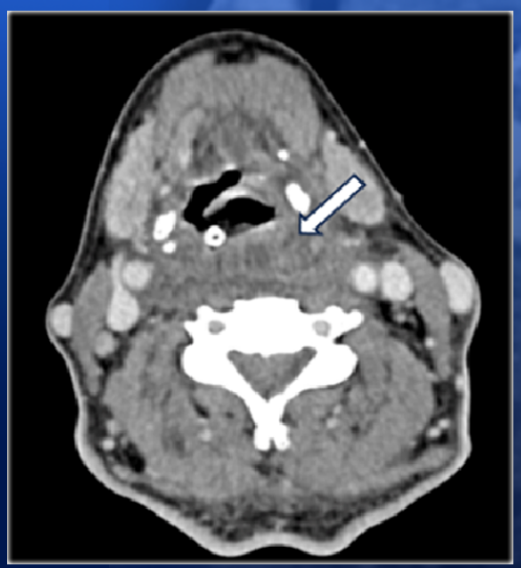
IMJM

VOLUME 25 NO 2
APRIL 2026 ISSUE
IIUM MEDICAL JOURNAL MALAYSIA

ISSN : 1823-4631
E-ISSN : 2735-2285

www.imjm.my



IMJM
IIUM MEDICAL JOURNAL MALAYSIA

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IMJM
IIUM MEDICAL JOURNAL MALAYSIA
Volume 25, Issue 2, April 2026
https://doi.org/10.31436/imjm.v25i02

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EDITORIAL

Volume 25 Number 2, April 2026

Closing the Perioperative Temperature Gap: Lessons from Implementation Science

Busy clinicians are faced with a constantly expanding body of published literature. The wealth of evidence available to improve patient outcomes and health system efficiency is enormous and growing. The prospect of applying best practice based on a mass of data, even with consensus of certain themes, is usually characterized by significant delays from bench to bedside. Most published data will not achieve widespread adoption. When scientific evidence does make the transition to practice improvement the lag between generating evidence and routine clinical use is estimated to be 17 years.[1] Addressing this evidence-to-practice gap is the primary focus of implementation science.

The evidence-to-practice gap is not merely academic. Experienced clinicians can typically cite examples of fundamental safety practices that fail to occur reliably in their institutions. Perioperative temperature management is a case in point. A period-prevalence study of five Australian hospitals (1,690 surgical patients) observed that more than half of the patients had just two or fewer temperature measurements during the entire surgical pathway.[2] Notably no temperature was recorded at any stage before the Post-Anaesthetic Care Unit (PACU) arrival in one third of patients. In PACU, temperature monitoring was near-universal but in many ways not soon enough, with approximately one third of patients unintentionally hypothermic post-operatively. This is the "perioperative temperature gap". Guidelines and devices are at hand, yet systems fail to deliver routine, risk-aligned warming and monitoring that would benefit our patients and healthcare systems.

The most sobering finding in this multi-site prevalence study is that emergency and ASA IV patients had the lowest monitoring rates.[2] Closing the temperature gap is therefore also an equity agenda. Implementation plans should prioritise high-risk operating lists and shifts (after-hours, weekends), stratify dashboards by urgency and severity of illness, and make equity an explicit success criterion, not a post-hoc consideration.

Effectiveness research determines whether an intervention works and provides the foundation for evidence-based practice. Implementation science is defined as the scientific study of methods to promote the systematic uptake of research findings and other evidence -based practice into routine practice, and hence improve the quality and effectiveness of health services and care.[3] Implementation research asks how people and organisations will do an evidence-based intervention sustainably and at scale.

Quality improvement activities are important and complement implementation science but are distinct.[4] Quality improvement tackles local problems with methods that may not be broadly applicable or scalable. Implementation science seeks generalisable, assessable methods to embed and spread change across settings. Perioperative practice needs both, but only an implementation lens will close a persistent, system-level issue, such as the perioperative temperature gap.

Implementation science has been criticized for inconsistent strategy, terminology and under-measurement of implementation outcomes (acceptability, appropriateness, feasibility, adoption, fidelity, sustainability).[5] Perioperative programs should also resist 'black box' bundles without characterizing components transparently.

Effectiveness research and implementation science can be brought together. The GLOW trial operationalises a hybrid study design with co-primary outcomes (PACU hypothermia, as well as the extent of monitoring and warming).[6] Team-based facilitation, local adaptation

within a common framework, and an economic evaluation are proposed. This approach may develop templates that can be adopted by perioperative services beyond the study sites. By reporting implementation outcomes alongside clinical outcomes, results should be generated that other services can reproduce and regulators can recognise.

Detailed guidelines can overwhelm busy clinical teams. As a prerequisite of the GLOW trial, a national, multidisciplinary consensus distilled the perioperative thermal care evidence and guidelines into three simple principles: (1) monitor core temperature frequently; (2) warm actively; (3) minimise exposure throughout the perioperative pathway.[7] These principles established non-negotiables, against which fidelity can be determined. Local teams can adapt workflows including device selection, handover checklists, and electronic medical record (EMR) automations. This 'principled adaptation' preserves predictability without succumbing to idiosyncratic alteration that dilutes the intervention.

Improvements that depend on champions tend to fade. Contemporary implementation rationale emphasises building scalable units.[5] To address the perioperative temperature gap, this could include a local multidisciplinary 'warmth' team (including an internal facilitator) supported by a regional facilitation hub that coaches sites, maintains fidelity, and curates a concise set of indicators. Further support could be added as a broader (perhaps national) learning network that spreads and sustains effective implementation strategies.

Closing the gap also requires stopping practices that are unsafe or wasteful. One example of this would be the use of active warming without concurrent temperature monitoring. This appears to be regular practice and is at odds with the basic principle of titrating treatment based on response. Another example may be skipping pre-anaesthesia temperature checks due to an emphasis on throughput, only to 'discover' hypothermia in PACU and prolong discharge due to rewarming requirements. De-implementation (stopping things that do not help) and avoidance of mis-implementation (the mistake of de-implementing things that work) should be anticipated and strategies embedded as components of perioperative temperature programs.[4]

Artificial intelligence, continuous monitoring devices, and automated data-capture systems promise to accelerate improvements in perioperative care by reducing documentation burden, signaling risk earlier, and supporting real-time decision making. Emerging large language model (LLM) tools can help generate concise handover summaries, translate complex guidelines into simple checklists, and provide rapid access to evidence.[8] Reliable, passive background processes may also be provided by integrated temperature dashboards and EMR-linked sensors.[9]

Highly capable innovations may be abandoned when they are difficult to use, poorly integrated, or misaligned with clinical workflow. By looping implementation science principles back into technology selection, perioperative teams may ensure they adopt innovations because they fit the clinical problem, integrate cleanly with workflows, minimise cognitive load, and deliver quantifiable value.[8] In this way, AI and digital systems may become enablers rather than distractions. By making the right thing easier to do and reinforcing fidelity to best-practice, thermal care could become a dependable property of the system rather than vulnerable to the effort of individuals.

Measured early and often, warmed wisely, and implemented scientifically, perioperative temperature management can move from well-meaning intention to reliability. Even if the only improvement was fewer chills and shivers in the recovery room, patient experience would justify the effort. Beyond that, closing the perioperative temperature gap will result in fewer perioperative complications, faster recovery, and a standard of care that keeps people warm and safe by design, not by chance.

CONFLICT OF INTEREST

Prof. Sturgess serves as a Key Opinion Leader for Solventum (previously 3M Healthcare). No financial support was received for the preparation of this editorial, and Solventum had no role in its content.

