3898	43%	Survey
5	Aldebasi et al. ¹⁰ ,2018	Retrospective	Saudi Arabia	Patient records reviewed = 2601	N/A	N/A	Analytical, record-based study
6	Barret and Loughman ¹² ,2018	Cross-sectional	Ireland	Optometrist	n=737	27%	Survey
7	Alrasheed ¹⁴ , 2019	Cross-sectional	Sudan	Optometrist	n=300	97.90%	Survey
8	George et al. ¹⁸ , 2019	Cross-sectional	Singapore	Optometrist	n=766	30%	Survey
9	Carneiro et al. ⁸ , 2020	Cross-sectional	Portugal	Optometrist	n=1288	24%	Online survey
10	Muma and Obonyo, ¹⁶ ,2020	Cross-sectional	Kenya	Optometrist	n=146	62%	Survey
11	El-Abiary et al. ¹⁵ , 2021	Cross-sectional	Scotland	Optometrist	n=76	89%	Survey

Table 2. Scope of Practice by Optometrists

Study	Refraction	Dispensing	Anterior Segment	Posterior Segment Evaluation	Perimetry	Tonometry	Contact Lens	Low Vision	Binocular Vision	Pre & Post Operative
NEEDLE ET AL. ⁹ , 2008	P	N/A	P	P	O	P	N/A	N/A	N/A	N/A
BOADI-KUSI ET.AL ¹⁹ , 2015	P	P	P	P	P	P	P	P	P	P
HARPER ET.AL ¹¹ , 2016	P	N/A	P	P	P	P	N/A	N/A	N/A	N/A
KIELY ET AL. ¹³ , 2017	P	P	P	P	P	P	N/A	N/A	N/A	N/A
ALDEBASI ET AL. ¹⁰ , 2018	P	P	P	P	N/A	P	N/A	N/A	N/A	N/A
BARRET AND LOUGHMAN ¹² , 2018	P	P	P	P	P	P	N/A	N/A	N/A	N/A
ALRASHEED ¹⁴ , 2019	P	P	P	O	O	O	N/A	N/A	N/A	N/A
GEORGE ET AL. ¹⁸ , 2019	P	P	P	P	P	P	P	N/A	P	P
CARNEIRO ET AL. ⁸ , 2020	P	P	P	P	P	P	P	P	P	P
MUMA AND OBONYO, ¹⁶ , 2020	P	N/A	P	P	P	P	N/A	N/A	P	N/A
EL-ABIARY ET AL. ¹⁵ , 2021	P	N/A	P	O	O	O	N/A	N/A	N/A	N/A

(P-services provided by optometrists; N/A – no information available; O - no service available by optometrist)

Table 3. WCO Classification of Optometric Services Categories.

No.	Author/ Year	WCO category	Therapeutic agents	Referral
1	Needle et al. ⁹ , 2008	3 (b)	Use of diagnostic agents; stains	General practitioners and ophthalmologist
2	Boadi-Kusi et.al ¹⁹ , 2015	3 (b)	Diagnostic agents; pharmaceutical agents	N/A
3	Harper et.al ¹¹ , 2016	3(b)	Diagnostic agents; pharmaceutical agents	Ophthalmologist
4	Kiely et al. ¹³ , 2017	4	Diagnostic agents; pharmaceutical agents	Ophthalmologist and non-ophthalmic specialist
5	Aldebasi et al. ¹⁰ ,2018	3(a)	Diagnostic agents;	Ophthalmologist
6	Barret and Loughman ¹² , 2018	4	Diagnostic agents; pharmaceutical agents	Ophthalmologist
7	Alrasheed ¹⁴ , 2019	3(a)	Diagnostic stains;	Ophthalmologist
8	George et al. ¹⁸ , 2019	3 (a)	N/A	General practitioners and ophthalmologist
9	Carneiro et al. ⁸ , 2020	3(b)	Diagnostic agents;	Ophthalmologist
10	Muma and Obonyo, ¹⁶ , 2020	3 (a)	N/A	Ophthalmologist
11	El-Abiary et al. ¹⁵ , 2021	3 (a)	N/A	General practitioners and ophthalmologist

Management

Beyond prescribing glasses and contact lenses, optometrists in the reviewed studies were also involved in the management of ocular abnormalities. From the reviewed studies, common conditions managed included dry eye syndrome, glaucoma, diabetic retinopathy, and

macula-related disorders. In all studies, optometrists referred patients to ophthalmologists or general practitioners for further management when ocular pathology was detected. An overview of management practices by the optometrists is summarised in Table 4.

Table 4. Management by Optometrists.

Study	Dry eye	Anterior segment abnormalities	Diabetic	Glaucoma	Macula	Referral
Needle et al. ⁹ , 2008	✓	✓	N/A	✓	N/A	GP and ophthalmologist
Boadi-Kusi et.al ¹⁹ , 2015	N/A	N/A	N/A	N/A	N/A	N/A
Harper et.al ¹¹ , 2016	✓	✓	✓	✓	✓	Ophthalmologist
Kiely et al. ¹³ , 2017	✓	✓	N/A	✓	N/A	GP and ophthalmologist
Aldebasi et al. ¹⁰ , 2018	N/A	N/A	N/A	N/A	N/A	Ophthalmologist
Barret and Loughman ¹² , 2018	N/A	N/A	✓	✓	✓	Ophthalmologist
Alrasheed ¹⁴ , 2019	N/A	N/A	N/A	N/A	N/A	Ophthalmologist
George et al. ¹⁸ , 2019	✓	✓	✓	✓	✓	GP and ophthalmologist
Carneiro et al. ⁸ , 2020	✓	✓	✓	✓	✓	Ophthalmologist
Muma and Obonyo, ¹⁶ , 2020	✓	✓	N/A	N/A	N/A	Ophthalmologist
El-Abiary et al. ¹⁵ , 2021	✓	✓	N/A	N/A	N/A	GP and ophthalmologist

(✓- areas managed by optometrists; N/A – no information available; GP – General Medical Practitioner.)

DISCUSSIONS

This systematic review synthesised published evidence describing the scope of optometry practice worldwide. Findings indicate that the scope of practice varies considerably across regions and has evolved over time, as reflected in more recent studies. Earlier research, such as Needle et al. (2008), reported that optometric practice was largely confined to refraction, with no evidence of sub-specialisation in areas such as binocular vision or contact lenses. In contrast, studies from 2019 to 2020 demonstrate that optometrists are increasingly practising beyond refraction, incorporating binocular vision assessment, contact lens fitting, low vision services, and comprehensive anterior and posterior segment evaluation, in addition to dispensing. While basic optometric practice remains centred on refraction and dispensing, the evidence shows a clear progression toward broader primary eye care services in alignment with the World Council of Optometry (WCO) model. These services include not only refraction and dispensing but also detection, diagnosis, and management of ocular diseases, as well as rehabilitation for conditions affecting the visual system.¹

The scope of primary eye care was found to vary significantly according to geographical location, particularly between optometrists practising in developed countries and those in underdeveloped nations (e.g., Kenya). Access to primary health care is especially crucial in poorer and rural communities, where health outcomes are generally worse than in urban areas. Rural populations experience approximately 1.5 times higher rates of illness and injury compared to city dwellers, with some cases resulting in premature mortality.¹⁹ One of the major challenges for health services is ensuring equitable access, especially in underserved or remote areas, where limited healthcare facilities, transportation barriers, and financial constraints can delay timely access to appropriate care. In such contexts, integrating optometrists into the primary healthcare team is essential to enable early detection of visual and ocular abnormalities.

This review shown that optometrists have expanded their roles beyond refraction to include ocular diagnostics,

disease management, and referrals. Comprehensive vision care provided by optometrists generally includes evaluation, assessment, management, and coordination of a wide range of eye health needs, with appropriate referrals to ophthalmologists or general practitioners when required. Many optometrists have invested in advanced technology, diagnostic instrumentation, and therapeutic capabilities.¹⁵ Being equipped with the necessary training and skills, optometrists are able to manage visual and ocular abnormalities effectively, positioning them as the first point of contact for patients with vision concern.

In addition to early detection and preventive care, optometrists play a vital role in patient education on vision and eye care.¹² Their contributions include advising patients on when to seek professional help, promoting healthy lifestyle choices, discussing visual ergonomics, identifying environmental risks to vision, and educating the public on ocular safety and preventive measures.¹⁸ Optometrists can detect eye conditions with high accuracy and provide timely referrals when necessary.⁶ Collaboration between optometrists, ophthalmologists, and other healthcare or rehabilitation professionals enhances patient management, reduces waiting times in public eye care facilities, and alleviates the burden on ophthalmologists, especially in cases involving minor eye diseases.² In many developing countries, healthcare systems remain heavily focused on tertiary care, resulting in the neglect of primary and secondary eye care services. This imbalance places additional strain on tertiary facilities and increases demand for quality eye care at the primary level.

This review found that, despite the diversity of optometric roles, they remain underutilised, particularly in community healthcare, where their potential to detect, manage, and treat vision and eye disorders is not fully realised.^{18,20,21} This review emphasised on the inventory of optometry practices and a wide scope of services provided by optometrists. Optometrists play a crucial role in early detection and referral.³ This highlighted the need for revamp in primary health care services, whereby vision care and eye care should be shifted to the optometrists.¹⁸

Optometry education generally produces competent practitioners, well-trained to deliver comprehensive vision care. However, some studies reported that services remain limited due to factors such as a country's economic status, rural versus urban practice location, and infrastructure constraints.^{4,19,21,22} The cost of eye care can also be prohibitive, particularly when it involves advanced diagnostic testing, heavy reliance on ophthalmologists, or uneven distribution of optometrists across regions. While this review focuses on the scope of practice, the findings cannot be generalised to specific legal frameworks, insurance coverage systems, or healthcare models worldwide. Nevertheless, the evidence underscores the importance of rethinking primary healthcare delivery so that optometrists can be more fully integrated into vision and eye care at the primary level. Further research is needed to explore barriers such as professional regulations, resource limitations, and public awareness that constrain the scope of optometric practice in primary eye care.

LIMITATIONS

As with any research, this systematic review has limitations. First, linguistic bias may have been introduced, as only studies published in English were included, potentially excluding relevant evidence from non-English sources. Second, methodological biases may exist, including possible sampling and selection bias, as well as low response rates in several of the included studies. Despite these constraints, a comprehensive search strategy and a systematic approach were employed to address the review questions using the best available evidence.

CONCLUSION

This systematic literature review demonstrates the diverse roles and practices of optometrists globally. Their scope extends well beyond refraction and dispensing, encompassing anterior and posterior segment evaluation, perimetry, and the diagnosis and management of vision-related conditions at the primary care level. The findings reaffirm that optometrists function as primary eye care providers, equipped to deliver comprehensive ocular assessments and initiate appropriate management.

While notable advancements have been achieved in certain regions, disparities persist, highlighting the need for greater harmonisation of training, stronger legislative support, and deeper integration into healthcare systems. Future research should expand the evidence base through larger, multi-centre studies and meta-analyses to explore barriers and challenges related to professional recognition, optometric education, and training. Furthermore, international collaborative efforts aimed at developing a standardised framework for the scope of optometry practice may enhance care quality and promote consistent professional standards worldwide.

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Scientific Evidence of Prophetic Medicine: Exploring Its Role in Integrative Medicine – A Review and Bibliometric Analysis

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ABSTRACT

Prophetic medicine embodies teachings by Prophet Muhammad ﷺ regarding health and well-being. Despite its historical significance, there is a growing global interest in traditional medicine in the context of modern medicine, necessitating a comprehensive and critical analysis of its relevance today. This study aimed to evaluate the scientific landscape and research trends surrounding prophetic medicine through a bibliometric approach, complemented by a review of recent evidence on key natural remedies. Literature from the Scopus database was retrieved using relevant keywords. Inclusion and exclusion criteria were applied, with the final selection of 171 articles for bibliometric analysis using VOSviewer software. The analysis identified 15 authors, 9 countries, 15 journals, 14 documents, and 157 keywords that fulfilled the chosen threshold. Although article publication fluctuated over the years, an upward trend emerged, with rapid growth from 2022 to 2023, reflecting the recent surge in scholarly attention. Salah Mohamed El Sayed was identified as the most prolific author, while Evidence-based Complementary and Alternative Medicine was the leading journal. Saudi Arabia emerged as a recent key contributor to prophetic medicine research and had the closest collaboration with Malaysia. Common research hotspots included “black cumin” and “antioxidant activity,” with recent interest focusing on honey and olives. The bibliometric findings highlight the novelty of this study by quantitatively mapping the current research landscape, identifying gaps, and highlighting emerging areas of focus. This review also integrates scientific evidence supporting the bioefficacy of prophetic remedies, reinforcing their relevance as complementary components of integrative medicine. The findings encourage further in-depth investigations to substantiate their therapeutic benefits.

Keywords

Tibb al-Nabawi, Bibliometric, Integrated medicine, Natural remedies

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INTRODUCTION

Prophetic medicine, also known as “Tibb al-Nabawi”, encompasses a body of literature that elucidates the lifestyle practices and viewpoints on well-being endorsed by Prophet Muhammad ﷺ. These teachings are rooted in centuries-old wisdom and guided by a profound understanding of the intricate connections between physical, mental, and spiritual well-being. A significant contribution to this field was made by Ibn Qayyim al-Jawziyah, who dedicated a comprehensive work to prophetic medicine, highlighting its importance in Islamic tradition. Prophetic medicine has gained increased attention among academic scholars and the public due to

its holistic approach to health and wellness.¹

Emerging from the intersection of faith, tradition, and health, the principles of prophetic medicine encompass a diverse array of health-related recommendations, dietary guidelines, and natural remedies that were advocated by the Prophet Muhammad ﷺ. These teachings, confined within the framework of hadiths (the sayings and actions of the Prophet), provide a roadmap for maintaining a balanced and harmonious existence. While the roots of prophetic medicine can be traced back to the early period of Islam, its principles continue to persist in finding

favour among individuals who are pursuing comprehensive methods for enhancing health and averting illnesses.²

In recent years, there has been a growing interest in the integration of traditional healing practices into contemporary healthcare systems.³ Prophetic medicine, with its emphasis on preventive care, moderation, and natural remedies, offers a unique perspective that aligns with many of the principles sought after in the modern health system.⁴ However, despite the growing body of literature on prophetic medicine, there has yet to be a comprehensive bibliometric analysis that maps the current research landscape, identifies influential contributors, and uncovers emerging research trends.

While individual narrative reviews and clinical studies have explored specific remedies such as *N. sativa* and honey, limited bibliometric studies have focused on this domain, and those available tend to concentrate on narrow themes or single plants. This highlights the need for a broader, more systematic mapping of research activity in prophetic medicine to support evidence-based investigations and identify future directions.

This study aims to analyse the scientific literature on prophetic medicine through bibliometric methods to uncover publication trends, leading authors and journals, collaborative networks, and emerging areas of research focus. This dual-method approach, combining bibliometric mapping with qualitative review, offers valuable insights into the evolving interest and scientific validation of prophetic medicine in the context of modern integrative healthcare.

To guide this investigation, the following review questions are proposed:

1. What are the publication trends in the field of prophetic medicine?
2. Who are the most prolific contributors (authors, institutions, countries), and which journals are leading in this field?
3. What are the key topics and frequently studied remedies within prophetic medicine?

4. Which areas show emerging research interest or gaps that warrant further exploration?

METHODOLOGY

Data collection and analysis

Publications related to the topic of interest were retrieved from the Scopus database using relevant keywords ("Medicine of the Prophet" OR "Prophet* medicine" OR "Tib* Nabawi" OR "Tibb Al-Nabawi" OR "Islamic medicine" OR "Arab medicine"). The papers were retrieved up to 2024. A total of 445 articles were initially identified from the database. Inclusion and exclusion criteria were applied to the search.^{5,6} The inclusion criteria involved literature with the search keywords mentioned in the title, abstract, or keywords. This approach was chosen to ensure that the retrieved articles had a central focus on prophetic medicine, as the presence of keywords in these fields typically indicates that the topic is a core aspect of the research. The exclusion criteria excluded non-English articles, irrelevant subject areas (e.g., engineering, social sciences, computer science, business), and any document type other than articles. Upon applying these criteria, a total of 171 articles were selected for the subsequent bibliometric analysis. The search strategy is depicted in Figure 1, illustrating the process of identifying and selecting relevant studies based on a modified PRISMA flowchart.⁷

Bibliometric analysis of the selected articles was conducted using VOSviewer 1.6.19, a software tool specifically designed for constructing and visualizing bibliometric networks.⁸ VOSviewer creates various types of maps and offers advanced clustering techniques to identify research themes, as well as network visualisation (to show relationships among items) and overlay visualisation (to illustrate temporal trends or average publication years). In this study, the analysis covered the author (threshold: a minimum of 5 documents per author), country (a minimum of 5 documents per country), keyword (a minimum of 2 occurrences per keyword), source (a minimum of 5 documents per source), and document (a minimum of 100 citations per document) analyses. The thresholds were determined

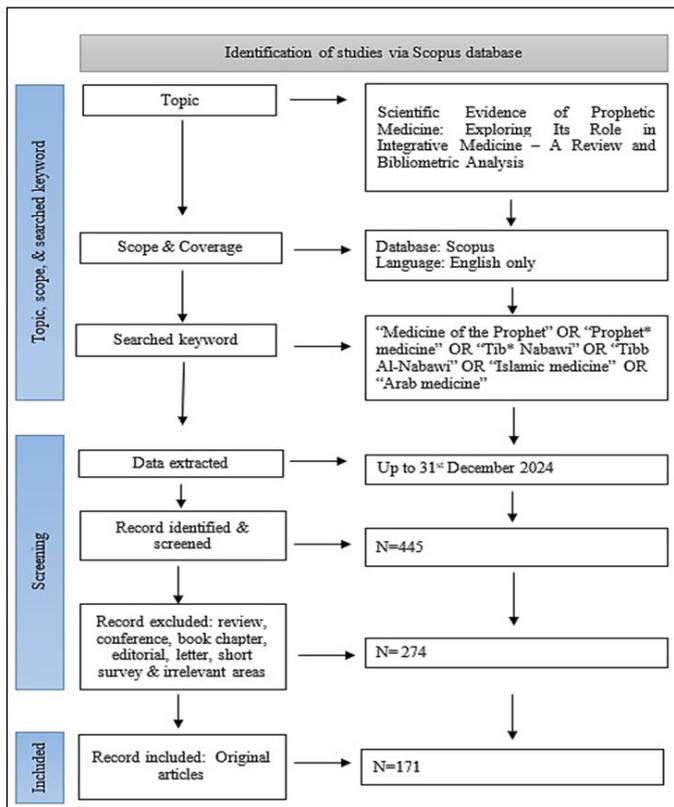


Figure 1: Modified PRISMA flowchart for selection of studies

based on the total number of items retrieved in each analysis. As a larger dataset tends to include many infrequent or less significant items, higher thresholds were applied to filter out such data and to focus on the most relevant, influential, and frequently occurring items. This approach improves the clarity, readability, and interpretability of the bibliometric maps. The results were visualised using network maps to illustrate thematic clusters and overlay maps to show publication trends over time.

RESULTS AND DISCUSSION

Author, country, and journal analysis

The connections between various authors, countries, journals, and study areas can be mapped out with the use of bibliometrics. In addition to allowing researchers to uncover key patterns and knowledge gaps, this tool can provide a visual representation of how various theories and concepts in the topic relate to one another.⁹ Based on the chosen threshold, there were 5 authors, 12 countries, and 4 journals that fulfilled the criteria. Among these analysed authors, countries, and journals, the top five prolific items are listed in Table 1. Saudi Arabia and

the United States emerged as the leading countries in terms of prolific publication with 22 articles in the field of prophetic medicine, as evidenced by the largest nodes in Figure 2A. This indicates a significant interest and expertise in this field within the country. Following Saudi Arabia and the United States, Egypt, Israel, and Iran were the next prolific countries in the field. Collaborations between these countries, as shown in Figure 2A, may explain their substantial contributions to prophetic medicine research. The author analysis further supports this trend by identifying a prolific contributor from Saudi Arabia, El Sayed, Salah Mohamed. Saudi Arabia demonstrated strong international research collaboration, particularly with Malaysia. This reflects recent bilateral efforts in academic research and may be attributed to shared interest in Islamic medicine, cultural alignment, and active research partnerships between institutions in both countries. The positioning and linkage strength suggest Saudi Arabia's central role as a collaborative hub in prophetic medicine research, influencing emerging contributions from Southeast Asia. The analysis also revealed strong collaboration among the other prolific authors, except for El Sayed, Salah Mohamed (Figure 2B). This isolation may be due to his more recent entry into the field, as indicated by the yellow hue denoting more recent publication years, and possibly due to publishing independently or with different research groups that did not meet the threshold for co-authorship network visualisation in this analysis.

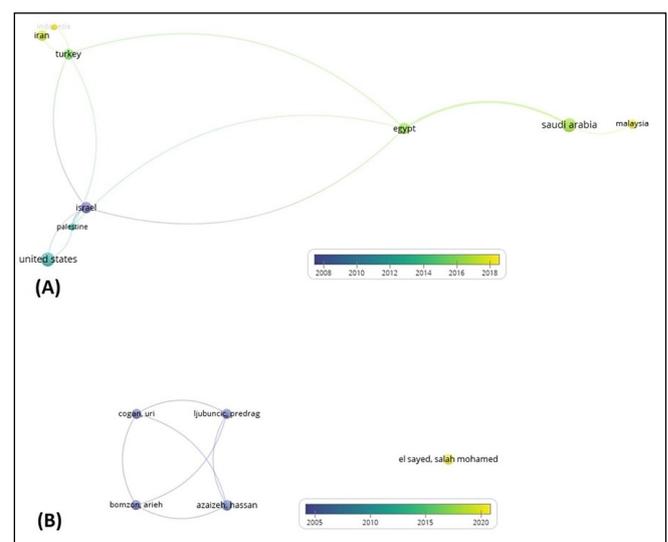


Figure 2: Overlay visualisation of (A) country and (B) author collaboration networks. The node size represents the number of documents, and the colours indicate the average year of publication. The lines between nodes reflect co-authorship or collaborative links. The closer and thicker the lines, the stronger the collaboration.

In terms of journals, Evidence-based Complementary and Alternative Medicine, and Journal of Ethnopharmacology stand out as the most prolific sources with the highest number of documents (6) among the identified sources (Table 1). Both of these journals have become preferred platforms for researchers to disseminate their findings in the field. Other notable sources for prophetic medicine studies include Journal of Religion and Health, and Studies in History of Medicine and Science with a total of 5 documents each. These sources have also been instrumental in contributing to the body of knowledge in prophetic medicine.

Table 1 List of productive authors, countries, and journals.

No.	Author	TP	Country	TP	Journal	TP
1.	El Sayed, Salah Mohamed	6	Saudi Arabia	22	Evidence-based Complementary and Alternative Medicine	6
2.	Azaizeh, Hassan	6	United States	22	Journal of Ethnopharmacology	6
3.	Bomzon, Arieh	5	Egypt	15	Journal of Religion and Health	5
4.	Cogan, Uri	5	Israel	15	Studies in History of Medicine and Science	5
5.	Ijubuncic, Predrag	5	Iran	12		

TP= Total of publication

Document analysis

The publication trend for prophetic medicine studies shows a gradual rise over the decades, with very few publications before the 2000s (Figure 3). From 2000 to 2010, research activity remained modest but steady. A noticeable increase began around 2011, with annual publications consistently ranging between 6 and 10. The most significant growth occurred from 2021 onward, peaking at 15 publications in 2023. This recent surge indicates a growing academic interest in prophetic medicine, likely driven by a broader recognition of traditional and holistic health practices within modern scientific research. Following this trend analysis, the documents were further examined based on the citation counts. A threshold of 100 citations per document was applied to identify the most impactful and widely referenced studies in prophetic medicine. This selection strategy filtered out lower-impact papers and focused on those that have significantly shaped the field. The five documents listed in Table 2 were deemed influential due to their topical novelty, particularly their focus on prophetic medicinal plants such as *N. sativa* and *Teucrium*

Table 2. List of prolific documents.

No.	Document title	Citation
1.	Chemical investigation of <i>Nigella sativa</i> I. seed oil produced in Morocco	147
2.	Traditional Arabic and Islamic medicine, a re-emerging health	120
3.	Aqueous extract of <i>Teucrium polium</i> possess remarkable antioxidant activity in vitro	116
4.	Antioxidant activity and cytotoxicity of eight plants used in traditional Arab medicine in Israel	109
5.	Antioxidant activity of <i>Crataegus aronia</i> aqueous extract used in traditional Arab medicine in Israel	108

polium, and their strong methodological approaches, including phytochemical analyses, antioxidant assays, and cytotoxicity evaluations. These studies not only reinforced the scientific basis of prophetic remedies but also paved the way for future investigations, as evidenced by their high citation counts.

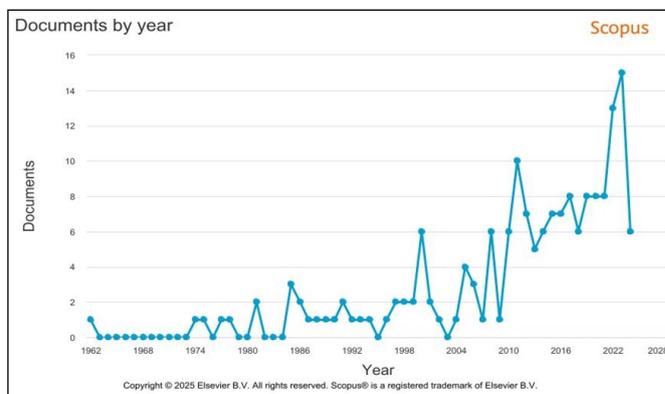


Figure 3: Publication trends of the prophetic medicine articles.

Research keyword analysis

The keyword analysis produced a total of 157 items distributed across six distinct clusters, each reflecting unique thematic areas within the research landscape of prophetic medicine (Figure 4A). The green cluster predominantly captures the sociocultural and ethical dimensions of prophetic medicine. Keywords such as religion, traditional medicine, psychology, cultural anthropology, mental health, food intake, anaesthesia, and medical ethics suggest a thematic focus on the spiritual, historical, and ethical foundations of health practices rooted in Islamic tradition.

The yellow cluster reflects a biochemical and pharmacological investigation, with particular emphasis on *N. sativa*. Keywords such as leukocyte count, malonaldehyde, alanine aminotransferase, ferritin,

essential oil, and thymoquinone indicate a strong focus on the anti-inflammatory, antioxidant, and hepatoprotective effects of black seed. This theme points to a growing body of experimental studies examining its therapeutic potential through specific biochemical markers. Meanwhile, the purple cluster showcases the contemporary relevance of prophetic remedies during the COVID-19 pandemic. Terms such as black cumin, prophetic medicine, SARS-CoV-2, COVID-19, olive oil, and garlic link traditional remedies to current global health concerns. The presence of antiquity as a keyword also connects modern exploration with the historical roots of these treatments, highlighting their re-emergence in times of crisis.

The blue and turquoise clusters highlight the application of prophetic and herbal medicine in disease-specific and therapeutic contexts. The blue cluster includes keywords such as alternative medicine, cancer therapy, *Ficus carica* extract, *T. polium* extract, pomegranate, colorectal cancer, depression, quality of life, and diet therapy, indicating a strong focus on using plant-based remedies for chronic conditions, particularly cancer and psychological well-being. Complementing this, the turquoise cluster includes keywords such as antineoplastic activity, medicinal plant, and phytotherapy, reflecting a broader interest in the pharmacological potential of traditional botanicals for anticancer and therapeutic applications.

Lastly, the red cluster encompasses themes related to experimental toxicology and cellular mechanisms. It includes keywords such as cytotoxicity, antioxidant activity, protein expression, liver homogenate, animal tissue, and oxidative stress, pointing to preclinical studies that investigate the safety, efficacy, and cellular impact of plant-based compounds, often using animal models. This cluster supports mechanistic insight into how prophetic remedies interact with biological systems.

Together, these clusters offer a comprehensive picture of the multidimensional research directions in prophetic medicines. Among the prophetic medicines, “black cumin” was the most frequently mentioned keyword, appearing 10 times. Its frequent occurrence suggests a

particular emphasis on the medicinal properties of black cumin. In terms of bioactivities, “antioxidant activity” emerged as the most mentioned keyword, with 12 occurrences. Antioxidants are essential for combating oxidative stress and supporting overall health, highlighting their importance in the study of prophetic medicine.^{10,11} Based on the time trend analysis, the recent keywords reflect a growing focus on studies involving honey and olive oil (Figure 4B). Researchers were also interested in understanding the potential health benefits of Prophetic medicines in the context of alternative medicine for COVID-19 and mental health.

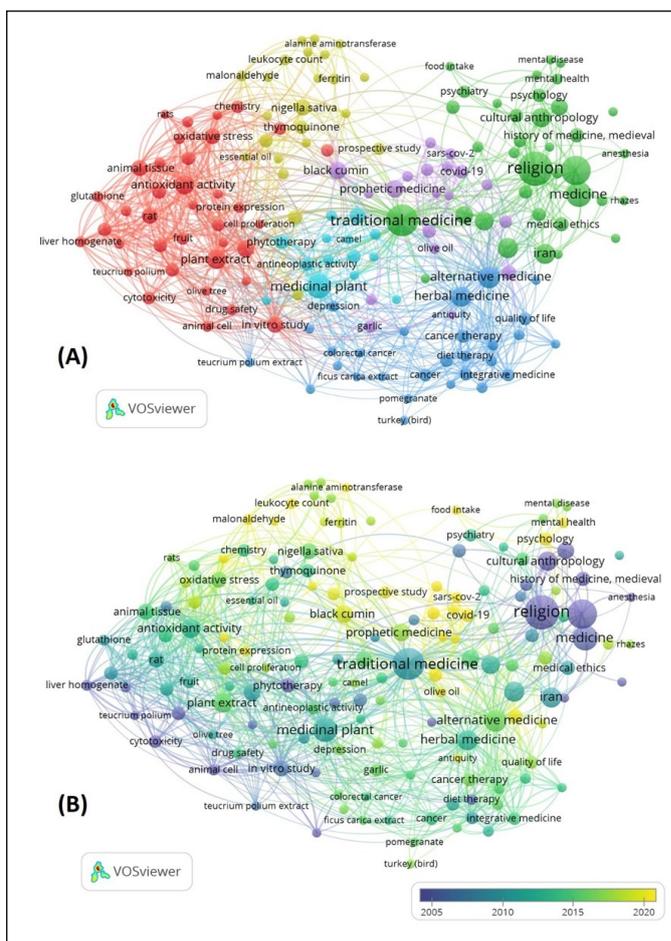


Figure 4: Network (A) and Overlay (B) visualization of keyword analysis, in which the size of clusters represents the occurrence number of the items. The colours of nodes represent the different thematic clusters (A) and average years (B) of studies.

Phyto-therapeutics in prophetic medicine

Following the bibliometric and keyword analysis, which revealed dominant research themes centred around antioxidant, anti-inflammatory, and antineoplastic properties of various prophetic remedies, a more in-

depth exploration of these commonly cited natural agents is warranted. Traditional medical systems, such as prophetic medicine, hold significant historical and cultural value. Nevertheless, it is crucial to evaluate the effectiveness and safety of herbal remedies through scientific research and clinical evidence. Tibb al-Nabawi, which draws upon various natural resources, references several noteworthy ones, including *N. sativa* (black cumin), *Hordeum vulgare* (barley), honey, *Olea europaea* (olives), *Salvadora persica* (Miswak), and *Phoenix dactylifera* (dates). Hence, the chemical compositions, pharmacological properties, clinical trials, and safety of these prophetic medicines were reviewed to align the bibliometric insights with current biomedical evidence.

N. sativa (black seed or black cumin) is valued in prophetic medicine for its diverse pharmacological benefits. As narrated by Abu Hurairah (Sahih al-Bukhari, Hadith No. 5688; Sahih Muslim, Hadith No. 2215a), the Prophet Muhammad ﷺ said:¹² "Use the black seed, for indeed it contains a cure for every disease, except death." Its main bioactive compound, thymoquinone, exhibits antioxidant, anti-inflammatory, analgesic, anticarcinogenic, antimicrobial, hypoglycaemic, antihypertensive, immune-boosting, hepatoprotective, and anti-diabetic properties.¹³ Preclinical studies have shown thymoquinone's anti-inflammatory action through inhibition of IL-1 β , TNF- α , IFN- γ , and IL-6.^{14,15} Additionally, black seed extracts demonstrated neuroprotection by reducing inflammation and oxidative stress in Alzheimer's disease models.¹⁶ Thymoquinone also activated caspase 8, which plays a central role in initiating and executing apoptosis in myeloblastic leukaemia HL-60 cells. Caspase activation results in a series of events that eventually cause cell death.¹⁷

Several human clinical trials have been conducted to investigate the anti-inflammatory properties of *N. sativa*. In a trial involving rheumatoid arthritis patients, it was discovered that supplementing with black seed oil significantly reduced levels of several inflammatory markers, such as C-reactive protein (CRP) levels, erythrocyte sedimentation rate (ESR), and disease activity scores.¹⁸ In addition, the administration of *N. sativa* oil

capsules to asthmatic patients was examined. According to the study, supplementation with black seed oil has reduced the symptoms of asthma and enhanced lung function, potentially as a result of the anti-inflammatory and bronchodilatory properties of black seed oil.¹⁹ Meanwhile, a study found that black seed supplementation contributed to a reduction in inflammation markers and improved glycemic control for patients with type 2 diabetes.²⁰

Barley (*Hordeum vulgare*) is rich in soluble fibres such as pectin and β -glucan, which have been shown to alleviate gas, bloating, and stomach discomfort.^{21,22} Barley or Talbinah has been mentioned in many narrations of the Prophet . For example, as narrated by Sahih Bukhari and Muslim in Mishkat al-Masabih 4179 (hadith no. 18), and on the authority of 'Aisha (may Allah be pleased with her) who said: I heard the Prophet Muhammad ﷺ said: "Talbinah gives rest to an invalid's heart and removes some of his grief".²³ Talbinah is a meal made from powdered barley that was traditionally consumed during the time of the Prophet Muhammad to alleviate stomach discomfort.¹² A cardioprotective effect of β -glucan was evaluated in patients having coronary artery bypass grafting (CABG). β -glucan has also been found to support probiotic activity and showed cardioprotective effects in patients undergoing coronary artery bypass grafting by reducing ischemia-reperfusion injury and creatine kinase isoenzyme levels.^{24,25} Barley is also rich in antioxidants, which help protect body cells from oxidative stress and damage. Preclinical studies have demonstrated its antioxidant potential, which may contribute to various health benefits.²⁶⁻²⁸ Research in animal models has also suggested the positive outcomes of barley intake on cardiovascular health. The consumption of barley can improve heart health markers and lower cholesterol levels and blood pressure.^{29,30}

Honey has a prominent place in prophetic medicine within the Islamic tradition. Honey is mentioned in several narrations (hadiths) of the Prophet Muhammad, highlighting its therapeutic properties.¹² It is narrated from Abu Huraira that Prophet Muhammad ﷺ said: "Whoever licks honey three mornings each month,

will not be afflicted by a major calamity (fatal disease)," (Sunan Ibn Majah, hadith no. 3450). The Prophet Muhammad referred to honey as a wholesome and nutritious food. He recommended its consumption as a part of a healthy diet, pointing to its natural sweetness and health benefits as a source of strength and energy. Honey is regarded as a natural source of antioxidants and is linked to several health benefits, including a potential role in lowering the risk of chronic diseases and increasing general well-being. The presence of phenolic compounds in honey supports its antioxidant properties, preventing cells from oxidative damage caused by free radicals.³¹

Honey has also been extensively explored in preclinical studies for its wound-healing characteristics. Its potent antimicrobial properties also contribute to its effectiveness in wound treatment.³² Besides, the effects of honey on nocturnal cough and sleep quality in children with upper respiratory tract infections were studied in a clinical study.³³ According to the study, children who have infections and nocturnal coughs may benefit from using honey as a natural therapy. Additionally, it improved sleep quality for both children and parents.³³ Prophet Muhammad ﷺ advised combining honey with warm water or herbal teas to relieve cough.¹² Honey also contains bioactive compounds like chrysin, which has demonstrated cancer-preventive effects by suppressing early hepatocarcinogenesis and inducing apoptosis in liver preneoplastic lesions.³⁴

Olea europaea (olive) contains bioactive compounds like oleocanthal and oleacin, known for their anti-inflammatory and antioxidant effects, supporting its traditional use in prophetic medicine for inflammatory conditions. It was narrated from Umar that the Prophet Muhammad ﷺ said: "Season (your food) with olive oil and anoint yourselves with it, for it comes from a blessed tree" (Sunan Ibn Majah 3319, hadith no. 69).

Olive oil's antioxidants, including polyphenols and vitamin E, help prevent oxidative cell damage.³⁵ Hydroxytyrosol, the main polyphenol, makes up about 50% of the phenolics in virgin olive oil and has the

highest antioxidant potency among olive polyphenols.³⁶ Preclinical studies show that olive-derived compounds regulate blood sugar and improve insulin sensitivity.³⁷ Dietary interventions confirmed their role in lowering metabolic syndrome risk by improving blood pressure and glucose levels, and reducing LDL oxidation.³⁸ Hydroxytyrosol and oleuropein also inhibit cancer cell growth, angiogenesis, and metastasis while protecting DNA and regulating BCL-2 and COX-2 expression, offering protection against various cancers, including colon, breast, lung, and skin.³⁹

Salvadora persica (miswak or siwak), commonly known as the miswak or siwak, is mentioned in several narrations (hadiths) of the Prophet Muhammad, ﷺ highlighting its dental and oral hygiene benefits. Abu Huraira reported: The Messenger of Allah, peace and blessings be upon him, said, "Were it not a burden upon my nation, I would have ordered them to use the toothstick before every prayer" (Sahih al-Bukhari 847 and Sahih Muslim 252).

Furthermore, Huzaifah (r.a.) narrated that "Whenever the Prophet (s.a.w.) got up at night, he used to clean his mouth with Siwak" (Sahih Bukhari, Book of Ablution, hadith no. 246).

It has been reported that the extract of miswak contains a wide range of organic and inorganic compounds. The Prophet Muhammad ﷺ recommended it as a natural toothbrush for cleaning the teeth and mouth.¹² Miswak contains various organic and inorganic compounds and is believed to help prevent tooth decay, gum disease, and bad breath by removing food particles, plaque, and bacteria.⁴⁰ Its antimicrobial effects have been demonstrated when chewed or applied, supporting its traditional use in preventing dental infections.⁴¹ Studies also show its anti-inflammatory properties, which help reduce gum inflammation and prevent gingivitis.^{42,43} Other pharmacological benefits include hypolipidemic, antiulcer, antifertility, and anticonvulsant effects.^{44,45}

Phoenix dactylifera (dates) are rich in bioactive compounds, including tannins, flavonoids, phenolic acids, and carotenoids like beta-carotene and lutein, contributing to

their antioxidant and anti-inflammatory effects.⁴⁶ Phytosterols in dates may also help lower cholesterol and support cardiovascular health.⁴⁷ In prophetic medicine, dates are valued for boosting endurance and vitality, especially during illness or physical exertion, and serve as a natural sweetener in traditional foods.⁴⁸ Narrated by Sa'd, the Prophet Muhammad ﷺ said, "He who eats seven 'Ajwa dates every morning, will not be affected by poison or magic on the day he eats them" (Sahih al-Bukhari 5445, hadith no. 74).

In vitro and *in vivo* studies, such as those on four Tunisian date cultivars, showed the highest antioxidant activity at the Besser (early ripeness) stage, with key compounds like caffeic, ferulic, and catechin identified.⁴⁹ Date seeds have demonstrated anti-inflammatory effects by downregulating IL-1 β , TGF- β , COX-1, and COX-2, and may enhance immunity and prevent chronic diseases.⁵⁰ Moreover, dates and *N. sativa* were also discovered to have a synergistic effect on hepatocyte structure and function when subjected to aflatoxin B-1-induced hepatotoxicity.⁵¹

Hence, phytotherapeutics in prophetic medicine represent a rich resource of natural remedies. Key components of black seed, barley, honey, olive, miswak, and dates have demonstrated diverse pharmacological properties, from anti-inflammatory and neuroprotective effects to blood sugar regulation and cardiovascular benefits. Clinical trials have confirmed their therapeutic potential in conditions such as rheumatoid arthritis, asthma, diabetes, and oral hygiene.

Despite the promising evidence, several limitations and conflicting findings have emerged in the literature regarding the efficacy and standardization of prophetic remedies. For instance, while *N. sativa* has been widely studied for its anti-inflammatory and antioxidant effects. Some clinical trials have reported inconsistent outcomes, possibly due to variations in dosage, formulation (oil vs. powder), patient population, or duration of intervention. Similarly, although honey shows potent antimicrobial and wound-healing effects *in vitro* and *in vivo*, clinical trials

in humans often lack standardization in honey types and purity, which may influence reproducibility and therapeutic outcomes.

Moreover, olive oil's health benefits, though well-established in Mediterranean diet studies, are often confounded by lifestyle and dietary factors, making it difficult to isolate the effects of olive-based remedies as used in prophetic medicine. Likewise, for miswak, while antimicrobial effects are evident, some systematic reviews have questioned its superiority over modern dental products due to limited high-quality clinical trials with standardised endpoints.

Another challenge lies in the lack of regulatory frameworks and standard quality control measures for herbal products derived from prophetic medicine. Variability in preparation methods, dosage, and lack of standardised outcome measures across studies pose a major barrier to translating these traditional practices into evidence-based complementary therapies.

These findings highlight the need for well-designed, large-scale randomised controlled trials (RCTs) with a rigorous methodology, validated biomarkers, and longer follow-up periods to confirm the clinical relevance of these remedies and to bridge the gap between traditional knowledge and modern clinical standards.

CONCLUSION

This review presents a qualitative and quantitative evaluation of the prophetic medicine by analysing its scientific landscape using a bibliometric approach to identify publication trends, key contributors, collaborative networks, and research hotspots, complemented by a narrative review of key natural remedies to provide a comprehensive overview of the field. The bibliometric findings highlight key contributors, countries, journals, keywords, and documents with a notable rise in publications in 2023. Throughout history, numerous natural remedies, herbs, and practices recommended by the Prophet have been explored for their therapeutic benefits. While scientific research has validated some of these remedies, much of the knowledge remains rooted in

tradition and faith. The therapeutic benefits of prophetic medicine include the use of natural remedies such as black seed, olive oil, and honey, among others. These remedies have shown promise in areas such as anti-inflammatory properties, immune system support, digestive health, and disease prevention.

However, several limitations remain in the current body of clinical evidence. These include small sample sizes, short trial durations, heterogeneity in formulations, and limited reproducibility of findings. Additionally, a lack of standardised outcome measures and insufficient regulatory oversight pose challenges to the widespread acceptance and integration of these remedies into modern medical frameworks. Hence, it is imperative to view prophetic medicine from a well-rounded perspective, acknowledging both its cultural and historical importance and the need for more robust scientific validation. Prophetic medicine offers valuable complementary insights into health and well-being, but its integration into evidence-based medicine should be guided by rigorous, high-quality research and clinical standards.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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***Streptococcus Gallolyticus* Infection and its Interrelation with Colorectal Cancer: Diagnostic Accuracy of Statistical and Machine Learning Models for Early Detection Algorithm**

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ABSTRACT

INTRODUCTION: Epidemiological studies have emphasized the role of *Streptococcus gallolyticus subspecies gallolyticus* (*Sgg*) infection in the development of colorectal cancer (CRC), yet it remains underappreciated. While statistical and machine learning (ML) models can enhance CRC prediction, direct comparisons between them are rare. This study aims to assess the diagnostic accuracy of stool polymerase chain reaction (PCR) for *Sgg* and immunochemical fecal occult blood test (iFOBT) for CRC detection and to compare multivariable statistical and ML models in predicting CRC. **MATERIALS AND METHODS:** A hospital-based case-control study with a reversed flow design was conducted, involving 33 CRC cases and 80 controls. The analysis incorporated Asia Pacific Colorectal Screening (APCS) risk factors into three predictive models: logistic regression (LR), decision tree (DT), and ensemble Bayesian boosted decision tree (BDT). **RESULTS:** Combined testing achieved a net sensitivity of 54%, outperforming individual tests (iFOBT=12.1%, Stool PCR=48.5%). Among the models, the ensemble BDT approach demonstrated the highest classification accuracy for CRC (BDT=78.1%; DT=72.4%; LR=69.9%). The DT model identified iFOBT as the sole predictor, while the BDT ensemble model prioritized positive stool PCR for *Sgg* as the primary predictor, followed by normal to overweight body mass index and individuals aged over 53 years. **CONCLUSION:** The ensemble ML model incorporating *Sgg* infection demonstrated superior predictive performance. Screening for *Sgg* in stool samples has the potential as an early CRC detection strategy, particularly for individuals with a normal to overweight BMI and those above 53 years old.