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Prof. Dr. David Sturgess
Professor of Anaesthesiology & Critical Care Medicine
Princess Alexandra Hospital Southern Clinical School,
The University of Queensland, Brisbane, Australia

EXPERT OPINION

Ethical and Legal Issues at the End of Life for Critically Ill Patients

Ibrahim NA[a], Mat Nor MB[b]

[a]Faculty of Medicine, Universiti Putra Malaysia

[b]Department of Anaesthesiology and Intensive Care, Kulliyyah of Medicine, IIUM.

CASE VIGNETTE

Mr. A, a 68-year-old man with advanced metastatic colon cancer, was admitted to the intensive care unit following respiratory failure. Despite maximal ventilatory support, his prognosis was poor, with no realistic chance of recovery. His oncologist had previously discussed about palliative care, but the family insisted on "doing everything possible" in the hospital. After two weeks of mechanical ventilation, Mr. A remained sedated, dependent on artificial nutrition, and developed recurrent infections. The treating team faced a dilemma: should life-sustaining treatment be withdrawn to allow a natural death, or should it be continued in deference to the wishes of the family?

This case illustrates the ethical and legal complexities of end-of-life (EOL), where cultural expectations, religious beliefs, and legal uncertainties converge.

INTRODUCTION

Medical progress has transformed the natural course of illness and death. Life-sustaining technologies such as ventilators, dialysis and artificial nutrition can extend the physiological function of critically ill patients long after the body's natural capacity has waned.[1] While these life-prolonging interventions save lives, they also create ethical and legal dilemmas when applied to patients with no realistic prospect of recovery. Clinicians in Malaysia, face uncertainty due to limited legislation, diverse cultural expectations, and strong religious influences. This article provides an expert opinion on ethical and legal issues at EOL, contextualised within Malaysian practice but informed by global discourse.[2]

MORALS, ETHICS, AND LAW

EOL decision-making is shaped by three overlapping domains: morals, ethics, and law. Morals represent the personal values and convictions of individuals, often deeply influenced by religion, culture, and social norms. Ethics refers to the professional codes that guide medical conduct, such as the Malaysian Medical Association's *Code of Ethics* and the Malaysian Medical Council's *Code of Professional Conduct*.[3] These codes provide a framework for acceptable practice, though they are not legally binding. Law differs in that it comprises statutory rules enforced by government institutions, carrying penalties for any violation. At the bedside in hospital wards, these domains frequently intersect: a physician may feel morally compelled to continue treatment, ethically bound to respect patient autonomy, and legally constrained by the absence of clear provisions on withdrawal of treatment. The conflict between these spheres creates the crucible in which EOL dilemmas must be resolved. [5]

ETHICAL FRAMEWORKS

The four principles of biomedical ethics articulated by Beauchamp and Childress, namely autonomy, beneficence, non-maleficence, and justice, remain central to EOL care. Autonomy requires respect for patient choice, beneficence obliges physicians to act in the best interests of patients, non-maleficence demands the avoidance of harm including futile interventions, and justice calls for fair allocation of resources. These principles are not hierarchical and may be in conflict, requiring nuanced judgment and sensitive communication.

ETHICAL ISSUES IN END-OF-LIFE CARE

Decisions at the EOL often involve whether to continue life, withhold, or withdraw treatment. Ethically, withdrawal and withholding are considered equivalent, yet they carry different emotional weight. Families may perceive withdrawal as an active step of "giving up" or

abandoning care, which makes the process more emotionally problematic and can lead to conflict.

Artificial hydration and nutrition are frequently regarded as basic care rather than medical intervention, and their withdrawal is often resisted even when it prolongs suffering without meaningful benefit. Terminal sedation, when used to relieve intractable symptoms, is ethically defensible under the principle of double effect, provided the intent is comfort rather than hastening death.[4,5]

In Malaysia, euthanasia and physician-assisted suicide are not legally permitted. Physicians, therefore, focus on ethically sound alternatives, particularly comprehensive palliative care, to relieve suffering and uphold the dignity of the patients. The actual challenge lies in balancing beneficence and non-maleficence by providing interventions that genuinely benefit the patient while avoiding harm through futile or burdensome treatments. Ultimately, ethical decision-making at the end of life requires sensitive communication, respect for patient autonomy, and recognition of the emotional complexities faced by family members. Structured approaches such as planning for advanced care and family conferences can help bridge these gaps, ensuring that decisions about patient care reflect both ethical principles and patient values.

RELIGIOUS AND CULTURAL PERSPECTIVES

Malaysia's plural society adds complexity to this conundrum. Islamic jurisprudence emphasises regarding the sanctity of life but permits withdrawal of medically inappropriate treatments.[6] Christian and Buddhist traditions emphasise compassion and dignity. Cultural norms often prioritise family-centred decision-making, sometimes overshadowing patient autonomy. Clinicians in charge must navigate these sensitivities by engaging in dialogue with family members and religious authorities to ensure that care aligns with the patient's values.[7]

SURROGATE DECISION-MAKING IN END-OF-LIFE CARE

Surrogate decision-making is a defining feature of EOL care in Malaysia, where family members frequently assume responsibility when patients are incapacitated. This practice reflects cultural expectations of filial duty and collective decision-making; however, this also raises ethical concerns when surrogates' preferences diverge from those of the patient.

Mr. A's case illustrates this dilemma vividly. Although his prognosis was poor and his oncologist had previously discussed regarding palliative care, his family members insisted on "doing everything possible." Their role as surrogate decision-makers effectively overrode the patient's earlier openness to comfort-focused care, resulting in prolonged interventions that may not have aligned with his wishes.

A study published in April 2022 entitled *"Differences in Attitude towards End-of-Life Care among Haemodialysis Patients and their Family Members in Two Malaysian Hospitals,"* highlighted this issue. The findings revealed that those patients were generally more receptive to limiting aggressive interventions, whereas family members tended to favour continuation of treatment. This divergence underscores the risk that surrogate decision-makers may unintentionally override patient autonomy, perpetuating interventions that the patient might not have desired.[8]

International evidence reinforces this concern. Shalowitz and colleagues, in their systematic review of surrogate decision-making accuracy, found that surrogates correctly predicted patients' treatment preferences only about two-thirds of the time, with accuracy declining further in complex scenarios involving life-sustaining treatment. Their work demonstrates that even in societies where family involvement is deeply valued, surrogate decision-making is inherently limited and prone to error.[9]

These findings highlight the importance of Advance Care Planning (ACP**)** in Malaysia. ACP provides a structured process for patients to articulate their values, preferences, and goals of care before they become incapacitated. By documenting these preferences, ACP reduces reliance on surrogate interpretation and ensures that medical decisions

reflect the voice of the patients. In a plural society like Malaysia, ACP also facilitates dialogue between patients, family members, and healthcare providers, bridging cultural expectations with ethical safeguards. Institutionalising ACP within hospitals and dialysis units would help mitigate conflicts, reduce moral distress among clinicians, and align care more closely with patient autonomy.

EVIDENCE FROM ETHICUS TRIALS AND MALAYSIAN CONTEXT

The Ethicus I trial (2003), conducted across 37 European intensive care units (ICU), revealed that nearly half of ICU deaths involved some limitation of treatment, either withholding or withdrawing life-sustaining interventions. Importantly, the study highlighted striking regional differences: clinicians in Northern Europe were more likely to withdraw treatment, while those in Southern Europe tended to withhold treatment rather than withdraw, reflecting cultural and religious influences on medical decision-making.[10]

Nearly two decades later, the Ethicus II trial (2021) demonstrated a significant evolution in decision-making. Physicians reported greater acceptance of treatment withdrawal, more structured communication with families, and increased patient involvement in decision-making. The trial concluded that EOL practices had become more standardised across Europe, with clearer institutional protocols and reduced variability between regions.[11]

For Malaysia, these findings are highly relevant. Local ICU audits, such as those conducted at Universiti Malaya Medical Centre and Hospital Kuala Lumpur, suggest that decisions to limit treatment remain relatively uncommon compared to those in Europe. Malaysian intensivists often favour withholding rather than withdrawing interventions, echoing the Southern European pattern seen in Ethicus I. This reluctance is driven by cultural sensitivities, strong family involvement, and fear of litigation. Physicians have reported moral distress when continuing intervention, which they considered futile, but felt constrained by family expectations and legal uncertainty.[12,13]

Taken together, the Ethicus trials and Malaysian studies highlight the importance of structured communication and documentation of patient preferences. Ethicus II showed that family engagement, when guided by clear institutional protocols, reduces conflict and aligns decisions with patient values. In the Malaysian context, the absence of such structures means that family surrogates often exert dominant influence over end-of-life decision-making, which can perpetuate overtreatment. Institutionalising advance care planning and family conferences could help ensure that patient voices remain central, even when they are incapacitated, while balancing cultural sensitivities and family expectations.[10,11, 12,13]

LEGAL CONSIDERATIONS IN MALAYSIA

In Malaysia, the absence of clear legislation on end-of-life care creates significant uncertainty, often resulting in overtreatment as healthcare professionals seek to avoid potential legal repercussions. While this legal vacuum poses challenges, it should not prevent clinicians from acting in accordance with ethical standards. The Malaysian Medical Association (MMA) Code of Ethics 2023 provides a crucial framework, emphasising that ethical duties remain paramount even in the absence of statutory support. Healthcare teams must therefore strive for consensus in their decision-making, ensuring that choices are both ethically defensible and clinically appropriate. Once a unified position is reached, it should be communicated transparently and compassionately to the patient's family, allowing for family concurrence and alignment with the care plan. This approach not only safeguards professional integrity but also fosters trust between healthcare providers and families, bridging the gap left by the lack of legislative clarity.[2,3,14,15]

INSTITUTIONAL CHALLENGES

Hospitals in Malaysia face systemic challenges, including a lack of standardised protocols, limited palliative care resources, inadequate ethics training, and physicians' fear

of litigation. These challenges contribute to inconsistent practices and moral distress among healthcare providers.

RECOMMENDATIONS

Authorities in Malaysia's medical sector should consider legislative reform to clarify the legality of withdrawing futile treatment and to protect physicians who act ethically. Strengthening palliative care services nationwide would ensure that patients receive holistic support addressing physical, psychological, social, and spiritual needs while improving the quality of those dying and reducing unnecessary interventions. Education in ethics should be expanded to train clinicians in communication and cultural competence. Hospitals should adopt clear institutional protocols for EOL decisions, and structured family engagement should be prioritised to align expectations and reduce conflict.

Equally important is the institutionalisation of Advanced Care Planning (ACP). ACP allows patients to articulate their values and preferences before they become incapacitated, reducing reliance on surrogate interpretation and minimising conflict between families and clinicians. In Malaysia's plural society, ACP provides a culturally sensitive framework for dialogue between patients, families, and healthcare providers. Incorporating ACP into routine practice, particularly in dialysis units, oncology clinics, and intensive care settings, would ensure that patient autonomy is respected, decisions are guided by documented preferences, and care at the EOL reflects the values and wishes of individuals rather than being driven solely by surrogate interpretation or institutional uncertainty.

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Dr. Noor Airini Ibrahim
Consultant Intensivist,
Faculty of Medicine,
Universiti Putra Malaysia

National Coordinator
End-of-Life Care Malaysian Society of Intensive Care
2015 to 2025

Prof . Dato' Dr. Mohd Basri Mat Nor
Consultant Intensivist,
Department of Anaesthesiology and Intensive Care,
Kulliyyah of Medicine,
International Islamic University Malaysia

REVIEW ARTICLE

A Systematic Literature Review on ICU Nurses' Experience and Family Interactions during Death and Dying from an Islamic Perspective

Ludin SM[a], Ramli SA[b]

[a]Department of Critical Care Nursing, Kulliyyah of Nursing, International Islamic University Malaysia, Pahang, Malaysia
[b]Klinik Mamad Sdn Bhd, Lot 295 & 296, Jalan Besar Kuala Berang, Terengganu, Malaysia

ABSTRACT

The growing complexity of death and dying in Intensive Care Units highlights nurses' critical role, particularly concerning family interactions and spiritual needs from an Islamic perspective. However, there is a gap in understanding the nuances of these interactions, how nurses can best facilitate them, and how potential conflicts arising from differing interpretations of religious beliefs may impact care; this area remains underexplored. This systematic literature review aims to synthesize existing studies on ICU nurses' experiences with critically ill patients during death and dying, focusing on Islamic perspectives or spiritual care, employing a qualitative synthesis approach. The Scopus database was used to retrieve relevant documents published between 2005 and 2024. The review followed PRISMA guidelines for identification, screening, exclusion, and inclusion. Qualitative, quantitative, mixed-method studies, and review articles were included, with only qualitative papers appraised using the Joanna Briggs Institute's criteria. Initially, 378 records were identified. After removing unavailable files and screening, 113 titles and abstracts were assessed. Of 84 reports reviewed for eligibility, 68 were excluded, leaving 14 studies that met the inclusion criteria for the final review. This review emphasizes the crucial need for better training, policies, and institutional support for ICU nurses. Such measures would enable them to manage the complexities of culturally sensitive care for family members during loved ones' death and dying. Implementing standardized guidelines addressing Islamic perspectives can significantly improve care quality and patient-family satisfaction.

Keywords:
Critical care, spiritual care, nurses, Islamic perspective, death and dying

Corresponding Author
Prof. Dr. Salizar Mohamed Ludin
Department of Critical Care Nursing, Kulliyyah of Nursing, International Islamic University Malaysia,
Kuantan, Pahang, Malaysia.
Email: msalizar@iium.edu.my

Received: 13th May 2025; Accepted: 30th January 2026

Doi: https://doi.org/10.31436/imjm.v25i02.2958

INTRODUCTION

Critical care nurses face challenges in integrating Islamic cultural and religious values into their practice, especially during death and dying. They work closely with patients to provide essential care, with the goal of end-of-life care, ensuring patients' final moments are peaceful, dignified, and comfortable.[1] However, achieving this goal can be difficult due to challenges in the critical care environment, such as burnout out which may lead to psychological problems for the nurses involved.[2] Nurses also face obstacles like doctors being overly optimistic about patient recovery and families not fully understanding life support measures, making communication and decision-making harder.[3] It is a common occasion for a critical care nurse to experience different kinds of emotions during caring, including sadness, anger, and frustration, as they try to provide compassionate care in emotionally charged situations.[2,4] For newer nurses, experiences such as anticipating death, witnessing the transition from life to death, supporting the family during these moments, and continuing with their duties afterwards can be incredibly challenging.[5,6]

The importance of addressing the Islamic perspective in end-of-life care is particularly pronounced due to documented cultural practice gaps and known misalignments with standard Western ICU procedures. Islamic values emphasize kindness and compassion, influencing nurses' approach in culturally diverse settings and enhancing the healthcare experience for all involved, emphasizing the importance of compassion until the end.[7]

However, healthcare providers often demonstrate a lack of knowledge regarding the specific needs and beliefs of Muslim patients and their families concerning end-of-life care, indicating a critical gap in cultural competence training for nurses. Issues regarding organ donation are also frequently mentioned, as they usually affect patients in the process of death and dying. It includes the ethical decision made by the family member and the patients themselves. Studies on death and dying processes in Islamic countries are limited due to a focus on Western contexts, indicating a lack of studies on Islamic or spiritual practices in hospital settings for nursing patients.[5]