Keywords

Streptococcus gallolyticus, colorectal cancer, diagnostic accuracy, machine learning, bayesian

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INTRODUCTION

Colorectal cancer (CRC) is one of the most common cancers in developing countries.¹ Various studies look for lifestyle factors but do not highlight infection as the potential driver for CRC development. Many epidemiological studies highlighted the importance of the *Streptococcus gallolyticus subspecies gallolyticus* (*Sgg*) infection in carcinogenesis of CRC.²⁻⁵ It is regarded as a highly important and treatable disease. However, it is not often examined.

An increasing incidence of CRC coupled with late detection of the disease due to poor screening practice leads to a high burden of disease.⁶ This is made worse by variable results of immunochemical faecal occult blood (iFOBT) as the first line screening which leads to false positive and false negative results. *Sgg* infection detected has been shown to increase the risk for CRC in many epidemiological studies.^{4,5,7} However, there is a paucity of studies on screening diagnostic accuracy related to *Sgg*.

More and more patients are referred for unnecessary invasive colonoscopy that resulting from false positive iFOBT. Furthermore, current guidelines follow stratification based on family history. There has been a lack of risk stratification based on modifiable factors. Thus, in order to have more people correctly classified as having CRC, this infection should be highlighted and included as one of the risk factors apart from presence of blood in the stool (source).² In view of the multifactorial nature of CRC, a combination of risk factors is a more plausible explanation for its occurrence, which can be explained not just by statistical but machine learning models (ML).

ML has been used to predict cancers but not specifically looking at multivariable infection models. Various techniques such as decision tree, artificial neural network and naive bayes have been utilised, but suffers from either underfitting or overfitting. One potential technique to improve model accuracy is by ensemble methods such as bagging, boosting and stacking.⁸ However, small sample sizes often deter the ability to make good predictions. Hence, the bayesian method of looking at prior knowledge helps to overcome this problem.

The research objectives in this study are twofold; First objective is to determine diagnostic accuracy of simultaneous testing of stool PCR for *Sgg* with iFOBT in detecting CRC and second objective is to predict the likelihood of CRC by comparing multivariable statistical and machine learning models. We hypothesised that the overall accuracy of bayesian ensemble machine learning model is better than the statistical model.

MATERIALS AND METHODS

This research was carried out over 3 year duration (from September 2019 until July 2022). It was a case-control study with reversed flow design with an allocation ratio of 1 case to 2 controls which followed Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement checklist. The study population were patients who came to the surgical clinic of Sultan Ahmad Shah Medical Centre IIUM (SASMEC @ IIUM) for colonoscopy. A case was defined as patients who

attended the colonoscopy and diagnosed as histopathologically-confirmed CRC and controls were patients who attended the colonoscopy but were diagnosed as not having CRC.

Sample size was calculated based on PASS software version 19.03. For objective 1, the calculation for estimation of the minimum sample size for this study was calculated with estimated prevalence of 20% for 1 university hospital in peninsular Malaysia with similar setting,⁹ power of 88.5% and sensitivity of 90%, the minimum sample size required is 95.¹⁰ The power was chosen as it is the highest achievable power to detect to reject the null hypothesis of no association, hence able to reach up to 90% sensitivity based on the simulation.¹⁰ For objective 2, the sample size was calculated based on 6 predictors using logistic regression formula,¹¹ where the number of predictors were multiplied by 15 to get 90. Since objective 1 has a higher estimated sample size (95), this estimated sample size is chosen as it can answer objective 1 and 2, thus final sample size after adjusting for 20% attrition rate, total sample size was 120. Thus, approximately 40 cases and 80 controls were required.

Quality control

For iFOBT, ABON FOB test was used, which is a simple, rapid qualitative immunochemical assay that detects 50 ng/ml of human blood haemoglobin done in controlled laboratory environment. If both test and control lines were visible, it indicated that the test was positive. If only the control line was visible, then the test was deemed negative. If only the test line is visible, the test was taken as invalid.

Concurrently, stool PCR were tested for evidence of *Sgg* infection. Two sets of primers were tested in the PCR assay. Following PCR optimization of both primers and gel electrophoresis, amplification using primer set 2 resulted in non-specific and multiple bands, while primer set 1 exhibited a specific and single band of DNA without primer dimer and the needs of pure culture bacteria. The PCR with primer set 1 showed an optimum outcome with the gradient annealing temperatures of 55°C to 62.9°C. DNA sequence alignment of randomly

selected samples showed 100% similarity without any nucleotide mutation. BLASTN analysis of the targeted 167 bp amplified gene segments demonstrated that DNA sequences were 100% identical to the *tanB* gene of *Sgg* found elsewhere.¹²

The background characteristics of patients, which are age, gender, family history, BMI and smoking status were taken based on the validated modified Asia Pacific Colorectal Screening (APCS) score.¹³

Univariate data analysis

Chi square test and fisher’s exact test was employed for univariate analysis in RStudio version 2022.07.2. Accuracy parameters were calculated for iFOBT and stool PCR in terms of sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy. The calculations were split into single testing for each test and simultaneous testing of both tests.

Multivariable data analysis

Data was analysed using RapidMiner Studio version 9.10.011. Continuous data was reported as mean (SD) and categorical as frequency (%). Classical logistic regression (LR) was used for the statistical model. For ML prediction, bayesian boosting operator methods were utilised using ensemble machine learning, where we compared bayesian-decision tree (BDT) ensemble versus decision tree (DT) model alone, to improve the accuracy and generate screening algorithm. The Bayesian boosting operator builds an ensemble of classifiers to predict boolean target attributes. During each iteration, the training data was reweighted to reduce the influence of previously learned patterns and incorporate prior knowledge. A base classifier, usually a rule-based or decision tree algorithm, was applied repeatedly in sequence, and the resulting models were merged into one comprehensive model. The total number of models generated was determined by the specified number of iterations. The steps involved were feature engineering, threshold setting, cross validation and model performance evaluation. After the data collection, the data was pre-processed and missingness was handled via multiple imputation techniques. The feature selection

involved the variables identified by the APCS risk factors, as well as the main laboratory markers namely the iFOBT (in line with CPG) and Stool PCR for *Sgg* as the feature of interest. The threshold for prediction was fine-tuned at 0.6. If the prediction probability is greater than this, the class label to be predicted is CRC. A 10-fold cross validation method was done with shuffled sampling, coupled with random seed number to randomly choose the subsets for the training and testing model. Accuracy parameters were the same as the univariate data analysis, adding in another parameter which is area under the curve (AUC).

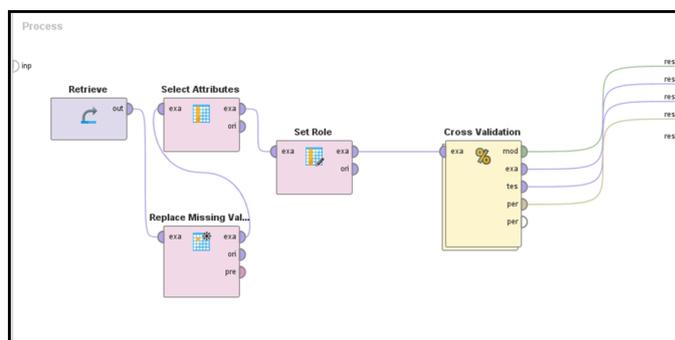


Figure 1: Process canvas for multivariable analysis using boxes called operators. The grey “retrieve” operator signifies the original dataset, the red “select attribute” operator signifies the variables selected for analysis, the red “replace missing values” operator signifies the imputation of missing values, the red “set role” operator is setting the CRC as the case and non-CRC as the control (Boolean) and the yellow “cross validation” operation is the method for data validation.

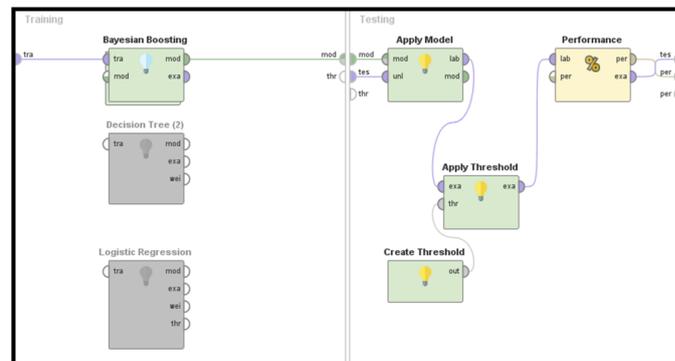


Figure 2: Cross validation for the three models (LR, DT and BDT)), tested at different stages. The training section on the left signifies the model used (the green is the active model), while the testing section on the right signifies the execution of the model based on 30% testing data (green operator) and performance metric generation (yellow operator such as sensitivity)

RESULTS

Objective 1

Thirty-three (33) CRC cases were obtained instead of 40 due to patient loss to follow-up. The proportion of cases with a positive iFOBT and stool PCR was higher than a negative test ($P < 0.05$). Post hoc power analysis using

48.5% sensitivity of stool PCR for *Sgg* obtained shows the actual power was 92% even though there was loss to follow up. The simultaneous testing produced net sensitivity that was higher compared to a single test.

Table 1: Distribution of case and control according to iFOBT and stool PCR for *Sgg*

Test	Classification		P value
	Case, n(%)	Control, n(%)	
iFOBT			
Positive	4(80.0)	1(20.0)	0.03*
Negative	29(26.9)	79(73.1)	
Stool PCR for <i>Sgg</i>			
Positive	16(50.0)	16(50.0)	0.005*
Negative	17 (21.0)	64(79.0)	

*Significant at P<0.05

Table 2: Accuracy parameters for single and simultaneous testing

Accuracy parameter	iFOBT	Stool PCR for <i>Sgg</i>	Simultaneous testing
Sensitivity ^a (%)	12.1	48.5	54.7
Specificity ^b (%)	98.8	80.0	79.0
Positive predictive value (%)	80.0	50.0	-
Negative predictive value (%)	73.1	79.9	-
Diagnostic accuracy (%)	73.5	70.8	-

^aFor simultaneous testing, net sensitivity was calculated

^bFor simultaneous testing, net specificity was calculated

Objective 2

The performance of the BDT ensemble approach was superior (BDT accuracy=78.1%; DT accuracy=72.4%; LR accuracy=69.9%). The DT algorithm generated only iFOBT as the predictor without the inclusion of *Sgg*, whereas the ensemble approach produced positive stool PCR for *Sgg* as the main branch followed by normal to overweight body mass index and adults above 53 years of age.

Table 3: Performance metrics of the models compared

Parameter	Logistic Regression (LR)	Decision Tree (DT)	Bayesian-Decision Tree (BDT)
Accuracy (%)	69.0	72.4	78.1
Sensitivity (%)	36.0	15.8	56.6
Specificity (%)	82.2	96.0	85.8
Positive predictive value (%)	39.3	62.5	62.5
Negative predictive value (%)	76.5	73.2	84.3
Area under the curve (AUC)	0.74	0.53	0.74
Significant predictors (categorical unless stated otherwise)	Gender Stool PCR iFOBT	iFOBT	Stool PCR BMI (kg/m ²) Age (years)

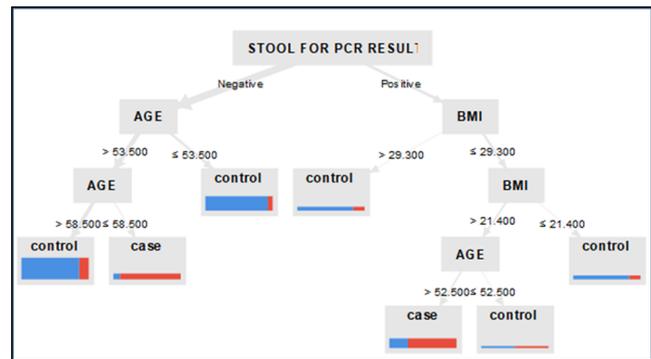


Figure 3: Best model algorithm generated from the BDT ensemble method.

DISCUSSION

Gist of the research

The sustainable development goals (SDG) number 3 focuses on ensuring wellbeing in terms of reducing burden due to NCDs. Goal 3.4.1 states the importance of reducing premature mortality from cancer by one third by early detection and prompt treatment.¹⁴ This includes detecting the agents triggering cancer formation such as the *Sgg* infection. If the infection is detected early, it can be treated with antibiotics and prevents the occurrence of disease. Furthermore, the current evidence to risk-stratify the patients for screening does not consider infective agents such as *Sgg*.¹⁵ Risk stratification allows for risk prediction to tell patients that early screening is important as it increases the risk for cancer. This in turn will assist the patients in making good decisions towards their health and wellbeing. Hence, it is of utmost importance for this research to detect new risk predictions for people to know and to act early. For clinicians, clinical decision support model and system can help in stratifying those who require invasive diagnostics such as colonoscopy.^{16,17}

Outcome on single and simultaneous testing

Currently the clinical practice guideline focuses on iFOBT as the asymptomatic screening for CRC. Here, the proportion of CRC among positive iFOBT was higher than negative iFOBT by almost 60%, indicating the relevance of screening asymptomatic population in the guidelines. For stool PCR, it is not routinely done worldwide as a screening tool. However, our study proved its relevance as a potential screening marker as it was detected more in CRC cases, similar with previous studies.²⁴ The sensitivity of iFOBT was low at 12.1% as compared to a systematic review by the Malaysian Health

Technology Assessment Section team.¹⁸ The iFOBT sensitivity depends on yield quality, timing of sample collection, even though the respondents have been briefed regarding the sample collection procedure. The briefing followed standard informed consent procedure and the enumerators were trained. On the other hand, the sensitivity of stool PCR was higher than iFOBT, indicating a negative test will rule out CRC. In addition, the negative predictive value was higher than iFOBT by almost 7%, signifying the probability of not having CRC following a negative test was higher. This gave a promising clue for stool PCR as a screening tool rather than diagnostic tool. However, the screening is predicted to be better in certain population such as those with high red meat consumption, where the bacteria reside and gets into the human gut. The challenges of using stool PCR are the testing requires PCR machines that are not readily available in all healthcare setting and stool sampling is yield-dependent as it may not contain the causative agent, if any.

When both tests are done simultaneously, gains in sensitivity were observed indicating that iFOBT and stool PCR, if done concurrently, can improve early detection rates for CRC. A systematic review showed the usefulness of simultaneous testing in detecting CRC.¹⁹

Statistical model building

Many research has focused on statistical models.^{20,21} One of the most used is logistic regression. The model's ability to predict binary outcomes such as cancer and non-cancer has made it a popular choice for classification problems. Here, our model showed that male patients and positive iFOBT are independent risk factors of CRC. These risk factors are in favour of the current epidemiology of CRC in Malaysia.⁶ However, the stool PCR here is of interest as a positive test will increase the odds to get CRC by 4 times as compared to a negative test controlling for APCS risk score and iFOBT. The method of detection here is improved by detecting the subspecies (*S. galloyticus subsp. galloyticus*) which are more accurate for Sgg-CRC interaction. Thus, molecular detection here plays an important role in establishing that interaction.^{2,22} However, other microbiota such as

Fusobacterium nucleatum, also linked with CRC are not tested here which might serve as a marker for carcinogenesis as well, hence serving as a selection bias.¹ This becomes the limitation in the study. Nevertheless, these findings were made after data cleaning and multiple imputation, which improved the model fit and accuracy in one study.²³

Machine learning model building

Feature engineering has become one of the most important steps in building machine learning models. In our research, the missingness, if left untreated, could lead to biased estimates. Multiple imputation method was chosen as the multivariable nature of the data would benefit more from this method as compared to single imputation.²³

Threshold for predicting the case class was set higher at 0.6 than the default 0.5 because we wanted to correctly detect true CRC cases and minimise the false positive rate, similar with a previous study.²⁴ This would in turn increase the precision of the model.

In terms of the performance metric, the most important parameter would be the AUC. The use of AUC is known to be best used when there is an imbalance in outcome because it measures the quality of the model's predictions irrespective of what classification threshold is chosen.²⁵ Thus, it is a robust performance measure.

When compared to the LR statistical model, ML outperforms it in few key areas such as accuracy, specificity and positive predictive value. This shows the value of ML models in multivariable analysis, which is more practical in real-world applications such as clinical decision support system (CDSS) for diagnosis of CRC. A study revealed the use of ML to aid diagnosing cancer and estimating prognosis to aid decision-making.²⁶

We used the decision tree model as the base ML model because of the classification nature of the outcome. It has shown to be robust but tends to overfit. To overcome this, ensemble method which combined bayesian boosting and cross validation was utilised to combat overfitting.⁸

Performance evaluation of the three models

The main interest here is to determine which model is the best in predicting CRC. Here we had a variety of performance metrics but the gain and losses in these parameters were evaluated more in terms of its value in clinical decision making. For example, to diagnose high-burden diseases such as cancer requires more specificity than sensitivity. For screening, sensitivity is preferred. It is a trade-off. The statistical LR model showed good predictive power, whereby being male, positive stool PCR and positive iFOBT had significantly higher odds to get CRC. However, its other metrics are poorer than ML models. Statistical models are sometimes not as good as machine learning models in terms of optimization,²⁶ and quite strict in their test assumptions. ML models, on the other hand, are more robust but require model optimization to increase prediction accuracy.²⁷

For the DT model, the best performance was specificity (96%) and iFOBT as the significant predictor. When BDT ensemble method was used, there was a positive trade-off where improvement in almost all parameters except specificity, as well as having stool PCR, age and BMI as the significant predictors. Thus, it can be inferred here that DT model accurately detects CRC by only iFOBT, but BDT was able to accurately predict CRC much better with multivariable inputs. Bayesian boosted decision trees integrate the advantages of Bayesian optimization and boosting with decision trees to build highly effective and resilient machine learning models. Bayesian optimization aids in selecting the best hyperparameters for the boosted trees, enhancing both accuracy and the ability to generalize. Boosting works by sequentially combining multiple weak decision trees to form a strong overall model capable of capturing intricate patterns in the data. Together, these techniques produce models that are typically more accurate, less prone to overfitting, and well-suited for handling complex datasets. The other traditional machine learning methods such as random forest and gradient-boosted machines lack this. The superiority of ensemble learning here was similar with another study on e-learning performance prediction²⁸ albeit in a different context. The BDT algorithm provided clues that a positive stool PCR patient should be further

risk-stratified into normal and overweight BMI and age more than 53 years old to be advised for early colonoscopy. We also tested for other CRC risk factors based on APCS criteria but was not significant in the BDT algorithm.¹³

Novel theories/knowledge

The tool to detect *Sgg* infection as a marker for CRC can be classified to be either for diagnostic purpose or as a screening tool based on the diagnostic accuracy parameters. As described earlier, the results show promise more towards screening tool rather than diagnostic tool, as the *Sgg* infection is mainly asymptomatic. The availability of the primer for testing and the prevalence of SGG that is fairly high serves the potential for this organism to be developed as a rapid test kit for early clue and detection of CRC, especially when simultaneous testing with iFOBT is done as per result findings.⁹

The Bayesian prediction model that incorporates *Sgg* infection allows for a more accurate prediction for CRC. The advantage lies in the ability of Bayesian prediction to cater for small sample size using prior probability, posterior probability and likelihood.^{29,30} Hence, a more realistic prediction and better risk stratification for early colonoscopy for patients can be shown.

Potential real-world application

CDSS can be implemented at clinic and hospital level to risk-stratify those going for colonoscopy. Antibiotic treatment can be given to patients with *Sgg* infection. Future development of vaccines towards *Sgg* may be able to prevent the infection to either induce CRC formation or delay the progress of the disease. A cost-effective screening that reduces cost of treatment will benefit the people in low socioeconomic status by correctly screening those at risk, where early diagnosis such as at stage I of the disease will advert the need for high-costing treatment such as chemotherapy.⁶ Potential vaccine against the *Sgg* infection can be developed which will prevent CRC development. This promotes a healthier and more productive nation.

LIMITATIONS

The research has several limitations. First, causality cannot be ascertained for *Sgg* and CRC interaction. The single centre experience in obtaining the case and control might be limiting the strength of the relationship. The results for simultaneous testing, although better than single testing, were not proven with cost effectiveness calculations. The prediction using machine learning is data-dependent and operator-dependent, thus is prone to biases just like the statistical model. The missing data, although imputed, might be missing not at random but are difficult to prove. Hence, better primary data collection method and guidelines for testing should be outlined and developed in hospital setting for quality *Sgg* and CRC data to be obtained for more precise results. Having no external validation using external data serves as our limitation. Since this study is done mainly for model development, the error risk was reduced by including training (70%) and testing (30%) data using the same dataset. Together with cross validation, this serves to reduce overfitting and provide a better valid model.

CONCLUSION

Ensemble ML model incorporating *Sgg* infection was superior to the standard ML and statistical model in predicting CRC. *Sgg* screening for early CRC detection in those with normal to overweight BMI patients and aged above 53 years old has potential, provided further research with more robust techniques to minimize error is done in the future. Future studies are recommended to use the ensemble ML model to explore the dietary and environmental source of this infection towards CRC which may pose an undetected one health problem, as well as external validation using other CRC cohorts to enhance the model validity.

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CONFLICT OF INTEREST

There were no conflicts of interests between the contributors of this research.

INSTITUTIONAL REVIEW BOARD (ETHICS COMMITTEE)

The study protocol was approved by the Medical Research Ethics Committee (MREC), Ministry of Health Malaysia (NMRR-19-3062-51372) and IIUM research ethics committee (IREC) (IREC2020-109) before the study.

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The Avoidance Practice and Its Association with Self-Efficacy, Knowledge and Attitude among Mothers with Children under 6 Years Old on Environmental Tobacco Smoke Exposure to Their Children in Selangor

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ABSTRACT

INTRODUCTION: Environmental tobacco smoke (ETS) poses significant health risks globally, particularly for children. This study aimed to determine levels of self-efficacy, knowledge, attitude, and avoidance practices regarding ETS exposure among mothers with children under six and identify factors associated with avoidance practices.

MATERIALS AND METHODS: A cross-sectional study was conducted using the validated Malay SE-KAP-ETS questionnaire among 321 mothers. Higher scores indicated better self-efficacy, knowledge, attitude, and avoidance practices. Multiple linear regression (MLR) analysis was performed to determine associations. **RESULTS:** Participants had a mean age of 33.4(±5.57), and 67.9% had tertiary education. Mean scores were: self-efficacy 36.41(±9.7), knowledge 38.26(±3.76), attitude 48.58(±3.75), and avoidance practices 28.33(±3.27). MLR revealed that no smokers at home [B=0.700, 95%CI: 0.304, 1.462; p=0.003], higher self-efficacy [B=0.058, 95% CI: 0.028, 0.088; p<0.001], and positive attitudes [B=0.414, 95%CI: 0.336, 0.491; p<0.001] were positively associated with avoidance practices. Conversely, primary and secondary education [B=-0.750, 95% CI: -1.449, -0.051; p<0.035] and self-employment [B=-1.517, 95%CI: -2.584, -0.450; p=0.005] were negative predictors. **CONCLUSION:** Findings indicate that although ETS knowledge is high among mothers of young children in Selangor, it does not predict avoidance practices. Instead; self-efficacy, attitude, and smoke-free homes are critical determinants, underscoring the need for empowerment-focused interventions, particularly for mothers with primary and secondary education.

Keywords

Environmental tobacco smoke (ETS), self-efficacy, attitude, avoidance practice, mother of young children.

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INTRODUCTION

Environmental tobacco smoke (ETS), or second-hand smoke, is a toxic byproduct of tobacco use, comprising both exhaled mainstream smoke and side stream smoke from burning tobacco. ETS contains over 4,000 harmful compounds, including oxidizing agents, heavy metals, cyanide, and at least 50 carcinogens.¹ Exposure to ETS is hazardous at any level, increasing risks of respiratory diseases and other health issues, especially for children, who are often more vulnerable due to their developing systems and higher respiratory rates.² Therefore, creating completely smoke-free environments is the most effective strategy to protect children from these hazardous chemicals.³ This can be achieved through comprehensive

measures such as legislation and, crucially at the household level, through the active avoidance practices implemented by caregivers.

Tobacco use leads to approximately 8 million deaths globally each year, with 1.2 million attributed to ETS exposure. Children are particularly vulnerable, with high ETS prevalence reported across Southeast Asia.¹ In Malaysia, the problem is severe, with over 10,000 deaths annually linked to smoking-related illnesses.⁴ Crucially, this risk extends to the nation's youngest, as a national survey revealed that 52.8% of children under the age of six are exposed to ETS at home.⁴ This alarming statistic

highlights a critical public health gap and forms the primary justification for the present study.

ETS exposure in children is primarily due to smoking within the home. Studies have linked ETS to various health issues, such as respiratory infections, asthma, middle ear infections, and even sudden infant death syndrome. Additionally, ETS exposure has been associated with developmental and cognitive issues, including high blood pressure, behavioral problems, and increased hospitalization rates for respiratory conditions.⁷⁻⁹

To combat ETS exposure, the WHO's Framework Convention on Tobacco Control (FCTC) recommends implementing smoke-free legislation (SFL) in public spaces. Malaysia has made efforts to restrict smoking in eateries, schools, and other public areas and has launched educational programs to promote smoke-free homes. However, these measures have had limited impact on reducing ETS exposure within homes, where children face the greatest risk. Studies show that children in lower socioeconomic households and those with parents who smoke face increased ETS exposure risks.^{2, 10}

Mothers, as primary caregivers, play a crucial role in shaping household behaviors, including ETS avoidance practices. Mothers' knowledge, attitude, and self-efficacy significantly influence their practices in avoiding ETS exposure, with higher self-efficacy linked to better avoidance behaviours.¹¹ Research indicates that mothers with higher knowledge about ETS risks are better able to implement effective avoidance strategies.¹² Nonetheless, despite high levels of knowledge, attitudes and behaviours often remain poor, highlighting the complexity of ETS avoidance practices among mothers in Malaysia.¹³

This study fills the gap by focusing on Malaysian mothers with children under six, aiming to explore their self-efficacy, knowledge, and avoidance practices. The findings align with Malaysia's public health goals, highlighting the need for targeted interventions, particularly towards mothers, to improve ETS avoidance and protect children from its harms.

MATERIALS AND METHODS

Study Design and Population

This cross-sectional study was conducted from January to March 2024 across six government health clinics in Hulu Langat, Selangor, targeting Malaysian mothers aged 18 and above with children under six years old. Exclusions included mothers who were unable to read Malay or those with psychiatric conditions affecting questionnaire responses.

Sample Size Calculation

Using a sample size calculator, with a power of 80% and significance level of 0.05, we calculated a sample size of 337 participants, accounting for 20% attrition based on standard deviations reported.³

Sampling and Data Collection

Participants were selected using multistage sampling to ensure district representation, followed by convenience sampling at each clinic. Targeted quotas per clinic were based on annual maternal-child health visit data. Eligible mothers received study details and consent forms before completing questionnaires with researcher assistance available as needed.

Study Instrument

The SE-KAP-ETS questionnaire was used, containing 17 items across four domains: self-efficacy (5 items), knowledge (4 items), attitude (5 items), and avoidance practice (3 items), scored on a 10-point interval scale.¹⁴ Higher scores indicate stronger self-efficacy, knowledge, positive attitude, and avoidance practices. The development of this questionnaire involved a comprehensive validation process, including content validation by experts, face validation with mothers, and confirmatory factor analysis (CFA).¹⁴ The instrument has demonstrated strong psychometric properties, showing excellent internal consistency (Cronbach's alpha ranging from 0.755 to 0.887).¹⁴ The CFA confirmed its construct validity with a good model fit, achieving a root mean square error of approximation (RMSEA) of 0.053, a goodness-of-fit index (GFI) of 0.932, and a comparative fit index (CFI) of 0.968.¹⁴

Statistical Analysis

Data were analysed using SPSS version 28. Simple linear regression (SLR) assessed associations between independent variables and avoidance practice. Variables with p-value <0.25 were included in multiple linear regression (MLR) with stepwise selection. Multicollinearity was assessed with variance inflation factors (VIF).

RESULTS

A total of 321 mothers participated in the study. Table I presents the descriptive analysis of the sociodemographic characteristics and smoking history of mothers with young children among the study participants. Participants had a mean age of 33.4 years, with the majority being Malay (89.1%) and most having a tertiary education (67.9%). Occupations varied, with 33% in the government sector, 30.5% in the private sector, and 28.3% as housewives. Most households (61.1%) were in the B40 income group, and nearly all mothers were non-smokers (99.7%). In terms of household smoking, 43.3% reported a smoking spouse, and 48.4% had no smokers at home. Indoor smoking restrictions were common, with 64.8% reporting total restrictions, 24.6% partial, and 10.6% none.

Table I: Sociodemographic Characteristic and Smoking History of Mothers with Young Children on Environmental Tobacco Smoke (ETS) Exposure to Their Children in Hulu Langat (N=321).

Sociodemographic characteristic	Mean (±SD)	n (%)
Age (year)	33.4 (5.57)	
Race		
Malay		286 (89.1)
Non-Malay		35 (10.9)
Education level		103 (32.1)
Primary & Secondary		218 (67.9)
Occupation		
Government sector		106 (33)
Private sector		98 (30.5)
Self-employed		25 (7.8)
Housewife		92 (28.7)
Household income		
RM4849 and below (B40)		196 (61.1)
RM4850 - RM10959 (M40)		87 (27.1)
RM10960 and above (T20)		38 (11.8)
Smoking status		
Current/daily smoker		1 (0.3)
Non-smoker		320 (99.7)
Household smoking history*		
Self		1 (0.3)
Husband		145 (43.3)
Child's older siblings		5 (1.5)
Babysitter		10 (3)
Others		12 (3.6)
No smoker in the house		162 (48.4)
House smoking restriction		
Total		208 (64.8)
Partial		79 (24.6)
None		34 (10.6)

*Multiple responses analysis

Table II: Mean scores of Self-efficacy, Knowledge, Attitude and Avoidance Practice of Mothers with Young Children on Environmental Tobacco Smoke (ETS) Exposure to Their Children in Hulu Langat (N=321).

Domains	Score in Mean (±SD)	Participant's Score		Score Interpretation
		Lowest	Highest	
Self-efficacy	36.41 (9.70)	5	50	Min: 5, Max:50
Knowledge	38.26 (3.76)	17	40	Min: 4, Max: 40
Attitude	48.58 (3.75)	5	50	Min: 5, Max: 50
Avoidance practice	28.33 (3.27)	11	30	Min 3, Max: 30

±SD: standard deviation

Mothers generally demonstrated high levels of self-efficacy, knowledge, positive attitudes, and ETS avoidance practices, with mean scores of 36.41/50 (±9.70), 38.26/40 (±3.76), 48.58/50 (±3.75), and 28.33/30 (±3.27), respectively (Table II). Differences in avoidance practice scores were observed across education, occupation, and household smoking history (Table III). Mothers with tertiary education scored higher in avoidance practices than those with only primary and secondary education. Self-employed mothers scored lower in avoidance practices than other occupational groups. Households

Table III: Avoidance Practice Mean Scores Comparison of Sociodemographic Characteristics and Smoking Status of Mothers with Young Children on Environmental Tobacco Smoke (ETS) Exposure to Their Children in Hulu Langat.

Characteristic	n	Mean (±SD)	F(df)	p-value
Race			1.512 (1,319)	0.220
Malay	286	28.25 (3.254)		
Non-Malay	35	28.97 (3.382)		
Education level			4.203 (1,319)	0.041
Primary & Secondary	103	27.89 (3.722)		
Occupation			3.486 (3,317)	0.016
Government sector	106	28.41 (3.309)		
Private sector	98	28.66 (2.536)		
Self-employed	25	26.36 (4.462)		
Housewife	92	28.42 (3.417)		
Household income			0.326 (2,318)	0.722
RM4849 and below (B40)	196	28.39 (3.182)		
RM4850-RM10959 (M40)	87	28.10 (3.606)		
RM10960 and above (T20)	38	28.55 (2.956)		
Smoking status				
Current/daily smoker	1	30(-)	-	-
Non-smoker	320	28.36 (3.202)		
Household smoking history*				
Self				
Yes	1	30 (-)	-	-
No	130	28.33(3.274)		
Husband				
Yes	145	27.54 (4.047)	16.259(1,319)	<0.001
No	176	28.98 (2.266)		
Child's older sibling				
Yes	5	25.60 (6.387)	3.568 (1,319)	0.060
No	316	28.37 (3.198)		
Babysitter				
Yes	10	28.90 (2.807)	0.313 (1,319)	0.576
No	311	28.31 (3.287)		
Others				
Yes	12	27.50 (3.920)	0.803 (1,319)	0.371
No	309	28.36 (3.246)		
No smoker				
Yes	162	29.13 (1.822)	20.745(1,319)	<0.001
No	159	27.52 (4.118)		
House smoking restriction			8.361 (2, 318)	<0.001
Total	208	28.85 (2.497)		
Partial	79	27.15 (3.926)		
None	34	27.91 (4.795)		

One-way ANOVA

*Separate analysis of each parameter

with no smokers and those with total smoking restrictions at home also reported higher avoidance practice scores.

In the multivariate analysis (Table IV), five factors were significantly associated with ETS avoidance practices. Positive associations included having no smokers in the home (B=0.700, 95% CI: 0.304, 1.462; p=0.003), mothers with higher self-efficacy (B=0.058, 95% CI: 0.028, 0.088; p<0.001), and mothers with more positive attitude toward ETS avoidance (B=0.414, 95% CI: 0.336, 0.491; p<0.001). In contrast, mothers with primary and secondary education level (B=-0.750, 95% CI:-1.449,-0.051; p<0.035), and self-employment (B=-1.517, 95% CI: -2.584, -0.450; p=0.005) were negatively associated with avoidance scores. The model explained 37.7% of the variance in ETS avoidance practices, with 62.3% likely due to other factors.

DISCUSSION

This study found that the majority of mothers in the sample were of Malay ethnicity, with only 0.3% reporting

ever smoking, a much lower figure compared to the 1.5% prevalence of smoking among adult Malaysian females as reported by the Global Adult Tobacco Survey of 2023. This lower prevalence is likely a reflection of the specific characteristics of our study sample, which is composed of mothers with a high level of educational attainment (67.9% had tertiary education). This finding is consistent with established evidence showing a strong inverse relationship between education level and smoking rates. Furthermore, as participants were recruited from government health clinics during child health visits, the sample may also represent a subgroup of mothers who are more engaged with the healthcare system and potentially more health-conscious.

Sociodemographic factors significantly influence ETS exposure in children, including living with smokers, family socioeconomic status, parents' education and occupation, as well as household smoking restrictions. Our study, revealed that the absence of smokers in the household was associated with higher avoidance practices, which is consistent with other studies.^{12,15,16} It

Table IV: Simple Linear Regression and Multiple Linear Regression Analysis of the Factors Associated with Avoidance Practice.

Variables	Univariate analyses		Multivariate analyses	
	B (95% CI)	p-value	B (95% CI)	p-value
Age (year)	0.018 (-0.046, 0.083)	0.575	-	-
Race				
Malay	Ref.	Ref.	Ref.	Ref.
Non-Malay	-0.720 (-1.871, 0.432)	0.220	0.090 (-0.857, 1.036)	0.852
Educational level				
Tertiary	Ref.	Ref.	Ref.	Ref.
Primary & Secondary	-0.650 (-1.285, -0.015)	<0.041	-0.750 (-1.449, -0.051)	<0.035
Occupation				
Government sector	Ref.	Ref.	Ref.	Ref.
Private sector	0.258 (-0.634, 1.149)	0.571	0.196 (-0.543, 0.935)	0.602
Self-employed	-2.046 (-3.460, -0.631)	0.005	-1.517 (-2.584, -0.450)	0.005
Housewife	0.018 (-0.888, 0.925)	0.968	0.220 (-0.602, 1.042)	0.598
Household income				
RM4849 and below (B40)	-	Ref.	-	-
RM4850-RM10959 (M40)	-0.284 (-1.115, 0.546)	0.501	-	-
RM10960 and above (T20)	0.165 (-0.978, 1.308)	0.777	-	-
Smoking status				
Current/daily smoker	Ref.	Ref.	Ref.	Ref.
Non-smoker	2.360 (-0.873, 5.592)	0.152	0.975 (-2.047, 3.998)	0.526
Smoking history *				
Self	2.347 (-4.240, 8.935)	0.484	-	-
Husband	-0.141 (-2.187, 1.905)	0.892	-	-
Child's older sibling	-1.996 (-5.079, 1.086)	0.204	1.437 (-0.964, 3.838)	0.240
Babysitter	1.170 (-1.011, 3.351)	0.292	-	-
Others	-0.499 (-2.693, 1.694)	0.655	-	-
No smoker in the house	1.481 (0.596, 3.558)	0.162	0.700 (0.304, 1.462)	0.003
House smoking restriction				
Total	Ref.	Ref.	Ref.	Ref.
Partial	-1.694 (-2.526, -0.863)	<0.001	-0.543 (-1.326, 0.241)	0.174
None	-0.934 (-2.098, 0.229)	0.115	-0.363 (-1.360, 0.634)	0.474
Self-Efficacy	0.272 (0.056, 0.127)	<0.001	0.058 (0.028, 0.088)	<0.001
Knowledge	0.498 (0.350, 0.516)	<0.001	0.107 (-0.014, 0.229)	0.084
Attitude	0.524 (0.375, 0.539)	<0.001	0.414 (0.336, 0.491)	<0.001

There were no interactions and multicollinearity between independent variables. VIF ≤ 1.054.

*Separate analysis of each parameter.

demonstrated that mothers living in smoke-free households have more proactive behaviours in shielding their children from ETS exposure. In our study, nearly half of the women had smoking husbands (43.3%). Even though it was not a significant predictor for avoidance practice, but the comparison of avoidance practice mean scores between smoking and non-smoking husband group were significant. Fathers were identified as the primary source of ETS exposure within households, underscoring the influence of family members who smoke on children's health outcomes.¹² Similarly, previous studies observed higher ETS exposure among children whose primary caregivers smoke and reside in homes with multiple smokers.^{15, 16} As a consequence, living with smokers has a negative impact on a non-smoker's ability to avoid exposure to ETS. Additionally, our study found that mothers with older children who smoke had the lowest avoidance practices mean score, although this was not statistically significant. This trend suggests that maintaining a smoke-free environment is more challenging for these mothers when living with smokers. This highlights a need for smoking prevention strategies that also target adolescents to protect younger siblings within the same household. Despite knowing the risks, mothers find it difficult to stop their spouses or household members from smoking indoors due to feelings of powerlessness and fear of causing family conflict.¹⁷ Cultural gender norms lead women to accept male smokers and prioritize family harmony over personal beliefs.¹³ To address this, it is crucial that fathers, as the typical family leaders, play a more important role by setting a positive example and enforcing a smoke-free household rule. Therefore, interventions could be more effective by promoting smoking cessation programs specifically for men who are about to get married or have young children. If the family leader smokes indoors, it becomes harder to prevent ETS exposure from other household and visitors.¹⁸

Based on our study, the participants generally demonstrated high mean scores for self-efficacy, knowledge, attitude, and avoidance practice, all of which were above average, indicating good self-efficacy, knowledge, attitude, and avoidance practice concerning

ETS exposure. However, only self-efficacy and attitude were found to be significantly positive association with the mothers' avoidance practices. These results align with previous research, which has consistently shown that mothers who exhibit higher self-efficacy and maintain positive attitudes are more likely to adopt behaviours that protect their children from ETS exposure.¹¹ Self-efficacy has been found to be the strongest predictor of ETS avoidance behavior.¹¹ A key finding from our regression analysis is that while mothers in our sample had high knowledge scores, knowledge itself was not a significant predictor of avoidance practices. Instead, a mother's self-efficacy was the crucial factor. This suggests that even with full knowledge of the risks, mothers who lack self-efficacy struggle to translate that knowledge into protective actions, especially when facing a smoking spouse. Even though knowledge was not a significant predictor in our study, but several studies reported that nonsmoking parents have more knowledge about ETS, and parents with greater understanding regarding ETS have more effective avoidance practices.^{12, 19, 20} Previous studies support our findings, showing that non-smoker parents and those who practice completely smoke-free homes have higher self-efficacy than parents who smoke or have only partial restrictions.^{19, 21} Similarly, a positive attitude is crucial for effective avoidance.¹¹ Because mothers with high self-efficacy and positive attitudes demonstrate better avoidance behaviours,²² it is clear that promoting strict, smoke-free home rules is a vital public health strategy to empower mothers and protect children from ETS exposure.

Numerous studies have established a strong link between educational attainment and health behaviours. Higher education levels are often associated with better health literacy, leading to more effective health practices and behaviours. Our study found that mothers with only primary and secondary school education were significantly less likely to engage in avoidance practices compared to those with higher educational attainment. A study found that, individuals with higher levels of education generally enjoy better health outcomes, demonstrated by greater self-reported health, and lower rates of illness, disability, and mortality. Conversely, lower

educational attainment is linked to poorer self-reported health, reduced life expectancy, and shorter survival rates when facing illness.²³ Align with our findings, a study revealed that parents with lower educational attainment are more likely to have children who are heavily exposed to ETS.⁷ This is because individuals with lower education levels tend to engage in fewer health-promoting behaviours and have higher smoking rates compared to those with higher education levels.²⁴ This indicated that mothers with lower education levels often have gaps in knowledge regarding the health impacts of ETS on children.¹⁹ Less educated mothers may have limited access to health information and resources, which can affect their awareness of the dangers of ETS and the importance of avoidance practices. Additionally, educational attainment is closely linked with socioeconomic status.⁷ Mothers with lower educational attainment often belong to lower socioeconomic backgrounds, which may limit their ability to create smoke-free environments. A study reported that 31.9% of individuals with less than high school education attainment had a complete no-smoking policy at home, compared to 45.6% of college graduates.²¹ Factors such as housing conditions, cohabitation with smokers, and economic constraints can hinder the implementation of avoidance practices.

In addition, our study revealed that self-employment was a significant negative predictor of ETS avoidance practices. Many self-employed women work in informal or less-regulated environments where smoking restrictions are often not enforced. This contrasts with government and private sector workplaces, where anti-smoking measures have created a culture that encourages non-smoking, which employees may extend to their personal lives.²⁵ Furthermore, self-employed mothers may face economic pressures, such as a perceived need to refrain from asking clients or business partners to smoke elsewhere in order to maintain professional relationships.²⁵

RESEARCH IMPLICATIONS

Our findings call for a significant shift in the approach to protecting children from ETS. Given that our study demonstrated that knowledge alone is not a significant

predictor of avoidance, future interventions must move beyond general awareness campaigns and instead focus on building mothers' self-efficacy. This can be achieved through practical, skill-based training where mothers learn and practice assertive communication to negotiate smoke-free spaces. Healthcare providers can use motivational interviewing not just to convey information, but to specifically bolster a mother's confidence in her ability to enforce these boundaries. Additionally, establishing peer support groups can provide a powerful platform for mothers to share successful strategies and reinforce their resolve. Crucially, our results indicate that the burden of protection cannot fall on mothers alone. Interventions must actively engage the primary sources of household ETS: fathers and older siblings. Public health programs should reframe fathers as essential partners and role models in maintaining a smoke-free home. This includes creating targeted smoking cessation initiatives for men at key life stages, such as during pre-marital counselling or when they become expectant or new fathers. To address the risk from older siblings, school-based smoking prevention programs are vital to stop them from introducing tobacco into the home. Finally, policymakers and stakeholders should align their efforts with this evidence. Support should be directed towards funding family-centred cessation programs and implementing comprehensive smoking bans that create an environment supportive of a mother's efforts. By focusing on empowerment and a whole-family approach, we can translate these findings into a real impact for mothers and children.

LIMITATIONS AND RECOMMENDATIONS

The study's reliance on self-reported data introduces the possibility of recall bias. Additionally, the study's geographic limitation to the Hulu Langat district may have restricted the generalizability to other regions with different sociodemographic profiles. To address these limitations, future research should incorporate objective measures of ETS exposure to minimize recall bias and enhance data accuracy. Expanding the study to include multiple regions with diverse sociodemographic profiles would improve the generalizability of the findings. Besides that, including both parents in future research

would allow for a comparative analysis of fathers' and mothers' behaviours. High smoking prevalence among fathers highlights the importance of including fathers in future research on ETS avoidance practices. This could explore how fathers' behaviours influence household exposure and how targeted interventions for smoking cessation and behaviour change among fathers might reduce ETS risks for children. Understanding these dynamics will enable the development of more targeted and effective interventions to reduce ETS exposure. Additionally, employing a longitudinal design could provide a deeper understanding of the causal relationships between self-efficacy, knowledge, attitude, and avoidance practices regarding ETS exposure.

CONCLUSION

The study found that mothers with no smokers in the household, higher levels of self-efficacy, and positive attitudes towards ETS avoidance were more likely to engage in avoidance practices to protect their children from ETS exposure. In contrast, self-employed mothers and those with lower education levels were associated with lower avoidance practices. Based on these findings, interventions should move beyond traditional education and focus on empowering mothers, particularly those who are self-employed or have lower education levels. This can be achieved through practical sessions like role-playing to build assertive communication skills, alongside counselling and support group activities designed to boost their self-efficacy. Furthermore, to be truly effective, these clinic-based interventions must expand to include the entire family by engaging fathers as role models for a smoke-free home and addressing the risk posed by other smoking household members.

CONFLICT OF INTEREST

The authors report there are no competing interests to declare.