In Islamic contexts, cultural and religious values further shape these dynamics of death and dying, often diverging from conventional hospital protocols. Practices like Qur'anic recitations, *Shahadah* (declaration of faith), and continuous family presence at the bedside are integral to ensuring a dignified death and dying and are deeply valued. Yet, these core Islamic practices can often conflict with, or be hindered by, standard ICU procedures and hospital restrictions, as evidenced during periods like the COVID-19 pandemic.[8,9] Furthermore, specific issues such as organ donation, embalming, and autopsy frequently present ethical dilemmas for Muslim families and healthcare providers due to differing religious interpretations and traditional post-mortem practices.[10] The reliance on life-sustaining technologies for religious reasons, even against clinical advice, also highlights potential areas of conflict in ICU settings.[11] Critically, spiritual care, though essential and valued in Islamic traditions, often remains neglected for critically ill Muslim patients, despite the proven benefits of Islamic spiritual practices as non-pharmacological interventions.[12]

Studies on death and dying processes in Islamic countries are limited due to a focus on Western contexts, indicating a lack of studies on Islamic or spiritual practices in hospital settings for nursing patients.[13,14] This significant gap in existing literature and the scarcity of high-quality evidence underscore the need for further research in this area.[13,14] This systematic review aims to address this critical gap by synthesizing existing studies to understand ICU nurses' experiences in dealing with critically ill patients during death and dying, specifically focusing on Islamic perspectives and spiritual care. This exploration is vital for developing culturally sensitive care models that respect and incorporate the unique values of Muslim patients and their families.

METHODS

Search strategies

This review exclusively used Scopus as its data source, valuing its high-quality, consistent, and reliable data for accurate trend and citation analysis. Scopus was chosen over other databases for its comprehensive coverage, structured information, and robust analytical tools, making it the ideal primary source for the review, which involved a detailed keyword search. The study selection process involved Scopus screening articles based on availability and relevance, assessing suitability, and selecting studies on ICU nurses' experiences, spirituality, family interactions, and death and dying, ensuring the most relevant and eligible studies were included for the systematic review.

Inclusion criteria are: i) Articles encompassing qualitative studies and mixed-method studies. However, only qualitative and mixed method papers were appraised as it is more suitable for this topic of interest; ii) Articles published in English only; iii) Studies in the ICU setting; iv) Studies related to spiritual care, religion, or the Islamic perspective; v) Articles published between 2005 and 2024; and vi) Studies pertaining to nurses and family interaction.

The exclusion criteria are: i) Articles only consisting of abstracts; ii) Studies that are outside the scope of the topic; and iii) Studies involve nursing students.

Identify Relevant Studies

Search Results

The study followed PRISMA guidelines as explained in Figure 1 below.

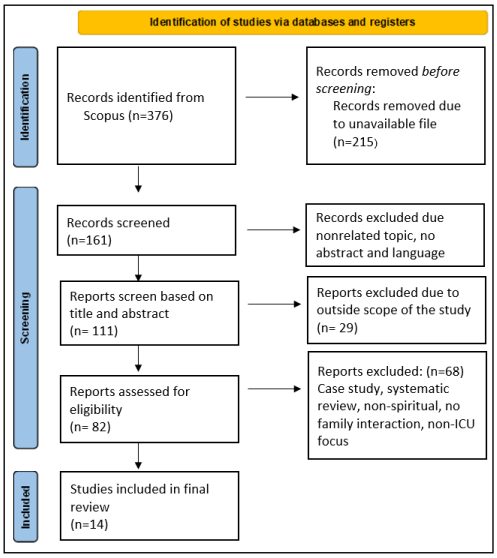

Figure 1: PRISMA flow diagram of the documents search, selection process, and reason for exclusion.

Critical Appraisal of the Sources of Evidence

Critical appraisal of papers was conducted using the JBI tool. Table I summarizes the methodological quality of included studies, allowing researchers to identify strengths and weaknesses against standardized criteria quickly. Each row specifies a research study by author(s) and publication year. Column headers represent individual criteria from a specific JBI Critical Appraisal Checklist. "Y" signifies the study met the criterion, indicating strength; "UC" means it was unclear if the criterion was met due to insufficient reporting; and "N" indicates the study did not meet the criterion, suggesting a methodological weakness or risk of bias.

Table I: JBI Quality appraisal for qualitative studies

Author (year of publication)	Individual Criteria from a Specific JBI Critical Appraisal Checklist.									
	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10
Mani, (2024)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Sadeghi et al., (2016)	Y	Y	Y	Y	Y	Y	UC	Y	Y	Y
Betriana & Kongsuwan (2019)	Y	Y	Y	Y	Y	Y	UC	Y	Y	Y
Adistie et al., (2020)	Y	Y	Y	Y	Y	U C	UC	Y	Y	Y
Lima & Rosa (2008)	Y	Y	Y	Y	Y	Y	N	Y	Y	Y

In this review, the author critically appraises only qualitative data because the review was done for several justifiable reasons. Firstly, the alignment with the research question is key, as qualitative studies are best suited for exploring experiences, perceptions, meanings, or processes, and for answering "what," "how," or "why" questions. Secondly, such an appraisal is part of a qualitative evidence synthesis or systematic review, which specifically aims to synthesize qualitative findings to enhance their credibility and transferability or to complement systematic reviews of clinical trials. Lastly, the review will serve as a complementary role, providing qualitative insights to inform policy and practice without necessarily integrating quantitative measures of effectiveness or prevalence. For a comprehensive explanation of each criterion, refer to Table II, which presents the JBI Critical Appraisal Checklist.

Table II: Checklist of JBI critical appraisal

CRITE	QUESTION
C1	Is there congruity between the stated philosophical perspective and the research methodology?
C2	Is there congruity between the research methodology and the research question or objectives?
C3	Is there congruity between the research methodology and the methods used to collect data?
C4	Is there congruity between the research methodology and the representation and analysis of data?
C5	Is there congruity between the research methodology and the interpretation
C6	Is there a statement locating the researcher culturally or theoretically?
C7	Is the influence of the researcher on the research, and vice versa, addressed?
C8	Are participants, and their voices, adequately represented?
C9	Is the research ethical according to current criteria, or for recent studies, and is there evidence of ethical approval by an appropriate body?
C10	Do the conclusions drawn in the research report flow from the analysis or interpretation of the data?

Data Extraction

The standardized data extraction chart included the following information for each study: Author's year, country, study design, objectives, recruitment, and main findings, as shown in Table III.