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Job Satisfaction Among Medical Officers in a University Hospital: A Qualitative Study

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ABSTRACT

INTRODUCTION: Job satisfaction among medical officers (MOs) in university hospitals is crucial for both healthcare delivery and medical education. High job satisfaction is linked to improved productivity and mental well-being, while dissatisfaction can lead to errors, lower patient satisfaction, and higher employee turnover. Although many studies have examined job satisfaction in Malaysian healthcare settings, most have focused on public hospitals. This qualitative study aimed to explore the experiences of MOs actively working in a Malaysian university hospital to gain a better understanding into the factors influencing their job satisfaction. **MATERIALS & METHODS:** Using a phenomenological approach, 18 MOs were interviewed through semi-structured, in-depth interviews. The interviews were audio-recorded, transcribed verbatim, and analysed using thematic analysis. Guided by Herzberg's Two-Factor Theory, we explored motivators and dissatisfiers in the MOs' work environment. **RESULTS:** Four main themes emerged: (1) enjoyment in patient care including aspects of diagnosing, treating, and communicating with patients, (2) personal fulfilment in relations to family time and educational responsibilities, (3) positive work culture comprising of teamwork and hospital facilities, and (4) distress related to hospital systems, salary, and career advancement. **CONCLUSION:** This study elucidated how different factors contribute to job satisfaction and dissatisfaction among service and postgraduate MOs. These findings underscore the need for targeted strategies by hospital management and policymakers to address these dynamics, in order to sustain a motivated medical workforce in university hospitals.

Keywords:

Satisfactions, Job, Physicians, Hospitals, University

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INTRODUCTION

University hospitals serve dual functions, providing both medical care to patients, and offering clinical training to current and future health professionals.¹ These institutions are also frequently known as teaching hospitals and they are widely recognized for their contributions to quality care, particularly for managing complex cases using advanced technologies, while conducting clinical innovations.² However, these achievements come at a cost. In the Malaysian setting, healthcare workers in university hospitals encounter different challenges from those working in government hospitals, which can contribute to psychological stress and job dissatisfaction.³ Studies have shown that the training and the dual demands of education and clinical service may lead to fragmented care processes, contributing to workplace stress and dissatisfaction among healthcare providers.³ When left unaddressed, these gradients can

negatively affect both patient care and the quality of medical education provided in these institutions.⁴

Internationally, teaching hospitals face similar challenges related to dual service and academic missions. Studies conducted in the West have shown that doctors working in university hospitals often operate in high-stress environments due to the concurrent demands of patient care and academic obligations, leading to dissatisfaction due to high workloads and stress.^{5,6} Apart from the training responsibility, unique to Malaysian university hospitals are the financial constraints and discrepancies in remuneration compared to private sectors or government hospitals.⁷ This aligns with findings from other developing nations, such as Vietnam, where resource limitations in addition to dual-role expectations exacerbate job dissatisfaction.⁸

Job satisfaction is a complex concept, with various definitions depending on the perspective. Earliest definitions describes job satisfaction as an affective feelings arises from individual's work experience.^{9,10} However, in recent years, many authors have defined job satisfaction based on the positive or negative variables that influence individual's overall appraisal of their job.¹¹⁻¹³ In healthcare setting, job satisfaction has a profound effect on both healthcare professionals and patients, as the experiences of both groups can be interlinked, particularly during medical consultations.¹⁴ High job satisfaction among healthcare workers is associated with improved productivity, lower turnover rates, and better mental health, whereas dissatisfaction can result in higher error rates, decreased patient satisfaction, and higher employee turnover.¹⁵⁻¹⁷

Numerous studies on the job satisfaction of physicians have been done in Malaysia, but many of them focuses on the government sectors. Some research has shown high levels of satisfaction, while others indicate significant dissatisfaction in relation to working conditions such as administrative burden and benefits provided.¹⁸⁻²⁰ Thus, this study aims to explore experiences of job satisfaction among medical officers (MOs) in one of the university hospitals in Malaysia. By exploring this issue, we would like to describe the underlying reasons of satisfaction and dissatisfaction, besides suggesting improvement for them. In this study, we adopted Herzberg's well-established Two-Factor Theory of job satisfaction.¹² Herzberg's theory distinguishes between hygiene and motivator factors as two components in job satisfaction among workers in general. According to Herzberg, while hygiene factors can prevent dissatisfaction, true job satisfaction arises from the presence of motivators. The ideal situation is when both factors are met, employees are not only free from dissatisfaction but are also highly motivated and satisfied with their jobs.

MATERIALS AND METHODS

This study employed a qualitative approach using a phenomenological methodology to explore job satisfaction among MOs in university hospital. The study was conducted at one of the teaching university hospitals

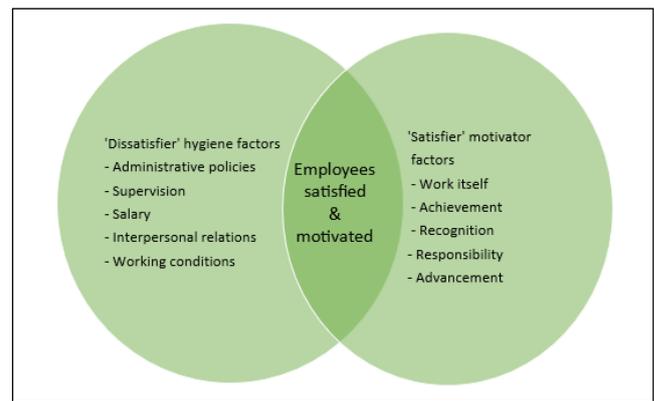


Figure 1 Herzberg's Two-factor Theory

at northeastern regions of Peninsular Malaysia. This hospital housed both service and postgraduate MOs currently pursuing Master's degree in medicine. Participants were recruited using purposive sampling including snowball sampling. A total of 18 participants were interviewed until thematic saturation was reached. Saturation was identified when no new codes, subthemes, or themes emerged during data analysis, as assessed through an iterative review of the transcripts and a comparison of codes generated from subsequent interviews.

Study advertisements and Google forms were distributed to MOs from various medical and surgical departments. Those who agreed to participate were then contacted, consented and interviewed from March to August 2023 in person or online. One-to-one interviews were conducted in the mother tongue of the 18 participants and audio-recorded.

There were two tools used in this study which were socio-demographic form and semi-structured interview guide. Firstly, socio-demographic information of participants was documented. The researcher employed a semi-structured interview guide to conduct in-depth interviews. Open-ended questions were used for participants to share stories in their own words. Probing questions were used to explore specific aspects of the interview more deeply. The interview primarily focused on participants' perceptions of job satisfaction, their experiences working in the university hospital, factors affecting their job satisfaction, and areas that need improvement.

A pilot study involving three participants were conducted,

and the transcripts were reviewed by researchers with experienced in qualitative studies to assess question clarity. Based on feedback, adjustments were made to the interview guide questions. All interviews were transcribed verbatim and analysed using N-Vivo software, following Braun and Clarke's six-step thematic analysis method.²¹

To achieve methodological rigor, steps were taken to ensure reliability and validity of this study. Regular discussions among researchers were done to prevent any drift in the definition of the codes and themes. A master table of main themes was created by grouping generated codes from the interview transcriptions, and selected themes were chosen based on the consensus of all researchers. In addition, member checking by sharing themes derived from the analysis with some participants to verify the accuracy of the research findings were also done, and all agreed on the themes derived from their interviews.

RESULTS

A total of eighteen MOs participated in the study.

Table I Demographic information of participants

Demographic information		Total
Gender	Female	14
	Male	4
Age (years old)	30 - 40	18
Types of MOs	Service	8
	MMed	10
Departments	Medical-based	12
	Surgical-based	6
Working duration in university hospital (years)	1 – 2	9
	3 - 5	6
	> 5	3

The thematic analysis of the interviews revealed four themes as shown in Table II and Figure 2. These include: (1) enjoyment in patient care; (2) personal fulfillment; (3) positive work culture; and (4) Distress with system, salary and career opportunities.

Table II Job satisfaction experiences among MOs in university hospital

Themes	Sub-themes	Axial coding	
Enjoyment in patient care	Ability to treat patient optimally	Correct diagnosis	
	Communication with patient	Active interaction with patients Patient's education	
	Seeing progress of patient's condition	Patient's compliant to treatment Shared decision with	
Personal fulfillment	Work-life balance	Spending time with family	
	Educational responsibilities	Improvement in knowledge and skills Teaching junior doctors and medical students	
Positive work culture	Good team work	Supportive colleagues Guidance from lecturers and specialists Helpful supporting staffs	
		Hospital supportive environment	Conducive studying Advanced medical equipment Non-burdensome clinical works compared to KKM hospitals
			Distress with system, salary and career development
	Salary and allowances	Underpaid salary Low oncall allowances rate	
Career advancement difficulties	Career advancement difficulties	Limited slot for service MO to further study Stress-coping in post-graduate study	

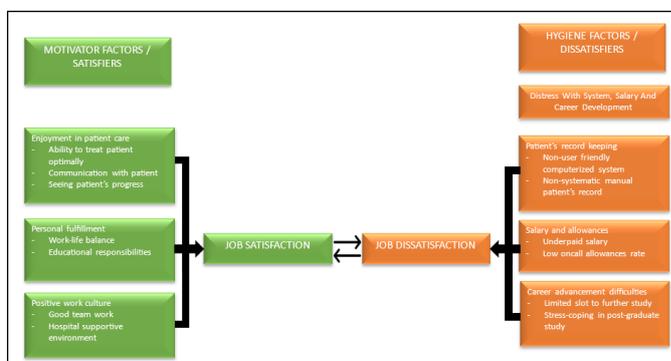


Figure 2 Factors influencing job satisfaction among MOs.

Theme 1: Enjoyment in Patient Care

Most of the MOs attributed their satisfaction to their work in providing the best patient-care. Both service and MMed MOs shared the same values despite having different job responsibilities.

Ability to Treat Patients Optimally

A significant aspect of job satisfaction for MOs is their ability to provide quality care. Many MOs expressed that accurately diagnosing and effectively treating patients contributes greatly to their satisfaction as doctors.

"For me, job satisfaction is when we can use our knowledge to diagnose patients. When a patient comes with various complaints, we can come up with the correct diagnosis and treat the patient." (P10, MMed MO)

Communication with Patients

Other MOs expressed that active interaction with patients brings joy in their work. As one participant compared her previous nature of work that lack of communication with patients:

"When I was in the administration office, we were only in charge of management tasks. After experiencing that, I felt unsatisfied. I didn't have contact with patients." (P13, service MO)

Educating patients about their illnesses and treatment plans was also highlighted as this allows MOs to impart knowledge and see the impact of their efforts, as mentioned by P7:

"Providing knowledge to patients. Giving them an understanding of their illness. At that point, that is my satisfaction." (P7, service MO)

Patient's Progresses Well

As a result of their effective management and interactive relationships with patients, many MOs are able to see significant progress in their patients which is another major contributor to job satisfaction.

"When my patients are healthy or improved... when they are discharged in good health, I feel that is my satisfaction. Because what I provided, helped my patients to recover." (P12, service MO)

Many MOs find it rewarding to witness the progress of their patients as a result of shared decision-making with patients to make informed choices about their treatment plans, which subsequently leads to patient compliance with the treatment. This enhances job satisfaction by

fostering a sense of partnership and trust. One participant expressed this sentiment:

"I feel happy when the patient understands and accepts what we discussed. And then they followed the advice we gave regarding the necessary treatment and other aspects related to their illness." (P19, service MO)

Theme 2: Personal Fulfilment

Achieving personal fulfilment by balancing career development and family life is essential for MOs. Many participants found self-contentment through both career growth and fulfilling family responsibilities.

Work-Life Balance

The ability to balance work demands with family time highlights the importance of family among MOs as their pillars of support. P18 emphasized the importance of this balance:

"Because balancing work and family is important for me. That is my happiness even though I am busy at work, but I still have time with my family." (P18, MMed MO)

Educational Responsibilities

As MOs in a training centre, many valued the opportunities available at the university hospital to improve their knowledge and skills. Even though they are not bound by academic requirements as MMed MOs, majority of service MOs felt the responsibility to improve themselves.

"So when I joined here (university hospital), I was able to learn more to improve my knowledge in this field. I learned procedures. So when I accomplish a skill or gain new knowledge in my field, I feel satisfied." (P17, service MO)

Additionally, actively engaging in educational roles by teaching junior doctors is also fulfilling for most of them.

"Being able to share knowledge with the houseman makes me feel satisfied as a medical officer. Oh, today I was able to share something with my houseman. Hopefully, they gain something when they followed my rounds." (P12, service MO)

Theme 3: Positive Work Culture

A positive work culture, encompassing both human resources and workplace environment, are also highlighted.

Good Teamwork

All participants expressed that effective teamwork is crucial in their demanding work environment, particularly collegial support, which helps MOs navigate challenging situations, as shared by P14:

"And (I have) teammates who can help when we face problems or dilemmas in managing patients...there are teammates who are willing to help us even when their shift is over... When we are post-call, our colleagues are willing to help with our work." (P14, service MO)

The guidance from specialists, who also serve as lecturers in this training hospital, are highly valued by all MOs.

"They give me a lot of guidance. If there's anything I need to consult on, they are very willing to guide us... especially in managing complicated cases, and I have learned a lot from the lecturers about managing those cases." (P2, MMed MO)

However, concerns were raised regarding the quality of house officers, who were seen as incompetence and increasing the work burden of MOs.

"I feel dissatisfied. MOs have to do everything. The work that housemen should be doing is also done by MOs." (P10, MMed MO)

Many participants agreed that house officers need to be more proactive and take full advantage of the benefits of working in a university hospital. Additionally, hospital should invest in better training for house officers to ensure they perform effectively and uphold the standards of a university hospital.

Supportive Hospital Environment

A supportive environment with adequate facilities also contributes to satisfaction among participants. They

appreciated the conducive learning facilities and advanced medical equipment, noting the benefits of working in a university hospital. P16 noted the advantage of having advanced equipment:

"Especially the endoscopic lab, the equipment is complete. There are even extras that other places don't have. So the lab here is quite advanced." (P16, MMed MO)

Despite having top-notch learning and patient-care facilities, many participants felt that certain hospital infrastructures need improvement, particularly the on-call rooms and parking facilities. Although some stated that these issues do not lead to dissatisfaction, a facilitative environment can add values to the working conditions.

"Overall, I am satisfied with the infrastructure provided here. However, what could be improved is the number of parking spaces... perhaps designated parking for staff so that we don't have to park far away and spend time searching for parking before starting work." (P2, MMed MO)

In addition to the physical facilities, number of patients and workload in the university hospital were more manageable compared to other facilities, allowing them more time for academic activities.

"The difference at HUSM is that there aren't as many patients as in KKM, in my opinion. So we have more time to study." (P5, MMed MO)

Theme 4: Distress with System, Compensation and Career Development

This theme highlights emerging issues from the participants that, when unmet, lead to significant sources of their dissatisfaction.

Patient's Record Keeping

Inefficient computerized systems were frequently cited by MMed MOs as a significant frustration, as expressed by P10 regarding the challenges of using multiple online systems to access patient records:

"The HUSM system has too many components and is very confusing. It's not easy. It's not user-friendly." (P10, MMed MO)

Compared to service MOs, the majority of whom received their undergraduate and housemanship training in this hospital, they felt familiar with the system and had no issues with it. However, addressing these issues by integrating into a single main system is deemed beneficial to facilitate MOs' workflows, as suggested by another participant:

"I think all those applications need to be integrated into one system. And all the investigations should also be included in the online system." (P11, MMed MO)

Compensation

Inadequate salary and allowances are also main reason for dissatisfaction among MOs. Most participants highlighted the disparity between workload and compensation received.

"We are paid less than what we work for... The workload keeps increasing and not decreasing, but the salary for doctors remains the same." (P6, MMed MO)

Other MOs also voiced out pay difference between government and private sectors.

"In comparison, when doing locum work outside (private clinic), you can get forty, sometimes fifty or sixty (Ringgit) in one hour. And for one day of on-call (hospital), we get two hundred (Ringgit)... the on-call allowance is still low when compared with the workload." (P19, service MO)

Career Advancement Difficulties

Five service MOs shared challenges in pursuing further studies, which are specific to those working in the university hospital. One participant noted the issue of limited slots for the Master's program:

"In my department, there is only one slot per year... For the KKM Master's programme, many can get in, but the slots for service MOs here are very limited." (P14, service MO)

However, some participants agreed that the university has made efforts to address these barriers so that more of their MOs can join the Master's programmes.

"So, like last year and the year before, only one or two people from a department were able to continue their studies. But luckily this year, they've started accepting more. Even in [Department P], there are five people this year. I am grateful to be one of those who got the slot." (P19, service MO)

Unlike service MOs, MMed MOs face unique challenges in their career development. Many experienced difficulties coping with the stress of postgraduate studies while also maintaining their regular work duties.

"Since we are postgraduate MOs, we still have to work while studying. So the responsibility to provide service is still there. But we also have to meet other academic requirements like classes, CME, research, and many other things." (P4, MMed MO)

DISCUSSIONS

This qualitative study explores job satisfaction among medical officers (MOs) in a university hospital setting, revealing several themes on MOs' perspectives of job satisfaction aligning with Herzberg's Two-Factor Theory. A significant motivator identified in this study was the satisfaction derived from patient care, including aspects of diagnosing, treating, and communicating with patients. This aligns with Herzberg's Two-Factor Theory, where achievement and recognition through meaningful patient interactions enhance their satisfaction.¹² Various international studies showed similar findings, whereby the quality of patient care and the ability to spend adequate time with patients are significant predictors of job satisfaction among physicians.²² Furthermore, effective communication by fostering patient's understanding and compliance, was essential component that reinforced job satisfaction as this was seen as a direct outcome of their dedication to patient care.²³

Achieving balanced work-life dynamics and personal fulfilment has emerged as a vital component of job satisfaction as demonstrated not only in local contexts but also on a global scale. A study conducted in India had a

similar finding, that work-life balance among doctors is significantly shaped by factors such as working hours and the time dedicated to family and personal activities.²⁴ While not directly tied to Herzberg's Two-Factor Theory, maintaining a balance between work and family life reduces conflicts and promotes greater job satisfaction.²⁵ Maintaining this balance enhances productivity and engagement, as employees are less prone to burnout and better equipped to manage professional and personal responsibilities – findings echoed in both local and studies from the West.^{26,27} On the other hand, poor work-life balance is associated with adverse effects on both physical and mental health.²⁸

Another key motivator for MOs in this setting is the opportunity to share knowledge with juniors which aligns with Herzberg's motivator factor of recognition, where acknowledgment for their efforts in mentorship fosters job satisfaction.¹² Sharing knowledge not only leads to satisfaction, but job satisfaction itself is a strong predictor of knowledge-sharing behaviour.²⁹ Availability of educational opportunities create positive experiences for doctors, and this is not only significant for those pursuing Master degrees like the MMed MOs, but also to service MOs who are planning to pursue their studies in the university hospitals. These findings resonate with another study conducted among interns in Australia that showed quality supervision, teaching and clinical exposure in the hospital contributes to their satisfaction.³⁰

Working environment including interpersonal relationship and working conditions are typically viewed as hygiene factor preventing dissatisfaction, however, in this study it was also seen as a satisfier.¹² Cohesive teamwork between team members and supportive hospital facilities is crucial for reducing work-related stress and burnout, particularly in a high-demand profession like medicine.³¹ Despite this, negative impact contributed by non-user friendly of hospital electronic system can hinder job satisfaction, a challenge similarly observed in other developing countries like India.³² This dual role of working environment highlights the complexity of Herzberg's Two-Factor Theory in a university hospital setting, where factors traditionally seen as preventing dissatisfaction also actively

contribute to job satisfaction.

In the Malaysian medical community, concerns about the competency of house officers are not new as many have raised issues regarding the quality of these young doctors.³³ This concern also extends to university hospital, where the inadequate role of house officers, coupled with their unsatisfactory performance, has been a source of dissatisfaction for MOs. In Malaysia, studies on clinical competency have primarily focused on medical students, revealing low perceived competency in performing clinical procedures.^{34,35} In contrast, overseas research has extended to junior doctors, highlighting significant concerns regarding inadequate competency, particularly in basic procedures.³⁶ Although there are no studies directly correlating MOs' job satisfaction with the incompetency of house officers, a satisfying interprofessional relationship at work can prevent dissatisfaction, highlighting the importance of interpersonal relationships as hygiene factor.³⁷

Salary is a prominent dissatisfying factor identified in this study, aligning with Herzberg's hygiene factors.¹² This is consistent with existing local and international studies showing salary and benefits are critical factors influencing job satisfaction, particularly when the compensation does not meet employees' expectations.^{31,38,39} The comparison between government and private sector's compensation further exacerbates dissatisfaction.⁴⁰ This dissatisfaction can lead to increased turnover rates of MOs, particularly those aspiring specialists, may look for better-paying opportunities elsewhere and contribute to higher rate of resignations from government service.^{41,42} However with the recent salary revision in Malaysia and on-call allowances increment announced by the government it is hoped to alleviate financial stress and improve the overall well-being and performance of medical officers.⁴³

Opportunities for career development is seen as a dissatisfier among MOs in contrast to Herzberg's theory.¹² Limited slots and perceived inequities in educational opportunities can contribute to frustration and hinder personal and professional development.⁴⁴ These findings align with a local studies noting the need to address governance issues and resource limitations in medical

specialty training in Malaysia in comparison to a more structured post-graduate training in oversea countries.^{45,46} Additionally, academic challenges and the need to balance clinical duties with academic responsibilities play significant role in satisfaction among post-graduate trainees. The demanding nature of their work, combined with the pressures of post-graduate medical training, can create a stressful working environment for these trainees^{47,48} Therefore, providing adequate educational opportunities for service MOs and implementing welfare interventions to enhance coping skills for MMed MOs are both essential for ensuring job satisfaction across these groups.^{49,50}

CONCLUSION

Despite differing career roles and goals, job satisfaction among both service and MMed MOs in the university hospital is largely similar, consistent with Herzberg's Two-Factor Theory. The dynamic interplay between motivator factors, such as personal fulfilment, patient care, and teamwork, and hygiene factors, including salary, career development, and systemic support, highlights their critical role in shaping job satisfaction among medical officers. The findings of this study are consistent with both local and global research, underscoring the universal importance of addressing dissatisfaction stemming from hygiene factors while enhancing motivators to foster a more balanced and fulfilling work environment.

To address these findings, hospital management should prioritize improving the usability of patient record systems, improve allowances policies, and expanding postgraduate training opportunities. Policymakers must consider aligning financial incentives with the workload and revising career development pathways to retain skilled medical professionals. Such measures will not only boost job satisfaction but also improve healthcare delivery and the training of future health professionals. By focusing on these targeted strategies, stakeholders can foster a more supportive environment, ultimately benefiting patient outcomes and the quality of medical education.

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Study on the Effectiveness of Integrating Religious Approaches in Health Interventions for Transgender Individuals in Malaysia

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ABSTRACT

INTRODUCTION: Transgender women (mak nyahs) are biological males who self-identify as females and often face discrimination in education, employment, and healthcare. Economic marginalisation frequently pushes them into sex work, heightening risks of HIV infection, depression, anxiety, and substance abuse. While interventions for Muslim transgender communities exist, their effectiveness is underexplored. This study evaluated a health program integrating Islamic elements to reduce HIV-related risk behaviours among mak nyahs. **MATERIALS AND METHOD:** A cross-sectional study was conducted among 50 participants recruited via respondent-driven sampling. A validated, self-administered questionnaire assessed religiosity and HIV-related risk behaviours. The intervention, delivered in a 3-day, 2-night motivational camp (Mukhayyam), incorporated Islamic talks, tazkirah (religious reminders), songs, videos, slides, and quizzes. Participants completed questionnaires at baseline (Day 1) and post-intervention (Day 3). **RESULTS:** The mean age of respondents was 39.9 years (SD=9.46). One-fifth reported sex work, and only one-third reported no HIV-related sexual risk behaviours. The intervention significantly improved knowledge and attitudes related to ibadah ($z=-2.317, p=0.021$) and akhlak ($z=-2.900, p=0.004$), with an overall increase in Islamic religiosity scores ($z=-3.038, p=0.002$). Health knowledge also improved, particularly on the negative effects of cosmetic procedures ($z=-2.848, p=0.004$). **CONCLUSION:** The Mukhayyam-based intervention incorporating Islamic teachings enhanced religious knowledge and showed potential in reducing HIV-related risks among Muslim transgender women. Longitudinal studies and controlled trials are warranted to evaluate sustainability and scalability.

Keywords:

Male-to-Female Transgender, HIV, Sex Worker, Religion, Mukhayyam

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INTRODUCTION

According to the fifth edition of Diagnostic and Statistical Manual of Mental Disorders, transgenders are individuals who transiently or persistently identify with a gender different from their natal or anatomical gender. In local language, a male-to-female transgender is known as a mak nyah. The Joint United Nations Programme on HIV/AIDS (UNAIDS) reported that transgender women are disproportionately affected by HIV where new HIV infections increased annually by 3% from 2010 to 2022.2 The relative risk of acquiring HIV was 20 times higher for transgender women than for people in the wider

population globally in 2022, a significant increase from the 11 times higher risk in 2010. Accurate data on the number of transgender individuals in Malaysia is difficult to obtain due to societal and legal challenges. The number of transgender individuals in Malaysia is estimated to be 24,000 to 50,000., Studies in Malaysia suggested that as many as 80% of transgender women in Malaysia are Malays and are Muslims., In Malaysia, an estimated 9.7%–12.4% of transgender women are HIV positive, with higher estimates among those engaged in sex work. According to the 90–90–90 Joint United Nations

Programme on HIV/AIDS strategy, HIV testing is the first crucial step in curbing the HIV epidemic.

Studies have suggested that the inclusion of religious elements into health promotion programs could be effective in bringing health-related behaviour changes. A systematic review analysed fifty-seven studies that examined how sexual HIV risk varied according to religious affiliation, 31 of them showed religious affiliation to be associated with reduced sexual risk for acquiring HIV. This was supported by previous studies suggesting the fusion of religious elements into health services, so that people could benefit in terms of psychological health, physical health, and thus attain a happier, more meaningful life.

The Department of Islamic Development Malaysia (JAKIM) as well as universities have been organizing Mukhayyam-an Arabic term meaning "camp," which in this context refers to motivational or team-building programs that require participants to commit several days to structured courses. The Mukhayyam program places particular emphasis on religious education and formal ritual practices (ibadah). Participation is entirely voluntary and conducted without any element of coercion. Importantly, Mukhayyam is not a rehabilitation centre established under any statutory rehabilitation or treatment-related legislation, such as a drug court or criminal justice mandate.

The purpose of the Mukhayyam program is to educate the transgender individual community on religious knowledge, religious obligations, to increase their spirituality, and to give them a sense of belonging in a spiritual environment. The transgender community had expressed the need to seek religious and spiritual guidance, but they often avoid religious authority in fear of being discriminated.

There has been so far, no study on the effectiveness of Mukhayyam as one of the religious approaches in modifying the high-risk behaviour of transgender individuals. The objectives of this study therefore, were to assess the effectiveness of Mukhayyam in changing HIV-

related risk behaviours and to measure the knowledge on negative effects of feminization, substance abuse and mental health symptoms among transgender individuals participating in Mukhayyam.

MATERIALS AND METHODS

A cross-sectional study was carried out among Malaysian transgender individuals or mak nyahs using validated questionnaires that include parameters like knowledge of HIV/AIDS, attitude towards HIV/AIDS, HIV-related risk behaviours and Islamic religiosity.

Participants

This study included self-identified adult Muslim transgender individuals in Malaysia aged 18 and above, using the respondent-driven method. The inclusion criteria included Malaysian citizens with a producible Malaysian identity card, able to communicate in Bahasa Malaysia and/or English language and consented to the study. For illiterate subjects, the survey form was read out loud to them. Exclusion criteria were cisgender lesbian, gay, and bisexual individuals and female-to-male transgenders (transmen).

Sample size

The sample size was calculated to be 38 by using the online sample size calculator in OpenEpi software, version 3.01. With a prevalence of 0.61, precision of 5% and confidence interval of 95%, the design effect was taken to be 4.0, since the respondent-driven sampling method was used.

Instrumentation

The questionnaire to study the effectiveness of Mukhayyam programs was designed by the topic experts from amongst religious scholars and medical specialists. The steps of preparing the questionnaires roughly followed the 7-step guidelines provided by Artino Jr. and colleagues. Participants completed the questionnaires at baseline (Day 1) and post-intervention (Day 3).

Program Design

The Mukhayyam in this study was designed through a

formal partnership formed between JAKIM, Ministry of Health and volunteers 6 months before the program, assisted by Persatuan Insaf Pahang, Pahang Islamic Religious Department (Malay: Jabatan Agama Islam Pahang), and International Islamic University Malaysia (IIUM). Persatuan Insaf Pahang is a non-governmental organization that looks after the medical, psycho-social, and religious welfare for the transgender community.

Intervention Sessions and Activities

Table 1 showed interventions which were delivered through talks, short advice, music or songs, videos, slides and quizzes.

Instrumentation

There was no previously designed questionnaire to study the effectiveness of Mukhayyam programs, therefore it was designed by the topic experts consisted of religious scholars and medical specialists who have been involved in Mukhayyam previously. The steps of preparing the questionnaires roughly followed the 7-step guidelines provided by Artino Jr. and colleagues. The steps include conducting a literature review, discussing the topics of interest with the population of interest, developing the potential constructs into comprehensive items, undergoing expert or face validation, discussing the clarity of the items with the population of interest, and carrying out the pilot test. The designed questionnaire in Bahasa Malaysia was distributed to 12 mak nyah subjects who did not participate in the Mukhayyam. Internal consistency of the items were calculated. The overall Cronbach alpha was 0.71. Internal consistency of the religion domain was 0.88, while health awareness was 0.83, both were adequate.

Measuring Health Awareness

Knowledge on health issues were assessed on the following areas; knowledge on HIV prevention, knowledge on complication of using feminizing hormone, knowledge on complications of feminizing surgical procedures and implants and knowledge on negative health effects of alcohol and substance abuse.

Table I. Intervention sessions in *Mukbayyam*

INTERVENTION SESSIONS	CONTENT
1 Talks on HIV/AIDS and Sexually Transmitted Diseases	<ul style="list-style-type: none"> HIV/AIDS STD Methods of prevention
2 Health Quiz	<ul style="list-style-type: none"> Health risks of feminizing hormones Complications of feminizing surgical procedures and implants Negative impacts of alcohol on physical and mental health Negative impacts of substance abuse on physical and mental health Prevention, symptoms, diagnosis, treatment, and complication of HIV and sexually transmitted diseases
3 Psychological Support and Self-Help Methods	<ul style="list-style-type: none"> Negative impacts of substance and alcohol abuse Depression and anxiety Stress management How to attain positive habits Self-love and self-respect
4 Prayers as Spiritual Therapy	<ul style="list-style-type: none"> Ablution (Wudhu) Congregational prayers during the program (voluntary basis) Short religious reminders (tazkirah) after each prayer . Correction of recitations during prayers.
5 Religious Talks (Ceramah)	<ul style="list-style-type: none"> Aqidah (the basic knowledge of Islamic belief a Muslim should have) Ibadah (the basic knowledge of obligatory religious practices a Muslim should know) Akhlak (the basic knowledge of the attitude a Muslim should portray in daily life to reflect his understanding towards religion) Death and Akhirah (life after death)
6 Physical Exercises	<ul style="list-style-type: none"> Aerobic exercise Sports competition Jungle trekking Spring cleaning.
7 Work Opportunities	<ul style="list-style-type: none"> Participants provide insights to their needs. Exchange of contact numbers between agency and participants to keep each other updated and informed.

Measuring Religiosity

Items examined under this construct include *Aqidah* (6 items); *Ibadah* (6 items) and *Akhlak* (5 items). *Aqidah* in this context refers to the basic knowledge of Islamic belief a Muslim should have. *Ibadah* refers to the basic knowledge of obligatory religious practices a Muslim

should know. *Akhlak* refers to the basic knowledge of the attitude a Muslim should portray in daily life to reflect his understanding towards religion. Likert scales were used to allow for observation of changes in their knowledge and motivation before and after the intervention program.

Measuring the Motivation to Improve Lifestyle

Two items were asked to assess motivation to change lifestyle. In the pre-program questionnaire, the two items aimed to record the participants' current status in sex work and fulfilling the obligatory daily prayers. For the post-program questionnaire, the two items assessed their willingness to change in these two items. The purpose of keeping only two items under this construct was to simplify the questionnaire as much as possible so the participants would cooperate better in answering the questionnaires.

Data Analysis

Descriptive data were analysed and displayed through frequency, mean with standard deviation, and median with interquartile range. The pre-program and post-program results were compared with Wilcoxon test since the results generally had non-normal distribution when tested for normality. In addition, when the respondents were divided into two groups based when comparing for a certain condition (e.g. having multiple sexual partner), the number of respondents for each group becomes smaller. Therefore, the non-parametric test was used. Mann Whitney test was used to compare the independent pre-program and post-program variables.

RESULTS

50 self-identified adult Muslim transgender individuals completed the study as full participants of *Mukhayyam*. The mean age among the respondents was 39.9 (SD = 9.46) years, where majority of them (62.0%) were between the ages of 30 to 39. About one-fifth of them (18.0%) were 50 years and above. Although 64% of them had no financial dependents, as many as 30% had to share their income with 2 to 3 dependents, while 6% had to support from 4 up to 6 dependents. More than half (60.5%) of the respondents received secondary education while 20.0% of

them received tertiary education. The median of their income was MYR1250 (IqR=1100).

Comparison of knowledge before and after intervention programmes

Medical and Islamic Religious Knowledge in all participants

Table II showed significant improvement in knowledge about *Ibadah* ($z=-2.317, p=0.021$) and *Akhlak* ($z=2.900, p=0.004$), resulting in improvement in the total score for Islamic religiosity ($z=-3.038, p=0.002$). For knowledge of health issues, the knowledge on negative effects of cosmetic procedures improved after the program ($z=-2.848, p=0.004$). Detailed descriptions are illustrated in Table III.

Table II Pre-Program and Post-Program Scores for Medical and Islamic Religious Knowledge among Transgender individuals (N=50)

	Pre-program median score (IqR)	Post-program median score (IqR)	Z stat	p value	r (effect size)	Interpretation
Aqidah	20 (8)	21 (7)	-1.510	0.131	0.213	Small
Ibadah	20 (4)	21 (5)	-2.317	0.021*	0.328	Medium
Akhlak	20 (7)	20 (4)	-2.900	0.004*	0.410	Medium
Total score for Islamic religiosity	58 (19)	61 (15)	-3.038	0.002*	0.430	Medium–Large
HIV prevention	9 (6)	10 (4)	-1.456	0.145	0.206	Small
Hormone use	8 (7)	8 (8)	-1.012	0.312	0.143	Small
Cosmetic procedures	5 (4)	6 (6)	-2.848	0.004*	0.403	Medium
Substance abuse	9 (5)	11 (4)	-1.504	0.132	0.213	Small
Total score for medical knowledge	31 (17)	34 (17)	-2.441	0.015*	0.345	Medium
Total for both religiosity and medical knowledge	86 (29)	96 (30)	-3.152	0.002*	0.446	Medium–Large

* $p < 0.05$

Medical Knowledge and Islamic Religious Knowledge among Transgender individuals in Sex Trade and those not involved in sex trade

Table III compared the knowledge score before and after *Mukhayyam* for participants who were involved in sex trade. There was significant improvement in *Ibadah* ($z=-2.059, p=0.039$) and *Akhlak* ($z=-2.205, p=0.027$) knowledge scores after the program. This has translated

Table III Pre-Program and Post-Program Scores for Medical Knowledge and Islamic Religious Knowledge among Transgender individuals in Sex Trade (n=32)

	Pre-program median score (IqR)	Post-program median score (IqR)	Z stat	p value	r (effect size)	Interpretation
Aqidah	20 (8)	20.5 (10)	-0.242	0.809	0.043	Negligible
Ibadah	20 (9)	21 (5)	-2.059	0.039*	0.364	Medium
Akhlak	19.5 (7)	20 (4)	-2.205	0.027*	0.390	Medium
Total score for Islamic religiosity	58 (19)	58.5 (18)	-2.086	0.037*	0.369	Medium
HIV prevention	9 (6)	9 (4)	-0.880	0.379	0.156	Small
Hormone use	8 (8)	7.5 (7)	-0.350	0.726	0.062	Negligible
Cosmetic procedures	5 (4)	6 (5)	-1.541	0.123	0.273	Small-medium
Substance abuse	9.5 (6)	11 (5)	-1.075	0.202	0.190	Small
Total score for medical knowledge	31 (16)	32 (16)	-1.707	0.088	0.302	Medium
Total for both religiosity and medical knowledge	87 (28)	89.5 (28)	-2.197	0.028*	0.388	Medium

*p < 0.05

into significant increase in total score for Islamic religiosity. However, there was no significant improvement in overall health knowledge scores.

Table IV depicted result of the group not involved in sex trade. Only knowledge on Aqidah improved significantly after the program (z=-2.092, p=0.036) with significant increase in total score for Islamic religiosity. The knowledge on negative effects of cosmetic procedures also improved after the program.

Motivation in Changing Lifestyle

In further sub analysis, the respondents were divided into 2 groups, those who were involved in sex trade and those who were not involved in sex trade. The first group include 32 participants who had noted that they “work part time in sex trade” or “working in the sex trade is my only source of income” while the second group of 18 participants clearly noted that they “do not work in the sex trade”.

Sex work status

Figure 1 shows sex work status of the 50 respondents. There were 18 (36.0%) who chose “not involved in sex trade”, 16 (32.0%) who were “part time in sex trade”, and another 15 (32.0%) who were “full time in sex trade”.

Table IV Pre-Program and Post-Program Result of Medical Knowledge and Islamic Religious Knowledge Scores among Transgender individuals Not Involved in Sex Trade (n=18)

	Pre-program median score (IqR)	Post-program median score (IqR)	Z stat	p value	r (effect size)	Interpretation
Aqidah	21 (9)	23 (4)	-2.092	0.036*	0.493	Medium-Large
Ibadah	21 (4)	21 (5)	-0.985	0.325	0.232	Small
Akhlak	20 (9)	20 (4)	-1.863	0.063	0.439	Medium
Total score for Islamic religiosity	62 (18)	64 (16)	-2.160	0.031*	0.509	Large
HIV prevention	9 (6)	11 (4)	-1.437	0.151	0.339	Medium
Hormone use	8 (7)	9 (6)	-1.140	0.254	0.269	Small-Medium
Cosmetic procedures	4 (4)	9 (5)	-2.733	0.006*	0.644	Large
Substance abuse	9 (4)	11 (3)	-1.116	0.264	0.263	Small-Medium
Total score for medical knowledge	33 (18)	36 (15)	-1.943	0.052	0.458	Medium
Total for both religiosity and medical knowledge	86 (30)	97 (31)	-2.398	0.016*	0.565	Large

*p < 0.05

Daily obligatory prayers

For daily obligatory prayers (Figure 2), 13 (26.0%) respondents chose “not performing obligatory prayers at all”, 16 (32.0%) chose “sometimes performing obligatory prayers”, while another 21 (42.0%) chose “always performing obligatory prayers”.

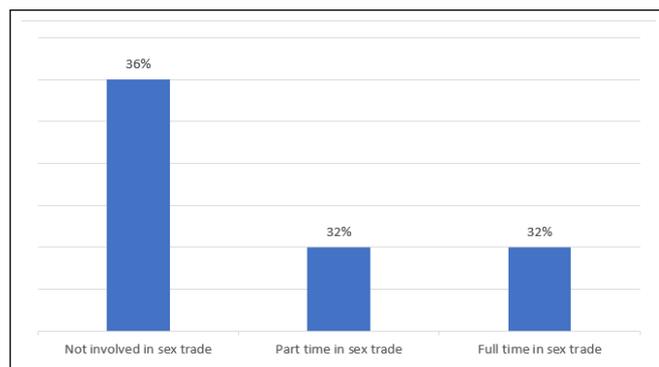


Figure 1: Sex Trade Involvement among transgender individuals (N = 50)

Transgender individuals Motivation in Changing Lifestyle after Program

Figure 3 compared the willingness to complete five times obligatory prayer. From the the 26 % of of respondents who did not perform obligatory prayers at all before the program (Figure 2), post Mukhyyam intervention resulted in only 14.0% respondents who were not sure if

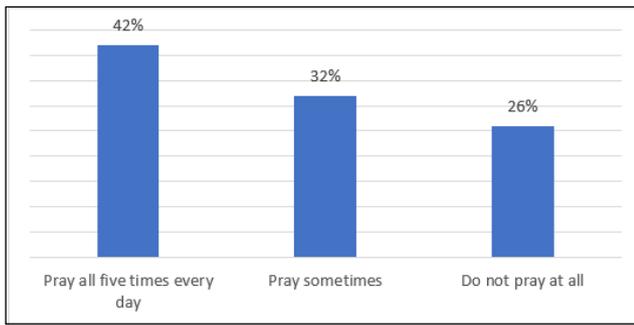


Figure 2: Daily Prayers Performance of Transgender individuals (N=50)

they could perform obligatory prayers. There was increased in behavioural changes of able to complete all prayers (46% post intervention as opposed to 42% before program) and willingness to pray (34% vs 32%).

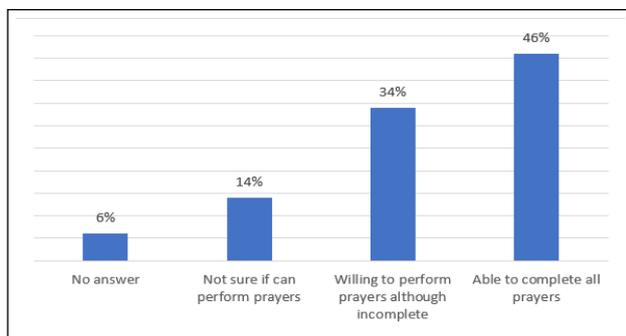


Figure 3: Transgender individuals willingness to complete five times of obligatory prayers

Figure 4 depicted that among the 64.0% respondents in the sex trade (refer Figure 1), 38% believed they were able to discontinue involvement in sex work, 42.0% now believed that they could try to do so, while 14.0% admitted that they were not able to discontinue involvement in sex work.

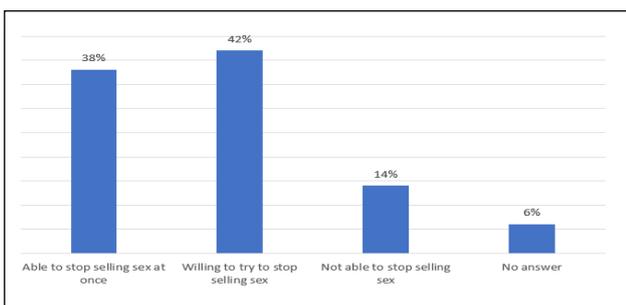


Figure 4: Transgender individuals willingness to discontinue involvement in sex work

DISCUSSIONS

This study, which was one of the first to investigate the effectiveness of health intervention program with religious approach, suggested that the Mukhayyam program is effective in motivating transgender individuals to change their high-risk behaviour. The increment in

total scores for Ibadah and Akhlak indicated that the program could motivate them to practice Islam better and to live a healthier lifestyle, therefore reduce their risk to HIV transmission. As evident from the study by Dowshen and colleagues, formal practices in religion were significantly associated with reduced HIV sexual risk. After the program, as many as 42.0% of the respondents self-reportedly were willing to discontinue involvement in sex work, and 38.0% were willing to abstain from sex trade as well. This result, considering that 64.0% respondents were involved with the sex trade, is a positive improvement.

There has been evidence suggesting that religious belief and behaviours could be protective factors against HIV-related sexual risk behaviours., Transgender sex workers are at a higher risk for HIV infection compared to transgender persons who do not engage in sex work., In this study, it was shown that transgender sex workers had a significantly lower score in religious practice in comparison to those who did not engage in sex work. This implies that encouraging religious awareness and practice in this community would be helpful in reducing HIV-related sexual risk behaviours and supporting transgender sex workers to quit sex trade. This study was able to document the subjects' frequency of religious actions commonly performed by Muslims, thus providing some insight towards areas that require more attention when preaching to this community. For daily prayers, 46.0% were willing to complete all daily prayers, while 34.0% were willing to perform prayers although incomplete. In comparison to the findings before the program began, where 26.0% of the respondents did not pray at all, and 32.0% who only prayed sometimes, it could be said that there were some motivations among the respondents to perform prayers after the program.

According to a study carried out among Christian black and Latino men who have sex with men (MSM), religion and spirituality benefits the stigmatized community. Religion and spirituality have brought positive changes in terms of the individuals' decision-making ability and self-respect. For some members of the community, religion and spirituality increased their level of self-worth and self-discipline, which made them feel less tempted by sex and

drugs. Also, increased self-esteem made them more aware of the potential consequences to their actions, thus preventing them from taking a risk. They also used sex as a tool to make them seek worthy and deserving of love.⁷ Religion and spirituality were able to fill up this void with the individuals' mental health seemed to be improved, therefore making them more empowered to avoid high risk sexual behaviours.

Therefore, religious approach, when implemented correctly, could be helpful as an effective HIV prevention method. In a Mukhayyam event such as this study, it is aimed at promoting and educating a group of Muslim involved in lesbianism, gay, bisexual and transgender (LGBT) the basic tenets of Islam. Participation is completely voluntary with no elements of coercion involved and is far from the conversion therapy practised by other countries, which involves an element of forced participation. In fact, the Mukhayyam underscores the non-discriminatory nature of the religious authorities in providing education and awareness building as part of Islam's rich religious traditions. An Islamic scholar has also highlighted the importance of Mukhayyam in providing the religious rights of transgender individuals to meet their spiritual needs. Mukhayyam also acts as a barrier to prevent all means leading to various harmful consequences (sadd al-dhari'ah).

The outcomes of the Mukhayyam program in this study suggest that it holds potential for broader implementation beyond the initial study sites. To facilitate scaling, strategic collaboration with religious institutions, public health agencies, and civil society organizations is essential to ensure cultural and contextual relevance. Adaptations may be necessary for different target populations, such as transgender youth, rural communities, or individuals with intersecting vulnerabilities (e.g., HIV-positive or undocumented individuals).

In terms of future research, we recommend conducting longitudinal studies to assess the sustainability of behavioural, psychological, and spiritual outcomes over time. This would allow researchers to examine whether observed improvements-such as in religiosity, self-

acceptance, and reduction in high-risk behaviours-are maintained in the medium to long term. Furthermore, randomized controlled trials (RCTs) could help establish stronger causal inferences by comparing outcomes between intervention and control groups. Mixed-methods designs could also explore how and why certain components of the Mukhayyam framework (e.g., group support, spiritual guidance, medical education) resonate with participants and influence behavioural change. Such future studies would provide more robust evidence to support the institutionalization or policy-level endorsement of the Mukhayyam model.

This study has several limitations. First, the relatively small sample size may limit the generalizability of findings to the broader transgender population. Second, the non-randomized, pre-post design precludes causal inferences, as other unmeasured variables could have contributed to the observed changes. Third, outcome data were collected within a short follow-up period, and therefore long-term effects remain unknown. Additionally, the reliance on self-reported measures may be subject to response bias, particularly given the sensitive nature of the topics addressed. Lastly, as the Mukhayyam program is grounded in Islamic principles, its applicability to transgender individuals from other religious or secular backgrounds may be limited, warranting culturally adapted models for broader implementation.

INSTITUTIONAL REVIEW BOARD (ETHICS COMMITTEE)

The research protocol was approved by Universiti Sains Islam Malaysia Research Ethics Committee with the code USIM/REC/0816-17. Participation in the study was fully voluntary. All participants received an information sheet explaining the purpose of the study, what it involved, potential risks and benefits, confidentiality, and their right to withdraw at any time without consequence. This information was presented in clear, accessible language, with translations provided where needed. Written informed consent was obtained from all participants before the study began. Given the potential for discrimination and stigma among transgender individuals, several measures were taken to protect participants well-being. Recruitment was carried out through a trusted local

NGO, Persatuan Insaf Pahang, and outreach workers to reduce any sense of coercion. Anonymity and confidentiality were strictly upheld; no identifying information was collected, and participants used self-chosen pseudonyms or codes.

All interviews and surveys were conducted in neutral, participant-selected locations to ensure comfort and safety. The research team was trained in gender sensitivity, trauma-informed practices, and cultural competence. Throughout the study, continuous reflection and care were taken to respect and uplift the voices and dignity of all participants.

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Effects of *Sauropus Androgynus* Extract on Cognitive Function Improvement and Neuron Enhancement in Trimethyltin Chloride-Induced Rats

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ABSTRACT

INTRODUCTION: This study examines the effects of *Sauropus androgynus* on cognitive function, Bax expression, and neuronal number in the hippocampus and prefrontal cortex of rats induced by Trimethyltin chloride (TMT). TMT is a compound utilized to induce neurotoxicity. **MATERIALS AND METHODS:** This is an experimental study. Twenty-five male *Rattus norvegicus* were divided into five groups: Group 1, no treatment (G1); Group 2, TMT-induced (G2); and Groups 3, 4, and 5, TMT-induced with ethanol extract of *S. androgynus* at doses of 75, 150, and 300 mg/kg body weight, respectively (G3, G4, and G5). The TMT is at a dose of 6 mg/kg body weight. The cognitive function of rats was measured by using the Y-maze spontaneous alternation test. Brain tissues of killed rats were collected for histological preparations using toluidine blue staining and immunohistochemistry with Bax antibody. Microscopic observations were performed to count the number of neurons and Bax expression. **RESULTS:** The percentage of alternation in the *S. androgynus* extract groups (G3, G4, G5) was higher than in the TMT group (G2). The number of neurons in the CA1 area of the hippocampus, dentate gyrus, and prefrontal cortex in the three groups (G3, G4, and G5) was higher than in group G2. The expression of Bax in groups G4 and G5 was lower than that in group G2. Different doses of 75, 150, and 300 mg/kg body weight did not provide significant differences in the percentage of alternation and the number of neurons. **CONCLUSION:** The *S. androgynus* extract could improve memory function, inhibit Bax expression, and increase the number of neurons in the CA1 area of the hippocampus, dentate gyrus, and prefrontal cortex in rats induced with neurotoxicity using TMT.

Keywords:

Sauropus androgynus, Trimethyltin, memory, hippocampus, prefrontal cortex.

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INTRODUCTION

Sauropus androgynus is a tropical plant known for its edible leaves and medicinal properties in Indonesia. It contains various phytochemical compounds, including vitamin C, which enhance its antioxidant capabilities.^{1,2} *S. androgynus* is rich in bioactive substances such as sterols, saponins, alkaloids, terpenoids, phenols, tannins, flavonoids, and catechol. Traditionally, it has been used to boost lactation, treat diabetes and diabetic ulcers, and manage obesity.^{2,3,4} Case reports have documented successful recoveries from heart stroke induced by ischaemic stroke using *S. androgynus*-based traditional therapies without serious complications.⁵

This study investigates the effects of *S. androgynus* on cognitive function, neuron counts in the hippocampus and prefrontal cortex, and Bax expression in rats induced with neurotoxicity using trimethyltin (TMT). TMT is a toxic compound used to induce neurodegeneration, causing extensive damage across various brain regions, including the hippocampus, olfactory area, cerebellum, pons, mammillary nucleus, and others.^{6,7} Rats treated with intraperitoneal TMT exhibited impaired learning and memory, increased aggressive behavior, and hyperactivity.⁸ TMT administration reduces acetylcholine levels, impacting cognitive function, similarly seen in Alzheimer's

disease.⁹ TMT alters biomarkers linked to memory formation, including cAMP response element-binding protein (CREB), protein kinase C (PKC), neuronal nuclear protein (NeuN), nerve growth factor (NGF), and ionized calcium-binding adaptor molecule 1 (IBA1) within the hippocampus.¹⁰

TMT can help impair memory function and decrease the number of neurons in the hippocampus's CA1, CA3, and dentate gyrus areas.^{11,12} TMT can cause pathological changes in the dentate gyrus and lead to an increase in necrotic neurons. Administering TMT at a dose of 6 mg/kg body weight to rats can result in brain damage characterised by necrosis and cell death in the hippocampal region, accompanied by heightened activity of glial cells. TMT-induced neurotoxicity in the brain is linked to mitochondrial dysfunction, affecting Na⁺/K⁺ ATPase function in cell membranes, disrupting adenosine triphosphate (ATP) synthesis, and triggering neuroinflammation. This inflammation is marked by significant activation of glial cells and the production of proinflammatory cytokines, contributing to neurodegenerative damage.^{13,14}

The toxic effects of TMT in the brain involve elevated calcium levels, excitotoxicity, mitochondrial dysfunction, oxidative stress, and neuroinflammation processes. Increased oxidative stress produces reactive oxygen species (ROS), which can damage mitochondria by causing swelling, reducing mitochondrial membrane potential, and activating pathways that initiate apoptosis. Elevated ROS levels affect apoptosis-related proteins like Bcl-2, BAX, and caspase-3.^{15,16} TMT administration could lead to increased expression of caspase 3, oxidative stress, elevated calcium levels, and mitochondrial damage, especially in the CA1 area of the hippocampus, resulting in a decrease in the number of neurons.¹⁷ This compound can induce cytotoxicity, evidenced by a lower ratio of phosphorylated Akt (p-Akt)/Akt compared to controls. Akt commonly promotes cell survival by phosphorylating proteins such as glycogen synthase kinase-3 α (GSK-3 α), BAD, and caspase 9. TMT can also upregulate BAX expression, leading to increased mitochondrial permeability, release of cytochrome c, and activation of the caspase cascade, ultimately leading to

apoptosis.⁹ Moreover, TMT can enhance microglial activation, increasing proinflammatory cytokines such as Tumor Necrosis Factor alpha (TNF α), interleukin-1 β (IL-1 β), and Interleukin (IL-6). It also elevates mRNA levels of pro-inflammatory microglial markers like TNF α , IL-1 β , IL-6, and nitric-oxide synthase-2 (NOS2). Additionally, TMT may reduce cholinergic immunoreactivity (ChAT, AChE), brain-derived neurotrophic factor (BDNF), and cAMP-response element-binding protein (CREB) in the hippocampus, affecting choline acetyltransferase (ChAT) and acetylcholinesterase (AChE).⁸

MATERIALS AND METHODS

This experimental study was conducted using a post-test-only group design. It was approved by the Ethics Committee of the Faculty of Medicine, Universitas Islam Indonesia. The experimental animals used consisted of 25 male rats of *Rattus norvegicus* (Wistar strain), aged 2-3 months. They were divided into five groups: Group 1, no treatment (G1); Group 2, TMT-induced (G2); and Groups 3, 4, and 5, induced with TMT and administered with ethanol extract of SA at doses of 75, 150, and 300 mg/kg body weight, respectively (G3, G4, G5).

Ethanol Extract of *Sauropus androgynus*

S. androgynus leaf simplicia was obtained from local farmers in Tegalyasan Farm, Tegalarum Village, Sempu District, Banyuwangi Regency, East Java Province, Indonesia. The leaves of *S. androgynus* were extracted using a maceration technique. The leaves were dried under sunlight until thoroughly dehydrated and completely dry. Next, the dried leaves were made into powder. Subsequently, the powder was mixed with 96% ethanol in a ratio of 1:10. The mixture was soaked for 72 hours and stirred every 24 hours. The mixture was filtered using filter paper. Next, a rotatory vacuum evaporator and a water bath evaporator were utilized to concentrate the filtrate at approximately 60 degrees Celsius until the extract concentration was 100%.¹⁸

Intervention of Ethanol Extract of *S. androgynus* and Induction of TMT

The rats were housed in cages measuring 40 cm x 45 cm x 15 cm, with one rat per cage. The cages were maintained

at room temperature between 24-26 degrees Celsius and with a 12-hour light-dark cycle. The light cycle began at 6 am, while the dark cycle started at 6 pm. Food and water were provided ad libitum. TMT (Sigma-Aldrich) was administered via intraperitoneal injection at a dose of 6 mg/kg body weight on the first day of the study. Rats in groups G1 and G2 were injected with normal saline. Meanwhile, groups 3, 4, and 5 (G3, G4, and G5) were treated with the ethanol extract of *S. androgynus* leaves using a probe daily for 28 days.

The Measurement of Cognitive Function

The cognitive function of the rats was assessed using the Y-maze spontaneous alternation test. The spontaneous alternation referred to the number of rats entering the arms of the Y-maze within 8 minutes, with the condition that all four legs enter the arms of the Y-maze. Next, the researchers calculated the percentage of alternation by using a formula: $\text{Alternation\%} = \frac{\text{Number of Alternations}}{(\text{Total number of arm entries} - 2)} \times 100$.¹⁹

In this study, the Y-maze test was conducted on the 28th day. It measured 50 cm x 10 cm x 20 cm and was placed in a closed room. Before assessment, the rats were acclimatized to the experimental room for 30 minutes. Then, the experiment was conducted on the Y-maze using the spontaneous alternation method to assess their spatial working memory. The researchers recorded and placed the Wistar rats at label A, facing towards the center, allowing them to explore the sides of the Y-maze for 8 minutes. After 8 minutes, the rats were returned to their respective cages. The researchers calculated the percentage of alternation by using the formula: $\text{Alternation \%} = \frac{\text{Number of Alternations}}{(\text{Total number of arm entries} - 2)} \times 100$.¹⁸

Necropsy and Histological Preparation

On the 29th day, the rats were anesthetized with Tiletamine + Zolazepam (Zoletil™) via intramuscular injection, followed by transcardial perfusion. Transcardial perfusion was done by inserting sodium chloride fluid through the heart to flush and cleanse the blood from the tissues. The brain tissue was then taken and fixed for 24 hours using a 10% neutral buffered formalin solution.

The brain tissue was embedded in paraffin blocks and sectioned using a microtome with a thickness of 3 μm. The brain tissue sections were stained with Toluidine Blue (TB) and immunohistochemical staining with Bax antibody.

Observation of histopathological specimens

Observation of histopathological specimens to count the number of neurons and Bax expression was conducted using a light microscope connected to a camera, with a magnification of 400x across the entire field of view. The observations were performed in all CA1 hippocampus, dentate gyrus, and prefrontal cortex areas. The number of neurons was counted by observing the entire CA 1 area of the hippocampus, dentate gyrus, and prefrontal cortex. Next, the average number of neurons from that area was calculated for each research subject (rat).

Data Analysis

A One-Way ANOVA statistical analysis was performed to determine the difference in the alternation percentage and mean number of neurons.

RESULTS

Figures 1, 2, and 3 illustrate these findings of the study, including the percentage of alternation, counts of CA1 neurons in the hippocampus, dentate gyrus, and prefrontal cortex, and BAX expression.

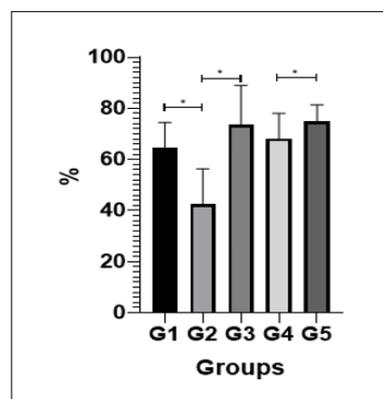


Figure 1. Alternation percentage G1: Group without TMT induction. G2: Group with TMT induction. G3, G4, and G5: Groups with TMT induction and administration of ethanol extract of SA leaves at doses of 75, 150, and 300 mg/kg body weight per day, respectively.

*significant difference between G1 and G2 (indicate as p=0.046), G2 and G3 (indicate as p=0.003), G2 and G4(indicate as p= 0.016), G2 and G5(indicate as p=0.002)

The difference in *S. androgynus* doses of 75, 150, and 300 mg/mg/kg body weight did not show significant differences in the Alternation percentage. No significant difference between G3 and G4 (indicated as $p=0.944$), G3 and G5 (indicated as $p=1.000$), and G4 and G5 (indicated as $p=0.887$).

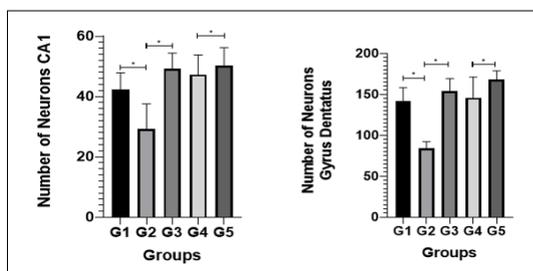


Figure 2. Number of hippocampal neuron and dentate gyrus neuron. G1: Group without TMT induction. G2: Group with TMT induction. G3, G4, and G5: Groups with TMT induction and administration of ethanol extract of SA leaves at doses of 75, 150, and 300 mg/kg body weight per day, respectively. *significant difference in the number of hippocampal neurons between G1 and G2 (indicate as $p=0.039$), G2 and G3 (indicate as $p=0.01$), G2 and G4 (indicate as $p=0.002$), G2 and G5 (indicate as $p=0.000$). *significant difference in the number of dentate gyrus neurons between G1 and G2 (indicate as $p=0.000$), G2 and G3 (indicate as $p=0.000$), G2 and G4 (indicate as $p=0.000$), G2 and G5 (indicate as $p=0.000$).

The difference in *S. androgynus* doses of 75, 150, and 300 mg/mg/kg body weight did not show significant differences in the number of hippocampal neurons. No significant difference between G3 and G4 (indicated as $p=1.000$), G3 and G5 (indicated as $p=1.000$), and G4 and G5 (indicated as $p=1.000$). The difference in *S. androgynus* doses of 75, 150, and 300 mg/mg/kg body weight did not show significant differences in the number of dentate gyrus neurons. No significant difference between G3 and G4 (indicated as $p=1.000$), G3 and G5 (indicated as $p=1.000$), and G4 and G5 (indicated as $p=0.422$).

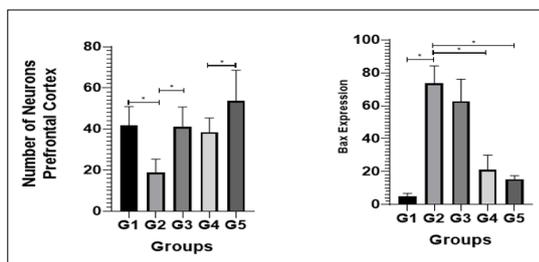


Figure 3. Number of Neuron in the prefrontal cortex and BAX expression. G1: Group without TMT induction. G2: Group with TMT induction. G3, G4, and G5: Groups with TMT induction and administration of ethanol extract of SA leaves at doses of 75, 150, and 300 mg/kg body weight per day, respectively. *significant difference in the number of neurons in the prefrontal cortex between G1 and G2 (indicate as $p=0.014$), G2 and G3 (indicate as $p=0.019$), G2 and G4 (indicate as $p=0.049$), G2 and G5 (indicate as $p=0.000$). *significant difference in BAX expression between G1 and G2 (indicate as $p=0.000$), G2 and G4 (indicate as $p=0.000$), G2 and G5 (indicate as $p=0.000$).

The difference in *S. androgynus* doses of 75, 150, and 300 mg/mg/kg body weight did not show significant differences in the number of prefrontal cortex neurons. No significant difference between G3 and G4 (indicated as $p=1.000$), G3 and G5 (indicated as $p=0.549$), and G4 and G5 (indicated as $p=0.236$). *S. androgynus* doses of 150 and 300 mg/mg/kg body weight did not show significant differences in the Bax expression (indicated as $p=1.000$). *S. androgynus* doses of 75 mg/mg/kg body weight cannot reduce BAX expression. No significant differences in BAX expression between G2 and G3 (indicated as $p=0.5999$).

DISCUSSION AND CONCLUSION

Extract from *S. androgynus* enhances memory function. The study observed higher alternation percentages in groups G3, G4, and G5 treated with *S. androgynus* extract compared to group G2 treated with trimethyltin alone. Significant differences in alternation percentage were noted between group G2 and groups G3 (indicate as $p=0.003$), G2 and G4 (indicate as $p=0.016$), G2 and G5 (indicate as $p=0.002$). These findings suggest that cognitive function was better in the trimethyltin-induced group treated with *S. androgynus* extract at doses of 75, 150, and 300 mg/kg body weight per day (G3, G4 and G5) compared to the group induced with trimethyltin only (G2). There was no significant difference between G3, G4, and G5. This shows that the difference in *S. androgynus* doses has no effect on improving cognitive function. A *S. androgynus* dose of 75 mg/kg body weight per day can improve cognitive function due to trimethyltin exposure.

A previous study supports these results, indicating that *Sauropus androgynus* leaf extract, administered at 150 mg/kg and 300 mg/kg, improves cognitive function in rat models of Alzheimer's disease by reducing β -amyloid plaques in the hippocampus.¹⁸ The ethanol extract of *S. androgynus* leaves contains flavonoids and steroids, which may mitigate neuroinflammation, decrease β -amyloid production, and enhance insulin sensitivity, positively influencing memory.¹

S. androgynus extract mitigates neuronal loss and reduces BAX expression.

The number of neurons in the hippocampus, dentate gyrus, and prefrontal cortex was higher in the groups treated with both trimethyltin and *S. androgynus* (G3, G4, and G5) compared to the group treated with trimethyltin only (G2). Significant differences in the number of CA1 hippocampal neurons between G1 and G2 (indicated as $p=0.039$), G2 and G3 (indicated as $p=0.001$), G2 and G4 (indicated as $p=0.002$), and G2 and G5 (indicated as $p=0.000$) were seen. Significant differences in the number of dentate gyrus neurons between G1 and G2 (indicated as $p=0.000$), G2 and G3 (indicated as $p=0.000$), G2 and G4 (indicated as $p=0.000$), G2 and G5 (indicated as $p=0.000$) were seen. Significant differences in the number of neurons in the prefrontal cortex between G1 and G2 (indicated as $p=0.014$), G2 and G3 (indicated as $p=0.019$), G2 and G4 (indicated as $p=0.049$), and G2 and G5 (indicated as $p=0.000$) were seen. This study suggests that *S. androgynus* extract administration at doses of 75, 150, and 300 mg/kg body weight per day may prevent neuronal loss caused by TMT exposure. Additionally, BAX expression was significantly lower in groups G4 and G5 compared to group G2. Significant difference in BAX expression between G2 and G4 (indicated as $p=0.000$), G2 and G5 (indicated as $p=0.000$). This study implies that *S. androgynus* extract administration at doses of 150 and 300 mg/kg body weight per day inhibited pro-apoptotic protein BAX expression induced by TMT exposure.

No significant difference in the number of neurons in the hippocampus, dentate gyrus, and prefrontal cortex between G3, G4, and G5. This shows that the difference in *S. androgynus* doses does not inhibit neuronal loss. *S. androgynus* dose of 75 mg/kg body weight per day can inhibit neuronal loss due to trimethyltin exposure. No significant difference in the Bax expression between G4 and G5. *S. androgynus* doses of 150 and 300 mg/kg body weight per day can inhibit Bax expression due to trimethyltin exposure. *S. androgynus* dose of 75 mg/kg body weight per day cannot inhibit BAX expression due to trimethyltin exposure. Researchers found no side effects at higher doses (300 mg/kg body weight per day). *S. androgynus* dose of 300 mg/kg body weight per day is safe to use.

According to phytochemical analysis, *S. androgynus* (SA) leaf extract contains alkaloids, flavonoids, saponins, polyphenols, quinone, monoterpene, and sesquiterpene.²⁰ Flavonoids identified include catechin, rutin, myricetin, quercetin, apigenin, and kaempferol.²¹ Previous studies investigating the antioxidant properties of SA, using rats induced with sodium nitrite, demonstrated its ability to reduce malondialdehyde (MDA) levels, indicating antioxidant potential.²² The antioxidants present in *S. androgynus* include vitamin C and flavonoids, particularly kaempferol and quercetin.¹ Studies suggest that β -carotene, tocopherols, and ascorbic acid may also mitigate oxidative stress.²³

Vitamin C plays a role in myelination during both the initial development of nerves and their recovery following injury.²⁴ In rat models of neurodegeneration, giving vitamin C (ascorbic acid) improved cognitive function and enhanced cellular proliferation, neuronal differentiation, and maturation. Vitamin C also prevented the decline in protein expression related to neuroplasticity in the hippocampus, including synaptophysin, phosphorylated Ca^{2+} /calmodulin-dependent protein kinase II, and brain-derived neurotrophic factor (BDNF).²⁵ Additionally, it prevented the decline in Purkinje cell count and the decrease in osteopontin expression in the cerebellum caused by exposure to lead. Osteopontin is a protein crucial for axonal myelination and neuron development.²⁶

Intake of *S. androgynus* may elevate vitamin E levels in the liver and boost coenzyme Q10 (CoQ10). CoQ10, also known as ubiquinol in its reduced form, is a potent lipophilic antioxidant that can regenerate other antioxidants such as tocopherol and ascorbate.²⁷ Vitamin E, known for its antioxidant, anti-inflammatory, and neuroprotective properties crucial for brain health, has been shown to benefit Alzheimer's therapy.²⁸ Vitamin E may help inhibit neurodegeneration in the brain by reducing the number and activity of microglia in cortical areas.²⁹ High levels of γ -tocopherol in the brain have been linked to presynaptic proteins in mid-frontal brain regions, suggesting that vitamin E may help maintain presynaptic protein levels.³⁰

S. androgynus contains the flavonoid quercetin. The antioxidant effect of quercetin operates through several mechanisms, including increasing glutathione (GSH) synthesis, regulating antioxidant enzyme activity, modulating signal transduction pathways, and inhibiting reactive oxygen species (ROS) production.³¹ Studies in rat models of hypoxia have demonstrated that quercetin administration increases levels of GSH, glutathione reductase (GR), glutathione-S-transferase (GST), glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase (CAT) while decreasing malondialdehyde (MDA) concentrations.³² Quercetin has been found to exhibit neuroprotective effects by inhibiting proinflammatory cytokines like NF- κ B and iNOS, enhancing motor function, preventing synuclein fibrillization, preserving neurons in the hippocampus, and promoting neuroplasticity. It also shows potential in inhibiting β -amyloidosis, improving cognitive and emotional function, and reducing tauopathies, astrogliosis, and microgliosis in the hippocampus and amygdala.³³ In elderly adults aged 65-75, quercetin may inhibit the decline in cerebral blood flow and reduce the accumulation of amyloid β (A β).³⁴ Additionally, in rat models induced with neurotoxicity using Lipopolysaccharide (LPS), quercetin has been observed to inhibit gliosis and neuroinflammation in the cortex and hippocampus, suppress the apoptosis pathway in mitochondria, hinder neurodegeneration, improve memory function, and preserve synapses in these brain regions.³⁵

S. androgynus contains the flavonoid kaempferol, demonstrating neuroprotective effects on striatal neurons in rat models induced with neurotoxicity via LPS. Its mechanisms of neuroprotection include suppressing neuroinflammation and preserving the integrity of the blood-brain barrier (BBB). Kaempferol has been observed to increase levels of tyrosine hydroxylase (TH) and postsynaptic density protein 95 (PSD95) in the rat striatum. Additionally, it inhibits the production of proinflammatory cytokines such as interleukin 1 β (IL-1 β), interleukin 6 (IL-6), and tumor necrosis factor α (TNF- α). It reduces levels of monocyte chemoattractant protein-1 (MCP-1), intercellular cell adhesion molecule-1 (ICAM-1), and cyclooxygenase-2 (COX-2) in the striatum.³⁶ In a rat

model of cerebral ischemia/reperfusion (I/R) injury, kaempferol administration improved neurological deficits, reduced infarct volume and brain water content, and inhibited cell apoptosis.^{37,38} It also modulated protein expressions related to apoptosis, increasing anti-apoptotic Bcl-2 and Akt phosphorylation while decreasing pro-apoptotic Bax and P53 in the hippocampus and cortex.³⁷ Kaempferol enhanced neuron arrangement, distribution, and morphology, and inhibited neuronal apoptosis in this injury model. Furthermore, it exhibited antioxidant effects by increasing superoxide dismutase (SOD) and glutathione (GSH) activity while decreasing malondialdehyde (MDA) levels in serum and brain tissue.³⁸ In rat models of traumatic brain injury (TBI), kaempferol administration improved sensorimotor behavior, preserved mitochondrial function, prevented degeneration of dopaminergic neurons in Parkinson's models by inhibiting lipid peroxidation, mitigating mitochondrial damage, and enhancing lipophagy. It also inhibited motor dysfunction and increased dopamine levels in the striatum.³⁹ In SH-SY5Y cell culture models induced with apoptosis, kaempferol inhibited cell apoptosis by reducing Bax expression, increasing Bcl-2 expression, and decreasing caspase-3 expression.⁴⁰

LIMITATIONS OF THE STUDY

The reduction in cell number can be caused by apoptosis. Apoptosis can be assessed from the increase in BAX and caspase-3 expression or the TUNEL assay. This study only assessed BAX expression. Further studies can assess BAX expression, Bcl2 expression, BAX/bcl2 ratio, caspase-3 expression, and TUNEL assay. The hippocampus includes the CA1, CA2, CA3, and dentate gyrus areas. In this study, only the CA1 area of the hippocampus and the dentate gyrus were examined, while the CA2 and CA3 areas were not evaluated. Further studies can assess the entire hippocampus area. This study has not evaluated the toxicity of *S. androgynus*. Further studies can assess the toxicity of *S. androgynus*.

CONCLUSION

Sauropus androgynus at doses of 75, 150, and 300 mg/kg body weight per day improves cognitive function and increases the number of neurons in the CA1

hippocampus, dentate gyrus, and prefrontal cortex of rats induced neurotoxicity using TMT. *S. androgynus* dose difference did not affect the increase in the number of neurons. *S. androgynus* at doses of 150 and 300 mg/kg body weight per day inhibits Bax expression. *S. androgynus* dose difference of 150 and 300 mg/kg body weight per day did not inhibit Bax expression. *S. androgynus* at 75 mg/kg body weight doses cannot inhibit Bax expression.

CONFLICT OF INTEREST

There is no conflict of interest in this study.

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Spatial and Temporal Intensity of HFMD Cases in Pulau Pinang, Malaysia between 2017 and 2022

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ABSTRACT

INTRODUCTION: Hand, foot and mouth disease (HFMD) remains a significant public health concern in Malaysia, persisting despite existing control measures. This study aimed to assess the spatial and temporal dynamics of HFMD in Pulau Pinang, a north-western state of Malaysia. **MATERIALS AND METHODS:** Data were retrieved from the Communicable Diseases Control Information System (CDCIS) E-Notification Version 2011, including all notified HFMD cases in Pulau Pinang from 2017 to 2022. The number of cases by district was estimated using the points-in-polygons function in the sf package in RStudio. Kernel Density Estimates (KDE) were used to assess spatial intensity, while spatial clustering was evaluated using the nearest neighbor index (NNI). **Results:** A total of 15 586 notified HFMD cases reported in Pulau Pinang between 2017 -2022. Temporally, the spatial intensity of cases fluctuated, with a peak in 2018, followed by a marked decline in 2020 and 2021 and a resurgence in 2022. Spatially, the highest intensity of infections was consistently observed in the district of Timur Laut, particularly in urban subdistricts such as Bandar Georgetown and Mukim 13 (Paya Terubong). Over time, high-intensity areas expanded to include Barat Daya and parts of Seberang Perai, including Mukim 12 (Bayan Lepas) and central areas of Seberang Perai Tengah, Utara, and Selatan. Evidence of significant spatial clustering was detected across all years based on nearest neighbor index values (NNI: 0.21–0.50). **CONCLUSION:** HFMD cases in Pulau Pinang showed marked spatial clustering and shifting intensity patterns, especially in densely populated and newly developed areas. These findings highlighted the need for targeted, locality-specific prevention strategies to curb HFMD transmission.

Keywords:

HFMD, Spatial Analysis, Spatial Intensity, Malaysia

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INTRODUCTION

Hand, foot, and mouth disease (HFMD) is a common infectious disease in childhood caused by various enteroviruses.¹ Patients typically presented with fever, malaise, rashes, skin eruptions on the hands and feet, and vesicles in the mouth which are usually mild and self-limiting.² However, few infected children develop systemic complications including neurological and cardiorespiratory complications, and even death.³

In the last decades, HFMD infections have widely spread in Asian region with multiple major outbreaks reported.⁴⁻⁶ Apart from clinical treatment given to the patient, various

public health measures such as isolation of infected children, school closure and social distancing implemented as response towards large HFMD outbreak.⁷ Several countries develop surveillance system to continuously monitoring the trend of HFMD infections locally.^{4,8,9} Despite careful attention given to distribution of HFMD infections, the incidence of HFMD continue to rise particularly in Western Pacific Region including Malaysia.¹⁰

According to report published in 2016, large outbreaks in Malaysia tend to occur in cyclical pattern for every 2 to 3

years.¹¹ This has necessitated improvement to the existing surveillance system towards HFMD infections. The application of spatial and temporal analysis can assist public health authorities to differentiate intensity of infections between different geographical areas.¹² However, there has been a lack of studies that analyze the geographical distribution and temporal trend of HFMD in Malaysia. This knowledge gap may lead to delayed responses and impacting the overall management of HFMD outbreaks. This study aimed to analyze the spatial and temporal intensity of HFMD infections in Pulau Pinang, Malaysia.

MATERIALS AND METHODS

Study Area

The study was conducted in Pulau Pinang, Malaysia. Pulau Pinang located at Northwest part of Malaysian Peninsula between 5 8' and 5 35' in latitude and between 100 8' and 100 32' in longitude. The state comprises two halves: Penang Island, where the capital city of George Town is located; and a strip of land on the peninsula, named Seberang Perai. The estimated population in Pulau Pinang is about 1,740,405 individuals.¹³ Pulau Pinang has 5 administrative districts where 2 districts are located in Penang Island (Timur Laut and Barat Daya) and the other 3 districts in Seberang Perai (Northern, Middle and Southern Seberang Perai) (Figure 1). The ethnic composition in Pulau Pinang shows that 42% are of Malay and Chinese, 9% are of Indian and 0.6% are of other races. About 13% or 225 000 of the whole population are children under the age of 10 years.

Data Source

This study was a state-wide retrospective secondary data review involving 6 years of quantitative data from 2017 to 2022. Data were obtained from national electronic communicable disease notification system known as Communicable Diseases Control Information System (CDCIS) E-Notification Version 2011. It contained variables from age, age group, gender and ethnicity for each notified HFMD case. The data of geographical location of the notified cases was captured in WGS 84 coordinate reference system (CRS). The CRS were then converted into the projected coordinate system, the

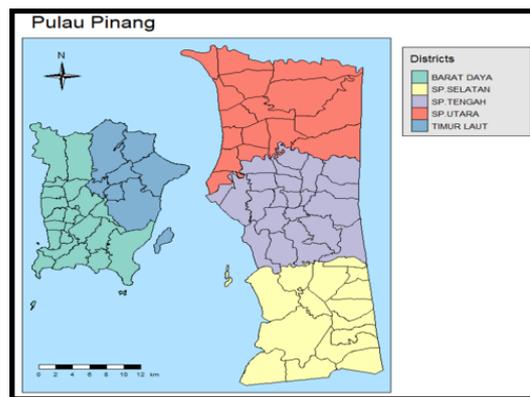


Figure 1 Map of Pulau Pinang, Malaysia, showing the five administrative districts: Barat Daya, Seberang Perai Selatan (SP Selatan), Seberang Perai Tengah (SP Tengah), Seberang Perai Utara (SP Utara), and Timur Laut

Kertau Rectified Skewed Orthomorphic (RSO) Malaya (EPSG:3168). Census tract data contain the variables for yearly population census for state, district and subdistrict of Pulau Pinang were obtained for comparison and analysis purposes.

Data Analysis

The coordinates of each notified HFMD cases were entered to R-Software for data cleaning and analysis using *sf package*.¹⁴ Spatial point distribution was performed to show distribution of notified HFMD cases in Pulau Pinang. Each point will represent geographical coordinates projected in RSO format for each notified HFMD cases. Subsequently, a series of spatial point maps indicating the yearly distribution of data point data from 2017 until 2022 were projected using *tmap package* in R-software version 4.2.3.¹⁴

Kernel Density Estimates (KDE) was one of the density-based approach (first-order effect) in spatial point pattern analysis.¹⁵ KDE refers to the probability density function that follow this equation.

$$\hat{f}(x) = \hat{f}(x, y) = \frac{1}{nh_x h_y} \sum_i k \left[\frac{x - x_i}{h_x}, \frac{y - y_i}{h_y} \right]$$

Where, (x,y)- projected coordinate reference system of HFMD cases using Kertau RSO/RSO Malaya (m) or EPSG:3168 as the coordinate reference system.

hx and hy: referred as the fixed bandwidths in the x and y direction.

KDE functions were used to estimate the intensity of HFMD infections in Pulau Pinang according to specific bandwidths. In this study, the bandwidths smoothing was adjusted to 2 Kilometers radius giving better visualization of the kernel smoothing effect. KDE analysis was performed using spstatat package in R-software 4.2.3 and the outcomes of the analysis were visualized using series of maps representing spatial intensity of HFMD infections in Pulau Pinang.¹⁶ The sequential Kernel maps were produced according to KDE analysis were plotted using raster package in R-software.¹⁴

Next, we used the point pattern analysis to examine the spatial spread (clustered, dispersed, or random) based on the Nearest Neighbour Index (NNI) analysis.¹⁷ The NNI measures the spatial distribution from zero (clustered pattern) to one (randomly dispersed pattern) to 2.15 (regularly dispersed/uniform pattern).¹⁸ NNI value interpretations are as follows, where NNI close to 1.0 indicates random pattern, while NNI value of less than 1.0 suggests clustering. In contrast, NNI value of larger than 1.0 suggests a dispersion pattern.¹⁹

We identified yearly cumulative NNI for HFMD infections from 2017-2022 with p-value less than 0.05 to be significant. Package spatialeco in R-software 4.2.3 was used for this analysis.²⁰

RESULTS

There was a total of 15,586 cases of HFMD in Pulau Pinang notified to CDCIS between 2017 until 2022. Table 1 provides information on the characteristics of HFMD infections in Pulau Pinang according to age, age group, gender, ethnicity, and administrative districts. The mean age of infections was 3.5 years and the majority of the infections (83%) occurred among preschool-aged children (0-4 years), followed by children aged 5-10 years (14%) and those older

than 10 years (2.9%). Male children accounted for 54% of the overall cases, while the remaining 46% were female children. Among the ethnic groups, most of the infections occurred among the Malay ethnicity (65%), followed by the Chinese ethnicity (29%), and other ethnicities (6%)

Table 1 Characteristic of Notified HFMD Infections in Pulau Pinang, 2017-2022 (N=15 586)

Characteristic	2017, n=1,378	2018, n=4,793	2019, n=2,752	2020, n=534	2021, n=205	2022, n=5,924	Overall, N=15,586
Age	3.11 (2.51)	3.42 (2.74)	3.15 (2.43)	2.93 (2.56)	2.24 (1.69)	4.00 (1.32)	3.53 (2.21)
Age Group							
0-4	1,202 (87%)	3,930 (82%)	2,379 (86%)	464 (87%)	197 (96%)	4,774 (81%)	12,946 (83%)
5-10	152 (11%)	726 (15%)	325 (12%)	60 (11%)	6 (2.9%)	918 (15%)	2,187 (14%)
>10	24 (1.7%)	137 (2.9%)	48 (1.7%)	10 (1.9%)	2 (1.0%)	232 (3.9%)	453 (2.9%)
GENDER							
Female	612 (44%)	2,184 (46%)	1,269 (46%)	243 (46%)	86 (42%)	2,699 (46%)	7,093 (46%)
Male	766 (56%)	2,609 (54%)	1,483 (54%)	291 (54%)	119 (58%)	3,225 (54%)	8,493 (54%)
ETHNICITY							
Chinese	726 (53%)	1,710 (36%)	1,223 (44%)	134 (25%)	17 (8.3%)	772 (13%)	4,582 (29%)
India	96 (7.0%)	228 (4.8%)	134 (4.9%)	22 (4.1%)	2 (1.0%)	182 (3.1%)	664 (4.3%)
Malay	542 (39%)	2,768 (58%)	1,365 (50%)	375 (70%)	186 (91%)	4,924 (83%)	10,160 (65%)
Non-Malaysian	9 (0.7%)	54 (1.1%)	11 (0.4%)	1 (0.2%)	0 (0%)	30 (0.5%)	105 (0.7%)
Others	5 (0.4%)	33 (0.7%)	19 (0.7%)	2 (0.4%)	0 (0%)	16 (0.3%)	75 (0.5%)
DISTRICT							
Barat Daya	177 (13%)	1,074 (22%)	621 (23%)	115 (22%)	63 (31%)	1,339 (23%)	3,389 (22%)
S.Perai Selatan	219 (16%)	780 (16%)	345 (13%)	49 (9.2%)	21 (10%)	784 (13%)	2,198 (14%)
S.Perai Tengah	214 (16%)	710 (15%)	374 (14%)	123 (23%)	63 (31%)	1,253 (21%)	2,737 (18%)
S.Perai Utara	58 (4.2%)	353 (7.4%)	368 (13%)	84 (16%)	14 (6.8%)	1,165 (20%)	2,042 (13%)
Timur Laut	710 (52%)	1,876 (39%)	1,044 (38%)	163 (31%)	44 (21%)	1,383 (23%)	5,220 (33%)

Mean (SD); n (%)

The trend of HFMD in Pulau Pinang follows an annual cyclical pattern, except for the years 2020 and 2021 as shown in Figure 2. The yearly cases exhibited a bimodal distribution with the first and taller peak usually starting in April and lasting until July or August, while the second and lower peak starting in November and lasting until December or January of the following year. The highest peak of HFMD cases was recorded in 2022, followed by 2018. However, the trend of HFMD cases dramatically reduced during the pandemic period of COVID-19 in 2020 and 2021.

Mean (SD); n (%)

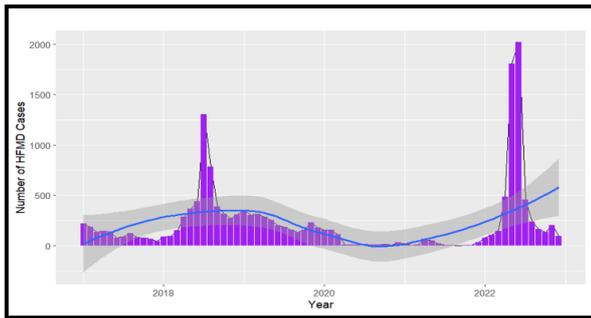


Figure 2 Trend of Notified HFMD Infections in Pulau Pinang between 2017-2022
Spatial and Temporal Intensity of HFMD infections between 2017-2022 estimated by
Kerned Density Estimates (KDE) approach

The spatial intensity of notified HFMD infections in Pulau Pinang was mapped using KDE functions with a bandwidth of 2 km (Figure 3).

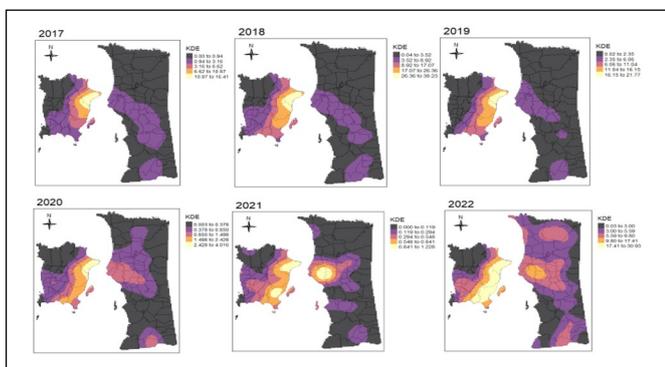


Figure 3 Spatial and Temporal Intensity of Notified HFMD Infections in Pulau Pinang
between 2017-2022

The KDE values (cases per km²) exhibited fluctuations from 2017 to 2019, with the highest recorded value in 2018. However, the values were significantly reduced in 2020 and 2021, which could be attributed to the implementation of COVID-19 pandemic lockdown measures. The spatial intensity of infections mainly concentrated in the Penang Island area, specifically in Subdistrict Bandar Georgetown and Mukim 13 (Paya Terubong). The areas with high spatial intensity also extended to the industrial settlement areas of Subdistrict Mukim 12 (Bayan Lepas) between 2017 and 2019. In 2022, prominent spatial intensity was observed central areas of Seberang Perai Tengah, Seberang Perai Utara and Seberang Perai Selatan area, along with higher KDE values (cases per km²).

Nearest Neighboring Index (NNI)

The study observed a clustering pattern in the HFMD cases over the study period, with NNI values ranging from 0.20 to 0.51 (Table 2). A smaller value of NNI

Table 2 Nearest Neighboring Index (NNI) of Notified HFMD Infections in Pulau Pinang

Year	n	Mean Distance		NNI	z score	p-value*
		Observed	Expected			
2017	1378	163.48	503.67	0.32	-47.96	< 0.001
2018	4793	63.45	279.62	0.22	-102.39	< 0.001
2019	2752	99.2	637.85	0.26	-73.28	< 0.001
2020	534	342.68	794.17	0.43	-25.13	< 0.001
2021	205	635.01	1225.33	0.51	-13.19	< 0.001
2022	5924	50.63	252.08	0.20	-117.66	< 0.001

*p-value for Nearest Neighboring Index (NNI)

indicates a more significant clustering of cases. For instance, in 2022, the NNI value was 0.20 (p-value <0.001), which suggests that the cases were clustered, with an observed average distance of approximately 50.63 meters towards nearest neighboring case. Table 3 shows that the results were significant with a p-value <0.001 for every year, indicating a consistent significant cluster pattern in HFMD cases throughout the study period.

DISCUSSION

HFMD remains a significant public health concern in Pulau Pinang, particularly among young children aged 0-4 years old, who accounted for 83% of all reported cases. This finding is consistent with previous studies that have also identified young children as a high-risk group for HFMD.¹⁰ Although infants under one year old are initially protected by maternal immunity, this protection may decrease over time, making them more susceptible to new HFMD infections.²¹ In contrast, older children may have developed herd immunity through previous infections, which could explain the decrease in HFMD infections with increasing age.²² These findings highlight the need for targeted prevention and control measures, especially for young children, to reduce the burden of HFMD in Pulau Pinang.