RESULTS

Theme 1: Cultural and Spiritual Sensitivities Islamic Principles and End-of-Life Spiritual Support

Islam, the world's second-largest religion, teaches that death is a divine will and an inevitable transition to the afterlife.[15] Islamic traditions emphasize the connection between death and faith, requiring families to honour religious practices through presence, prayer recitation, and ensuring a peaceful passing in accordance with Islamic

Table III: Summary of the selected articles

No	Author (Year), Country	Design (Data Collection Method)	Phenomenon of Interest	Recruitment	Main findings
		Title: Bridging cultural gaps in end-of-life care: the experiences of international charge nurses in Saudi Arabia			
1	**Mani (2024), Saudi Arabia**	• Qualitative descriptive design • Semi-structured interview • Interview guide	To understand the unique cultural and religious considerations that shape end-of-life care practices within the Islamic context.	Eight participants who are international ICU charge nurses from different countries.	• The Weight of Unspoken Truths • Clashing Worldviews • The Family's Agony • The Burden on Nurses • Bridging the Divide • A Call for Change • The Importance of Family Presence • Honouring Faith in Absence: Peaceful and Compassionate Passings
		Title: The life meaning of the parents of the critical patient			
2	**Lima & Rosa (2008), Salvador**	• Qualitative approach • Semi-structured interview	To understand the life meaning of critical patients' relatives, in view of the Tragic Triad: guilt, suffering, and death; to identify the contents of these individuals' life meanings, based on Existential Analysis.	10 interviews were conducted, and only six of them were selected based on the content criteria.	• The existential void: unveiling the relatives' concrete situation. • The suffering: unveiling the relatives' gravity and the unconscious God • Guilt: being guided by responsibility • Death: unveiling moments of reflection • Meaning of life: unveiling the eternal file • Assistance to the critical patients' relatives: unveiling the ICU as a health care space.
		Title: Spiritual Needs of Families with Bereavement and Loss of an Infant in the Neonatal Intensive Care Unit: A Qualitative Study			
3	**Sadeghi et al., (2016), Iran**	• Exploratory qualitative study • Semi-structured interview	To explore the spiritual needs of Iranian families at the end of their baby's life and through bereavement, from families' and professional health care providers' perspectives in the NICU.	25 participants (15 interviews with family members and 10 interviews with professionals).	• Belief In a Supernatural Power • The Need for Comfort of The Soul • Preserving the Human Dignity of the Newborn.
		Title: Grief reactions and coping strategies of Muslim nurses dealing with death			
4	**Betriana & Kongsuwan (2019), Indonesia**	• Qualitative phenomenological approach • Individual interview	To describe the grief reactions and coping strategies of Muslim intensive care nurses in dealing with the death of patients.	14 ICU nurses participated. Three were male and 11 were female.	• Reactions of grief • Factors influencing grief reactions • Coping strategies
		Title: The Needs of Children with Terminal Illness: A Qualitative Study			
5	**Adistie et al., (2020), Indonesia**	• Qualitative descriptive study • Focus group and in-depth interview	To examine the needs of children with terminal illness from the perspective of nurses and parents.	15 nurses from paediatric ward, PICU and NICU. 11 parents of children with terminal illness.	• Biological needs in children with terminal disease • Psychological needs in children with terminal illness • Social needs in children with terminal illness • Spiritual needs in children with terminal illness
		Title: The Dying Process and Death of Patients with Covid-19: A Reflection In The Light of Spirituality			
6	**Silva et al., (2020), Brazil**	• Reflective article	To reflect on the dying process and death of patients with Covid-19 in the light of spirituality.	Not applicable	Understanding the sense of spirituality on the part of health professionals, in search of support for dying patients and bereaved families, is important, as spirituality can be a potential factor of integration and harmonization of interpersonal relationships.
		Title: Perinatal and Paediatric Issues in Palliative and End-of-Life Care from the 2011 Summit on Compassionate Care			
7	**Youngblut & Brooten (2012), United States**	• Review paper	To convey a summary of research on infant/child ICU death and parent experiences, needs, and responses used to stimulate discussion of perinatal and paediatric palliative/EOL care issues and to provide recommendations for future research and clinical practice generated by those attending this session.	Not applicable	• Family/Parent Needs and Responses • Palliative and EOL Care Issues • Communication Issues • Communication between • Health Care Delivery System
		Title: The Investigation of Death Anxiety and Spiritual Well-Being Levels of Family Members of Patients Admitted to the Intensive Care Unit			
8	**Görücü and Arslan (2024), Turkey**	• Quantitative • Descriptive correlational • Face-to-face interview and survey	To investigate the death anxiety (DA) and spiritual well-being (SWB) levels of first-degree family members of patients hospitalized in the intensive care unit (ICU).	308 family members who came to visit family members treated in the ICU.	In this study, a positive and significant correlation was found between the DA levels and SWB levels of the family members. According to this result, as family members' DA increases, their spiritual needs also increase.
		Title: Religious and spiritual support in the conception of nurses and families of critical patients: a cross-sectional study			
9	**Santos et al., (2021), Brazil**	• Exploratory and descriptive, cross-sectional • Quantitative study	To assess the religious and spiritual support in critical care according to the conception of patients' family members and nurses.	22 nurses participated, 11 from hospital A and 11 from hospital B. Regarding family members, there were 34 from ICU A and 27 from ICU B (n=56).	Nurses and family members recognized religious/ spiritual support as significant to the process of caring for critically ill patients, even though professional qualification is required for greater integration of this support in daily intensive care.
		Title: Intensive Care Registered Nurses' Role in Bereavement Support			
10	**Kurian et al., (2014), United States**	• Quantitative • post-test-only survey design	To ascertain ICU registered nurses' (RNs') current practice and beliefs about bereavement care, their role in bereavement support, and interest and education related to bereavement.	A total of 110 RNs working in the MICU (n=28), TSICU (n=39), NICU (n=29), and CCU (n=14).	Most of the nurses agreed with items indicating it is the nurses' role to provide bereavement support to relatives. Almost half (46%) indicated they have not had sufficient education, training, and experience with bereavement care. The ICU nurses who had received bereavement program training more strongly agreed that nurses should be involved in initiating and maintaining contact with newly bereaved families.

cont'd

		Title: How do intensive care clinicians ensure culturally sensitive care for family members at the end of life? A retrospective descriptive study			
11	**Brooks et al., (2022), Australia**	• Quantitative • Descriptive study utilising a retrospective medical record audit	To examine whether clinicians provided culturally sensitive care for family members of patients from culturally diverse backgrounds who died in an intensive care unit.	430 records used to analyse.	Despite the culturally diverse patient population, findings show that details about culturally sensitive end-of-life care are rarely documented. Comprehensive documentation is required of how clinicians assess patient and family member cultural wishes and preferences, in conjunction with how clinicians attempt to address these cultural needs.
		Title: Families' needs of critical care Muslim patients in Saudi Arabia: A quantitative study			
12	**Al-Mutair et al., (2018), Saudi Arabia**	• Quantitative study • A cross-sectional survey designs. • Self-administered questionnaire.	To identify the needs of families of adult intensive care unit (ICU) patients in Saudi Arabia as perceived by family members and healthcare providers.	176 family members and 497 intensive health care providers were recruited from eight adult mixed medical-surgical ICUs.	Family members and health care providers ranked assurance, information and cultural and spiritual needs as the most important, and support and proximity as least important.
		Title: "The Patient Is Dying, Please Call the Chaplain": The Activities of Chaplains in One Medical Center's Intensive Care Units			
13	**Choi et al. (2015), United States**	• Quantitative • Retrospective cross-sectional study	To describe the prevalence, timing, and nature of hospital chaplain encounters in the ICU	Among a total of 4169 admissions to adult ICUs over six months, 248 patients (5.9%) had documented chaplaincy care during their index ICU stay.	Chaplain visits are uncommon and generally occur just before death among ICU patients. Communication between chaplains and physicians is rare. Chaplaincy service is primarily reserved for dying patients and their family members rather than providing proactive spiritual support. These observations highlight the need to better understand challenges and barriers to optimal chaplain involvement in ICU patient care.
		Title: How Should Intensive Care Unit Nurses Organize End-of-life Care? A Mixed-methods Study			
14	**Jung et al., (2024), South Korea**	• Mixed-methods study • Focus group interviews and focus group interviews	To explore intensive care unit nurses' perceptions of end-of-life care and to identify strategies for improving patient comfort in the intensive care unit.	Focus group = 12 ICU nurses, Questionnaire 95 ICU nurses	• Focus group: • End-of-life care units: Connection with family and patients • Combining acute critical care with end-of-life care • Physical care: Physical care at the boundary between life and death with dignity • Linking spiritual/social/ psychological well-being to end-of-life care • Environmental considerations that dying patients deserve Questionnaires: The primary components of end-of-life care for ICU nurses in the FGI were centred around "comforting" and "connecting." The participants said that they aimed to provide comfort to patients by connecting them with their families, spiritual beliefs, social networks, and their life experiences, helping patients organize their thoughts and accept death without feeling isolated. These priorities were set in the context of the challenges faced in providing end-of-life care within the ICU's broader scope of care.

teachings. In Islam, both the dying and the deceased are treated with respect and dignity, and families often request healthcare providers to uphold these values.[16] Religious practices like Qur'anic recitation and prayer also provide spiritual comfort, as many Muslims believe that spiritual guidance is necessary to help a person die peacefully and in a state of faith.[16,17] Nurses are crucial in meeting spiritual needs while balancing medical responsibilities, navigating cultural sensitivities, and respecting religious beliefs without interfering with patient care.[16] For Muslim families, faith serves as a coping mechanism, helping them find comfort and strength during the process of death and bereavement.[18] Healthcare providers can foster a compassionate and spiritually sensitive environment by addressing religious needs while upholding medical ethics and Islamic traditions.