Although the proportion of Chinese and Malay populations in Pulau Pinang was almost similar, the proportion of notified HFMD infections was higher among the Malay ethnicity (65%) compared to the Chinese ethnicity (29%). This disparity in infection rates could be due to differences in knowledge and awareness about the transmission of HFMD infections among parents from the Malay ethnic group. Recent report suggests that some parents from this group may have a lack of knowledge about the disease, including failure to

recognize clinical symptoms of HFMD at an early stage.²³

The trend of HFMD infection in Pulau Pinang shows larger peaks in 2018 and 2022. The peak in 2018 was also reported in other states in Malaysia where in cumulative more than 76 000 cases were reported nationwide during that year.¹ According to molecular analysis, the emergence of CV-A6 as co-circulating agent along with known to be aggressive EV-71 and CV-A16 were among the contributing factors towards large outbreak in 2018 including Pulau Pinang.¹ The number of notified HFMD infections dropped incredibly for 2 years in 2020 and 2021 owing to the impact of non-pharmaceutical intervention (NPI) such as school and kindergarten closure during COVID-19 pandemic which reduced risk of transmission HFMD, as well as of other infectious diseases.⁹

The gradual easing of non-pharmaceutical interventions (NPIs) that followed during the COVID-19 pandemic may have contributed to the larger number of HFMD infections observed in Pulau Pinang in 2022. Similar increases in infections after the loosening of NPIs have also been observed in other countries.^{9,24} NPIs implemented during the pandemic may have reduced exposure to the circulating agents responsible for HFMD infections. However, this may have created an immunity gap among children, leaving them more vulnerable to HFMD infections.²⁵

According to a spatial point pattern analysis using KDE analysis, the District of Timur Laut has consistently recorded higher numbers of notified HFMD infections compared to other districts in the state, with the highest density of infections observed in the urban centers of Subdistrict Bandar Georgetown and Mukim 13 (Paya Terubong). These areas are primarily urban centers with higher population densities.¹³ Similar studies conducted in Sarawak and Terengganu, Malaysia have also linked higher population density to higher numbers of HFMD infections.^{26,27} This may be due to the higher rate of transmission among children in overcrowded schools or childcare centers in urban areas.²⁸

The study also found that the clustering of HFMD infections had begun to spread to the district of Barat Daya, particularly in Subdistrict Mukim 12. Subdistrict Mukim 12 is home to major industrial areas, highly dense settlements, and major international and domestic points of entry into the state through Penang International Airport. Additionally, it has emerged as a popular place for many Penangites to stay and is easily accessible to tourists and visitors. Collectively, this has increased the population density in the area, including the number of children, and has contributed to the higher intensity of HFMD infections. A study conducted in China reported that increasing population density had 52% influence on the reported number of HFMD infections compared to other parameters.²⁸

The pattern of HFMD intensity observed in 2022 began to resemble the map of Development Priority Areas (DPA) outlined in the Penang State Structure Plan 2030.²⁹ As the urban sprawl continues and more new settlement areas emerge, the number of child care centers will also increase to cater the children of working parents within the urbanized region. However, the lack of training among staff in newly operated child care centers can reduce the effectiveness of gatekeeping strategies, leading to mingling between sick, and healthy but susceptible children, and resulting in major outbreaks.²³ Comprehensive health education including basic knowledge of prevention of infectious disease should be emphasized to every child-care center especially in new settlement areas. Local district Health Office (DHO) should have accurate information on urbanization plan within the state to anticipate potential area with higher HFMD infections and prioritization of prevention strategies.

LIMITATIONS

The current findings highlight the importance of using spatial analysis in understanding spread of HFMD infections in Pulau Pinang. However, it should be noted that our study did not include environmental parameters that may influence the spatial risk of HFMD infections across the state. Therefore, further research is needed to validate our findings on spatial intensity using additional

spatial parameters such as climate variables, to enable a more detailed spatial profiling of the disease. Incorporating such parameters could improve the accuracy and completeness of our findings and enhance our understanding of the underlying factors driving the spatial distribution of HFMD infections.

CONCLUSION

The spatial analysis revealed that the highest intensity of HFMD infections was concentrated in urban areas, specifically in Subdistrict Mukim 13 and Bandar Georgetown in the district of Timur Laut. However, temporal clustering of HFMD intensity was also observed in other areas, such as Subdistrict Mukim 12 in the district of Barat Daya, as well as urban centers in each district within the Seberang Perai area. These findings suggest that HFMD infections are spreading to new locations and settlements, raising concerns of future outbreaks if appropriate measures are not promptly implemented. It is crucial to take prompt and targeted actions to mitigate the spread of HFMD and prevent further escalation of the disease in these areas.

CONFLICT OF INTEREST

The authors disclose that they have no conflicting interests.

INSTITUTIONAL REVIEW BOARD (ETHICS COMMITTEE)

Ethical approval was obtained from the Human Research Ethics Committee of Universiti Sains Malaysia (JEPeM), USM JEPeM Code: USM/JEPeM/22110717 (Appendix A) and the National Medical Research Registry (NMRR) Ethics Initial Approval: NMRR ID-22-02848-USX (IIR) (Appendix B), Ministry of Health Malaysia. Data confidentiality was maintained at the highest possible level. Only the researchers had access to the data. Individuals' names and identification numbers were not extracted from the data.

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Development and Validation of Menstrual Disorder of Adolescent (MenDA) Questionnaire in the Malay Language

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ABSTRACT

INTRODUCTION: Menstrual disorders negatively affect adolescents' quality of life, with physical discomfort and emotional distress often contributing to anxiety. To address this, the present study aimed to develop and validate the Menstrual Disorder of Adolescent (MenDA) questionnaire for assessing adolescents' knowledge, attitudes, and practices (KAP) regarding menstrual disorders. **MATERIALS AND METHODS:** The questionnaire was systematically developed through literature review, focus group discussions, and expert consultation. Six experts assessed content validity, while face validity was tested among 46 adolescents. A cross-sectional validation study was conducted with 485 adolescents. The MenDA tool comprised three domains: knowledge (23 items), attitude (18 items), and practice (21 items). Construct validity was evaluated using exploratory factor analysis with principal component extraction and varimax rotation. Internal consistency was determined using Cronbach's alpha coefficient. **RESULTS:** The finalized MenDA questionnaire contained 62 items, structured into three domains. The knowledge domain included 23 items and demonstrated good reliability with Cronbach's alpha of 0.739. The attitude domain, comprising 18 items, showed a Cronbach's alpha of 0.711, while the practice domain, with 21 items, achieved a Cronbach's alpha of 0.793. These results confirmed satisfactory internal consistency across all domains. Factor analysis further supported construct validity, reinforcing the appropriateness of the three-domain structure in evaluating adolescents' menstrual health KAP. **CONCLUSION:** The MenDA questionnaire has demonstrated strong validity and reliability as a tool to assess knowledge, attitudes, and practices regarding menstrual disorders among Malaysian adolescents. It provides an evidence-based framework for identifying gaps and guiding interventions to improve menstrual health education and management.

Keywords

Adolescent, Menstrual disorders, Knowledge, Attitude, Practice, Validated questionnaire, Malay language

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INTRODUCTION

Menstruation is a critical milestone in female adolescence, marking reproductive maturity while also introducing potential health challenges such as menstrual disorders. The onset of menstruation or menarche represents a hallmark event in the pubertal development of the adolescent girl. It signifies the maturation of reproductive potential and physiological growth. In 95% of girls, it generally occurs approximately 2 to 3 years after the initiation of puberty, between the ages of 11 and 14 years, depending on race, ethnicity, socioeconomic status, and nutritional status.¹ A normal menstrual cycle depends on a coordinated interaction between the hypothalamus,

pituitary, ovary, and uterus. When all these organs function well, the reproductive cycle's major events will occur in their normal sequence.²

However, individuals with interrupted menstrual cycles suffer from various menstrual disturbances, such as abnormal uterine bleeding, dysmenorrhoea, and irregular cycles. A previous study showed that menstrual disorders are the most common presenting complaints in physician office visits by adolescents, and dysmenorrhoea is the main reason for school absenteeism among girls.³

Menstrual disorders not only affect individual health but also contribute to school absenteeism, reduced academic performance, and social limitations. Menstrual disorders can have an adverse effect on the quality of adolescents' lives, both physically and emotionally, and they can be a source of anxiety. Hence, early recognition and strategies to overcome these disorders will improve a young woman's health and quality of life and lower her risks for future disease and ill health.⁴

Studies have reported that up to 50-70% of adolescent girls experience dysmenorrhea, with significant consequences on their daily activities.¹⁻⁴ Several studies have been conducted worldwide to assess the prevalence and effect of menstrual disorders on adolescents by using questionnaires as research tools.¹⁻⁴ However, most of the questionnaires used have not been accessible and are less relevant to our Malaysian community. Almost all the questionnaires are also not available in Malay, which makes them difficult to use in our local community.

A knowledge, attitude, and practice survey helps assess a target group's current knowledge, attitudes, and practices on a specific health topic to identify their needs, problems, and possible barriers before developing and implementing an intervention.⁵ Therefore, this study aims to develop and validate a Malay-language questionnaire to assess knowledge, attitudes, and practices (KAP) regarding menstrual disorders among adolescents, ensuring its reliability and applicability in Malaysia.

MATERIALS AND METHODS

Development of Menstrual Disorder of Adolescents (MenDA) Questionnaire

The MenDA questionnaire, developed in Malay, comprises three sections: demographic data, student menstrual pattern, and knowledge, attitude, and practice (KAP) towards menstrual disorders among adolescents. These sections were selected based on a review of existing validated questionnaires and relevant literature, reflecting commonly used domains for assessing menstrual health in adolescents. The principal researcher facilitated structured meetings in which the domains and their features were discussed, potential items in Malay

were proposed, and the initial version of the questionnaire was finalized. Item selection was guided by literature review findings and consensus among the experts, focusing on relevance, clarity, and coverage of key concepts. Three researchers specialising in adolescent health and survey development contributed to refining the questionnaire content. A three-point Likert scale was used for the knowledge section (e.g., true, false, not sure), while a five-point Likert scale was applied to the attitude and practice sections to capture a broader range of responses. Following the initial item selection, face validity testing was conducted with adolescents to ensure that the items were understandable, culturally appropriate, and relevant to the target population.

Development of the Knowledge Section in the MenDA Questionnaire

The initial 39 items were developed on a three-point Likert-type scale based on expert recommendations and previous validated menstrual health questionnaires to ensure comprehensive coverage of key concepts. It focused on both normal and abnormal menstrual patterns. Normal patterns include cycles ranging from 21-35 days, while abnormal patterns include conditions such as heavy menstrual bleeding or irregular cycles.^{6,7} Additionally, items related to adolescent growth and development were included.⁸ A three-point scale was used to reduce response bias and allow participants to acknowledge uncertainty, which is common in adolescent knowledge assessments. Each item allowed respondents to choose between "yes," "don't know," and "no," with only one correct answer per item. Correct answers received one point, while incorrect answers received zero points. Following face validity testing and exploratory factor analysis, 16 items with low factor loadings or redundancy were removed, resulting in a final set of 23 knowledge items. Scores were categorised into low (0-12), moderate (13-18), and high (19-23) knowledge levels based on percentile distributions.

Development of the Attitude Section in the MenDA Questionnaire

The attitude section of the questionnaire assessed adolescents' views on abnormal menstrual patterns, e.g.,

severe dysmenorrhea, menorrhagia, irregular cycles, drawing from the Menstrual Disorder of Teenagers questionnaire used in an Australian cross-sectional study.⁹ The items were based on a study by Houston et al., which examined adolescents' attitudes and expectations concerning their menstrual cycles. The 26 items were developed based on prior research and adapted to fit the Malaysian adolescent context, and each was evaluated on a five-point Likert scale, ranging from "strongly disagree" to "strongly agree." Following factor analysis and expert review, 8 items were removed due to redundancy or low factor loadings, resulting in a final set of 18 attitude items. For positively worded items, scores were assigned in increasing order (1 for strongly disagree to 5 for strongly agree), while 16 negatively worded items were scored in reverse order. For instance, the statement 'Menstrual pain should always be tolerated without medication' was reverse-scored, meaning that 'strongly agree' was assigned a lower score. The scoring system was categorised into three: more than 80%, 60-70% and less than 60%. Higher scores indicate a more informed and proactive attitude toward menstrual health, including a willingness to seek medical advice and manage symptoms effectively. A score less than 60% indicates of poor attitude toward menstrual health.

Development of the Practice Section in the MenDA Questionnaire

The practice section of the MenDA questionnaire focused on adolescents' daily practices in managing menstrual issues and their health-seeking behaviours related to menstrual disorders. It also assessed the impact of menstrual problems on school attendance and participation in social or sports activities. The initial 23 items were generated based on previous validated health behavior surveys and expert consultations to ensure a comprehensive assessment; each was rated on a five-point Likert-type scale ranging from "never" to "always." The practice items were categorized into four key areas: (1) self-care and menstrual hygiene, (2) symptom management, (3) medical help-seeking behavior, and (4) impact on school and activities. Following factor analysis and expert review, two items with low factor loadings were

removed, resulting in a final set of 21 practice items. Positive items were rated on a scale from 1 (never) to 5 (always) across 13 items, while ten negatively worded items were scored in reverse. For instance, the statement 'I avoid physical activity during menstruation, even if I have no pain' was reverse-scored, meaning that 'Always' received a lower score and 'Never' received a higher score. Following factor analysis and expert review, two items with low factor loadings were removed, resulting in a final set of 21 practice items. Higher scores indicate more proactive and effective menstrual health practices, such as regular symptom management, timely medical consultation, and minimal disruption to school or social activities. The cut-off score was 65.

Study Sample

In this cross-sectional study, a group of 46 students from a single school was chosen to assess the face validity of the MenDA questionnaire. Probability proportional to size sampling method to evaluate the questionnaire's validity and internal consistency. The sample size for the validation study (n=485) was determined based on guidelines for factor analysis, ensuring at least 10 participants per questionnaire item.

This study involved all female students aged 13 to 17 (form 1 to form 5) from selected secondary schools in Kelantan. Secondary schools were randomly selected from different districts in Kelantan to ensure geographic diversity. Schools were weighted based on enrolment size, and participants were randomly selected within each school to achieve proportional representation. Participants were from diverse socioeconomic backgrounds, representing both urban and rural schools in Kelantan. We excluded those with physical disabilities or illiteracy. Any incomplete responses were excluded from analysis, and missing data patterns were assessed to rule out systematic bias. The response rate was 96.5%.

Validity

Three types of validity were determined for the MenDA questionnaire: content validity, face validity, and construct validity.

Content Validity

We evaluated the content validity of the initial MenDA questionnaire by having six gynaecology experts with specialisations in pediatric and adolescent care assess each item using a four-point Likert scale: 1= not relevant, 2= somewhat relevant, 3= quite relevant, and 4= highly relevant. Six experts were selected in accordance with previous validation studies, where a panel of 5-10 experts is recommended for content validation. "Experts were selected based on their experience in adolescent gynecology and survey development, ensuring diverse perspectives in item evaluation.

Ratings were recorded in Microsoft Excel, and the item-level Content Validity Index (I-CVI) was manually calculated by dividing the number of experts who rated an item as 3 or 4 by the total number of experts. An I-CVI cutoff of 0.82 was used to determine acceptable item relevance.¹¹

Face Validity

The MenDA questionnaire was tested for face validity among 46 students at one school. Each student rated items on a 1-4 Likert scale and noted any unclear items. Ratings for clarity were recorded in Excel, and the item-level Face Validity Index (I-FVI) was manually calculated.¹¹ At least 30 students were recommended to achieve an acceptable FVI of 0.8.¹² Based on this feedback, the questionnaire was revised to include three domains and 81 items for construct validation. Items identified as unclear by more than 20% of students were reworded for clarity before the final validation stage.

Construct Validity

We conducted a construct validation session involving 420 students from Form 1 to Form 5 in selected secondary schools to assess the feasibility and understand how well the population responds to the questionnaire.

The data obtained from each knowledge, attitude, and practice section were analysed through exploratory factor analysis (EFA) using the Statistical Package for Social Sciences (SPSS) version 24 software to evaluate

the relationship within a group of observed variables, measured through questions or items.¹⁴ EFA acts as a data-reduction technique that reduces questions into sets of questions by assessing similar constructs using intercorrelation items. EFA was used instead of CFA due to the exploratory nature of the study and the need to identify underlying factor structures. Factors were retained based on eigenvalues >1.0 and factor loadings above 0.40, following established statistical guidelines.

Reliability

The internal consistency of each KAP section in the MenDA questionnaire was evaluated by calculating the reliability using Cronbach's alpha (α) value. Cronbach's alpha is a widely used method for determining the correlation between items, and it is frequently used in medical research.¹⁵ A Cronbach's alpha of >0.70 was considered acceptable for internal consistency. Domains with α between 0.60-0.69 were considered marginally acceptable for exploratory research, while those >0.70 indicated good reliability.

Statistical Analysis

The data underwent exploratory factor analysis (EFA) using IBM SPSS Statistics version 24. Descriptive statistics, including mean (SD) and frequency (%), were used for sociodemographic data. The Keiser-Meyer-Olkin (KMO) measure assessed sampling adequacy, with a value of ≥ 0.5 indicating sufficient correlation among variables.^{16,17}

Bartlett's test of sphericity determined variable relationships, with significance ($p < 0.05$), allowing factor analysis. Principal component analysis with Varimax rotation identified factors with eigenvalues >1.5 and factor loadings >0.4 for item significance.¹⁸ An eigenvalue cutoff of 1.5 was used to ensure that only strong factors were retained, minimizing the risk of including weak or redundant constructs. Items with factor loadings <0.40 or significant cross-loadings were excluded to ensure a distinct factor structure. Factors were retained based on the scree plot's elbow method, where the slope changes significantly, indicating the optimal number of factors.

Factor analysis iterations excluded items with poor correlations until optimal combinations were identified. Cronbach's alpha was used to assess internal consistency reliability. Domains with α between 0.60-0.69 were considered marginally acceptable for exploratory research, while those >0.70 indicated good reliability.¹⁹

RESULT

Sociodemographic Characteristics

Four hundred and eighty-five (485) female students participated in this study, with ages ranging from 13 to 17 years and a mean age of 16.004 (1.164). Participants were selected from both urban and rural schools in Kelantan to ensure diverse representation. The ethnic composition of the students was 96.9% Malay, 0.8% Chinese, 1.0% Indian, and 1.2% from other ethnicities. "Due to the high proportion of Malay participants, the findings may be less generalizable to non-Malay populations. The average age of menarche was 12.016 (1.160). Socioeconomic background was not directly assessed but may be an area for future research. Missing data were minimal ($<3.5\%$) and handled through mean imputation where applicable.

Content Validity

Six experts were selected following best practices in questionnaire validation, where panels of 5-10 experts are typically recommended for content validation. Items scoring below the CVI threshold (0.82) or showing redundancy were removed after expert consensus. While no items were deleted, minor wording adjustments were made based on student feedback to improve clarity. None of the items were deleted from the practice domain. Thus, 81 items remained, consisting of 35 items in knowledge, 23 in attitude, and 23 in the practice domain. Items scoring below the CVI threshold (0.82) or showing redundancy were removed after expert consensus.

Face Validity

None of the items was deleted in any of the three domains, with FVI values ranging from 40/46 (0.86) to 46/46 (1.0). While no items were deleted, minor wording

adjustments were made based on student feedback to improve clarity. An eigenvalue cutoff of 1.5 was used to strengthen factor retention and minimize weak constructs. Therefore, 81 items (35 in the knowledge domain, 23 in the attitude domain, and 23 in the practice domain) remained in the questionnaire.

Construct Validity

The KMO measure of sampling adequacy (>0.5) and Bartlett's test of sphericity ($p<0.05$) were appropriate for all of the KAP domains, where KMO was 0.712 for the knowledge section, 0.697 for the attitude section, and 0.852 for the practice section.

In the EFA for the knowledge section, we identified five dimensions with an eigenvalue >1.5 . This was supported by the scree plot, which also indicated five dimensions. EFA revealed four dimensions for the attitude section with an eigenvalue >1.5 . In the practice section, after applying EFA, 21 items were retained from the initial 23 items. Four dimensions were revealed in this section. Therefore, in the MenDA questionnaire's final model, 62 items were retained from the initial 81 items after EFA. Twenty-three items were under the knowledge section, 18 under the attitude section, and 21 under the practice section.

Internal Consistency Reliability

Cronbach's alpha was calculated for each domain and dimension under a specific domain. The Cronbach's alpha for the knowledge domain was 0.739, for the attitude domain was 0.711, and for the practice domain was 0.793, all of which were >0.70 . Hence, they were considered acceptable for internal consistency.

For the dimensions under the knowledge domain, Cronbach's alpha for dimensions 1 and 2 were 0.716 and 0.726, respectively. However, the Cronbach's alphas for dimensions 3, 4, and 5 were 0.431, 0.568, and 0.458. While Cronbach's alpha for some knowledge dimensions was below 0.60, these items were retained due to their conceptual importance and contribution to construct validity.

Table I: Summary results of factor analysis and reliability for knowledge, attitude, and practice of adolescents towards menstrual disorder

Section/dimension	KMO	Number of items	Eigenvalue	Percentage of variance explained	Range of factor loading	Reliability coefficient (Cronbach's alpha)
	Bartlett's test					
KNOWLEDGE	0.712 p-value < 0.05	23				0.739
Dimension 1 : premenstrual syndrome		8	4.308	10.20%	0.461-0.714	0.716
Dimension 2 : growth spurt		4	2.337	6.58%	0.668-0.792	0.726
Dimension 3 : general menses		5	1.797	6.27%	0.430-0.610	0.431
Dimension 4 : hormonal treatment		3	1.633	5.15%	0.617-0.731	0.568
Dimension 5 : menorrhagia		3	1.511	4.88%	0.420-0.709	0.458
ATTITUDE	0.697 p-value < 0.05	18				0.711
Dimension 1 : menorrhagia and dysmenorhea		5	3.255	10.314%	0.513-0.680	0.658
Dimension 2 : willingness to seek treatment		4	1.900	9.744%	0.522-0.775	0.616
Dimension 3 : obstacle to seek treatment		6	1.715	9.291%	0.437-0.605	0.569
Dimension 4 : menstrual cycle and flow		3	1.536	7.201%	0.523-0.703	0.548
PRACTICE	0.852 p-value < 0.05	21				0.793
Dimension 1 : school attendance, medications and health seeking practice		8	6.951	28.200	0.778-0.946	0.962
Dimension 2 : seeking treatment/advice from expert		4	2.852	12.334	0.476-0.864	0.793
Dimension 3 : general practice on health and menstrual issue		7	1.982	9.885	0.434-0.602	0.628
Dimension 4 : social and sport activity practices		2	1.682	8.131	0.854-0.905	0.849

In the practice domain, all dimensions met the minimum internal consistency reliability threshold of 0.60, which is considered acceptable for exploratory research.

Dimension 1 had a Cronbach's alpha of 0.962, dimension 2 of 0.793, dimension 3 of 0.628, and dimension 4 of 0.849. Table I summarises all the results.

DISCUSSION

To the best of our knowledge, this study is the first to develop and validate a new questionnaire in the Malay language to assess adolescents' KAP regarding menstrual disorders in Malaysia.

The MenDA questionnaire was designed to serve as an essential assessment tool because it covers a wide range of aspects related to menstruation problems in adolescence. It has also been designed and customised to suit adolescents' needs and lifestyles. Its content validity has been tested by an expert panel, face validity by the secondary students as the target group, and construct validity using EFA, and its internal consistency reliability has been verified (Table I). The instrument also shows promising reliability levels, with Cronbach's alpha values for dimensions and an overall score reaching a sum of >0.70 in almost all cases, as recommended by

another study.²⁰ Because of the relatively low rate of missing responses, the questionnaire appears to be well-accepted by adolescents.

Six experts were selected in line with recommendations that panels of 5-10 experts are ideal for robust content validation.²¹ After calculating the CVI, we found that the MenDA questionnaire can retain 81 of the initial 88 items (Table I). Most of the expert panels agreed that this questionnaire's items were relevant to the measured domains, as represented by the value of universal agreement of 0.56-0.73. These values indicate that more than half of the experts consistently rated items as relevant, which meets the minimum acceptable threshold for agreement. Other studies that used five or fewer experts should have a content validity index of at least 0.99 when accepting or retaining a specific item.^{22, 23}

When assessing face validity, it is essential to consider how clear and understandable each item is for the target group, particularly for tools developed for a specific population.²⁴ Hadie et al. suggested that at least 30 students are needed to achieve an acceptable FVI value of 0.8.¹³ We managed to get 46 students to participate in the face validity study, and the result was promising, as all 81 items met the FVI value of >0.8 and

were retained. Most of the students agreed that the items developed in the MenDA questionnaire were easily understood, easy to use, and acceptable, because most participants were able to complete the questionnaire in less than 20 minutes. The use of the Malay language in the questionnaire representing the adolescents' education language medium is the main contributor to its clarity and comprehensibility. This also supports the purpose of developing the MenDA questionnaire in Malay to provide an appropriate and reliable tool for assessing menstrual problems among adolescents in our local community. The importance of language in face validity in determining an instrument for a specific target group is also highlighted in a questionnaire developed in Cantonese for Hong Kong Chinese girls.²⁵

Through EFA, we saw a clear structure emerge from the data for the construct validity of the MenDA questionnaire. Five factors identified in the knowledge section, with 23 items retained, covered the most basic knowledge about menstrual health that adolescents should acquire.²⁶ For the attitude section, 18 of 23 items retained under four factors clearly explained their construct. The researcher may understand the adolescent's attitudes regarding their menstrual problem and their willingness to seek treatment based on the items retained.²⁷ The practice section also demonstrated a clear structure based on four identified dimensions, where 21 of 23 items were retained. All items had acceptable factor loadings between 0.42 and 0.94. The lower bound of 0.42 was chosen as it exceeds the standard minimum threshold (0.40) for meaningful factor loadings in exploratory research. Although factor analysis is one method used to identify items to be retained in the questionnaire, the researcher's judgement is still necessary to ensure that the items retained and grouped provide appropriate meanings.^{24, 28}

Testing the MenDA questionnaire in a larger sample of adolescents also showed that it is a reliable instrument, with Cronbach's alpha values >0.70 for knowledge (0.739), attitude (0.711), and practice (0.793) domains. Despite lower reliability scores for some knowledge dimensions, these items were retained due to their conceptual importance and their contribution to overall

construct validity, similar to other exploratory studies.²⁹ The overall Cronbach's alpha score of 0.738 proved that this instrument is reliable and suitable for use in our community.

The strength of the present study was its detailed assessment of knowledge, attitude, and practice (KAP) of menstrual disorders faced by adolescents. Implementing the KAP model in this questionnaire may help the researcher identify knowledge gaps, cultural beliefs, or behavioural patterns that may facilitate the understanding and action of adolescents toward menstrual health and eventually help us improve their treatment. The successful management of menstrual disorders among adolescents is significantly influenced by adolescents' education and motivation, which an adolescent's adequate KAP primarily governs.³⁰ KAP is also an essential component of the knowledge attitude behaviour model, which proposes that accumulated knowledge about a health aspect initiates a change in attitude and results in gradual behaviour change.³¹ In addition, this questionnaire may help to collect epidemiological data among adolescents in our local community and can also be used as a tool in medical health education focusing on menstrual issues. Future studies could adapt the MenDA questionnaire for use in other Southeast Asian countries with similar cultural and linguistic backgrounds.

This study has some limitations. This study was conducted in Kelantan, and the sample primarily consisted of Malay students, which may limit generalizability to other regions or ethnic groups. It should be noted that most adolescents who participated in this study, where most, including non-Malay individuals, can speak and understand Malay very well. Some students struggled with certain medical terms, requiring additional clarification during face validity testing. Future studies should validate the questionnaire in a larger and more diverse population to improve its generalizability.

CONCLUSION

In conclusion, the MenDA questionnaire is a validated and reliable tool for assessing the KAP on menstrual disorders among adolescents, and it is reproducible for

use, especially in the next step of our research. The MenDA questionnaire can aid healthcare providers and educators in screening adolescents for menstrual health issues, ensuring early intervention and support.

INSTITUTIONAL REVIEW BOARD (ETHIC COMMITTEE)

This study was approved by the Human Medical Research and Ethics Committee of USM dated 6 February 2020 (JEPeM code: USM/JEPeM/19110816).

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Prevalence of Diabetes Mellitus and its Associated Factors among Adults in Malaysia: Findings from the National Health and Morbidity Survey 2019

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ABSTRACT

INTRODUCTION: Diabetes mellitus (DM) is a major non-communicable health problem in both developed and developing countries, including Malaysia. This study aimed to determine the prevalence of DM and identify associated factors among adults in Malaysia. **MATERIALS AND METHODS:** A nationwide cross-sectional study was conducted in 2019 involving 10,464 respondents. A two-stage stratified sampling design was employed to select a representative sample of adults aged ≥ 18 years. Data was collected using structured and validated questionnaires administered through face-to-face interviews. Finger-prick fasting blood glucose tests were performed on respondents without a known DM diagnosis. All analyses were weighted to represent the Malaysian adult population. Chi-square tests and multiple logistic regression analyses were used to determine the associations between DM and the associated factors, with a significance level set at 0.05. **RESULTS:** The overall weighted prevalence of DM was 18.3% (n=2629). Higher prevalence was observed among individuals aged ≥ 60 years (41.5%), of Indian ethnicity (31.4%), physically inactive individuals (22.5%), obese individuals (27.1%), those with hypertension (36.0%), and those with high cholesterol levels (30.4%). Logistic regression identified age, ethnicity, obesity, hypertension, and cholesterol levels as significant factors associated with DM. **CONCLUSION:** The prevalence of DM among Malaysian adults remains high. Targeted strategies focusing on high-risk groups, particularly older adults, individuals of Indian ethnicity, those with obesity, hypertension, and dyslipidaemia, are important to reduce the national diabetes burden.

Keywords

Prevalence, Diabetes, Adults, Factors, Malaysia

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INTRODUCTION

Diabetes is a prioritised non-communicable (NCD) disease due to its significant public health problem all over the world, including in Malaysia. The World Health Organisation (WHO) states that 830 million people worldwide have diabetes, especially in low or middle-income countries. Diabetes is a major contributor to serious health complications, including blindness, kidney failure, heart attacks, strokes, and lower limb amputations. In 2021 alone, diabetes and diabetes-related kidney disease were responsible for more than 2 million deaths worldwide. Additionally, elevated blood glucose levels accounted for approximately 11% of all cardiovascular-related deaths.

The WHO's 2019 Global Health Estimates state that

seven of the top ten causes of death worldwide are NCDs.²

In Malaysia, the National Health and Morbidity Survey (NHMS) in 2006³ showed that the prevalence of diabetes mellitus (DM) was 11.6%. This figure increased to 15.2% and 17.5% in NHMS 2011⁴ and NHMS 2015⁵, respectively. The increase in the prevalence of overweight and obesity in people may be one of the factors contributing to the rise in diabetes.⁶

The increasing prevalence of diabetes from year to year around the world has raised concerns among many parties, especially those involved in the field of healthcare. According to the International Diabetes Federation (IDF),

in 2021 estimated that approximately 537 million adults (20-79 years) are living with diabetes worldwide, and the number is expected to rise to 643 million by 2030 and 783 million by 2045⁷. More worryingly, data shows that nearly 1 in 2 (240 million) adults with diabetes are undiagnosed.⁸ Untreated diabetes has a significant relationship with morbidity and mortality and can lead to microvascular (retinopathy, neuropathy, and nephropathy) and macrovascular (heart attack, stroke, and peripheral vascular) complications.⁹

Recent evidence indicates that a diet high in saturated fats and added sugars is significantly associated with increased risk of type 2 diabetes, whereas dietary patterns rich in whole grains, fruits, and vegetables are protective.¹⁰ In addition to lifestyle factors, genetic predisposition plays a crucial role in the pathogenesis of type 2 diabetes, particularly through its influence on beta-cell function and glucose metabolism.¹¹ Other studies also showed certain socio-demographics to be associated with diabetes, such as gender, age, higher Body Mass Index (BMI), and co-morbidities, such as hypertension.¹²

Although previous NHMS cycles (2006, 2011, 2015) have documented the rising prevalence of diabetes in Malaysia, these surveys provided limited analysis of sociodemographic determinants and lacked detailed stratification by clinical risk factors such as obesity, hypertension, and cholesterol. Furthermore, earlier studies did not explore associations using a fully adjusted multivariable model based on the latest national dataset.

This study aims to address these gaps by providing updated prevalence estimates of DM and a more comprehensive assessment of associated factors among the adult population in Malaysia using nationally representative data from NHMS 2019.

MATERIALS AND METHODS

Data collection

The NHMS 2019 was a cross-sectional nationwide survey conducted by the Institute for Public Health, Ministry of Health Malaysia. NHMS 2019 implemented a multi-stage

stratified sampling design proportionate to the population size throughout all states in Malaysia, covering both urban and rural areas. The target population was residents of all non-institutional living quarters (LQs) in Malaysia for at least two weeks before data collection.

This survey used structured and validated bilingual questionnaires (in Bahasa Malaysia and English), and it was administered by trained interviewers. The data collection team conducted face-to-face interviews using mobile devices with a system developed specially for this data collection.¹³ Completed questionnaires were sent to the data management team through the NHMS server in the Institute of Public Health whenever there was an internet connection. Quality control checks were performed (especially on the respondent ID, outliers, or incorrect data).

Dependent variable

The fasting blood glucose measurement was performed on finger-prick blood samples from respondents using the CardioChek® PA Analyzer portable blood test system. Only respondents who claimed to be non-diabetic were tested for glucose levels. For this study, a respondent was classified as having DM when the respondent self-reported it or was told to have diabetes by a doctor or assistant medical officer, or had a fasting capillary blood glucose (FBG) of ≥ 7 mmol/L.

Independent variables

This survey involved structured and validated questionnaires that covered information on general household, socio-demographic, and specific health problems. The categorical variables that were considered were "sex" (male, female), "age group" (18-39, 40-59, 60 & above), "residence" (urban, rural), "ethnic" (Malay, Chinese, Indian, other indigenous, others), "education level" (no formal education, primary school education, secondary school education, tertiary education, unclassified), "marital status" (single, married, widow/widower/divorcee) and "occupational status" (working, not working). Meanwhile, in the section on specific health problems, we've included "physical activity" (active, inactive, "obesity" (non-obese, obese), "blood pressure

status" (normotensive, hypertensive), and "cholesterol status" (normal cholesterol, high cholesterol).

Trained research assistants did the clinical anthropometric measurements while qualified nurses took the finger-prick biochemistry tests. Informed consent was obtained from all the respondents before the questionnaire was administered. All followed the protocol for blood glucose intake and blood pressure measurements.

This survey used blood pressure assessments of respondents using the Omron Japan Model HEM-907. Three readings were taken from each respondent, and an average of the second and third readings was computed for the findings. Respondents were considered hypertensive if their average systolic blood pressure was ≥ 140 mmHg and /or diastolic blood pressure ≥ 90 mmHg or were self-reported hypertensive.

The cholesterol level of respondents was measured using a finger-prick method with the CardioChek® portable blood test system. A validated and calibrated HemoCue® Machine Hb 201+ was used to measure haemoglobin level, and respondents were considered high cholesterol if they had a total cholesterol of 5.2mmol/L or more.

The weight of respondents was measured in kilograms using a digital weighing machine, Tanita Personal Scale HD 319, and height was measured in centimetres using SECA Stadiometer 213. Both tools had also been validated and calibrated before the survey was conducted. BMI was calculated as weight divided by height squared. Respondents with a BMI of 30.0 kg/m² or more were classified as obese.

The physical activity level of respondents was assessed using the short form of the International Physical Activity Questionnaire (IPAQ). Respondents were classified as physically active if they achieved a minimum combination of vigorous-intensity, moderate-intensity, and walking activities of 600 metabolic equivalent of task (MET) minutes/week.¹⁴

Statistical Analysis

Data were entered, cleaned, and analysed using SPSS (Statistical Package for Social Science) Version 20 (SPSS, Chicago, IL, USA). Descriptive statistics were calculated to describe the data as frequencies and percentages. All analyses were weighted using sample weights provided by the Department of Statistics Malaysia (DOSM) to ensure that the estimates were representative of the Malaysian adult population. Crude and adjusted odds ratios (ORs) were calculated with 95% confidence intervals (CIs) and standard deviations (SDs). Pearson's chi-square test was used to determine the association between categorical variables.

Multiple logistic regression analysis was performed to identify factors associated with DM while controlling for potential confounders. Variable selection was based on significant changes in the -2 log-likelihood ratio. The outcome variable was DM, and the predictor variables included age group, ethnic group, education level, marital status, occupational status, physical activity level, obesity, blood pressure status, and cholesterol status. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were estimated. Statistical significance was set at a P value < 0.05 .

RESULTS

Socio-demographic characteristics of the study respondents

The total number of respondents to the DM questionnaire was 10,472. The proportion of female respondents was slightly higher, comprising 54.3% of the total sample. Based on age, respondents aged 18-39 made up 41.3%, and the majority of the respondents (60.9%) were from the urban population. Respondents who were Malays were the majority ethnic group with 64.8%, followed by Chinese (12.7%) and other indigenous groups (10.3%). More than 60.0% of respondents had received either a primary or secondary school education. Nearly 70.0% of respondents were married, and more than 50.0% of respondents were still employed (Table I).

Table I: Socio-demographic characteristics of the respondents (N= 10,472)

Socio-demographic characteristic	N	%
Gender		
Male	4785	45.7
Female	5687	54.3
Age group (mean, sd): (45.6, 16.9)		
18-39	4322	41.3
40-59	3697	35.3
60 & above	2453	23.4
Residence		
Urban	6380	60.9
Rural	4092	39.1
Ethnic group		
Malay	6787	64.8
Chinese	1327	12.7
Indian	662	6.3
Other indigenous	1078	10.3
Others	618	5.9
Education level		
No formal education	644	6.2
Primary school education	2379	22.8
Secondary school education	4969	47.6
Tertiary education	2425	23.2
Unclassified	31	0.3
Marital status		
Single	2186	20.9
Married	7154	68.3
Widow/widower/divorcee	1132	10.8
Occupation status		
Working	5944	56.8
Not working	4520	43.2

Prevalence of diabetes mellitus by socio-demographic characteristics

The prevalence of DM in this study was 18.3% (95% CI: 17.08, 19.58). There were differences in the various age groups, ethnic groups, education status, marital status, occupational status, physical activity, obesity, status of hypertension and cholesterol. However, gender and rural/urban status were not important factors in this study.

Factors associated with diabetes mellitus

The risk factors identified using the logistic regression model based on sociodemographic and health characteristics were like those identified using the fully adjusted model. There was a positive association between older age groups and the risk of DM. The risk of DM was significantly higher in individuals aged 40-59 years [aOR 1.95(95% CI: 1.68,2.27)] and 60 years old and above [aOR 2.68 (95% CI: 2.23,3.20)]. In addition, the risk of DM was significantly associated with ethnic groups [Malays: aOR1.77 (95% CI: 1.50,2.09) and Indians: aOR 3.02 (95% 2.38, 3.83)], educational level [no formal education: aOR

1.37 (95% CI: 1.07, 1.76) and secondary education: aOR1.20 (95 CI: 1.04, 1.38)], marital status (married: aOR 1.79 (95% CI: 1.49, 2.16)] and widow/widower/divorced: aOR1.83 (95 CI: 1.45, 2.31)], physically inactive: aOR 1.21 (95% CI: 1.07,1.36)], obese: aOR1.63 (95% CI: 1.45,1.83)], hypertensive: aOR 2.19 (95% CI: 1.95, 2.45) and high cholesterol: aOR 1.93 (95% CI: 1.73,2.15)]. No significant associations were found for gender, residence (rural/urban), and occupational status.

Table II: Prevalence of Diabetes Mellitus Among Adults Aged ≥18 Years by Sociodemographic and Clinical Characteristics

Demographic Characteristics	Diabetes Mellitus			
	count	Prevalen (%)	% (95 CI)	
			Lower	Upper
National	2629	18.3	17.08	19.58
Gender				
Male	1191	18.2	16.63	19.90
Female	1438	18.4	16.99	19.89
Age group				
18-39	438	8.4	7.16	9.75
40-59	1129	25.3	23.27	27.47
60 & above	1062	41.5	38.54	44.55
Residence				
Urban	1519	18.3	16.8	19.8
Rural	1110	18.3	16.48	20.4
Ethnic group				
Malay	1868	21.6	20.02	23.17
Chinese	276	15.1	25.85	37.53
Indian	250	31.4	25.85	37.53
Other indigenous	160	11.6	9.15	14.62
Others	75	8.8	6.21	12.21
Education level				
No formal education	231	28.7	23.10	34.94
Primary school education	795	23.9	21.14	26.98
Secondary school	1196	18.1	16.59	19.77
Tertiary education	399	12.7	10.76	14.85
Unclassified	3	4.8	1.21	17.18
Marital status				
Single	195	7.7	6.27	9.53
Married	1975	21.3	19.74	22.94
Widow/widower/divorcee	459	33.2	29.27	37.30
Occupation status				
Working	1166	14.5	13.06	16.01
Not working	1461	24.9	23.23	26.65
Physical activity				
Active	1799	16.8	15.49	18.23
Inactive	796	22.5	20.26	24.81
Obesity				
Non-Obese	1702	16.0	14.76	17.38
Obese	747	27.1	24.31	30.05
Blood pressure status				
Normotensive	916	10.7	9.54	12.04
Hypertensive	1713	36.0	33.84	38.16
Cholesterol status				
Normal cholesterol	839	10.9	9.62	12.22
High cholesterol	1790	30.4	28.48	32.42

Note: Values represent the prevalence of diabetes mellitus in the general population, not proportions within the diabetic subgroup. Weighted analysis was applied to reflect national population estimates.

Table III: Factors associated with diabetes mellitus (using multiple logistic regression)

Risk Factors	Simple Logistic Regression		Multiple Logistic	
	Crude OR (95% CI)	p-value	adjusted Odds Ratio (aOR)*	p-value
Gender				
Male	1.00	-	-	-
Female	1.02 (0.94, 1.12)	0.629	-	-
Age group				
18-39	1.00	-	-	-
40-59	3.99 (3.45, 4.40)	<0.00	1.95 (1.68, 2.27)	<0.00
60 & above	6.76 (5.96, 7.68)	<0.00	2.68 (2.23, 3.20)	<0.00
Residence				
Rural	1.19 (1.09, 1.31)	<0.00	-	-
Urban	1.00	-	-	-
Ethnic group				
Chinese	1.00	-	-	-
Malays	1.45 (1.25, 1.67)	<0.00	1.77 (1.50, 2.09)	<0.00
Indians	2.31 (1.88, 2.84)	<0.00	3.02 (2.38, 3.83)	<0.00
Other Bumiputra	0.66 (0.54, 0.82)	<0.00	0.82 (0.64, 1.04)	0.103
Others	0.53 (0.40, 0.70)	<0.00	0.92 (0.68, 1.26)	0.616
Education level				
No formal education	2.84 (2.34, 3.45)	<0.00	1.37(1.07,1.76)	0.012
Primary education	2.55 (2.22, 2.93)	<0.00	1.18 (0.99,1.40)	0.061
Secondary education	1.61 (1.42, 1.83)	<0.00	1.20 (1.04, 1.38)	0.012
Tertiary education	1.00	-	-	-
Marital status				
Single	1.00	-	-	-
Married	3.89 (3.33, 4.54)	<0.00	1.79 (1.49, 2.16)	<0.00
Widow/widower/	6.95 (5.75, 8.39)	<0.00	1.83 (1.45, 2.31)	<0.00
Occupation status				
Working	1.00	-	-	-
Not working	1.96 (1.79, 2.14)	<0.00	-	-
Physical activity level				
Active	1.00	-	-	-
Inactive	1.39 (1.26, 1.54)	<0.00	1.21 (1.07, 1.36)	0.002
Obesity				
Non-Obese	1.00	-	-	-
Obese	1.86 (1.68, 2.07)	<0.00	1.63 (1.45, 1.83)	<0.00
Blood pressure status				
Hypertensive	4.38 (3.99, 4.81)	<0.00	2.19 (1.95, 2.45)	<0.00
Normotensive	1.00	-	-	-
Cholesterol status				
Normal cholesterol	1.00	-	-	-
High cholesterol	3.40 (3.10, 3.74)	<0.00	1.93 (1.73, 2.15)	<0.00

*Backward likelihood ratio multiple logistic regression was applied. Multicollinearity and interaction were checked and not detected. The Hosmer–Lemeshow test ($p = 0.074$), classification table (overall correctly classified percentage = 76.9%), and receiver operating characteristic (ROC) curve (77.0%) indicated acceptable model fitness.

DISCUSSION

In this cross-sectional survey, we provide information about the associated factors of diabetes mellitus (DM) among adults in Malaysia. The prevalence of DM in the current study was found to be high at 18.3% (95% CI: 17.08, 19.58), which means that 1 in 5 Malaysians has DM. The prevalence from our survey is highest compared to studies conducted in other countries, including China (13%), Indonesia (10.8%), Thailand (11.6%), Singapore (14.7%), Nepal (8.5%), and Brazil (7.5%).^{15,16,17}

However, when compared to countries in the Arab World, the prevalence studies are lower in Malaysia: e.g. the Kingdom of Arabia at 31.6%, Oman at 29.0%, Kuwait at 25.4%, and Bahrain at 25.0%.¹⁷ The International Diabetes Federation's (IDF) 10th edition of the Diabetes

Atlas reported that 537 million adults worldwide were living with diabetes in 2021, a figure projected to rise to 783 million by 2045. Even more concerning is the fact that approximately 240 million people, around 44.7% of all adults with diabetes, remain undiagnosed and unaware of their condition.¹⁸

The high prevalence of DM among Malaysian adults could be partly due to a lack of awareness of the necessity of health screening at an earlier age and of early diabetes symptoms. Another issue that prevents Malaysians from getting screened for diabetes is the high patient load in public primary healthcare facilities.¹⁹ Population increase, population ageing, growing urbanisation, rising obesity and physical inactivity rates, particularly seen in developing and developed nations, could all be contributing factors.

Based on Table II, the prevalence of DM rose with age and was substantially more significant (41.5%) in people 60 years and older. Furthermore, based on Table III, our findings reveal that age was the one factor that showed the highest effect on the risk of DM. This finding is similar to findings in other studies in Saudi Arabia, Kenya and Vietnam, where the disease has become more common among the elderly,^{20,21,22} which showed that further age-related glucose intolerance is related to decreased insulin sensitivity and decreased β -cell function.²³ This is most likely brought on by an ageing population's increased propensity to gain weight, loss of muscle mass, and being engaged in less physical activity. It is known that cells in the body are more resistant to insulin when there is a greater abundance of fatty tissue.²⁴

This study shows a high prevalence of DM among Malaysian Indians, followed by Malays and Chinese. This pattern has been consistently observed in previous NHMS cycles, including NHMS 2011⁴ and 2015⁵, where Indian respondents also had the highest prevalence rates. In the current analysis, Indian ethnicity was associated with a more than threefold increased risk of DM (aOR: 3.02, 95% CI: 2.38-3.83), while Malay ethnicity also showed a significantly elevated risk (aOR: 1.77, 95% CI: 1.50-2.09) compared to the Chinese population.

Several factors may contribute to this ethnic disparity. There is growing evidence of genetic susceptibility to insulin resistance and central adiposity within South Asian populations, especially Indians, which may further elevate diabetes risk.²⁵ As for Malays, dietary habits, increasing urbanisation, and rising obesity rates are likely contributing factors. In contrast, the relatively lower prevalence among Chinese Malaysians may be linked to healthier dietary patterns, greater health awareness, and possibly more proactive health-seeking behaviours.²⁶ These findings underscore the importance of culturally tailored diabetes prevention strategies that consider ethnic-specific risk profiles in the Malaysian context.

Table II's data indicate that married and widow/widower/divorced individuals have a greater frequency of DM than single individuals. The result in Table III shows that married individuals are 1.79 times more likely to have DM; meanwhile, widow/widower/divorced individuals are 1.83 times more likely to have DM compared to single individuals. Economic stability often changes with marital transitions. Widowed individuals may experience financial constraints due to the loss of a partner's income, impacting their ability to access healthcare and maintain a healthy lifestyle. Economic hardships have been associated with higher diabetes prevalence.²⁷

Regarding educational attainment, based on Table II, a higher prevalence was observed in those without formal education, followed by those with primary education. There was a statistically significant association between education status and DM. Lower awareness and fewer opportunities for prevention and control may be linked to lower education levels, but not higher education. However, the current study is unlike earlier studies that found no connection.²⁸ Further research is needed to confirm the association between DM and education level.

According to the findings in this study, obese people had a higher risk of DM. The results showed that the risk of DM was 1.63 times higher in obese individuals. A recent meta-analysis provides evidence of the strong association between obesity and type 2 diabetes mellitus (T2DM). The study highlights that obesity is the most

significant risk factor for the development and progression of T2DM, with excess adiposity leading to insulin resistance and β -cell dysfunction. Recent studies have elucidated the mechanisms by which abdominal fat accumulation contributes to insulin resistance. Excess visceral adipose tissue releases elevated levels of free fatty acids (FFAs) into the bloodstream, which can impair the insulin signalling pathways in the liver and muscle tissues, leading to decreased insulin sensitivity. Additionally, adipocytes secrete pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumour necrosis factor alpha (TNF- α), which further disrupt insulin action by interfering with insulin receptor signalling and promoting systemic inflammation.³⁰

The present study found that the risk of DM was 1.21 times higher among inactive individuals. Recent research underscores a significant inverse relationship between physical activity and the risk of developing T2DM. A 2025 population-based cohort study found that higher levels of physical activity across various domains were independently associated with a lower risk of T2DM.³¹ Notably, individuals who combined high physical activity with an anti-inflammatory diet experienced an even greater reduction in diabetes risk.³²

According to our study, respondents with hypertension had a 2.19-fold increased risk of having DM. Similar findings were reported in a study by Pakistan³³ and Ethiopia.³⁴ Hypertension and T2DM frequently co-occur due to shared pathophysiological mechanisms such as insulin resistance, endothelial dysfunction, chronic inflammation, and activation of the renin-angiotensin-aldosterone system (RAAS).³⁵ These conditions are also driven by overlapping risk factors, including obesity, physical inactivity, and unhealthy dietary patterns, contributing to their high rate of co-occurrence.³⁶ Similarly, these relationships significantly raise the risk of cardiovascular problems as a result of insulin resistance.³⁷ In older people, high blood pressure doubles the risk of developing diabetes.³⁸

Our results also showed respondents with high cholesterol had a 1.19-fold increased risk of having DM. This finding aligns with recent research indicating that dyslipidaemia,

particularly elevated levels of low-density lipoprotein cholesterol (LDL-C) and small dense LDL-C, is significantly associated with an increased risk of developing T2DM. For instance, a 2024 large-scale multicentre retrospective cohort study in China found a nonlinear positive association between estimated small dense LDL-C levels and the risk of developing DM, suggesting that even modest elevations in certain cholesterol subtypes can substantially impact diabetes risk.³⁹

Improving Diabetes Awareness in the Malaysian Population

In order to improve diabetes awareness in Malaysia, efforts undertaken must address existing gaps in knowledge dissemination, risk perception, and accessibility to screening services, especially among high-risk populations. While the National Strategic Plan for Non-Communicable Diseases (NSP-NCD) 2016-2025 outlines broad goals for NCD awareness, implementation on the ground remains fragmented and limited in reach.

One key area for enhancement is the integration of diabetes risk communication into routine community health activities led by *Klinik Kesihatan* and KOSPEN volunteers. Currently, KOSPEN's focus is primarily on general lifestyle advice. Expanding its scope to include personalised diabetes risk assessment and targeted messaging, particularly in communities with a high proportion of Indian or older adult populations, can increase its impact. Additionally, many community health promoters lack culturally tailored materials in different languages and dialects (Tamil, Mandarin, and indigenous languages), which can be addressed to improve engagement.

Secondly, Malaysia lacks a nationwide, easily accessible digital diabetes risk calculator, unlike Singapore's "Diabetes Risk Assessment Tool"⁴⁰ or the UK's "Know Your Risk" tool by Diabetes UK.⁴¹ A locally adapted version hosted on MySejahtera, or the Ministry of Health's website, could allow individuals to self-assess their risks and receive tailored advice or be prompted to undergo screening at the nearest clinics.

Thirdly, school-based diabetes education is currently minimal and often limited to general health promotion weeks. Embedding structured diabetes awareness content into the *Pendidikan Jasmani dan Kesihatan* (PJPK) syllabus, beginning from lower secondary school, can instil early awareness, particularly targeting students with family histories of DM.

Additionally, the use of religious platforms and Friday Mosque khutbahs,⁴² as has been successfully done for vaccination and smoking cessation awareness,⁴³ can be adapted in Malaysia for DM. This approach would help reach older males, a group often under-screened despite being at higher risk.

Lastly, while workplace health screenings are encouraged, they are not mandated or standardised across the public or private sector. Incentivising employers, through tax benefits or HRDF-linked programmes, to conduct annual diabetes risk assessments and provide follow-up education could close this gap, particularly among sedentary office workers.

In summary, improving diabetes awareness in Malaysia will require not only strengthening existing programmes but also adopting best practices from successful regional models, improving community outreach, and embedding structured risk communication across schools, workplaces, and digital platforms.

This study has several notable strengths. Firstly, this study utilises data from the NHMS 2019, a large-scale, population-based survey with high response rates and robust sampling design, ensuring national representativeness of the adult population in Malaysia. The use of trained interviewers, structured and validated bilingual questionnaires, and standardised data collection protocols has enhanced the reliability and consistency of the information gathered. Additionally, objective clinical measurements such as fasting blood glucose, blood pressure, and anthropometric indicators were incorporated alongside self-reported data, reducing sole reliance on subjective reporting. The application of sample weights provided by the Department of Statistics

Malaysia further strengthens the generalisability of the findings. Finally, the study's analytical approach, including the use of multivariable logistic regression, allowed for the comprehensive identification of independently associated risk factors for DM, offering valuable insight for targeted public health interventions.

This study has several limitations. Although NHMS 2019 was a nationally representative survey, the analysis was constrained by the limited number of variables available on potential risk factors for undiagnosed DM. In addition, the study relied partly on self-reported data, which may be subject to recall bias and underreporting, particularly regarding medical history and lifestyle behaviours. The cross-sectional design also limits the ability to establish causal relationships between the identified risk factors and DM. Furthermore, obesity classification in this study was based on WHO criteria ($\text{BMI} \geq 30 \text{ kg/m}^2$), in line with previous NHMS methodologies. However, we acknowledge that this may underestimate obesity-related risks among Asian populations, for whom lower BMI thresholds are recommended in the 2023 Malaysian Clinical Practice Guidelines (CPG) on obesity.

CONCLUSION

In Malaysia, the number of people with diabetes mellitus increased significantly in 2019. The findings of this study indicate that age, ethnicity, educational attainment, marital status, degree of physical activity, obesity, blood pressure, and cholesterol are significantly associated with diabetes mellitus. Awareness programs and interventions on diabetes need to be improved, especially related to behavioural change as a strategy for the prevention and control of diabetes and its complications. The public must be made more aware of the significance of early diabetic screening, particularly among individuals 60 years of age and older and among high-risk populations, to prevent more severe complications and lessen the burden of this disease.

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CONFLICT OF INTEREST

The authors declare no competing interests.

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INSTITUTIONAL REVIEW BOARD (ETHIC COMMITTEE)

This study obtained ethical approval from the Medical Research and Ethics Committee of the Ministry of Health Malaysia and was registered in the National Medical Research Registry, bearing registration number NMRR-18-3085-44207. Informed consent was obtained from all the respondents before the questionnaire was administered.

CONSENT FOR PUBLICATION

Not applicable

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

AUTHORS' CONTRIBUTIONS

HI oversaw all aspects of the study and was also involved in the writing of the manuscript. TAS was involved in supervising nationwide data collection and contributed significantly to the writing of the manuscript. TGRL was involved in data collection and writing. WSRH contributed to the data analysis and writing, NLAM were involved in the data collection and writing of the manuscript, MFMY was involved in cleaning the raw data and data analysis and contributed to manuscript writing.

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Effect of Antipsychotic on the Dimension of Auditory Hallucination Among Patients with Schizophrenia

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ABSTRACT

INTRODUCTION: Auditory hallucination (AH) is the most common type of hallucinations in individuals with schizophrenia. Assessing the multidimensional aspects of AH provides more precise insights, particularly regarding associated psychological sequelae. This study aimed to examine the short-term effects of antipsychotics treatment on the emotional, cognitive and physical dimension of AH. **MATERIALS AND METHODS:** A total of 74 patients with schizophrenia with relapsing episodes were recruited. The Psychotic Symptoms Rating Scale subscale Auditory Hallucination. (PSYRATS-AH) was administered at baseline, and after 2 weeks and 4 weeks of treatment. Patients were treated with atypical, typical, or a combination of both types of antipsychotics. The emotional, cognitive and physical components of PSYRATS-AH were analysed. **RESULTS:** Most participants were Malay (89.2%), single (63.5%), unemployed (70%), and on atypical antipsychotic treatment (71.6%). At 4 weeks, there was a significant reduction in overall AH scores compared to baseline. Both atypical and combination antipsychotic regimen showed a significant difference in all three components, namely emotional ($\chi^2=43.9$, $p<0.05$ and $\chi^2=27.8$, $p<0.05$), cognitive ($\chi^2=34.1$, $p<0.05$ and $\chi^2=19.0$, $p<0.05$), and physical ($\chi^2=39.5$, $p<0.05$ and $\chi^2=30.5$, $p<0.05$). However, those on typical antipsychotic showed a poorer response in the physical component ($\chi^2=5.4$, $p>0.05$). **CONCLUSION:** Atypical and combination antipsychotic regimen demonstrated greater effectiveness in improving the emotional, cognitive, and physical dimension of AH. Typical antipsychotics alone were less effective, particularly in addressing physical symptoms. These findings support the preferential use of atypical antipsychotics managing the multidimensional aspects of AH in schizophrenia.

Keywords

auditory hallucination, PSYRATS, antipsychotic, schizophrenia

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INTRODUCTION

Auditory hallucination (AH) is a prominent symptom of schizophrenia, accounting for 60% to 80% of all hallucinations.¹ Various theoretical models such as cognitive neurobiology, psychopathology, neuroimaging, and dimensional frameworks have been proposed to explain their occurrence.² These hallucinations are dimensional in nature, conceptualized through cognitive, perceptual, and emotional domains.³ The cognitive dimension involves an inability to control voices, the perceptual dimension refers to voices perceived as external; and the emotional dimension includes voices with a negative or derogatory tone. This emotional aspect often causes significant distress and is associated with depressive symptoms.⁴

Clinical evaluation of AHs is complex due to factors such as number of voices, their perceived origin, interactivity, and mood congruence. A thorough assessment of their content and context is crucial, as these symptoms significantly influence treatment decisions. Considerations typically include psychosocial background, patient's preferences, treatment costs, and tolerability. A multidimensional approach allows for more tailored treatment strategies. For example, a study applying this framework prior to mindfulness therapy demonstrated improved voice control and reduced distress at 12 weeks.⁵ Treatment efficacy is often measured using the Positive and Negative Syndrome Scale (PANSS), which is regarded

as the gold standard.⁵⁻⁷ However, PANSS provides only a general overview and does not address specific features of hallucination.⁸ In contrast, the Psychotic Symptoms Rating Scale (PSYRATS) evaluates eleven dimensions of AHs, grouped into emotional, cognitive, and physical categories.^{9,10} PSYRATS is widely used to assess the effectiveness of psychological interventions.^{5,11}

Although the pharmacological treatment of schizophrenia is well researched, there is limited focus on antipsychotic effects on individual hallucination dimensions. Some studies have used PSYRATS to evaluate delusional dimensions.¹² A six-month trial reported early improvements in distress and loudness, supporting the observation that hallucinations respond to treatment sooner than delusions.¹³ This further validates PSYRATS as a reliable tool for symptom-specific evaluation.

Given the limited data on the pharmacological effects on AH dimensions, this study aimed to fill that gap by investigating the short-term impact of typical, atypical, and a combination of both antipsychotics on AH dimensions in schizophrenia. The findings are expected to support the integration of dimensional assessments into treatment planning, complementing traditional measures of efficacy and tolerability. Additionally, this research will contribute valuable local data to inform future outcome studies on schizophrenia.

MATERIALS AND METHODS

This prospective observational cohort study involved 74 patients with schizophrenia with relapsing episodes, recruited through simple random sampling from the psychiatric unit of a tertiary care and referral hospital in Peninsular Malaysia. Eligible participants met DSM-5 criteria for schizophrenia, were aged 18 to 65, Malay-speaking, and free from severe medical conditions (e.g., CNS infection, cerebrovascular disease, head trauma). All participants had Brief Psychotic Rating Scale (BPRS) scores below 52 and presented with relapse symptoms, primarily AHs.⁴ Relapse was defined as at least one acute psychotic episode lasting seven days or more.¹⁴

The study was conducted between June and November

2019 in compliance with institutional and national ethical guidelines and regulations. Ethical approval was obtained from both institutional and national research ethics committees (FF-2019-206; NMRR-18-2548-42942). Written informed consent was obtained at the baseline visit from both patients and their caregivers once the patients were clinically assessed to have the capacity to understand and comprehend the nature and purpose of the study. Consent was only taken when participants were mentally stable and were able to engage in meaningful discussion.

Assessments were conducted at three time points: baseline (over three sessions), week 2, and week 4. This timeline aligns with recommendations by the British Association of Psychopharmacology and the National Institute for Health and Care Excellence (NICE) suggest a four to six weeks period for evaluating antipsychotic efficacy. Throughout the study, symptom severity, side effects, and patient well-being were closely monitored. All participants were managed by their treating psychiatrists according to standard clinical protocols, while AHs were directly assessed by the authorS.

Instruments

A sociodemographic questionnaire was used to collect information on age, gender, marital status, education level, employment status, duration of illness, and type of medication prescribed. Symptom severity was measured using the 18-item Brief Psychiatric Rating Scale (BPRS), a clinician-administered tool. Only patients with BPRS scores below 52 were included in the study. Patients with score of 52 and higher were excluded to avoid potential confounding effects from severe illness.⁴

Auditory hallucination (AH) dimensions were assessed using the Malay version of the Psychotic Symptom Rating Scales – Auditory Hallucinations subscale (MyPSYRATS-AH),¹⁵ a validated semi-structured interviewer-rated tool comprising of 11 items. These items evaluated key features over the past week, including frequency, duration, location, loudness, perceived voice origin, negative content (amount and degree), distress (amount and intensity), degree of disruption to life, and controllability.

Each item was rated on a scale from 0 to 4, with higher scores indicating greater severity. The items are grouped into three subscales: emotional (negative content, distress), cognitive interpretation (origin, disruption, controllability), and physical characteristics (loudness, frequency, duration, location).¹⁶ MyPSYRATS-AH has demonstrated strong validity and reliability within the local population and shows minimal socio-cultural bias.¹⁵

Statistical analysis

Statistical analyses were performed using SPSS version 25. Descriptive statistics were used to summarize the sociodemographic and clinical characteristic of respondents. Means and standard deviation (SD) were reported for continuous variables (e.g., age, PSYRATS scores), while frequencies and percentages were used for categorical variables.

Normally distributed data were analyzed using independent sample t-tests and one-way ANOVA. For non-normally distributed data, Mann-Whitney U and Kruskal-Wallis tests were employed. Friedman's test was used to assess changes in PSYRATS-AH scores across the treatment period and between different antipsychotic groups

RESULTS

Sociodemographic and clinical characteristics

A total of 74 respondents completed the four-week assessment. Table I presents the sociodemographic data of the respondents. The mean age was 38.53 (SD=11.4), with 54% being male. Majority of respondents were Malay (89.2%), single (63.5%), unemployed (70%) and all (100%) belonged to the low-income group (B40, with household income less than RM 3,000). Across the study, the mean PSYRATS-AH scores for male respondents were consistently lower than those for female, but this difference was not statistically significant at both baseline ($p=0.72$) and week 4 ($p=0.6$). A significant improvement in PSYRATS-AH scores over time was observed among single respondents ($p<0.05$). However, the improvements among married and divorced respondents were not statistically significant ($p>0.05$).

Table I: Sociodemographic and clinical characteristic dimension of AH according PSYRAT-AH score (n=74)

Variables	Number (n)	Frequency (n)	Mean (SD)	PSYRAT-AH Score		
				Baseline (mean, SD)	Week 2 (median, IQR)	Week 4 (median, IQR)
Age			38.53 (11.4)			
Gender						
Male	40	54.1		26.6 (6.93)	15.5 (24)	7.00 (20)
Female	34	45.9				
Marital Status						
Single	47	63.5		28.9 (6.8)	18.0 (23)	2.0 (20)
Married	19	25.7				
Divorced	8	10.8		28.3	23.0	13.0
Race						
Malay	66	89.2		28.6 (7.2)	18.0 (24)	8.5 (22)
Chinese	5	6.8				
Indian	2	2.7		30.8 (5.6)	21.0 (10)	1.0 (10)
Aborigine	1	1.4				
Education Level						
Primary school	14	18.9		27.8 (6.9)	17.0 (30)	18.0 (25)
Secondary	49	66.2				
	11	14.9		28.8	18.0	1.0
Employment Status						
Employment	22	30		28.6 (7.2)	19.0 (24)	8.0 (22)
Unemployed	52	70				
Salary						
B40	74	100				
M40						
Duration of Illness			11.11 (9.6)			

Antipsychotic Treatment

Antipsychotics used in this study included typical antipsychotics (Haloperidol, Perphenazine, Trifluoperazine, Zuclopenthixol decanoate, Flupenthixol decanoate) and atypical antipsychotics (Risperidone, Olanzapine, Quetiapine, Aripiprazole, Paliperidone, Clozapine, and Amisulpiride). Some respondents received a combination of both typical and atypical agents. At baseline, the majority of the respondents were prescribed atypical antipsychotics alone (71.6%), followed by combination therapy (16.2%) and typical antipsychotics alone (12%). By week 2, nine respondents (12%) had been switched to a different medication group, mainly to enhance treatment response by introducing an additional route of administration. Only one respondent (1.35%) was switched from a typical to an atypical antipsychotic due to extrapyramidal side effects. The medication switches involved several strategies, including transitions from atypical to combination therapy, atypical to typical, typical to combination, and typical to atypical antipsychotics. Following these changes, the newly assigned treatment group was maintained until week 4. The most common switch was from atypical to the combination therapy (n=6).

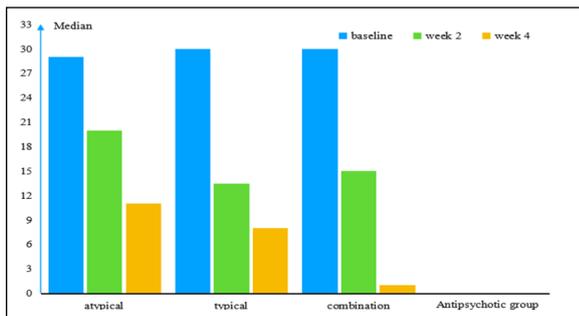


Figure 1: Total PSYRATS score (median) for 3 groups of antipsychotics over 4 weeks

The Effect of Different Antipsychotic Groups on AH Dimensions Based on PSYRATS-AH Scores

PSYRATS-AH scores were recorded at baseline, week 2, and week 4 of assessment. Overall, there was a statistically significant difference in PSYRATS-AH score from baseline to week 4 ($p < 0.001$). While this indicates general improvement, further analysis was conducted to determine whether any specific group of antipsychotics was superior to other antipsychotics at a certain time of treatment. Thus, separate comparisons were made at weeks 2 and 4 to evaluate the effects of all the three antipsychotic groups to the PSYRATS score. At week 2, there was no statistically significant difference in PSYRATS-AH scores among the three treatment groups, with a median score of 18 (IQR=24), $p = 0.066$. Similarly, at week 4, the differences remained statistically non-significant, with a median score of 8 (IQR=22), $p = 0.235$ T.

Further analysis was performed within each treatment group to assess the magnitude of change in PSYRATS-AH scores over time. For the atypical antipsychotics group, a significant reduction was observed from baseline (median=29, IQR=9) to week 2 (median=20, IQR=25) and further to week 4 (median=11, IQR=23), with $p < 0.001$. Similarly, for the typical antipsychotic group, scores decreased from baseline to week 2 (median=13.5, IQR=18) and week 4 (median=8, IQR=28.75), showing a statistically significant improvement ($p = 0.023$). The combination therapy group also demonstrated a significant reduction in scores over four weeks, from 30 (IQR=13) to 15 (IQR=23), and further to 1 (IQR=16), with $p < 0.001$ (Figure 1).

Table II presents improvements across all eleven dimensions of AHs from baseline to week 4 in patients treated with atypical antipsychotics and combination

therapy (all $p < 0.05$). These improvements include perceptual dimensions (e.g., frequency, location, loudness) and emotional-cognitive dimensions (e.g., negative content, distress, disruption, controllability). In contrast, the typical antipsychotic group showed significant improvements only in select dimensions, primarily related to emotional and cognitive aspects. No significant changes were observed in the frequency, location, loudness, and controllability dimensions ($p > 0.05$), suggesting a more limited impact on the full spectrum of AH symptoms.

Table II: Effect of atypical, typical and combination antipsychotics on the dimensions of AH

AH (dimension)	Statistical test, p value		
	Atypical antipsychotic (n=47)	Typical antipsychotic (n=8)	Combination (n=19)
Frequency	$\chi^2 = 38.70, p < 0.001^{**}$	$\chi^2 = 3.85, p = 0.146$	$\chi^2 = 29.10, p < 0.001^{**}$
Duration	$\chi^2 = 51.25, p < 0.001^{**}$	$\chi^2 = 11.40, p = 0.003^{**}$	$\chi^2 = 31.46, p < 0.001^{**}$
Location	$\chi^2 = 7.83, p = 0.02^{**}$	$\chi^2 = 2.00, p = 0.368$	$\chi^2 = 14.77, p < 0.001^{**}$
Loudness	$\chi^2 = 22.96, p < 0.001^{**}$	$\chi^2 = 0.43, p = 0.807$	$\chi^2 = 21.96, p < 0.001^{**}$
Origin of voice	$\chi^2 = 26.25, p < 0.001^{**}$	$\chi^2 = 6.28, p = 0.043^{**}$	$\chi^2 = 21.03, p < 0.001^{**}$
Amount of negative content	$\chi^2 = 39.56, p < 0.001^{**}$	$\chi^2 = 9.41, p = 0.009^{**}$	$\chi^2 = 24.11, p < 0.001^{**}$
Degree of negative content	$\chi^2 = 27.11, p < 0.001^{**}$	$\chi^2 = 7.47, p = 0.024^{**}$	$\chi^2 = 22.75, p < 0.001^{**}$
Amount of distress	$\chi^2 = 39.84, p < 0.001^{**}$	$\chi^2 = 7.72, p = 0.021^{**}$	$\chi^2 = 24.97, p < 0.001^{**}$
Intensity of distress	$\chi^2 = 40.28, p < 0.001^{**}$	$\chi^2 = 10.41, p = 0.005^{**}$	$\chi^2 = 24.04, p < 0.001^{**}$
Disruption to life	$\chi^2 = 37.71, p < 0.001^{**}$	$\chi^2 = 8.87, p = 0.012^{**}$	$\chi^2 = 18.25, p < 0.001^{**}$
Controllability	$\chi^2 = 29.64, p < 0.001^{**}$	$\chi^2 = 5.10, p = 0.078$	$\chi^2 = 15.50, p < 0.001^{**}$

*friedman test, p-value < 0.05**

The effect of antipsychotic treatment on the three main components of AH.

Figure 2 and 3 illustrate the effects of atypical and typical antipsychotics, respectively on the three main components (subscale) of AHs as defined by the PSYRATS-AH. These components were emotional, cognitive and physical. The emotional consisted of the amount and degree of negative content, and the amount and intensity of distress. The cognitive component consisted of perceived origin of the voice, disruption to daily life, and controllability.

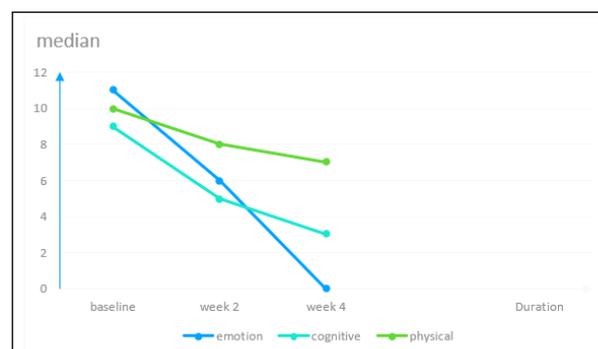


Figure 2: Effect of atypical antipsychotic on PSYRATS components

The physical component consisted of frequency, duration, location, and loudness of the voices. All antipsychotic groups (Figure 2, 3 and 4) demonstrated a significant reduction across all three components of AH, with the exception of the physical components in the typical antipsychotic (Figure 3). In this group, the reduction in the physical symptoms did not reach statistical significance ($\chi=5.448$, $p=0.066$).

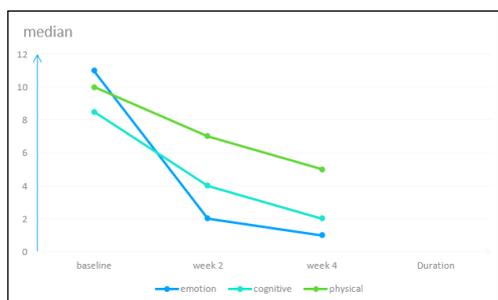


Figure 3: Effect of typical antipsychotic on PSYRATS components

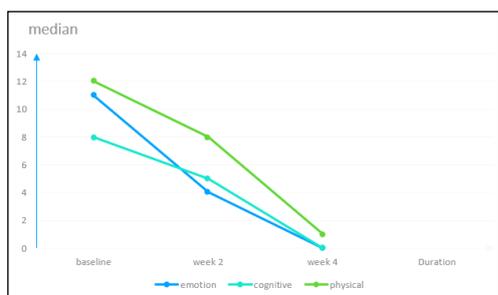


Figure 4: Effect of combination antipsychotic on PSYRATS components

DISCUSSION

This study investigated the short-term effects of antipsychotics on the dimensions of AHs in patients with relapsed schizophrenia. Antipsychotics were categorized into three groups: atypical, typical and combination therapy, with assessments conducted at weeks 2 and 4.^{17,18} The validated Malaysian version of the PSYRATS-AH¹⁶ scale was used for its ability to provide a detailed assessment of AH dimensions.

A total of 74 patients completed the study, with Malays comprising the majority (89.2%). This proportion is higher, though generally consistent with previous findings with one study reporting 66.2% Malay representation among patients with schizophrenia.¹⁸ Notably, another study on AH dimensions reported less Malay population representation at 36.7% which could possibly be due to regional differences and patterns of psychiatric service utilization.⁴ Local clinical data indicate that Malay patients account for approximately 66%-73% of

psychiatric unit visits, which may explain the higher representation observed in this study.

In this study, 71.6% of patients were treated with atypical antipsychotics, consistent with a retrospective analysis reporting that atypical antipsychotics accounted for 79.9% of all prescriptions to treat schizophrenia, with a steady increase in prescriptions times.¹⁹ The emergence of atypical antipsychotics, known for their superior efficacy in alleviating schizophrenia symptoms,²⁰ has led some clinicians to prefer them over typical antipsychotics. Atypical antipsychotics are also associated with fewer extrapyramidal side effects and improved cognitive function, making them a preferred option in clinical practice.²¹

Pharmacological treatment remains a cornerstone in managing schizophrenia, as evidenced by the improvements in AH scores observed in this study. However, no significant differences were found in AH dimension scores between the different antipsychotic types at both week 2 and week 4. These findings align with those from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) and subsequent meta-analyses, which found no substantial difference in overall efficacy between atypical and typical antipsychotics in treating schizophrenia.²² Although direct comparisons with the CATIE trial are limited due to differences in study design, both studies reported minimal differences in efficacy between the two antipsychotic classes during the observed periods.

One potential contributing factor to these findings may be genetic polymorphisms affecting antipsychotic drug metabolism, particularly those involving cytochrome P450 (CYP) enzymes.²³ Research indicates that Asian populations, including Malaysians, exhibit distinct CYP2D6 and CYP3A5 polymorphisms compared to Western populations. For instance, the CYP2D6*10 allele, which reduces enzyme activity, is prevalent in up to 50% of certain East Asian populations.²⁴ These genetic variations may influence the pharmacokinetics of antipsychotics, affecting therapeutic efficacy and side effect profiles.

While all antipsychotic groups showed overall

improvement in AHs, this study found that typical antipsychotics had a comparatively limited effect on the physical characteristic dimensions of AH, particularly frequency, loudness, and duration. It is hypothesized that each dimension of AH may respond differently to pharmacological treatment.²⁵ One possible explanation for this finding is the small sample size of patients receiving typical antipsychotics, which may have limited the power to detect significant changes compared to the atypical and combination groups.

Atypical antipsychotics exert their effects primarily through dopamine D₂ receptor antagonism in the mesolimbic pathway, reducing positive symptoms such as hallucinations. Additionally, their antagonism of serotonin (5-HT_{2A}) receptors enhances dopaminergic activity in the mesocortical pathway, potentially improving cognitive deficits²⁶ and negative symptoms.²⁶ Structural neuroimaging studies have implicated cortical thinning in the left middle temporal gyrus and disrupted connectivity between the right middle frontal gyrus and the left superior temporal gyrus in the pathophysiology of AH.^{27,28} The dorsal striatum, which receives input from speech-processing areas, is also thought to contribute to the misperception of internal thoughts as external voices.²⁹ Hyperactivity within the mesolimbic system further underpins the neurobiological basis of AH.³⁰

By modulating these neural circuits and neurotransmitter systems, atypical antipsychotics may influence both structural and functional brain changes. Evidence suggests that early treatment response may help restore disrupted connectivity, correlating with reductions in AH severity. This aligns with our study findings, where atypical antipsychotics produced broader improvements across all AH dimensions. These results are consistent with a 2016 study that had used the PSYRATS scale and reported similar outcomes.³¹ The same study also reported that similar to atypical agents, drugs with lower D₂ receptor affinity showed enhanced efficacy when combined with transcranial direct current stimulation.

Recent studies further support that typical antipsychotics, which primarily antagonize dopamine D₂ receptors, may be less effective in alleviating AH due to their limited

modulation of other neurotransmitter systems. In contrast, atypical antipsychotics with dual dopamine and serotonin antagonism, shows better therapeutic profile for AH.²⁶ A pragmatic randomized controlled trial comparing the efficacy of olanzapine, amisulpride, and aripiprazole in reduction of AH further supports this superiority among of certain atypical antipsychotics.³²

A small subset of participants underwent medication changes prior to the week 2 assessment, mainly involving the addition of depot typical antipsychotics to address adherence concerns. However, due to the limited number of cases, further subgroup analysis was not performed. Medication non-adherence remains a persistent challenge in the treatment of schizophrenia, with approximately 50% of patients demonstrating poor adherence.³³⁻³⁴ This limitation highlights the need to incorporate adherence monitoring in future studies, especially those with a longer follow-up period.

The short-term nature of this study presents a notable limitation, as it may not fully capture the longitudinal effects of antipsychotic treatment on AH. Moreover, there are limited research exploring the multidimensional aspects of AH using PSYRATS, thus making direct comparisons with existing literature challenging. Some studies have employed the PANSS for outcome assessment, which lacks the dimensional specificity provided by the PSYRATS.³⁵ Hence, the current findings may aid in the detailed evaluation of AH dimensions offered by PSYRATS and further enabling clinicians to tailor treatment based on specific symptom dimensions. For example, interventions such as cognitive behavioral therapy (CBT) and metacognitive training have shown efficacy in addressing distress-related dimension of AHs³⁶⁻³⁷ Therefore, the current study findings may aid clinicians in refining pharmacological strategies and integrating psychological therapies, while also taking into account tolerability and side effect profiles.

Future research should further explore the comparative effectiveness of pharmacological and psychological interventions across different AH dimensions. The present study provides preliminary evidence that may

serve as a catalyst for larger, long-term investigations in this area.

This study has several limitations. As an observational study design, treatment decisions including antipsychotic choice and dosage were based on clinical judgment, introducing selection bias and confounding by indication, particularly for patients with more severe symptoms. Variability in dosing and medication switching further complicate the interpretation of results. Without randomization or a standardized protocol, attributing outcomes solely to medication type is challenging.

The small sample size and short observation period limit the study's statistical power and its ability to draw long-term conclusions. The absence of a control group restricts causal inferences. Furthermore, factors such as medication adherence, polypharmacy, psychosocial variables, and comorbidities were not evaluated, despite their known impact on treatment outcomes.

Additionally, the study had only included patients who had episodes of schizophrenia relapses from a single district limiting generalizability to newly diagnosed patients or broader populations. Future research should employ randomized controlled, multicenter designs with larger samples and longer follow-up. In smaller populations, purposive sampling may offer a more efficient approach.

Despite these limitations, this study's strength lies in the standardized assessments conducted across three time points by a single rater, minimizing inter-rater variability. The findings provide early insights that may assist clinical decision-making in managing schizophrenia.

CONCLUSION AND RECOMMENDATION

This study underscores the importance of addressing the multidimensional nature of auditory hallucinations in schizophrenia to inform targeted treatment strategies. While all antipsychotic groups demonstrated short-term improvements, typical antipsychotics appeared less effective in alleviating the physical characteristics of hallucinations. Atypical antipsychotics, either alone or in combination, showed greater overall efficacy and may be

preferred in clinical decision-making alongside psychosocial interventions.

However, limitations such as a small sample size, short observation period, and the absence of a control group warrant caution in interpreting these findings. Thus, future research should emphasize larger, multicenter randomized controlled trials with extended follow-up periods and adherence monitoring. Additionally, evaluating the utility of PSYRATS in routine clinical settings may enhance its applicability and support more nuanced, dimension-specific treatment approaches.

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CONFLICT OF INTEREST

None

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Predictors to Mental Well-Being at Workplace: A Quantitative Case Study Among Administrative Staff of a Public University in Malaysia

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ABSTRACT

INTRODUCTION: The Malaysian Public Service Department reported many staff were at risk of mental health crisis or illness and an independent study revealed concerning rate of suicidal ideation. This study intends to: (a) describe the level of mental health literacy (MHL), mental health self-efficacy (MHSE), and mental well-being (MWB) among university administrative staffs, and (b) explore the dynamic influence between mental health literacy, mental health self-efficacy, and mental well-being. **MATERIALS AND METHODS:** A cross-sectional study using validated questionnaires was done on 91 administrative staff in one public university in Malaysia. The questionnaire consists of 37 items measuring MHL (subdimensions: knowledge, erroneous belief, first aid, and self-help), MHSE (subdimensions: optimism, factor coping, and advocacy), and MWB. Data was analysed using descriptive statistics, Pearson's correlation, and multiple linear regression. **RESULTS:** The mean scores for subdimensions of MHSE ranged from 14.2 to 28.6 (SD=2.73 to 4.45), subdimension of MHL from 6.1 to 25.5 (SD=2.17 to 3.35), and MWB was 18.5 (SD=3.36). Correlation analyses revealed all subdimensions of MHSE and MHL, as well as MWB showed significant weak to strong correlation ($r=0.22$ to 0.69). Only optimism subdimension of MHSE retained significance in predicting MWB ($B=0.43$) and among MHL subdimensions, only first aid retained significant prediction to optimism. **CONCLUSION:** The findings provide valuable insights to the dynamic role between subdimensions of MHL and MHSE, as well as their contribution towards MWB. Healthcare professionals should consider this dynamic into designing mental health promotion activity.

Keywords

mental well-being, mental health literacy, mental health self-efficacy, workplace

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INTRODUCTION

The importance of mental health or mental well-being has risen in both professional and public focus. According to the American Psychological Association, mental health is defined as *“a state of mind characterized by emotional well-being, good behavioral adjustment, relative freedom from anxiety and disabling symptoms, and a capacity to establish constructive relationships and cope with the ordinary demands and stresses of life.”*¹ On the other hand, mental well-being was proposed as an alternative terminology to represent mental health from the positive psychology perspective.² The two terminologies have been used interchangeably despite minor difference in wording and perspective. Sudden changes by the recent COVID-19 pandemic have

triggered the rise of mental health crisis and mental illness. Those from low-income communities, especially in urban areas, were more affected by mental illness as indicated by a higher prevalence for depression (24.2% vs 14.3%), anxiety (36.3% vs 8.0%), and stress (20.6% vs 0.9%) compared to national figures.³ These would have an impact on the workplace that may be reciprocal in nature. Surveys have indicated that the prevalence of high stress had shown an increasing trend among Malaysian workers and potentially lead to depression, anxiety, and burnout.⁴⁻⁶ The Malaysian Public Service Department have reported that more than 40,000 staff within the public service sector were at risk

of mental health crisis or illness and more than 11 % of healthcare workers reported suicidal ideation.⁷ This report added concerns over the mental well-being of workers.

Not surprisingly, the efforts to advocate for mental health at the workplace were numerous. Most notably was the recognition of the issue in the recent Mental Health Day theme for year 2024 that was “*It is Time to Prioritize Mental Health in the Workplace*”.⁸ Advocacy programs have been initiated by government agencies or corporate sectors to promote mental health among workers. Both the role of leadership and meaningful work seemed to significantly predict better mental health among staff in small and medium enterprises.⁹ The introduction of Employee Assistance Program (EAP) also showed significant contributions to improve mental well-being among staffs.¹⁰ This indicates that the organization can initiate impactful programs to maintain and improve the state of mental well-being among their staff.

Studies among university staff estimated prevalence of depression, anxiety, and stress were 28.7%, 50.1%, and 14.8% respectively.¹¹ Staff that are women, age less than 40 years old, and hold non-academic roles were reported to be prone to depression. Another study among academicians added high expectation and assuming multiple roles significantly contributed to high level of stress and burnout.¹² Studies involving non-academic staff were still lacking, especially in exploring factors related to mental health advocacy and its impact on mental well-being. Current available studies have focused on the prevalence of mental health crisis or illness, thus lacking the positive psychology perspective to the issue. This created a gap in operationalizing the concept of mental well-being in which understanding of the mental illness does not necessitate adequate to achieve good mental well-being. As far as the concept is concerned, a good mental well-being can also be achieved in the presence of mental illness.

Among the variables that are related to mental health advocacy are mental health literacy and mental health self-efficacy. Mental health literacy was defined as “*knowledge and beliefs about mental disorders which aid their recognition, management, and prevention*”.¹³ High level of

mental health literacy has been shown to predict good attitude towards mental health and help-seeking behaviour.¹⁴⁻¹⁶ Good mental health literacy can be achieved through advocacy and health education program that showed effectiveness among diverse populations such as adolescents and adults.^{13,17,18} Mental health literacy was less studied on its influence towards mental well-being among Malaysian population.

Mental health self-efficacy was defined as “*perceived ability to perform an act*”.¹⁹ The benefits of good mental health self-efficacy have been numerous and seem sustainable through encouraging social support, predicted less occupational stress, and building a conducive environment at work among Malaysian youths.^{20,21} Similar to mental health literacy, mental health self-efficacy can be shaped through advocacy program as evident by the *Sanubari* Optimal Health Program (Sanubari OHP) among junior doctors in Malaysia.²² This was only one study that linked mental health self-efficacy to mental well-being and currently, there is a lack of evidence among university administrative staff.

Therefore, this study aimed at addressing the above gaps. Specifically, the study intended to achieve the following objectives: (a) describe the level of mental health literacy, mental health self-efficacy, and mental well-being among university administrative staffs, and (b) analyse the role of mental health literacy and mental health self-efficacy onto mental well-being among university’s administrative staff.

MATERIALS AND METHOD

This study utilized a cross-sectional design using a validated questionnaire among university administrative staffs at the International Islamic University Malaysia. The questionnaire was self-administered to 91 staff that were chosen using purposive sampling among participants in a series of mental health advocacy workshops. The staff were included for data collection if they were on permanent employment and worked at least one year at the university. There was no exclusion criteria set. Multiple reiterations were made to express their right not to participate in the study to overcome possible

perceptions of coercion before consent was obtained. Sample size calculation using a-priori sample size calculator for multiple regression by Soper with anticipated moderate effect size from previous study and treating the subdimensions as individual predictor revealed a minimum sample size of 56 respondents.^{22,23} The questionnaire consists of four sections that measured: (1) sociodemographic characteristics, (2) mental health literacy, (3) mental health self-efficacy, and (4) mental well-being. Sociodemographic characteristics such as age, gender, highest education attainment, and household income.

The mental health literacy was measured using the Mental Health Literacy Questionnaire-Short Version for Adults (MHLq-SVa) consisting of 16 items measuring four dimensions: (a) knowledge of mental health problems, (b) erroneous belief/stereotypes, (c) help-seeking and first aid skills, and (d) self-help strategies. The instrument utilized a 5-point interval scale from “strongly disagree” to “strongly agree”. It has good content and construct validity and achieved 0.84 reliability index on Cronbach’s alpha.²⁴ Scores were obtained through summation of responses for each subdimension and for the whole construct. However, only scores for subdimensions were used for analysis in this study. Each subdimension has different number of items thus producing maximum score ranging from 15 to 30. All subdimensions reflected better outcomes with higher score except for erroneous belief subdimension.

Mental health self-efficacy was measured using the Mental Health Confidence Scale consists of 16 items measuring three dimensions that are: (a) optimism, (b) factor coping, and (c) advocacy.²⁵ The instrument utilized a 6-point interval scale with the extremes defined as “very not confident” and “very confident”, respectively. It has good content and construct validities as well as 0.94 reliability index on Cronbach’s alpha. Items can be scored by summation for each subdimension or the whole construct. Therefore, scores may range from 16 to 112 for the whole construct. Higher scores reflected higher mental health self-efficacy.