Spirituality plays a crucial role in supporting patients and families during death and bereavement.[19] A study found that spiritual and cultural needs are among the top three priorities for families.[20] However, research has mainly focused on patients, with less attention given to the families' spiritual needs.[21] Families of dying patients face heightened fear and emotional distress, making spiritual support crucial, especially in high-stress situations like the COVID-19 pandemic.[22] Factors influencing this need include employment status, income level, marital status, having children, and education level.[21] Many families view spirituality as a source of hope, believing in miracles or divine intervention for their loved ones.[23] Despite its importance, spiritual guidance is sometimes overlooked, particularly for children with terminal illnesses.[17] Providing spiritual support, whether through chaplaincy services or personalized care, helps address families' emotional and existential needs.[19] Critically ill patients receive frequent chaplain visits, while nurses, who form

close bonds with patients, often take the lead in providing spiritual care.[, 25] Families actively seek spiritual care from healthcare providers, believing that receiving religious guidance brings them peace.[16] Nurses play a key role in facilitating spiritual care by offering small yet meaningful gestures, such as providing a Qur'an to Muslim families.[18] They also invite religious leaders for additional support, helping patients feel closer to their Creator, though some families may decline such services.[18,25,26] Nurses are encouraged to incorporate spiritual interventions to support both patients and families.[22] Even after a patient's death, families require continued emotional support, including empathy, follow-up contact, and counselling.[27] Recording family wishes, including body handling and burial preferences, helps honour cultural and spiritual needs.[26] For Muslim families, respectful and careful handling of the body is a key aspect of spiritual care, helping to reduce stress and anxiety.[20]

Theme 2: Challenges occur during Grief and Coping

Family struggles

Families of critically ill patients often face intense emotional struggles, including anxiety, guilt, and existential distress, sometimes blaming themselves for their loved one's condition.[23] In the ICU, uncertainty about the patient's prognosis and exclusion from the care process often intensify families' distress. Denial is common, with families sometimes insisting that doctors and nurses do everything possible, even when the outcome is inevitable.[18,26] Communication gaps between medical staff and families can increase anxiety. While withholding information may respect cultural sensitivities, it can also erode trust and leave families feeling uninformed.[18] The emotional toll of these situations varies, but studies suggest that strong social support can help families cope better and even experience personal growth after grief.[13] Religious beliefs help families cope, as many see their loved one's illness as a test from God, finding solace in Qur'anic recitation and prayer.[16] Islam values patience (*sabr*) and discourages excessive mourning, which can emotionally challenge Muslim nurses supporting grieving families.[15] The level of grief experienced by families is influenced by demographic factors such as gender, employment status, income level, and past experiences with loss.[21] Recognizing these factors helps healthcare providers offer personalized support, ensuring families feel heard and included.

Nurse coping

ICU nurses face emotional strain from repeated patient deaths and family pressure, impacting their health, compassion, and care quality delivered.[18] Grief responses vary, with some showing detachment, empathy, or guilt, while others grieve privately.[8] Among nurses, factors like patient age, postpartum cases, and family involvement shape their grief, which ICU nurses manage through prayer and peer support to remain effective.[15] Muslim nurses, despite their Islamic values and personal faith, require structured support systems and training to effectively manage their emotional well-being.

Communication needs

Effective communication between healthcare providers and families is crucial in reducing stress and grief during the dying process. Transparent and empathetic communication helps families feel informed, supported, and involved in their loved one's care.[25] Nurses prioritize patient and family connections through active communication, but language barriers can hinder understanding, leading to miscommunication and distress.[26,27] Healthcare providers should ensure families are included in decision-making and kept well-informed about the patient's condition.[17,18] This involvement helps alleviate fear and uncertainty, making families feel more valued and reassured.[18] For those facing language difficulties, hospitals should provide translators or technology-based translation tools to ensure smooth and accurate communication.[18,26] This is particularly important when cultural expectations affect a family's understanding of medical care and end-of-life decisions.[27] Interestingly, in cases involving sick children, parents sometimes withhold medical information from them to protect them from emotional distress, which can complicate the communication process.[17] To address these challenges, healthcare institutions should continuously develop and improve communication tools to ensure effective dialogue between providers and

families.[18] Open discussions about religious and cultural beliefs foster trust, understanding, and comfort among families, reducing feelings of isolation and providing support to medical staff.[16,17] Chaplains and healthcare workers may face communication gaps due to differing perceptions of spiritual care needs, potentially hindering collaborative efforts.[24] Addressing these barriers to communication is essential in providing holistic, compassionate, and patient-centred care for both patients and their families.

Theme 3: Holistic and Family-Centred Care

Physical care

Nurses prioritize physical comfort and dignity during death and dying, especially in Islamic settings, ensuring care within a culturally and religiously sensitive framework. It stated that many nurses focus on meeting the patients' needs as well as providing them with emotional and spiritual support.[18] The example of basic physical care is the pain management from the nurses who received optimal infection prevention when hospitalized.[17,25] Nurses are also required to provide comfort as much as they can, as it can help to alleviate the suffering.[18]

Emotional care

Emotional care extends to both patients and their families, emphasizing the need to create a supportive environment, as there was distress on both sides.[22] For families, reassurance and acknowledgment of their grief are vital, while patients benefit from compassionate care that helps them accept death peacefully. Nurses often encourage the family members to be with the patient by their side, believing it to be the comfort the patients need.[17,18] This is including as act of visiting the sick relatives, as it is highly encouraged in Islamic teaching. It was stated that doing the emotional care shows respect for them, emotionally, spiritually, and psychologically.[18,20] During death and dying, nurses provide detailed patient information, especially for children, and encourage support through humour and treating them as sick individuals.[10] Nurses provide emotional support to patients by displaying family photos, making meaningful remarks, and organizing hospital programs to help them cope with sadness and fear.[25]

Training gaps

Nurses often report insufficient training in death and dying, particularly in addressing the spiritual and cultural needs of families.[19,28] The study highlights the significance of structured education programs on bereavement care and cultural competence in ICU nurses to enhance patient care and support.[18] It also highlights the need for resources and support mechanisms to acknowledge and address the emotional toll, as without support, nurses may experience burnout.[18]

Maqasid Al-Shariah: Guiding Islamic Perspectives on Death and Dying

The ethical considerations in Islamic healthcare are deeply rooted in *Maqasid al-Shariah*, which prioritize the preservation of life, intellect, faith, mind, and progeny.[29] Islam also emphasizes the integration of spirituality in health to maintain balance in the body, mind, and soul.[30] Islamic medical ethics emphasize truthfulness and trustworthiness in diagnosing patients, balancing patient autonomy with communal well-being.[29] This is particularly evident in Saudi medical settings, where family participation is emphasized to preserve emotional well-being and uphold *tawakkul* (reliance on God) in critical situations. This ethical framework ensures healthcare decisions consider both individual rights and family involvement.[29]