Mental well-being was measured using the WHO-5 mental

well-being questionnaire consisting of five items measuring one dimension. The response options utilized a 6-point interval scale from “none at all” to “all the time”. Total score may range from 0-30 points by summation of responses. It reported good content, factorial, concurrent, and convergent validity evidence and 0.91 reliability index on Cronbach’s alpha.²⁶ There was no categorisation proposed for the total score but higher score reflected higher mental well-being.

Descriptive analysis employed frequency and percentage for categorical variables and mean and standard deviation for numerical variables. Pearson’s correlation was used to analyse the relationship between scores of mental health literacy, mental health self-efficacy, and mental well-being. Correlation coefficient that are less than 0.2 was considered as very weak, 0.21 to 0.40 as weak, 0.41 to 0.60 as moderate, 0.61 to 0.80 as strong, and 0.81 to 1.0 as very strong.²⁷ Multiple linear regression was used to identify significant predictors to mental well-being. Ethical approval was obtained from the IIUM Research Ethics Committee [IREC 2024-292].

RESULTS

Most of the respondents were female (78%), with a mean age of 42.6 years old, married (74.7%), with household income between RM3,001 - RM6,000 (44%), and all respondents were of Malay ethnicity and subscribed to the religion of Islam. Over 60% of respondents attained at least an undergraduate education. Detailed descriptive statistics for demographic characteristics was presented in Table I below.

Table I: Respondents Sociodemographic Characteristics (n = 91)

Variable	n (%)
Age	42.6 (8.77)*
Gender	
Male	20 (22)
Female	71 (78)
Marital Status	
Deceased spouse	3 (3.3)
Married	68 (74.7)
Single	20 (22)
Household Income	
Less than RM 3,000	17 (18.7)
RM 3,001 to RM 6,000	40 (44)
RM 6,001 to RM 9,000	15 (16.5)
RM 9,001 to RM 12,000	12 (13.2)
More than RM 12,000	7 (7.7)
Highest education attained	
Primary school	2 (2.2)
Secondary school	34 (37.4)
Undergraduate	29 (31.9)
Postgraduate	26 (28.6)

* mean (SD)

Correlation between Subdimensions of Mental Health Self-Efficacy, Mental Health Literacy, and Mental Well-Being

Subdimensions under mental health self-efficacy showed several significant correlations. Optimism showed weak positive correlation with factor coping ($r=0.27$, $p=0.011$) and knowledge ($r=0.29$, $p<0.01$), moderate positive correlation with first aid ($r=0.44$, $p=0.008$) and self-help ($r=0.40$, $p<0.001$), and strong positive correlation with advocacy ($r=0.69$, $p<0.001$) and mental well-being ($r=0.67$, $p<0.001$). Factor coping showed weak positive correlation with advocacy ($r=0.38$, $p<0.001$) and mental well-being ($r=0.30$, $p=0.006$). Advocacy showed a weak positive correlation with knowledge ($r=0.36$, $p<0.001$), and moderate positive correlation with first aid ($r=0.55$, $p<0.001$), self-help ($r=0.52$, $p<0.001$), and mental well-being ($r=0.50$, $p<0.001$). Higher score of optimism may show higher scores of factor coping, knowledge, first aid, and self-help subdimensions. Higher score of factor coping may show higher scores of advocacy, and mental well-being. Higher score of advocacy may show higher scores of knowledge, first aid, self-help, and mental well-being.

Several subdimensions of mental health literacy showed several significant correlations. Knowledge showed weak negative correlation with erroneous belief ($r=-0.31$, $p=0.004$), weak positive correlation with mental well-being ($r=0.26$, $p=0.018$), and moderate positive correlation with first aid ($r=0.46$, $p<0.001$) and self-help ($r=0.60$, $p<0.001$). Erroneous belief showed a weak negative correlation with self-help ($r=-0.31$, $p=0.004$). First aid showed a weak positive correlation with mental well-being ($r=0.22$, $p=0.044$) and a moderate positive correlation with self-help ($r=0.58$, $p<0.001$). Finally, self-help showed a weak positive correlation with mental well-being ($r=0.32$, $p=0.003$). Higher score of knowledge may present with lower score of erroneous belief, and higher scores of mental well-being, first aid, and self-help. Higher score of erroneous belief may show lower score of self-help. Higher score of first aid may show higher scores of mental well-being and self-help. Finally, higher score of self-help may show higher score of mental well-being. These findings were summarized in Table II.

Table II: Descriptive Statistics and Pearson Correlations Analysis between Mental Health Self-Efficacy, Mental Health Literacy, and Mental Well-Being

Variable	Mean (SD)	Correlation coefficient						
		1a	1b	1c	2a	2b	2c	2d
Mental health self-efficacy								
Optimism (1a)	28.6 (4.45)							
Factor coping (1b)	23.5 (6.33)	0.27*						
Advocacy (1c)	14.2 (2.73)	0.69**	0.38**					
Mental health literacy								
Knowledge (2a)	25.5 (3.35)	0.29**	0.16	0.36**				
Erroneous belief (2b)	6.1 (3.02)	-0.10	0.09	-0.10	-0.31**			
First aid (2c)	12.9 (2.17)	0.44**	0.09	0.55**	0.46**	-0.16		
Self-help (2d)	18.2 (2.54)	0.40**	-0.07	0.52**	0.60**	-0.31**	0.58**	
Mental well-being	18.5 (3.36)	0.67**	0.30**	0.54**	0.26*	0.03	0.22*	0.32**

Note: Correlation is significant at the *0.05 or **0.001 level (2-tailed).

Predictors to Mental Well-being

Multiple linear regression revealed only optimism retained significant prediction of mental well-being scores ($F(6,78)=12.73$, $p<0.001$). For every unit of optimism score, mental well-being scores increase by 0.43 unit ($B=0.43$, 95% CI: 0.27–0.60, $p<0.001$). The prediction model was able to explain 45.6% (Adjusted R^2) variance in mental well-being scores. These findings were summarized in Table III below.

Table III: Multiple Regression Analysis for Predictors of Mental Well-being

Predictors	Univariate		Multivariate			
	B	p	B	95 % CI		p
				LL	UL	
Mental health self-efficacy						
Optimism	0.51	< .001	0.43	0.27	0.60	<.001
Factor coping	0.16	.016	0.05	-0.05	0.16	.378
Advocacy	0.66	< .001	0.18	-0.15	0.51	.335
Mental health literacy						
Knowledge	0.27	.008	0.05	-0.16	0.26	.601
Erroneous belief	0.04	.780	-	-	-	-
First aid	0.34	.059	-0.33	-0.67	0.00	.053
Self-help	0.42	< .001	0.16	-0.17	0.48	.292

Note: B – regression weight; CI – confidence intervals; LL – lower limit; UL – upper limit

Despite several predictors showing significance values less than 0.001 in the univariate analysis, only optimism retained its significance. This indicates that the influence of factor coping, advocacy, knowledge, and self-help onto mental well-being were a function of optimism. Subsequent analyses were done on subdimensions of mental health literacy as predictors to optimism. The multivariate analysis revealed only first aid ($B=0.63$, 95% CI: 0.14–1.12, $p=0.010$) retained its significance in predicting optimism. The prediction model was able to explain 19.4 % (Adjusted R^2) variance in optimism scores. These findings were summarized in Table IV below.

Table IV: Multiple Regression Analysis for Predictors of Optimism

Predictors	Univariate		Multivariate			
	B	p	B	95 % CI		p
				LL	UL	
Mental health literacy						
Knowledge	0.39	.002	0.04	-0.28	0.36	.762
Erroneous belief	-	-	-	-	-	-
First aid	0.89	< .001	0.63	0.14	1.12	.010
Self-help	0.70	< .001	0.35	-0.12	0.81	.157

Note: B – regression weight; CI – confidence intervals; LL – lower limit; UL – upper limit

Results of the predictors to optimism revealed that the influence of knowledge on mental health and self-help onto optimism was a function of first aid. Reflecting on the correlation between these predictors, it seemed probable that knowledge and self-help contributed to the development of first aid, which in turn predict optimism and subsequently mental well-being.

DISCUSSION

To recapitulate, most of mental health self-efficacy (MHSE) and mental health literacy (MHL) subdimensions were significantly correlated with each other, except for factor coping (MHSE) and erroneous belief (MHL). Advocacy subdimension of MHSE showed stronger magnitude of correlation with MHL subdimensions compared to optimism. These findings were in congruent with studies involving Chinese civil servants, Turkish nurses, and Australian sportsman.²⁸⁻³⁰ Mental health literacy was associated with some elements of mental health self-efficacy as operationalised in this study. In particular, emotional regulation self-efficacy was shown to be influenced by mental health literacy among Chinese civil servants, whereas Australian sportsman showed significant association between mental health literacy with confidence to support and help-seeking (conceptually related to optimism and advocacy, respectively). These coherent findings suggest that mental health self-efficacy and mental health literacy have associations across different culture and population. The stronger magnitude of correlation between advocacy and subdimensions of MHL suggests an opportunity for a tailored intervention that improves specific elements of MHL. This finding was novel in this study, especially within the target population.

Mental health promotion should focus on increasing knowledge on mental health, ways to seek help (first aid) and good self-help skills in hope to improve advocacy subdimension of MHSE. Different modalities can be

utilised in delivering the intervention. For example, a self-guided digital service has shown to improve both mental health literacy and mental health self-efficacy among Finnish patients with more relevance to younger population.³¹ Classical approach using educational module among young adults in Chennai showed a single 90-minute MHL module can lead to significant improvements in stigma, knowledge, and behaviour related to mental health up to 6 months post intervention.³² The refutation of erroneous belief may not be preferred to include in the mental health promotion. As indicated above, erroneous beliefs were not significantly correlated with advocacy or any other MHSE subdimensions. However, the negative correlation between knowledge and erroneous belief suggested that focusing mental health promotion on improving knowledge on mental health may provide additional benefit of reducing erroneous belief. Such approach of educating is much more desirable compared to antagonising approach to refute erroneous beliefs.

Bivariate analyses showed two subdimensions each of mental health literacy (MHL) and mental health self-efficacy (MHSE) showed significant prediction towards mental well-being. Knowledge and self-help of MHL and optimism and advocacy of MHSE predicted scores of mental well-being. This is consistent with studies that reported improvement in knowledge and self-help skills showed significant impact on mental wellbeing among various population.^{15,16,29,33} Optimism and advocacy predicted scores of mental well-being with the latter presented with higher magnitude of influence. The influence of MHSE onto mental well-being or precursors to mental well-being has been shown in studies involving parents, adolescents, and opioid users of overseas populations.^{22,34-36} This study extended the evidence of MHSE predicting mental well-being among working adults in university's administration.

This study found optimism, a subdimension of MHSE, as the sole significant predictor to mental well-being among administrative staff in a public university. This lends support to the full mediation role of optimism as seen among Spanish elderly population in previous study.³⁷ Optimistic individuals tend to have a positive outlook

on life, which may help them cope more effectively with work-related stressors, reduce negative emotions, and maintain better mental well-being. The influence of other mental health self-efficacy and literacy subdimensions on mental well-being may appear to be mediated by optimism as suggested by the change in regression weight and significance status from bivariate to multivariate regression analysis. This suggests that the benefits of mental health knowledge, first aid skills, and self-help strategies on mental well-being may operate through their effects on optimism. Individuals with greater mental health literacy and self-efficacy may be more likely to maintain an optimistic outlook, which in turn promotes their overall mental well-being.

The dissipating role of MHL onto mental well-being stimulated the quest to understand its role onto optimism. First aid was the only significant predictor to optimism among the subdimensions of MHL. Considering the strong positive correlation between the variables, the dynamic role of these subdimensions can be postulated. The formation of good MHL should be directed to improve first aid skills through collectively improving knowledge and self-care. First aid MHL may then resulted in better optimism among staff to manage their mental health, thus resulting in good MWB. This proposed mechanism of action was suggested after reviewing the results of correlation and regression analyses in tandem. Mental health literacy should be seen as precursors to developing good MHSE rather than being a direct contributor to mental well-being. Hence, this consideration should be reflected on how healthcare professionals assess the effectiveness of their intervention.

There are several limitations identified in this study. Firstly, this study was limited to administrative staff at a single public university, which may limit the generalizability. Future research should examine these relationships across broader samples of employees in different sectors and organizations. Secondly, a purposive sampling method during data collection may provide skewed picture among homogenous population. Therefore, future studies may consider using random sampling method to obtain a more representative data of the population. Thirdly, the dynamic between subdimensions

of MHL and MHSE, and its role towards MWB were analysed using linear regression technique due to the limited sample size and resources available for complex analysis. Future studies may consider using structural equation modelling to re-explore the role of these subdimensions as reported and discussed above. Fourthly, this study has focused on variables that were considered potential outcomes for mental health advocacy program as organised by the university and lack consideration of confounding variables. Future studies with better representativeness should consider including potential confounding variables such as history of mental illness, caregiving status for mental illness patient, and others.

CONCLUSION

The level of mental health literacy, mental health self-efficacy, and mental well-being among university administration staff were moderate with wide variation especially in factor coping of MHSE. Subdimensions of MHL and MHSE showed dynamic inter-relations and revealed that only first aid subdimension of MHL predicted optimism, and only optimism predicted MWB. These findings provided suggestions on how to focus the mental health promotion efforts and what to measure for assessing the effectiveness of specific interventions.

CONFLICT OF INTEREST

All authors declared no competing interests

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Ameliorative Effects of *Olea europaea* Oil on Morphine Withdrawal: Behavioural, Biochemical and Histological Evidence in Rats

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ABSTRACT

INTRODUCTION: Prolonged morphine use can trigger dependence and addiction leading to severe withdrawal symptoms upon cessation. Oxidative stress is a key factor in its pathogenesis. *Olea europaea* (olive) oil, rich in polyphenols and oleuropein, exhibits antioxidant, anti-inflammatory and neuroprotective properties. Thus, this study aimed to evaluate the effects of *Olea europaea* oil in alleviating morphine withdrawal symptoms in morphine-dependent rats. **MATERIALS AND METHODS:** A total of eighteen rats were randomly divided into three groups. The control group received normal saline, while the positive control group received intraperitoneal injections of morphine sulphate (2.5 mg/kg to 50 mg/kg) for seven days. The treatment group received the same morphine doses followed by oral administration of 250 mg/kg *Olea Europaea* oil for twenty-one days during morphine withdrawal period. Spontaneous morphine withdrawal behaviours of rats were observed. Subsequently the rats were sacrificed and the brain tissue was stained with H&E for histological markers. Blood serum and brain tissue were collected for Glutathione (GSH) level measurement using an ELISA kit. The findings were analysed using GraphPad Prism. **RESULTS:** The administration of *Olea Europaea* oil significantly reduced ($p < 0.05$) spontaneous withdrawal symptoms. Findings show that *Olea Europaea* oil ameliorated histological brain signs of morphine toxicity and GSH levels in the brain tissue of the treated group were significantly higher ($p < 0.05$) compared to the no-treatment group. **CONCLUSION:** This study demonstrates that *Olea Europaea* oil supplementation significantly alleviates morphine withdrawal symptoms and restores antioxidant capacity likely due to its potent antioxidant and neuroprotective properties.

Keywords

Antioxidant, Glutathione (GSH), *Olea Europaea* oil, Oxidative Stress, Morphine withdrawal

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INTRODUCTION

Morphine is known for its potent analgesic effects in Managing the withdrawal symptoms remain the most managing patients experiencing severe or chronic pain. difficult challenge in treating opioid addiction.² Despite However, repeated prolonged or abused administration of the pharmaceutical treatments used today such as morphine can trigger the development of dependence and methadone, buprenorphine, clonidine, and naltrexone are addiction, subsequently leading to a difficult withdrawal effective, they frequently have serious adverse effects that syndrome upon abrupt cessation.¹ Upon the cessation of increase the risk of relapse.³ Herbal medicines have drawn chronic morphine use, patients can experience severe more attention in recent times as viable therapeutic withdrawal symptoms including tremors, anxiety, muscle choices for a range of medical ailments. Herbal remedies aches, sweating, gastrointestinal distress, and more.² have long been used to relieve withdrawal symptoms, and

new studies suggest they could offer a promising alternative or addition to conventional treatment. This strategy could improve patient outcome and lower the chance of relapse by effectively relieving symptoms with fewer side effects.⁴

Olea europaea commonly known as olive is an abundant tree along the Eastern Mediterranean coastline, Western Asia and Northern Iran near the Caspian Sea which has been traditionally used in folk medicine to treat a variety of conditions.⁵ Due to its wide availability in local markets and low cost, *Olea europaea* oil presents a practical and economical option for therapeutic application. Emerging research demonstrates that *Olea Europaea* is enriched with a variety of polyphenolic antioxidants including oleuropein, hydroxytyrosol, tyrosol, and oleocanthal which can scavenge free radicals and attenuate oxidative stress implicated in multiple disease states. Several studies have linked oxidative stress to the development of both morphine tolerance and withdrawal.^{6,7} However, limited studies are available on the effectiveness of *Olea Europaea* oil to mitigate morphine dependence and withdrawal symptoms by restoring redox homeostasis. Therefore, the current study aimed to analyse the efficacy of *Olea europaea* oil supplementation in alleviating morphine withdrawal symptoms using a rat model of morphine dependence.

MATERIALS AND METHODS

Olea europaea oil

Olea europaea oil was purchased from the local market in Selangor.

Animals

This study included eighteen (n=18) Sprague-Dawley rats weighing between 180-220 grams on average. The sample size is calculated using the following formula:

$$E = \text{total number of animals} - \text{total number of groups}$$

$$E = [6 \times 3] - 3$$

$$E = 15$$

A sample size is deemed acceptable if it maintains E between 10 and 20. Thus, when the E is 15, the number of rats employed in this experiment is deemed appropriate.⁸ The rats were kept in the animal house at Management & Science University under

carefully monitored circumstances including $23 \pm 1^\circ\text{C}$, a 12-hour light/dark cycle, a generally humid atmosphere (30%–40%) and unrestricted access to food and water. The rats were acclimatized for one week before the study begin.

Induction of morphine dependence rats

Eighteen (n=18) rats were exposed to morphine sulphate (10 mg/mL; Merck, Germany) to induce morphine dependency in rats. Based on a study conducted by Sabuee et al. with some modifications, morphine was delivered intraperitoneally twice daily for seven days with gradually increasing doses to induce dependency.⁹ Morphine sulphate was administered incrementally from 2.5 mg/kg to a maximum dosage of 50 mg/kg. The doses were titrated as follows: Day 1–2.5 mg/kg, Day 2–5 mg/kg, Day 3–10 mg/kg, Day 4–20 mg/kg, Day 5–30 mg/kg, Day 6–40 mg/kg, and Day 7–50 mg/kg. When induction of morphine was completed, rats in the treatment group were given *Olea europaea* oil orally for 21 days. Withdrawal behaviour was observed on Days 1, 7, 14 and 21. After completing behavioural testing, the animals were sacrificed by cervical dislocation.

Animal grouping

The rats were divided into 3 groups consisting of 6 rats each as shown in Table I.

Table I: Animal grouping

Group	Exposure
Negative control (n=6)	Normal saline (200 μL /rat, i.p) daily for 7 days.
Positive control (n=6)	Morphine sulphate solution (i.p) twice daily for 7 days at incremental dose from 2.5 mg/kg up to 50 mg/kg, twice daily. The doses were titrated as follows: Day 1–2.5 mg/kg, Day 2–5 mg/kg, Day 3–10 mg/kg, Day 4–20 mg/kg, Day 5–30 mg/kg, Day 6–40 mg/kg, and Day 7–50 mg/kg. Withdrawal symptom observed for 21 days following morphine dependency.
Treatment group (n=6)	Morphine sulphate solution (i.p) twice daily for 7 days at incremental dose from 2.5 mg/kg up to 50 mg/kg, twice daily. The doses were titrated as follows: Day 1–2.5 mg/kg, Day 2–5 mg/kg, Day 3–10 mg/kg, Day 4–20 mg/kg, Day 5–30 mg/kg, Day 6–40 mg/kg, and Day 7–50 mg/kg. When morphine dependency has been established, oral <i>Olea europaea</i> oil (250 mg/kg) was once given daily for 21 days. Withdrawal symptom observed for 21 days following treatment.

Evaluation of spontaneous morphine withdrawal behaviour

Following the induction of morphine dependency, the rats were placed in cages for 30 minutes on Days 1, 7, 14 and 21, to observe signs of spontaneous morphine

withdrawal namely, i) wet dog shakes, ii) writhing, iii) face grooming, and iv) sniffing. After allowing 5 minutes for the rats to acclimatise to the cages, the above-mentioned withdrawal signs were continuously monitored and recorded on video for 30 minutes and the scores were averaged for each behavioural test.

Measurement of antioxidant level by ELISA test

All 18 rats were sacrificed upon completing the study. An enzyme-linked immunosorbent assay (ELISA) (Elabsience, USA) kit was used to quantify glutathione (GSH) in the blood and brain tissue. Blood was drawn via cardiac puncture before sacrificed and centrifuged at 3000 rpm for 10 minutes. To measure GSH levels, the serum was isolated and kept at -80°C. The rat brain was removed for tissue analysis, and rinsed with ice-cold phosphate buffer saline (0.01 M, pH 7.4) to eliminate excess blood. The GSH levels in the supernatant were ascertained, using the GSH ELISA test kit following the manufacturer's instructions.

Haematoxylin and eosin (H&E) staining of rat tissue sections

To assess neuronal integrity, histological analysis focused on identifying morphological changes including neuronal degeneration, fragmentation, and hyperchromatic features particularly in the hippocampal CA1 region. These structural characteristics were evaluated as potential indicators of apoptosis associated with escalating morphine dosages. Brain tissues were fixed in 10% neutral phosphate buffered formalin then dehydrated and stored in liquid paraffin. Tissue samples were sectioned at 5 µm thickness, deparaffinized, rehydrated and staining with haematoxylin and eosin (H&E).

Data analysis

For each group, the data are shown as the mean ± SEM. One-way ANOVA was used for statistical analysis, and Tukey's post hoc test was used for pairwise comparisons of group means. A P-value of less than 0.05 was deemed statistically significant.

RESULTS

Effects of *Olea europaea* oil on Morphine withdrawal

The effects of morphine and *Olea europaea* oil on withdrawal were investigated by observing exposed animals following the cessation of morphine. Withdrawal behaviour namely i) wet dog shakes, ii) writhing, iii) face grooming, and iv) sniffing were scored over a 30-minute period. Based on the results, the group receiving *Olea europaea* oil (Treatment Group) showed a significant improvement in the morphine withdrawal signs as compared to the untreated group (Positive Control) ($p < 0.05$), as depicted in Figure 1.

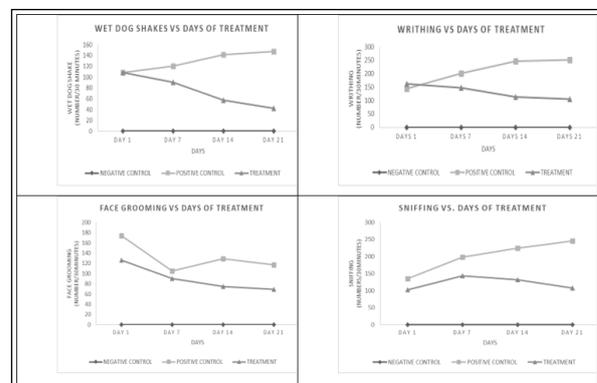


Figure 1: The effects of *Olea europaea* oil on morphine withdrawal signs after 21 days of morphine cessation. The data is expressed as the mean ± SEM.

Effects of *Olea europaea* oil on Glutathione (GSH) level in the brain and blood

An analysis of GSH concentration in the brain tissues and blood is displayed in Figure 2. The results demonstrate that the GSH levels in the brain tissue of the treatment group are significantly greater than those in the untreated group, and there is no significant difference in the GSH concentration of blood in all groups.

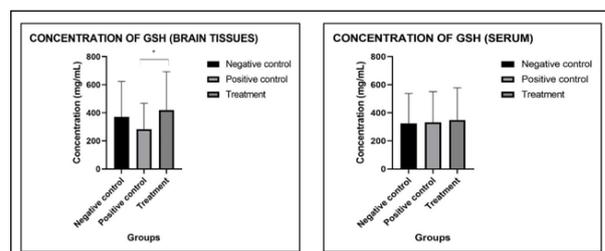


Figure 2: The effects of *Olea europaea* oil on GSH level in blood and brain tissue. Data are shown using the mean ± SEM.

Effects of *Olea europaea* oil on the histological changes in hippocampus

Figure 3 illustrates the effects of *Olea europaea* oil on the hippocampal region in brain sections. In this comparative histological study, the CA1 area of the hippocampus in the positive group exhibits tiny, fragmented hyperchromatic neurones during the examination of the effects of escalating morphine dosages (50 mg/kg), which suggests cellular death. In contrast, the group that received *Olea europaea* at 250 mg/kg showed noticeably reduced neuronal damage with more preserved neuronal morphology and fewer activated microglia, similar to the brain structure observed in the negative control group (saline only).

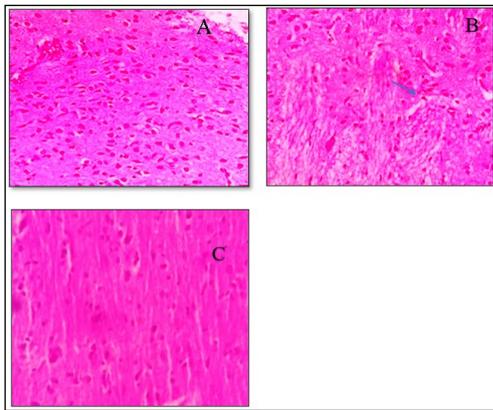


Figure 3: Histological section of neuron with haematoxylin and eosin at 40x magnification. (A) Negative control (normal saline only), (B) Positive control group (morphine sulphate only), (C) Treatment group (morphine sulphate and *Olea europaea* oil -treated with 250mg/kg). Neurons that have degenerated can be identified by their shrunken appearance, with condensed and darkly stained nuclei (blue arrow). The microglia present in this region are characterized by their small size, featuring elongated nuclei surrounded by minimal cytoplasm.

DISCUSSION

Effects of *Olea europaea* oil on morphine withdrawal

In agreement with our previous studies, administering daily intraperitoneal injection of increasing dosage until the maximum of 50 mg/kg morphine was effective in sustaining rats in a state of morphine dependence at Day 7.⁷ Small modifications were made to the morphine dependence model originally described by previous study.⁹ In the previous study, rats were treated with morphine at a higher dosage of 180 mg/kg on Day 6. However, in this study, rats that had been treated at Day 7 with a lower dosage (50 mg/kg) were enough to elicit the full spectrum of withdrawal signs. Reducing both the duration of treatment and the dosage significantly contributed to a notable decrease in the mortality rate.

Withdrawal symptoms became evident around 20 hours after the last morphine dose. In these recent investigations, various indicators of morphine withdrawal were employed to verify the physical dependence of rats on morphine. These included alterations in well-characterised and commonly observed behaviours associated with withdrawal, namely i) wet dog shaking, ii) writhing, iii) face grooming, and iv) sniffing. Rats that had been deprived of morphine for 20 hours displayed other characteristic signs of opioid withdrawal, such as physical withdrawal symptoms. Notably, these withdrawal indicators remained consistent throughout the duration of the study. The present study evaluated the impact of *Olea europaea* oil on the symptoms of morphine withdrawal syndrome in rats, using dosages of 250 mg/kg of the oil. Results showed that dosages of 250 mg/kg of *Olea europaea* oil decreased the amount of withdrawal-related wet dog shakes. Also, this dose reduced the number of writhing, sniffing, and face grooming due to withdrawal syndrome significantly.

Studies had demonstrated that calcium channel blockers, which function via mechanisms involving both the central and peripheral neural systems could mitigate the symptoms associated with morphine withdrawal.¹⁰ A previous study has demonstrated that T-type voltage-gated calcium channels played a crucial role in the development of morphine dependence and the manifestation of withdrawal symptoms.¹¹ It was proven that the symptoms of morphine withdrawal were lessened by calcium channel blockers which inhibited L-type voltage-gated calcium channels.¹² Another researcher had found that in rats, mecamlamine-precipitated nicotine withdrawal syndrome was lessened by calcium channel blockers. The development of tolerance and dependence as well as the antinociception induced by morphine and nicotine appeared to have been mediated by comparable calcium-dependent pathways. In the current study, we proposed *Olea europaea* oil could alleviate morphine withdrawal syndromes owing to its calcium channel blocking properties. Studies had revealed that olive leaf extract blocked calcium channels. This effect of the leaf extract from *Olea europaea* oil had been connected to oleuropein, which is the primary component of the extract.¹³ Oleuropein, which made up 35.6% of the extract was likewise the main ingredient of olive leaf

extract according to high-performance liquid chromatography (HPLC) studies.¹⁴

Antioxidant

Changes in the cellular antioxidant state revealed the oxidative stress induced by morphine in specific brain areas. Further research had demonstrated that morphine reduced the hippocampal enzymatic activity of glutathione (GSH), superoxide dismutase (SOD), and glutathione peroxidase (GPx).^{15,16} Results from this study showed that the quantities of GSH were much lower in the brains of rats that were given morphine alone (Positive control group) which was consistent with another research. This was because the administration of morphine caused an excessive number of free radicals to be produced, which led to oxidative stress and a reduction in antioxidant status. Thus, the levels of antioxidants like GSH were substantially diminished, signalling their depletion in neutralising free radicals.¹⁷ Morphine could alter intracellular GSH levels, which could therefore affect cellular redox state, S-adenosylmethionine levels, and ultimately global DNA methylation.¹⁸

A growing amount of research indicated that oxidative stress contributed to the development of addiction to a variety of drugs, including morphine and methamphetamine.^{19,20} In addition to causing the generation of free radicals, such as reactive oxygen species (ROS) or reactive nitrogen species (RNS), morphine, which was known to activate opioid receptors, also reduced the actions of antioxidants in target cells. Rats that were dependent on morphine demonstrated increased oxidative stress in the hippocampus and prefrontal cortex.²¹ The ratio of pro-oxidants to antioxidants determined the oxidative state of cells. Reactive oxygen species (ROS), another name for pro-oxidants, were divided into two groups: radicals and nonradicals. Radicals were very reactive because they could easily accept or give electrons in order to stabilize. Excess ROS was produced under oxidative stress in cells, and this excess ROS has the ability to oxidize DNA, lipids, and proteins. Damage to organs and cell death resulted from this oxidation. The present results indicated an elevation in brain

GSH levels in response to the influence of morphine. This observation aligned with previous evidence demonstrating that *Olea Europaea* oil had the capacity to boost GSH levels.²²

The protective ability of *Olea europaea* oil came from its polyphenols, which were known to be highly antioxidant. These polyphenols could neutralise ROS and other free radicals by donating electrons to them, hence protected cells from being damaged by the attack of ROS and free radicals.^{23,24} Phenolic acids, phenolic alcohols, flavonoids, and secoiridoids, were the four primary categories of phenolic chemicals identified in olive fruit. While many fruits and vegetables from other plant groups included phenolic acids, alcohols, and flavonoids, only the Oleaceae family contained secoiridoids. Many phenolic acids, including vanillic, syringic, caffeic, ferulic, p-coumaric, gallic, p-hydroxybenzoic, protocatechuic, and sinapic acids, were found in olive fruit. Tyrosol [(p-hydroxyphenyl) ethanol] and hydroxytyrosol [(3,4-dihydroxyphenyl) ethanol] were the most prevalent phenolic alcohols in olive fruit.²⁵ Flavonoids found in olive fruit include anthocyanins like cyanidin 3-O-glucoside and cyanidin 3-O-rutinoside, as well as flavonol glycosides such luteolin-7-glucoside and rutin.

Histopathology

The histological examination of the hippocampus after administering morphine (50 mg/kg) revealed signs of cellular apoptosis or programmed cell death. Particularly, in the hippocampal CA1 region, tiny, broken up, and hyperchromatic neurons were seen, which was indicative of neuronal death. *Olea europaea* oil treatment, however, did not result in these apoptotic alterations, indicating that *Olea europaea* oil could inhibit morphine-induced neuronal death. Apoptosis, or cell death, in nerve cells could be induced by amphetamines and heroin, as multiple investigations had shown. It had been established by earlier studies that these medications might have caused differentiated neurons to undergo apoptosis, which could have led to changes in intercellular dopamine levels.²⁶ It had been demonstrated that long-term or chronic morphine usage causes had caused oxidative stress, inflammation, and death in brain neurons,

especially in the hippocampus region of lab animals.²⁷

It had been suggested that the antioxidant polyphenol oleuropein which was present in olive leaf extract scavenged free radicals. Oleuropein was a phenolic molecule that had been shown in several studies to have a variety of pharmacological actions, including antioxidant, hypotensive, vasodilatory, anti-inflammatory, and neuroprotective activities.²⁸⁻³⁰ Furthermore, studies had demonstrated that oleuropein administration could have reduced oxidative stress and cognitive impairment caused by specific anaesthetic medications in the rat CA1 area of the hippocampal hippocampus.³¹ Oleuropein or olive leaf extract has been demonstrated in a number of earlier investigations to have anti-apoptotic effects in a variety of cell types, especially in the presence of oxidative stress. Furthermore, oleuropein administration following spinal cord injury has been shown to have a neuroprotective effect in rats, as shown by an increase in glutathione levels and a decrease in several apoptotic markers (Bax/Bcl2 ratio).³² According to previous study, oleuropein had lowered cleaved caspase-3 activation and the Bax/Bcl2 ratio, which in turn lowers the production of reactive oxygen species (ROS) and apoptosis in an in vitro model of Parkinson's disease.³³ Additionally, studies have demonstrated that oleuropein had neuroprotective effects against colchicine-induced cognitive impairment in the rat hippocampus CA1 region. These effects had been attained via lowering oxidative stress and activating caspase-3.²⁸

CONCLUSION

Our finding demonstrates that *Olea europaea* oil markedly alleviated withdrawal symptoms while augmenting cerebral antioxidant activity. Histological study revealed a decrease in apoptotic cells following 21 days of treatment. While *Olea europaea* oil exhibits therapeutic potential for detoxification syndrome, its underlying mechanisms require additional exploration.

CONFLICT OF INTEREST

The authors declare no conflict of interest

INSTITUTIONAL REVIEW BOARD (ETHIC COMMITTEE)

All animal studies were performed according to the guidelines endorsed by the Ethics Committee of MSU [MSU-RMC-02/FR01/08/L3/108].

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Locked Anterior Hip Dislocation with Ipsilateral Greater Trochanteric Fracture and Common Femoral Artery Compression: A Rare Case Report

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ABSTRACT

We report a rare case of post-traumatic anterior hip dislocation with ipsilateral greater trochanteric fracture and compression of the common femoral artery. To our knowledge, this is the first report that highlights a rare pubic anterior dislocation with greater trochanter fracture complicated with a pale, pulseless limb. Additionally, after two unsuccessful closed manipulative reduction (CMR) attempts, an urgent open reduction was performed, which resulted in an immediate recovery of the distal circulation. We emphasize the need for urgent open reduction following failed CMR. A delayed open reduction that was carried out 12 hours after the injury may have contributed to the surgical site infection, avascular necrosis, and heterotopic ossification that developed in our case.

Keywords

hip dislocation, avascular necrosis, pale pulseless limb

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INTRODUCTION

Traumatic hip dislocation in children is uncommon.¹ Anterior and posterior hip dislocations are two types of traumatic hip dislocations, with the latter being more prevalent.¹⁻⁵ There has never been a description of a pubic type anterior hip dislocation with ipsilateral common femoral artery compression and a pale, pulseless limb. Urgent reduction should be carried out to prevent complications such as avascular necrosis, heterotopic ossification, and arthritic changes of the joint.¹⁻⁵ Several closed reduction strategies can be used.¹⁻⁵ Failed closed reduction necessitates an urgent surgery to relocate the femoral head within six hours of injury.

CASE REPORT

An obese 17-year-old man who had allegedly been in a car accident arrived at the emergency room with a right thigh pain and deformity. Clinical examination revealed a pale and pulseless right leg with non-palpable dorsalis pedis, posterior tibial, popliteal and faint femoral arteries pulses. However, sensation over the femoral and sciatic nerve distribution were intact. A handheld Doppler scan showed absent signals at dorsalis pedis, posterior tibial and popliteal arteries while femoral artery showed biphasic signal. A right pubic type anterior hip dislocation

with fractured greater trochanter was visible on a plain radiograph (Fig. 1a, b). CTA on the right lower limb discovered the right femoral head was anteriorly displaced and pressing against the nearby right common femoral artery, which reduced the diameter of the vessels beyond the compression (Fig. 1c, d).

At the emergency room, Allis manoeuvre was performed in attempt to reduce the dislocation. Patient lay supine on the bed. Gentle traction and external rotation in hip flexion were performed while the assistant stabilised the pelvis. However, the hip failed to be reduced. The capillary refilling time was reduced to two seconds by periodic vascular assessments, and there was improved colour of the toes, but the pulses were still not detectable. Due to long list of emergency surgery cases taking place, we performed an open reduction and internal fixation on the right hip 12 hours after the injury.

The patient was positioned in a left lateral decubitus position. Hardinge approach is utilized. The muscles surrounding the hip joint were pale and had little contact bleeding during surgery. There was a displaced fracture of the greater trochanter. The femoral head protruded

through a buttonhole defect on the anterior capsule and caught at the superior surface of the superior pubic ramus. A T-shaped capsulotomy was performed, the hip joint was inspected, and the femoral head reduced with axial traction and internal rotation. The greater trochanter fracture was fixed using two 4.5mm cortical screws. Following reduction of the dislocation, there was immediate return of the pulse. The patient was given 5000cc heparin in one-pint normal saline and given oral aspirin 75mg daily for six weeks. In the ward a skin traction was applied to the right leg. Following surgery, a repeated plain radiograph revealed a repositioned femoral head with reduced greater trochanter fracture (Fig. 2a,b).

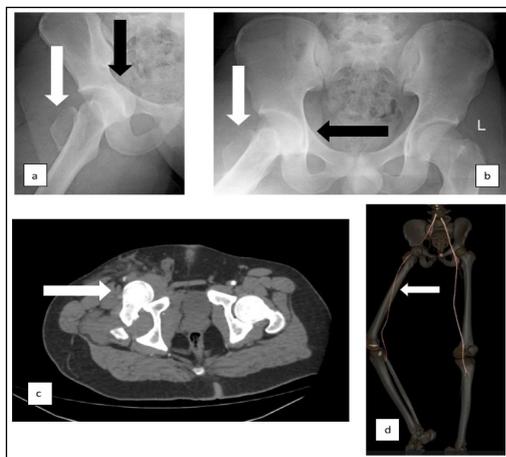


Figure 1: (a) and (b) Admission plain radiograph of the right hip and pelvis. White arrow refers to the greater trochanter fracture. Black arrow points to pubic type anterior right hip dislocation (c) axial cut of CT scan of the pelvis showed anteriorly dislocated right femoral hip that was caught at the superior pubic ramus (white arrow) (d) CTA of the lower limbs that showed compression of the right common femoral artery by the dislocated right femoral head leading to reduced calibre of the distal arteries (white arrow).

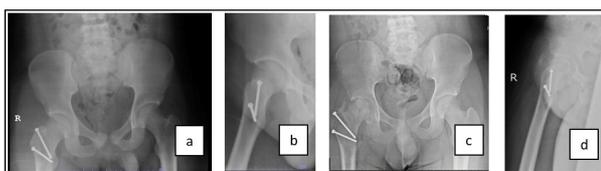


Figure 2: (a) and (b) Immediate post-operative radiograph of the pelvis and right hip. (c) and (d) Plain radiograph at 18 months after injury showed avascular necrosis changes of the femoral head, sclerotic acetabular wall edges and heterotopic ossification along the abductor muscles.

On day nine following surgery, the surgical incision developed purulent discharge and erythema. The white blood cell count was increasing in trend from $26 \times 10^3/uL$ to $32 \times 10^3/uL$. At $1617nmol/L$, the C-reactive protein also increased. Right thigh wound debridement and Collatamp® insertion then followed. At the site of the incision, there was a pus collection seen. Seropurulent discharge was seen inside the hip joint underneath friable joint capsule. Enterobacter species were grown in

intraoperative tissue cultures. Throughout admission, the patient received gentamicin and cefuroxime intravenously for seven and five days, respectively. Against medical advice, the patient was discharged from the hospital with oral antibiotics on day 14 following surgery.

Six weeks after the first surgery, there was a small sinus at the centre of the wound discharging minimal hemerosous collection. Six weeks later, plain radiograph revealed a united right femur greater trochanter fracture, reduced femoral head with no obvious avascular necrosis of the femoral head and osteomyelitis changes. The C-reactive protein decreased to $200nmol/L$. On his latest follow-up 18 months after the trauma the plain pelvis radiograph showed aspherical femoral head, sclerotic acetabular edges consistent with avascular necrosis and degenerative changes of the acetabular wall. Heterotopic ossification was also seen along the abductor muscle fibers (Fig. c,d). The patient complained of right hip pain and was able to walk unaided with a limping gait. Clinically there was healed sinus at the centre of the surgical scar (Fig. 3a). Limited active and passive range of motion was observed more marked on internal and external rotation. Assessment of the passive range of movement showed right hip flexion of 0-45, abduction 0-45 and adduction 0-15 (Fig. 3b,c,d). Due to the young age, we advised the patient for total hip arthroplasty in the future if pain becomes not tolerable and developed limited hip range of motion.



Figure 3: (a) On follow up there was a sinus formation at the centre of the surgical scar. The range of motion was grossly restricted. Flexion was from 0-45 degrees (b), while abduction was at 0-30 degrees (c). (d) The right lower limb attitude was in external rotation.

DISCUSSION

Hip dislocation can be divided into congenital and acquired.¹ Acquired cases can be further classified into native dislocation or dislocations that occur after total hip arthroplasty procedure.¹ A native dislocation typically

happens following motor vehicle accident and can be divided into posterior and anterior dislocation.¹

Anterior dislocation is not as common as the posterior type, approximately 10-15% of all dislocations.¹⁻⁵ The reason is possibly due to the mechanism of injury to produce an anteriorly dislocated hip being rarer.^{2,3} The direction of the anteriorly dislocated hip is either superior-anterior (pubic) or inferior-anterior (obturator).^{2,3} Superior-anterior dislocation is infrequent and usually resulted from extreme abduction, extension and external rotation force.^{2,3}

Immediate recognition of this injury is important to prevent complications.¹ A thorough assessment of the patient via primary survey should be performed as per protocol to avoid missing life-threatening injuries.^{1,4} As for local limb assessment, the position of the anteriorly dislocated hip is positioned in the abduction and external rotation.¹⁻⁵ The deformity would also depend on the types of dislocation, a superior-anterior type would produce a flexion deformity while inferior-anterior type would have an extended hip.^{1,2} Detailed assessment of the ipsilateral limb is also crucial to identify neurovascular damage.^{1,3} Furthermore, ipsilateral bone or soft tissue injuries could potentially lead to difficulty in joint reduction and exacerbates the initial injury.¹

Immediate reduction of the dislocated femoral head within six hours is paramount to prevent complications.^{1,3,5} A traumatic hip dislocation is commonly associated with concurrent ipsilateral fractures of the femoral head, femoral neck and acetabulum.¹⁻⁸ Avascular necrosis is one of the complications and may eventually lead to post-traumatic osteoarthritis in the future.¹⁻⁷ The incidence of avascular necrosis could be significantly reduced if the reduction is performed within six hours after injury.^{1,3} Although no functional impairment was reported, heterotopic ossification may potentially occur as a result of the production of bone in the soft tissues around the affected area.¹⁻⁵ For anterior hip dislocation, associated injury to neurovascular structures is rarely mentioned.¹ Only a few cases of anterior hip dislocation with concurrent ipsilateral femoral neck,

femoral head, and intertrochanteric fractures, as well as acetabular wall and pubic rami, were discussed.²⁻⁹ Anterior hip dislocation is a high-velocity injury that frequently co-occurs with injuries to other systems, including contralateral long bone fractures, cerebral hemorrhage, and intraabdominal injuries.⁵

The first imaging technique used to establish the clinical diagnosis and rule out related fractures is a plain radiograph. Typically, an anteroposterior pelvic radiograph suffices.¹⁻⁸ The femoral head that has been anteriorly dislocated typically seems greater in size, and the type of dislocation depends on how close it is to the pubic bone or the obturator canal.¹ Frog leg, Judet, or lateral views of the hip can be used to corroborate any unconfirmed findings.¹ The related fractures shown on the plain radiographs are confirmed and studied using a CT scan after the diagnosis has been made.¹⁻¹⁰ Since there were signs of vascular compromise in our instance, CT angiography was also done to rule out vessel tears or occlusion.

Various closed reduction techniques such as Allis maneuver, Bigelow maneuver, Leftkowitz maneuver, Captain Morgan technique, East Baltimore Lift technique, Skoff maneuver, Howard maneuver and piggy back technique had been described.¹ In our case we attempted Allis maneuver twice before surgery, once at the emergency department and after the patient had been induced under general anesthesia. We also performed Skoff maneuver after putting the patient in lateral position prior to open reduction. These techniques were chosen as the physicians are more familiar with them. Allis procedure is performed while the patient was on the floor. An assistant would stabilize the pelvis. The physician would flex the hip at 90 degrees and give ipsilateral traction with gentle extension and external rotation of the hip.¹ Skoff procedure is performed in lateral decubitus position while the affected leg is facing up with the hip and the knee is placed in 90 degrees flexion. Gentle traction is applied with internal rotation and adduction while one assistant would try to push the palpable femoral head to reduce it back into the acetabulum.¹ As for our patient, we were unable to

achieve reduction of the femoral head possibly due to the head being 'locked' at the superior pubic rami, the 'button-hole' effect of the head through the capsule.

Hip joint can be reached either around an intact gluteus medius tendon (medial, anterior, anterolateral or posterior approach) or through gluteus medius tendon (through the tendon or through the bone).^{11,12} Since the hip was anteriorly dislocated and involved ipsilateral greater trochanter fracture, author decided to avoid violation of the posterior and medial soft tissues by using lateral (Hardinge) approach. After skin incision and subcutaneous incision the gluteus maximus and tensor fascia lata was cut exposing the vastus lateralis and gluteus medius.^{11,12} The gluteus medius is split at the junction of middle and posterior thirds exposing the fractured greater trochanter, the torn capsule and anteriorly dislocated femoral head trapped at the superior pubic ramus.^{11,12}

CONCLUSION

Anterior hip dislocation is an orthopaedic emergency. While posterior hip dislocation is more common, a pubic-type anteriorly dislocated hip with concomitant greater trochanter compressing the adjacent femoral artery is rarer and has never been reported. A head protrusion through a buttonhole defect at the capsule may be the cause of a failed CMR in a hip anteriorly displaced of the pubic type. The femoral head could as well possibly be caught at the superior surface of the ipsilateral superior pubic ramus. Thus, the release of the capsule and the use of a skid are recommended to relocate the femoral head. As early as six months after the incident, our patient already showed signs of complications such avascular necrosis, arthritic changes in the hip joint, as well as heterotopic ossification. In our case septic arthritis of the hip might contribute to the complications. To avoid consequences like those we experienced, we advise immediate surgery for patients with unsuccessful closed manipulative reduction.

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Scissor-Induced Penetrating Brain Injury in a Child: A Case Report

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Keywords

Penetrating brain injury, pediatric trauma, scissor injury, craniotomy, foreign body, frontal lobe injury

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ABSTRACT

Penetrating brain injury (PBI) is a rare but severe form of traumatic brain injury, especially when caused by non-missile, low-velocity objects. We report a case involving a 12-year-old boy who sustained a penetrating frontal brain injury after falling with a scissor in hand during a school activity. The scissor penetrated the right orbital roof and entered the anterior cranial fossa, injuring the right frontal lobe and causing an intraparenchymal hematoma. Computed tomography (CT) confirmed the trajectory and extent of injury. The patient underwent emergency craniotomy and foreign body removal. Postoperatively, he recovered without neurological deficits, cerebrospinal fluid (CSF) leakage, or recurrent seizures. This case highlights the importance of timely imaging, careful surgical planning, and adherence to management principles to optimize outcomes in pediatric PBI.

INTRODUCTION

Penetrating brain injuries (PBIs) caused by foreign bodies are uncommon and carry a high risk of complications including vascular injury, seizures, intracranial infections, and CSF leakage. PBIs may be categorized as missile injuries (e.g., gunshot wounds) or non-missile injuries caused by sharp objects such as knives, scissors, or sticks. The removal of the penetrating object should only be performed under controlled surgical conditions. Preoperative planning, including the use of a similar object for trajectory estimation, may aid surgical precision. Stabilization of the object in situ is crucial to prevent further parenchymal damage during transport or imaging. Invasive injuries can result in hematomas, neurological deficits, or life-threatening infections if not promptly and appropriately managed.

CASE REPORT

History and Presentation

A 12-year-old boy with no prior medical history presented to the emergency department at Hospital Sultanah Bahiyah, Kedah, after a scissors-related injury during a school activity. While engaged in a craft task, he tripped and fell, causing the scissor to impale his right forehead just below the eyebrow. On initial evaluation, he was alert with a Glasgow Coma Scale (GCS) of 15/15. A 10 mm

laceration was noted, with the scissor partially embedded. He exhibited no visual disturbances, had full extraocular movements, and both pupils were 3 mm and reactive. No other injuries were observed. While awaiting imaging, the patient experienced a generalized tonic-clonic seizure. He was treated with intravenous diazepam and subsequently intubated for airway protection.

Imaging and Diagnosis

A skull X-ray confirmed intracranial penetration. Non-contrast CT scan revealed a metallic foreign body traversing the right supraorbital bone into the anterior cranial fossa, with associated right frontal intraparenchymal hematoma (~2.0 × 1.0 cm). No midline shift or cerebral edema was noted. The patient was initiated on empirical intravenous antibiotics (ceftriaxone and metronidazole) for central nervous system (CNS) infection prophylaxis. Surgical intervention was planned.

Surgical Management

An urgent right craniotomy was performed under general anesthesia. The patient was positioned supine, and an extended hemicoronal incision was made posterior to the hairline for optimal exposure. A 1.0 cm craniotomy was created above the frontal sinus. The scissor, extending

into the frontal lobe, was gently removed in a controlled fashion to minimize parenchymal trauma. The wound and hematoma site were irrigated, debrided, and hemostasis achieved. Dural tears were repaired, and the scalp was closed in layers. The patient was transferred to the intensive care unit for postoperative care.

Postoperative Course

A repeat CT on postoperative Day 1 showed no new hemorrhage or midline shift. The patient was extubated uneventfully and remained neurologically intact. He was continued on antibiotics for six weeks and received intravenous phenytoin for seizure prophylaxis. The patient made a full recovery and was discharged after two weeks without neurological deficits or signs of infection.

DISCUSSION

Penetrating injuries to the brain are rare, particularly those involving low-velocity objects in pediatric populations. Compared to closed head injuries, PBIs are associated with increased morbidity and mortality. Despite general principles for PBI management, each case necessitates individualized surgical planning. CT scanning remains the cornerstone in evaluating the extent of bone and parenchymal injury. If vascular injury is suspected, CT angiography is warranted to assess traumatic aneurysms or vessel disruption. Immediate removal of the foreign object should be avoided unless absolutely necessary, as abrupt extraction may exacerbate brain injury or hemorrhage. Surgical goals include controlled extraction of the foreign body, removal of necrotic tissue and debris, evacuation of hematoma, achieving hemostasis, and ensuring watertight dural closure to prevent CSF leakage. Retained bone fragments and debris increase the risk of intracranial abscess, which typically manifests within a month. In our case, skull X-ray (Figure 1) and CT imaging (Figure 2) provided crucial details regarding the trajectory and extent of penetration. The CT scan clearly delineated the metallic foreign body passing through the right frontal bone into the anterior cranial fossa, with associated right frontal hematoma.



Figure 1: Lateral skull X-ray showing the scissor penetrating through the right orbital roof into the anterior cranial fossa

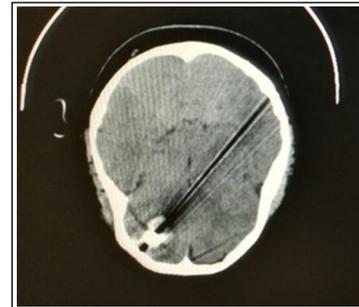


Figure 2: Axial non-contrast CT scan showing the metallic foreign body traversing the right frontal bone with associated intraparenchymal hematoma.

The surgical intervention was carefully planned, and an extended hemicoronal incision was used for optimal exposure (Figure 3). Early administration of prophylactic antibiotics is essential to reduce the risk of infection. Our patient was treated with six weeks of antibiotics due to the uncertain sterility of the scissor. Seizures are a common complication in PBIs, and the use of prophylactic antiepileptics is advisable even in patients without initial episodes. Serial imaging remains critical in detecting late complications such as hematoma expansion, cerebral edema, ventriculitis, or posttraumatic hydrocephalus.



Figure 3: Intraoperative image showing incision planning with an extended right hemicoronal approach

CONCLUSION

This case highlights the importance of adhering to established principles in the management of penetrating brain injuries. Stabilization of the foreign body, timely imaging, appropriate antibiotic prophylaxis, and definitive surgical intervention contribute significantly to favorable outcomes. Each PBI case is unique, and a tailored approach is critical to achieving optimal recovery, especially in pediatric populations.

CONFLICT OF INTEREST

The authors declare no conflicts of interest and no external funding.

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Remission of Hypertension Through Lifestyle Modification: A Case Study

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Keywords

Hypertension, remission, lifestyle modification, obesity

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ABSTRACT

Hypertension is a common comorbidity associated with obesity, and weight reduction offers numerous health benefits, including improved blood pressure control. This case study presents a 38-year-old man with an initial body mass index (BMI) of 35.5 kg/m² who achieved hypertension remission through comprehensive lifestyle modifications. A structured program incorporating dietary changes, regular physical activity, and behavioral therapy led to a sustained BMI reduction to 25.8 kg/m². This weight loss was accompanied by a gradual normalization of blood pressure, allowing for the discontinuation of three antihypertensive medications irbesartan, hydrochlorothiazide, and amlodipine after approximately one year of lifestyle modification. Remarkably, his blood pressure remained within the normal range for three years following medication cessation, which was maintained through continued adherence to lifestyle interventions.

INTRODUCTION

Hypertension is a major global risk factor for cardiovascular disease, and its strong association with obesity has been well documented. According to the Malaysian National Health and Morbidity Survey 2019 (NHMS 2019), the prevalence of hypertension among Malaysian adults is approximately 30%.¹ Obesity contributes to the development of primary hypertension through multiple physiological mechanisms, including neurohormonal activation, systemic inflammation and renal impairment.² These physiological mechanism leads to the expansion of extracellular fluid volume and an increase in cardiac output, primarily due to enhanced renal sodium reabsorption. This process is mediated by activation of the renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system overactivity, and mechanical compression of renal structure by adipose tissue. All these changes increase the renal blood flow and glomerular filtration rate, in which over time, they contribute to the development of hypertension.²

An increase in the prevalence of obesity, is associated with an increase in hypertension and related cardiorenal conditions. Lifestyle modification, including dietary changes and regular physical activity remains the mainstay treatment for obesity.³ However, its long-term

effectiveness in reducing adiposity, sustaining weight loss, and maintaining blood pressure control has been modest.⁴ Bariatric surgery has been proven effective in promoting substantial weight loss and improving other metabolic disorders. Nonetheless, it carries potential risks such as bleeding, infection, anesthetic risks, dumping syndrome, and long-term nutritional deficiencies.²

Hypertension remission is defined as the normalization of blood pressure (BP) without the need for antihypertensive medications.⁵ Although a universally accepted definition is lacking, growing research is beginning to explore this concept. Currently, comprehensive data on the long-term effects of intensive lifestyle intervention leading to sustained hypertension remission remain limited. Despite this gap, the present case study highlights how structured lifestyle modifications can result in significant weight loss and durable hypertension remission in an individual with obesity.

CASE PRESENTATION

A 38-year-old man with underlying hypertension and obesity was referred from a private clinic in 2020 for obesity management. He expressed concern about his

increased risk of COVID-19 complications due to his underlying health conditions. He had been diagnosed with primary hypertension at the age of 20 during a routine medical check-up for university admission. Initially managed with daily amlodipine, his antihypertensive regimen was later escalated to include three antihypertensive medications: amlodipine 5 mg and irbesartan/hydrochlorothiazide 300/12.5 mg daily. Despite medication adherence, his blood pressure remained sub-optimally controlled, consistently ranging between 140-150/80-90 mmHg.

Regarding his weight history, the patient reported significant weight gain beginning in adolescence, which progressively increased over time. Initially, his weight was not perceived as problematic, as it did not noticeably affect his daily functioning, social interactions, or mental well-being. He led a sedentary lifestyle with minimal physical activity largely due to his desk-based occupation, which involved sitting for approximately 8 to 9 hours per day. His dietary habits were characterized by excessive intake of carbohydrates, fat, and salt diet. His typical daily meal consisted of large portions, including 4-5 scoops of rice accompanied by generous servings of curry gravy, fried chicken, and red meat. He frequently enhanced the flavor of his meals with soy sauce or fermented fish sauce. Additionally, he regularly snacked between meals on high-calorie foods such as fried bananas, crispy crackers, cakes, and other processed snacks. He also had a strong family history of hypertension and diabetes.

On physical examination, his height was 176 cm, weight was 110 kg and body mass index (BMI) was 35.5 kg/m², consistent with obesity class II. Other system examinations were unremarkable. His laboratory investigations were all in the normal range as shown in Table 1.

The patient was diagnosed with obesity class II and uncontrolled hypertension. He was counselled for comprehensive lifestyle modification and a mutual agreement was reached regarding the implementation of these changes. A dietary plan introduced to him was based on the 'quarter-quarter-half' plate method comprising half of the plate filled with vegetables,

one-quarter with lean protein, and one-quarter with carbohydrates. He was advised to reduce his caloric intake by at least 500 kcal/day, primarily by eliminating high calorie snacks, from an estimated initial daily intake of approximately 2500-3500 kcal. Additionally, he was encouraged to limit the consumption of high-sodium foods, including processed foods, added sauces, and fermented foods, as well as sugary food and beverages. He was also referred to a dietitian for further support and individualized meal planning.

The patient was prescribed a personalized exercise regimen consisting of moderate-intensity aerobic activity, targeting 150-200 minutes per week. He began with 20-minute brisk walks twice a week, gradually progressing to 30 minutes per session, five days a week, within one month. The treatment goal was to achieve a 5-10% reduction in body weight over six months, with an emphasis on improving metabolic parameters.

Lifestyle modifications were introduced gradually, accompanied by substantial support through regular follow-up consultations aimed at providing motivation and addressing emerging challenges. Due to the constraints imposed by the COVID-19 pandemic, follow-ups were conducted every three months. These were supplemented with behavioral therapy, which included daily tracking of dietary intake and physical activity via mobile applications, weekly weight monitoring, goal setting, problem-solving strategies, and stimulus control techniques.

The patient demonstrated high motivation throughout the intervention, regularly monitoring his weight on a weekly basis. He adhered to a diet plan of 1800-2000 kcal per day, as prescribed by the dietitian, typically consuming 3-4 meals daily. Occasionally, he replaced his rice-based meal with salads. He also significantly reduced his intake of high-sodium foods, including soy sauce, processed food, and junk food. To manage hunger and food cravings, he employed coping strategies such as drinking water, engaging in focused tasks, and choosing healthy snacks. His physical activity included aerobic exercises such as cycling and jogging for at least 40-60 minutes, five days per week, and he increased his daily steps count

Table I: Progress of the parameters measured.

Parameter	Date	Oct 2020	Jan 2021	April 2021	June 2021	Oct 2021	Jan 2022	Sept 2022	Jan 2023	Oct 2023	Feb 2024
Weight (kg)		110.0	101.6	92.5	80.9	76.9	75.0	76.7	77.6	75.5	80.0
BP range (mmHg)		147/73	145-138/ 85-92	128/68	115-119 / 64-65	120-131/ 66-68	125-137/ 63-75		121-135 / 66-74		126-135/ 68-72
Lipid profile											
TC (mmol/L)		4.2				4.8		4.9		4.7	
HDL (mmol/L)		1.0				1.6		1.6		1.6	
LDL (mmol/L)		2.9				2.9		3.0		2.8	
TG (mmol/L)		0.7				0.6		0.6		0.7	
Renal function											
Creatinine (µmol/L)		79				68		72		79	
Serum uric acid (mmol/L)		0.49				0.39		0.47		0.43	
Antihypertensives		Aml0 5 mg, Irbesartan/ HCTZ 300/12.5mg		Irbesartan/ HCTZ 300/12.5mg	Irbesartan 150mg	off	off	off	off	off	off

Abbreviation: TC - total cholesterol, HDL - high-density lipoprotein, LDL - low-density lipoprotein, TG - total triglycerides

on non-exercise days. He used a smartwatch to monitor calorie expenditure. Support from family members further contributed to his adherence and success. After six months of consistent lifestyle changes, he achieved a weight loss of 17.5 kg.

At the seventh-month follow-up, he reported experiencing postural dizziness and noted low blood pressure reading (100/60mmHg). He also observed that his home blood pressure readings had ranged between 110-120/60-70 mmHg over the preceding month. These symptoms resolved after a reduction in his antihypertensive medication. Over subsequent visits, his medications were gradually tapered off as his blood pressure remained within the normal range. All antihypertensive medications were discontinued when he reached a weight of 80 kg at the 12-month of intervention. He continued with lifestyle therapy and further reduced his weight to 75 kg, achieving a total weight loss exceeding 30% of his original body weight. The patient expressed satisfaction with his progress.

Over the following three years, he remained under regular follow-up. His weight has been consistently maintained between 75 and 80 kg, with minor fluctuations of 3-5 kg. His blood pressure has remained within the normotensive range, and he has sustained his regular exercise routine and healthier dietary practices.

DISCUSSION

This case illustrates the significant effectiveness of lifestyle modification in managing obesity and achieving hypertension remission. Numerous clinical trials have

demonstrated that lifestyle interventions can improve blood pressure control and, in some instances, lead to complete remission of hypertension.⁶⁻⁷ For example, one study found that sustained dietary and lifestyle changes enabled 21.7% of obese hypertensive patients to discontinue antihypertensive medications entirely, highlighting the effectiveness of non-pharmacological approaches.⁸ In this case, the patient achieved a remarkable 30% reduction in body weight, which was associated with a progressive decline in BP and the eventual cessation of all antihypertensive medications. This outcome underscores the potential of structured lifestyle changes in reversing hypertension, particularly when implemented through shared decision-making, continuous healthcare provider support, and patient empowerment via self-monitoring.

Weight reduction has a well-established impact on BP. On average, a 1 kg weight loss is associated with a 1–2 mmHg reduction in systolic and diastolic BP, respectively.⁹ Several studies have linked weight loss to reduced activity in the sympathetic nervous system and the renin-angiotensin-aldosterone system, both of which play key roles in BP regulation.¹⁰ Furthermore, fat mass reduction improves adipocyte function and mitigates sympathetic overactivity, contributing to BP normalization.¹¹ However, the degree of weight loss needed to achieve hypertension remission varies based on individual factors such as baseline weight, overall health status, and the severity of hypertension.¹² In this patient, the absence of complications and a baseline classification of stage 1 hypertension likely contributed to the successful remission.

The fundamental elements of comprehensive lifestyle modification for weight reduction includes diet therapy, physical activity and behavior therapy. A daily calorie deficit of 500–750 kcal is recommended, which typically results in a weekly weight loss of 0.5–0.75 kg.³ For effective weight loss, moderate-intensity aerobic exercise for at least 150 minutes per week is advised, with longer durations necessary for weight maintenance. This can be complemented by resistance training 2-3 times per week, involving 8-10 exercises targeting major muscle groups. Behavioural therapy components include daily tracking of food intake and physical activity (using apps or diaries), weekly weight monitoring, goal setting, problem-solving strategies, stimulus control, and ongoing professional support.³ These elements should be tailored to each patient's preferences and daily routines to enhance adherence and sustainability.

Self-monitoring is a cornerstone of behavioral intervention, offering patients insight into their progress and reinforcing commitment to their goals.³ With the advent of digital health tools, wearable devices have made it easier to monitor physical activity, caloric expenditure, and other health metrics. Research shows that frequent monitoring of food intake and use of wearable technology (such as armbands) is associated with greater weight loss.³ In this case, the patient used a smartwatch to track calorie burn, which supported his efforts in maintaining a consistent energy deficit.

Despite the promise of lifestyle interventions, their long-term efficacy and sustainability remain limited in many cases. While lifestyle changes often result in weight loss and metabolic improvements, maintaining these changes can be difficult for most individuals.¹³ Successful long-term weight maintenance requires integrating healthy behaviors into daily routines and social contexts. This patient demonstrated strong intrinsic motivation, reinforced by positive outcomes, family support, and personal discipline. These factors, combined with regular healthcare provider follow-up and guidance, were crucial in sustaining his progress.

Continued support from healthcare professionals is essential in helping patients maintain lifestyle changes.

Regular follow-up enables individuals to address challenges, make informed decisions, and adjust their behaviors to ensure lasting health benefits. In this case, the patient's three-year sustained remission of hypertension and stable weight reflects the success of a comprehensive, patient-centred lifestyle intervention supported by multidisciplinary care.

CONCLUSION

This case highlights that intensive lifestyle modifications, supported by self-monitoring and continuous healthcare provider engagement can lead to significant weight loss and subsequent remission of hypertension. While long-term sustainability remains a challenge for many, this patient successfully maintained lifestyle changes and normotensive blood pressure for over three years. A patient-centred, integrated approach is essential in achieving and sustaining weight loss through therapeutic lifestyle interventions, offering a viable non-pharmacological strategy for managing obesity-related hypertension.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

DECLARATION OF PATIENT CONSENT

The authors certify that patient consent was obtained.

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Stroke Chameleon: Acute Bilateral Middle Cerebral Artery Infarct Complicated with Acute Pulmonary Oedema

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ABSTRACT

Acute bilateral middle cerebral artery (MCA) infarctions are an extremely rare event. However, it can cause disruption of bilateral corticothalamic networks leading to coma. Detection of this condition is challenging as the early ischemic signs found on the non-contrast CT (NCCT) is depending on comparison between infarcted region and its normal counterpart. We report a case of 60-year-old man presented with acute comatose state and pulmonary oedema secondary to hypertensive emergency. His NCCT brain showed acute infarction of bilateral MCA territories. His acute pulmonary oedema subsequently resolved with the treatment. However, he succumbed to his illness and its complications on day 7 of admission. In this case report, we explore the strategy to improve detection of bilateral infarction on NCCT and navigating the differential diagnosis of comatose state and acute pulmonary oedema brought about by the hypertensive emergency.

Keywords

bilateral infarctions, middle cerebral artery, acute pulmonary oedema

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INTRODUCTION

A stroke chameleon is a situation in which a stroke is revealed by clinical symptoms that are not usual in stroke patients. This leads to false negative diagnostic errors in which the incidence in Emergency Department (ED) varies between 2 to 26%. Most stroke chameleons involve posterior circulation strokes in which the common presentations are dizziness and altered mental status.¹ The commonest presentation of acute stroke cases is focal neurological deficits due to the sophisticated anatomy of cerebral arteries supplying one side of the brain. However, bilateral middle cerebral artery (MCA) occlusions are rare and the clinical presentations ranging from asymptomatic to fatal stroke. We report a case of acute simultaneous bilateral middle cerebral artery infarction presenting with coma and complicated by probable acute neurogenic pulmonary oedema.

CASE PRESENTATION

A 60-year-old male was found unconscious with copious oral secretions at approximately 7:30 AM. He had been seen in good health just a few minutes earlier by his

wife while they were together in the kitchen before he decided to go outside. According to the wife, the patient had been complaining of dizziness the day before the event. His underlying medical conditions were diabetes mellitus and hypertension and he has poor adherence to his medications. He was brought to an Emergency Department (ED) at 8:50 AM via an ambulance call.

Upon arrival to the ED, the patient remained unconscious. His blood pressure was 206/136 mmHg, heart rate of 100 beats per minute, respiratory rate of 30 breaths per minute, oxygen saturation (SpO₂) of 86% under room air, and afebrile with a body temperature of 37°C. There were frothy secretions coming out from his mouth and presence of crepitations on bilateral lower zones up to the midzones. However, there was no lower limbs oedema noted. His Glasgow Coma Scale (GCS) score was 3/15 and his pupils were equal and reactive bilaterally. His blood glucose level was 17.9 mmol/L. A bedside point of care ultrasound revealed poor cardiac

contractility with plethoric inferior vena cava. His lungs ultrasound shown bilateral B-profiles with no pleural effusion. His chest radiograph (Figure 1) showed features of pulmonary oedema.



Figure 1: Chest radiograph showing features of pulmonary oedema - alveolar opacification, air bronchograms, upper lobe diversions and right pleural effusion

The patient’s electrocardiogram revealed sinus rhythm with left ventricular hypertrophy, ST depression and T wave inversion at lateral leads. The patient was intubated for airway protection and respiratory distress and treated as acute pulmonary edema secondary to hypertensive emergency. He was started on nitrate infusion and sent for non-contrast computed tomography (NCCT) of the brain due to sudden onset of loss of consciousness. A consultation with the general medical and intensive care teams were made. Due to an access block, the patient was managed in the ED. An initial review of the CT scan by ED team was normal.

On the second day of hospitalization, the patient was treated as septic shock secondary to aspiration pneumonia, as there was newly documented fever. His total white cell count was 14.1×10^9 /L and his C-reactive protein more than 293.3 mg/L. He was started on antibiotic therapy and vasopressor support. A re-evaluation of the initial CT scan by the managing team raised suspicion of acute ischemic changes in the bilateral MCA territories, indicated by the dense bilateral MCA sign and blurring of both basal ganglia. The formal radiology report from the previous evening noted an ASPECT score of 0 on the right side and an ASPECT score of 2 on the left side (Figure 2). The patient then was started on antiplatelet and referred to the neurology team.

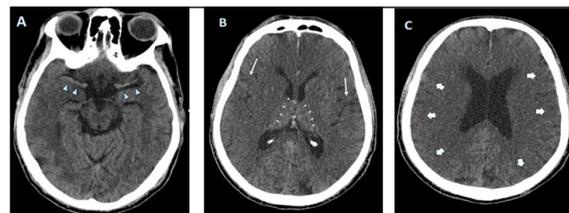


Figure 2: Initial NCCT shows (A) bilateral hyperdense MCA; (B) vanishing sylvian fissure (long arrow) and blurring of basal ganglia white matter and grey matter (arrowhead); (C) bilateral cortical sulcal effacement

A follow-up CT brain scan revealed generalized cerebral oedema with pseudo-subarachnoid hemorrhage (Figure 3).

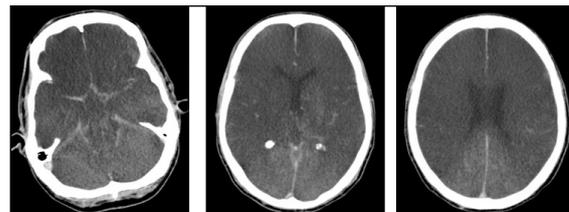


Figure 3: Repeated NCCT brain showing diffuse cerebral edema and appearance of pseudo-subarachnoid haemorrhage.

The treatment strategy was then modified to focus on cerebral protection, incorporating osmotic therapy and desmopressin infusion. A consultation on potential surgical intervention was made with neurosurgery team. However, a conservative medical management was decided upon. Despite the efforts, the patient succumbed to his illness seven days after the initial presentation. The final diagnosis was acute ischemic stroke with bilateral MCA infarcts, complicated by septic shock secondary to aspiration pneumonia.

DISCUSSION

A comatose condition can result from disturbances in the ascending reticular activating system or widespread insults to the bilateral brain hemispheres, such as occlusion of bilateral middle cerebral arteries (MCAs). Additionally, hypertensive emergencies may also induce coma due to posterior reversible encephalopathy syndrome (PRES) or brainstem infarctions. However, the decline in consciousness associated with these conditions is typically less abrupt.

Based on published case reports summarized in Table I, the initial presentation of bilateral MCA strokes varies from unilateral neurological deficits to comatose states, with the former being the commonest.² This variation arises as some patients may initially present with focal

Table I: Studies included in the literature review

Authors/Year	Design	Sex	Risk Factor	Pulmonary Oedema	Stroke Occlusion Site	Admission NIHSS	GCS	Initial ASPECTS	i.v. rt-PA	MT	mRS 90 days
Hu et al. 2007 ³	Medical	Female	Atrial fibrillation	NR	M1-M1	NR	4	NR	NR	NR	NR
Nawashiro et al.	Case report	Male	Atrial fibrillation	NR	MCA-MCA	NR	4	NR	NR	NR	NR
Pop et al. 2013 ²	Case report	Female	Atrial fibrillation	NR	MCA - ICA	26	NR	9	Yes	bilateral MT	0
	Case report	Female	Atrial fibrillation	NR	distal ICA -	18	NR	10	Yes	bilateral MT	3
Dietrich et al. 2014 ²	Case report	Male	Atrial fibrillation, hypertension	NR	M1-M1	NR	15	9	No	bilateral MT	NR
Ramos et al. 2018 ²	Case report	Female	Atrial fibrillation, Diabetes, hypertension	-	M1-M2	12	NR	NR	NR	NR	4
	Case report	Female	Atrial fibrillation, Diabetes, hypertension	-	M1-ICA	6	NR	10	Yes	NR	6
London et al. 2019 ²	Case report	Female	Atrial fibrillation, hypertension	NR	M1-M1	11	NR	NR	yes	bilateral MT	1
Braksick et al. 2018 ⁵	Case report	Female	NR	NR	M1-M1	NR	NR	10	Yes	bilateral MT	5
Storey et al. 2019 ²	Case report	Female	Atrial fibrillation	NR	M1-M2	NR	5	NR	NR	bilateral MT	NR
Escalard et al. 2020 ²	Case report	Female	Atrial fibrillation	NR	M1-M1	coma	3	NR	NR	bilateral MT	2
Heyworth et al.	Case report	Female	Atrial fibrillation	NR	M1-M1	12	NR	NR	NR	bilateral MT	NR
Khanna et al. 2021 ²	Case report	Female	Hypertension, COVID-19 infection	NR	M1-M2	NR	NR	NR	NR	bilateral MT	0
Wu et al. 2021 ²	Case report	NR	Atrial fibrillation, ischaemic cardiomyopathy	NR	M1-M1	28		7-10	NR	bilateral MT	5
Kaesmacher et al. 2020 ²	Case series of 10 patients	Female 60% (6/10)	Atrial fibrillation 50% Diabetes mellitus 10% Arterial hypertension 70%	-	M1-M1 = 2 M2-M2 = 2 M1-M2 = 1 ICA-M1 = 4 ICA-M2 = 1	21 (IQR 5.5-30)	-	7-10	7-10	-	20% mRS 0-2
Joyce et al. 2022 ²	Case report	Female	Atrial fibrillation, hypertension, hyperlipidaemia	NR	M1-M1	13	NR	8	NR	bilateral MT	6
Saad et al. 2022 ³	Case series	-	-	-	-	-	-	-	-	-	-
Govindappa et al.	Case report	Female	Aortic stenosis	NR	M1-M1	21	NR	8	Yes	bilateral MT	0
White et al. 2023 ⁷	Case report	Female	Diabetes, hypertension, hyperlipidaemia, previous cerebrovascular accident without neurological deficit	NR	M1-M1	12	NR	-	NR	bilateral MT	NR
Li et al. 2023 ⁸	Case report	Male	Atrial fibrillation	NR	M1-M1	15	NR	NR	Yes	bilateral MT	2
Srichawla et al.	Case report	Male	Atrial fibrillation	NR	M1-M1	7	NR	NR	No	bilateral MT	NR
Bernava et al. 2023 ²	Case report	Female	Atrial fibrillation	NR	M1-M2	6	15	NR	NR	bilateral MT	0
	Case report	Female	-	NR	M1-M1	29	5	NR	NR	bilateral MT	4
Current case	Case report	Male	Diabetes, Hypertension	Yes	M1-M2	NR	3	0-2	No	No	6

Abbreviation: NIHSS=National Institutes of Health Stroke Scale; GCS=Glasgow coma Scale; ASPECTS= Alberta stroke program early CT score; i.v. rt-PA=intravenous recombinant tissue plasminogen activator; MT=mechanical thrombectomy; mRS=modified Rankin score; NR=not reported; MCA=middle cerebral artery; ICA=internal carotid artery

neurological deficits and often have single-vessel occlusions, which subsequently progress to multivessel occlusions affecting both hemispheres, leading to a decline in consciousness. Therefore, clinicians must be vigilant for bilateral large vessel occlusions in cases of acute onset of coma or progression to coma from initial focal neurological deficits.

Acute ischemic stroke with simultaneous bilateral occlusion of the anterior circulation is a very rare event with a reported incidence around 0.3% with the commonest site of artery occlusion is internal carotid artery-middle cerebral artery, followed by MCA-MCA.² Cardioembolic stroke is more likely to cause acute simultaneous occlusion of both MCA in this case as compared to large artery atherosclerosis stroke subtype. The emboli has higher chance of affecting both MCA simultaneously as they branch off the internal carotid arteries.

A diagnosis of bilateral MCA infarctions based on NCCT scan is challenging. Hyperdense artery sign and hypoattenuation of ischemic parenchyma are among the early ischemic signs seen on NCCT and the detection relies on comparing them from their normal counterpart. Both hyperdense MCA sign and focal attenuation are of value in distinguishing unilateral MCA occlusion and thus very challenging in the case of bilateral MCA occlusion as in our case. The interpreter should be vigilant of other early ischemic signs on NCCT such as blurring of basal ganglia's grey and white matter, cortical sulcal effacement and vanishing Sylvian fissure so as to improve the recognition of multiple large vessels occlusion stroke.

Apart from the acute bilateral MCA infarction, the elevated blood pressure coincidentally causes acute pulmonary oedema in this case. Thus, the hypoxia-induced agitation commonly displayed in acute pulmonary oedema is absent in this case since the patient is already

comatose from the disruption of the neural networks responsible for the consciousness. Thus, it is possible that our patient had acute neurogenic pulmonary oedema (NPE) precipitated by bilateral MCA infarction. It is challenging to differentiate acute NPE and cardiogenic pulmonary oedema (CPE) as both conditions have similar presenting symptoms and signs with an abrupt onset and possibility of rapid resolution. However, the treatment strategy is slightly different in which control of circulating volume is an important aspect in CPE, whereas optimisation of the circulating volume is favourable in NPE to maintain perfusion in acutely ischemic brain tissue. However, both conditions are associated with high mortality rate with CPE has higher mortality rate compared to NPE.¹⁰

CONCLUSION

Acute simultaneous bilateral MCA infarctions with concurrent acute NPE makes the diagnosis of stroke chameleon more challenging. High clinical suspicion and early multi-disciplinary team approaches may improve the diagnosis and expedite the treatment.

CONFLICTS OF INTEREST

None.

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Cervical Intramedullary Cavernous Haemangioma: A Rare Cause of Acute Hemiparesis

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ABSTRACT

This case report describes a 45-year-old female who presented with acute hemiparesis and was initially diagnosed with acute ischemic stroke. Subsequent evaluation of her non-contrast computed tomography (NCCT) brain revealed a lesion in her spinal cord, which was further identified as intramedullary mass on cervical spine magnetic resonance imaging (MRI). This case underscores the importance of differential diagnosis in patients presented with acute hemiparesis, comprehensive assessment of NCCT scan, and the crucial role of MRI in diagnosing spinal cord lesions. Surgical intervention, involving laminectomy and excision of the lesion, was essential and resulted in significant postoperative improvement, highlighting the pivotal role of surgery in managing such conditions.

Keywords

Spinal Cord, Haemorrhage, Haemangioma
Cavernous

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INTRODUCTION

Intramedullary cavernous haemangioma is a rare vascular anomaly, accounting for approximately 3-5% of central nervous system lesions and 5-12% of spinal vascular abnormalities.¹ These lesions can present with a variety of clinical symptoms, including motor deficits (60%), sensory deficits (58%), pain (34%), and bladder and/or bowel dysfunction (24%).² Stroke mimics are medical conditions presenting symptoms akin to those of stroke but with different underlying causes.³ Unlike stroke which is caused by interrupted blood flow to the brain, stroke mimics may originate from various factors such as brain tumours, migraines, seizures, infections, or metabolic disturbances.⁴ The varied presentations of intramedullary cavernous haemangioma can mimic stroke symptoms, creating diagnostic challenges.

CASE PRESENTATION

A 45 year old female with no cerebrocardiovascular risk factors and no prior medical conditions presented with 2 days onset of right-sided upper and lower limb weakness associated with progressive left-sided neck pain radiating to the occipital and parietal areas, unaffected by movement or posture. Otherwise, she reported no infective symptoms, no neurological deficits, or notable family medical history.

Initial examination showed stable vital signs, with a blood pressure of 127/90 mmHg and a pulse rate of 63 beats per minute. She was fully conscious and orientated to time, place, and person. Her pupils were symmetrically reactive to light with normal cranial nerves findings, except for the hypoglossal nerve (12th cranial nerve) which showed right-sided deviation and twitching of the tongue. Strength on her right side was diminished (3/5) compared to the full strength (5/5) on her left; reflexes were brisk. Her sensory and cerebellar functions were normal.

Blood sugar level was 6.4 mmol/L. Blood tests, including a full blood picture, renal function, and coagulation profile, were also within normal limits. Her initial diagnosis was acute ischemic stroke. No stroke activation was done as she was not in the stroke activation window. A non-contrast computed tomography (NCCT) brain reviewed by the emergency team, showed multiple old infarcts, and she was started on a dual antiplatelet regimen and admitted. Further evaluation of the NCCT brain the next day by the neuromedical team in the ward revealed a spinal cord haemorrhage (Figure I), with no additional neurological worsening noted. An MRI uncovered an eccentric intramedullary mass at C2/C3, with associated spinal cord oedema and haemorrhage (Figure II).

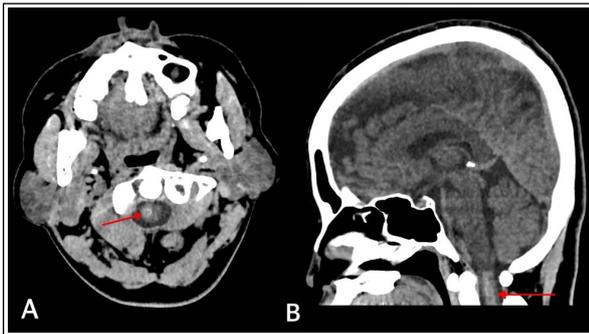


Figure I: Non-contrast computed tomography (NCCT) images reveal intramedullary hyperdensity consistent with spinal cord haemorrhage (red arrow). Axial view (A); Sagittal view (B)

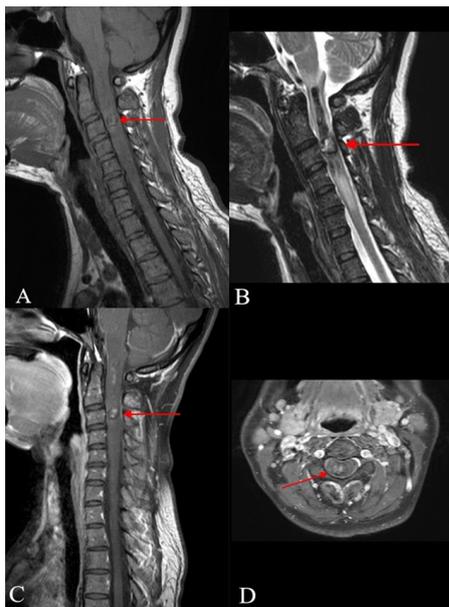


Figure II: Cervical magnetic resonance imaging T1-weighted(A), T2-weighted(B), post-gadolinium(C), post-gadolinium (D) sections showing an intramedullary lesion at the level of C2/C3 with spinal cord oedema and haemorrhage extending superiorly to the craniocervical junction. Sagittal view (A-C); Axial view D

An emergency C3 laminectomy, was performed. Intraoperatively, the lesion was dissected and a clean base was obtained (Figure III). A histological examination revealed the typical features of cavernous haemangioma.

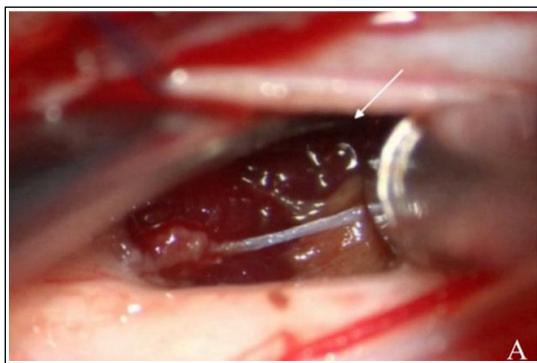


Figure III: Intraoperative photographs of cervical intramedullary cavernous haemangioma excision. Exposure of the cavernous haemangioma after C3 laminectomy and dural incision, showing the haemangioma within the spinal cord parenchyma (white arrow).

Postoperatively, her hemiparesis improved gradually with resolved 12th cranial nerve palsy, leaving residual paraparesis in her right upper limb. She was discharged on the 30th day, with a five-month follow-up with MRI planned.

DISCUSSION

Cerebral cavernous haemangiomas, which show no gender preference, spinal cord cavernous haemangiomas pose unique clinical challenges due to their tendency to haemorrhage and the diverse clinical manifestations they can induce.¹ Clinical manifestations of intramedullary cavernous haemangioma can range from asymptomatic to symptomatic. Motor deficits tend to involve only one limb or extremity, whereas hemiparesis was found in only 2 out of 26 cases.² Its clinical course tends to be chronic, except during haemorrhagic events, which are acute. These manifestations can be categorized into four distinct patterns, ranging from acute deterioration following haemorrhages to mild symptoms with gradual decline, illustrating the variability in disease progression and highlighting the critical importance of tailored management strategies.⁵ It is also prone to repeated haemorrhage and growth over time.

The initial evaluation of suspected acute stroke typically relies on NCCT brain, which serves as the primary imaging tool to differentiate between stroke subtypes (ischemic vs haemorrhagic) and to rule out conditions that mimic stroke,⁶ a step that was taken with our patient upon her presentation with acute right hemiparesis. However, the initial review of her NCCT brain focused solely on the cerebral hemispheres, inadvertently omitting a thorough examination of the spinal cord. Consequently, the spinal cord lesion remained undetected. It was only upon further assessment and evaluation in the ward that the spinal cord lesion was detected, leading to the performance of MRI.

Acute hemiparesis is a common clinical presentation of acute stroke. However, not all hemiparesis is due to acute stroke. One of the rarest causes of acute hemiparesis is intramedullary cavernous haemangioma, a rare vascular malformation within the central nervous system, defined

by abnormal sinusoidal spaces that are dilated and devoid of intervening nervous tissue.¹ It can be epidural, intradural, or intramedullary, with the latter being exceptionally rare.²

The hypoglossal nerve palsy (12th nerve palsy) observed in our patient supported the initial diagnosis of stroke. The potential causes of hypoglossal nerve palsy (HNP) encompass tumour, neck trauma, stroke, infection, skull base disorders, and craniocervical degenerative diseases.⁷ In our case, the hypoglossal nerve palsy was likely resulted from oedema in the lower medulla, which exerted pressure on the hypoglossal nerve. This conclusion is extrapolated from MRI findings that also revealed an extension of the haemorrhage to the craniocervical junction. This situation mirrors another case, where a gentleman presented with neck pain and hypoglossal nerve palsy; his MRI detected an atlantooccipital spinal cord cyst with compression to the hypoglossal nerve.⁷ Therefore, comprehensive evaluation, including MRI, is crucial for accurately diagnosing patients with neck pain, acute hemiparesis, and cranial nerve palsies.

MRI is the best imaging modality and plays a crucial role in achieving an accurate diagnosis by differentiating this haemangioma from inter-tumoral haemorrhages and other spinal cord pathologies.¹ A lesion of mixed signal intensity with a surrounding hypointense rim on T2-weighted MRI with minor contrast enhancement suggests cavernous haemangioma as seen in our patient. Adjacent intramedullary haemorrhage is a common finding. The presence of haemorrhage might narrow the differential diagnosis to include thrombosed arteriovenous malformation (AVM), telangiectasia, or spinal cord hemangioblastoma.⁸ The MRI is superior over NCCT in identifying lesions, with NCCT missing several lesions, emphasizing the diagnostic advantage of MRI. Thus, the possibility of missing spinal cord haemorrhage on NCCT is significant.⁹ However, since NCCT is always the first imaging modality for a suspected stroke case, clinicians should meticulously examine the entire scan, including the spinal cord, to eliminate the possibility of spinal cord lesions. This is a crucial practice, especially when the suspected stroke case involves a relatively young

patient with neck pain, normal blood pressure and without any cerebrocardiovascular risk factors.

Surgical intervention is essential for unstable spinal cavernous haemangioma to prevent neurological deterioration, with complete resection resulting in stable or improved outcomes in 92% of cases.¹ The typical procedure entails a laminectomy or hemilaminectomy at the appropriate spinal level. Following MRI confirmation, our patient underwent emergency C3 laminectomy for complete haemangioma excision. Postoperatively, with adequate physiotherapy, significant improvement in right hemiparesis was observed, aligning with outcomes in similar cases.² In a retrospective study, immediate postoperative neurological improvement was noted in 5 patients, with 46% reporting enhanced motor strength during follow-up.¹⁰

CONCLUSION

Intramedullary cavernous haemangioma has variable presentations, including acute hemiparesis, which mimics a stroke. Clinicians should thoroughly examine the entire scan in a relatively young patient who presents with neck pain, normal blood pressure, and no cerebrocardiovascular risk factors.

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