Additionally, Islamic spiritual care is crucial in modern healthcare, addressing physical, mental, psychological, emotional, and religious well-being.[30] Integrating spirituality and religion into patient care promotes holistic healing, comfort, and coping mechanisms in hospital settings. Engaging in prayer can help divert the mind from pain and promote relaxation through bodily movements.[30] Healthcare providers must practice spiritual care as a professional duty, respecting patients' values and beliefs, enhancing patient and family comfort.[30]

Islamic bioethics addresses ethical concerns in end-of-life decision-making, particularly regarding patient autonomy

and family roles. Physicians face dilemmas balancing truth-telling and psychological preparedness.[31] The integration of *Maqasid al-Shariah* in medical ethics ensures ethical, spiritually aware, and patient-centred healthcare, addressing both physical and metaphysical well-being.[31] This framework enables Muslim healthcare providers to navigate complex decisions while adhering to Islamic principles of justice, mercy, and public welfare.

DISCUSSION

The findings of this review highlighted the critical role of ICU nurses in managing the cultural and spiritual needs of patients and families during the death and dying process in Islamic contexts. Nurses serve as advocates, ensuring that the beliefs and values of Muslim patients and their families are respected and integrated into end-of-life care.[18] The approach to culturally sensitive ICU care emphasizes the importance of promoting a peaceful and dignified passing through key Islamic practices like Qur'anic recitation, *Shahadah,* and family presence, which provide spiritual and emotional comfort during a patient's final moments.[16,17] These rituals not only ease the patient's transition but also offer solace and closure to grieving families. Many Muslims find faith to be a source of strength during bereavement, believing in God's healing power and divine wisdom.[16]

However, a significant gap identified in this review is the lack of institutional guidelines addressing Islamic cultural and spiritual needs. Without formal policies, nurses are often left to rely on personal judgment or improvised approaches, leading to inconsistencies in care quality.[18,26] Nurses in ICU settings often engage with religious leaders for spiritual care, but may struggle due to a lack of awareness or training. Culturally tailored policies and standardized training programs are crucial for equitable and high-quality care. The review also highlights the emotional and psychological burden on ICU nurses providing care. Repeated exposure to grief and loss, coupled with the responsibility of supporting families in distress, can lead to stress, compassion fatigue, and burnout.[15,18] Nurses face challenges in dealing with young patients, denial-inducing families, and culturally sensitive cases, causing professional grief as they form emotional bonds with patients, making their deaths deeply affecting.[15]

ICU nurses in Islamic settings cope through prayer, faith, and religious practices for emotional strength, while peer support provides comfort through shared experiences.[8] ICU nurses experience burnout due to limited organizational support. Institutions should offer counselling, debriefing, and peer support to boost resilience. Cultural expectations and communication challenges further complicate care. Families of critically ill patients often experience heightened anxiety and stress, especially when faced with uncertainties about their loved one's condition.[16] In Islamic settings, illness is seen as a test of faith, leading families to seek spiritual reassurance and emotional support from healthcare providers, but communication gaps can exacerbate these challenges.[18,23] A lack of clear and empathetic communication regarding treatment options and prognosis can lead to frustration and mistrust, increasing the emotional strain on both families and nurses.

Some healthcare providers avoid discussing death and dying matters, fearing the topic is too sensitive or inappropriate.[18] Language barriers, cultural misunderstandings, and inadequate training in culturally sensitive communication complicate interactions in ICUs. Improving communication can be achieved through interpreters, translation technology, and cultural liaisons. Healthcare providers must also find a balance between cultural sensitivity and evidence-based medical practices, such as addressing traditional remedies like honey and oil for wound care while ensuring patient safety and medical efficacy.[18] Families in denial may struggle to accept a loved one's condition, often insisting on further medical interventions even when recovery is unlikely.[18] Effective communication not only reduces family distress but also eases the emotional burden on nurses, fostering a more supportive care environment.[18]

Holistic care is essential in death and dying management, addressing physical, emotional, and spiritual needs. While pain management is crucial, spiritual and emotional support are equally important in ensuring a dignified and compassionate death.[18] ICU nurses play a pivotal role in

this approach by facilitating religious rituals, involving chaplains, and providing spiritual care.[18,24] Many nurses lack training in cultural and religious aspects, making them unprepared to provide comprehensive spiritual care. Implementing educational programs on cultural competence, bereavement support, and spiritual care could equip nurses with the necessary skills.[18] These programs would not only boost nurses' confidence but also ensure that care practices align with the spiritual and cultural values of patients and families.

In summary, this discussion synthesizes the critical insights gleaned from the systematic review concerning the complex interplay between Islamic principles, spiritual care, and end-of-life experiences within Intensive Care Units. The findings underscore the indispensable role of ICU nurses in navigating cultural and spiritual sensitivities during the death and dying process for Muslim patients and their families.

A central theme emerging from the review is that Islamic traditions consider death an inevitable divine will and a transition to the afterlife. This foundational belief dictates a profound emphasis on honouring religious practices, including presence, prayer recitation, and ensuring a dignified passing in accordance with Islamic teachings. Both the dying and the deceased are to be treated with utmost respect and dignity, a value that families frequently ask healthcare providers to uphold. Religious acts such as Qur'anic recitation and prayer are not merely rituals but vital sources of spiritual comfort, believed to facilitate a peaceful and faith-affirming death. Faith itself serves as a crucial coping mechanism for Muslim families, providing strength and solace during bereavement. Nurses, therefore, hold a pivotal position in addressing these spiritual needs while balancing their medical duties, respecting diverse beliefs, and avoiding interference with patient care.

Despite the clear importance of spirituality, the review highlights significant challenges and gaps in current practice. Healthcare providers, including nurses, often demonstrate a lack of specific knowledge regarding the end-of-life needs and beliefs of Muslim patients and their families, pointing to a critical deficit in cultural competence training. This lack of understanding can lead to conflicts with standard ICU procedures, hindering deeply valued Islamic practices such as continuous family presence, Qur'anic recitations, and the Shahadah. Ethical dilemmas surrounding issues like organ donation, embalming, and autopsy further complicate care, often stemming from differing religious interpretations. While spiritual care is profoundly valued in Islamic traditions, it frequently remains overlooked for critically ill Muslim patients, despite its proven benefits as a non-pharmacological intervention.

The findings advocate for healthcare providers to foster compassionate and spiritually sensitive environments by actively addressing religious needs within the bounds of medical ethics and Islamic traditions. Nurses play a key role in facilitating spiritual care through gestures like providing a Qur'an and inviting religious leaders for additional support, though some families may decline such services. Critically ill patients benefit from chaplain visits, and nurses, due to their close patient bonds, often lead in providing spiritual care.

RECOMMENDATIONS

Future research should focus on Islamic perspectives in ICU end-of-life care, focusing on the cultural and spiritual needs of Muslim patients and families. Comparative studies between Islamic and non-Islamic settings could provide insights into how cultural differences impact care practices and patient outcomes. Culturally tailored training programs for ICU nurses are essential, covering bereavement support, spiritual care, and effective communication. Further investigation into institutional support mechanisms, such as counselling and peer support groups, is needed to manage the emotional burden of repeated patient deaths. Standardized guidelines integrating Islamic principles should be developed for culturally sensitive care.

LIMITATIONS

The review has limitations, including its reliance on a single database (Scopus) for literature search, which may have limited the scope of findings, and its inclusion of only English-language articles, potentially introducing

language bias and excluding studies conducted in non-English-speaking Islamic countries. Reviewing only qualitative papers may have caused incompleteness and a limited scope of evidence however, the decision to focus exclusively on qualitative studies, is valid for research questions aiming to explore experiences, perceptions, or meanings.

CONCLUSIONS

This review examines the experiences and difficulties faced by ICU nurses caring for dying Muslim patients. Nurses manage emotional, ethical, spiritual, and cultural complexities, providing both medical and spiritual support for patients, families, and themselves, which is a good practice to enhance the quality of care delivered. Family involvement and spiritual practices are crucial for patient comfort, yet nurses encounter communication barriers, a lack of spiritual care training, and support from the organizations. Therefore, improved training, policies, and support systems are needed. Culturally sensitive practices and better institutional support can enhance the end-of-life experience for patients and families, aligning with Malaysia Madani's vision.

FUNDING

This research was supported by the International Institute for Islamic Thought through the Strategic Research Programme Grant (ID IIIT-SRP24-049-0049).

CONFLICT OF INTEREST

The authors declares no conflict of interest.

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REVIEW ARTICLE

A Bibliometric Analysis of Chatbot or ChatGPT in Nursing Fields from 2022 to 2024

Ab Razak NI[a], Muhammad Yusoff MF[b], Nasharuddin NA[c], Soh KL[d], O.K. Rahmat RW[c]
[a]Human Physiology Unit, Department of Human Anatomy, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia
[b]Faculty of Quranic and Sunnah Studies, Universiti Sains Islam Malaysia
[c]Department of Multimedia, Faculty of Computer Science and Information Technology, Universiti Putra Malaysia
[d]Department of Nursing, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia,

ABSTRACT

Nursing education has undergone a significant transformation as a result of artificial intelligence (AI). Chatbots, specifically ChatGPT, have emerged as vital AI technologies within the nursing domain as it is a computer program designed to simulate human conversation through text or voice interactions. This study aims to conduct a bibliometric analysis to gain insights into the publication trends, citation impact, and thematic evolution in nursing education and practice concerning ChatGPT and chatbots. A comprehensive bibliometric analysis was performed using VOSViewer, concentrating on citation networks for data analysis and visualisation. A review of LENS.org identified 344 relevant research publications regarding chatbots and ChatGPT within the nursing discipline, all of which were utilised in the study. The study examined various aspects, including types of publications, prominent authors, leading journals, participating nations, institutions, and the impact of ChatGPT on nursing practice. The primary objectives included categorising the papers, identifying the most influential authors, delineating the prominent areas and institutions in the field, and examining the impact of ChatGPT on nursing education and practice. The findings indicate that ChatGPT positively impacts nursing education by enhancing learning experiences, improving communication, and aiding clinical decision-making. The findings indicate that journal articles accounted for 76% of publications, with the U.S. leading in research output. The findings indicate that ChatGPT positively impacts nursing education by enhancing learning experiences, improving communication, and aiding clinical decision-making. Future research should focus on establishing frameworks for integrating ChatGPT into nursing education, addressing ethical implications, and assessing the long-term impacts on patient care.

Keywords:
Chatbot, ChatGPT, Generative Artificial Intelligence, Nursing, Education

Corresponding Author
Dr. Nur Izah Ab Razak
Human Physiology Unit, Department of Human Anatomy, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 Serdang, Selangor, Malaysia.
Email: nurizah@upm.edu.my

Received: 21st April 2025; Accepted: 28th October 2025

Doi: https://doi.org/10.31436/imjm.v25i02.2809

INTRODUCTION

Artificial intelligence (AI) has been benefiting the educational landscape for numerous years, and nursing education is no exception. AI has been used to encourage student engagement in nursing programmes,[1,2] create personalised learning experiences,[3] and improve simulation training.[4,5] With the continuous advancement of AI technology, it is becoming more and more important to equip student nurses with the necessary skills to effectively adapt AI in their nursing practice.[6] Among various AI technologies, ChatGPT is gaining rapid adoption in nursing education and clinical support. ChatGPT produces human-like text responses and can thus be adopted as a learning assistant to help students effectively prepare for real patient interactions. [7,8] Furthermore, statistical analyses show that the integration of AI into simulation debriefing in nursing education improved student nurses' confidence, knowledge, and satisfaction, which can directly influence their performance. [1] Thus, it is important to develop a framework for conceptualising and promoting the use of ChatGPT in nursing education. Plus, just like other AI-based technologies, it is also important to raise awareness

about the advantages and limitations of chatbots[9,10] and to investigate effective ways to integrate them into the curriculum to maximise their benefits for student learning.

LITERATURE REVIEW

Chatbots/ChatGPT in Education

Teaching and learning are changing as technology advances. Education uses chatbots, recommendation systems, intelligent tutors, and learning analytics apps to provide customised assistance to students. Like humans, these chatbots can answer enquiries, give assignment comments, and offer study advice to improve learning.[11] It supports students who learn at different speeds in the classroom and through distance learning by helping them assimilate knowledge at their own pace.[12] Chatbots in education are not new, especially with the introduction of ChatGPT in 2022. The majority of chatbots in use prior to ChatGPT were rule-based, meaning that they reacted to user input in accordance with rules and guidelines that were preset and created by human developers.[13,14]

Chatbots/ChatGPT in Healthcare

In healthcare, ChatGPT has been used in many ways, such as providing personalised information on symptoms and treatments,[15,16] offering evidence-based recommendations for diagnosis and treatment planning[17] and even assisting in creating realistic healthcare simulation scenarios to help nursing educators.[8] Its ability to learn and adapt makes it a valuable tool for improving patient care and accessibility to medical information. ChatGPT is also helping management tasks in hospitals by making scheduling appointments and billing more accurate and efficient, which allows doctors to spend more time caring for patients.[18] Numerous studies have examined ChatGPT's impact on nursing education, but no bibliometric study has been done. With research in this subject, researchers can refer to it to identify domain-wide issues and trends. Thus, a bibliometric analysis is urgently needed to guide future research.

Chatbots/ChatGPT in Nursing Education

Nurses have historically depended on a range of technologies in education, simulation, and clinical practice. However, with the availability of advanced AI-enabled tools like big data analytics, ChatGPT, chatbots, and virtual reality, the nursing field is presented with both prospects and hurdles.[19] Technology has profoundly reshaped the healthcare industry, prompting changes in medical and nursing practices, enhancing workforce safety and efficiency, and advancing patient outcomes.[20]

AI-powered chatbots like ChatGPT can enrich problem-based learning, especially in nursing processes.[21] ChatGPT holds the potential to transform nursing education and research by simplifying the process.[22] It has transformed nursing by providing an efficient, accessible, and versatile tool.[23] Its integration into nursing practice holds the promise of enhancing patient care, streamlining administrative processes, and fostering the ongoing development of nursing professionals, ultimately elevating the overall quality of healthcare delivery. However, while AI technologies offer potential benefits such as aiding in patient documentation, reducing nurses' workload, and enhancing practice efficiency, they should not supplant human experience, discernment, personality, or responsibility.[24]

In nursing education, AI simplifies learning for students by aiding their understanding of complex topics. It can generate practice scenarios and enable nursing students to refine their communication and critical thinking skills.[25] AI can support students in assignments, provide realistic scenarios, and facilitate personalized learning, but concerns such as academic integrity, plagiarism, ethics, and misinformation must be addressed.[26] ChatGPT may improve nursing education results. Interactive learning scenarios with non-virtual or virtual patients are part of these experiences. ChatGPT can create patient scenarios and practice clinical decision-making skills to give students feedback on their decisions and create a more immersive and engaging learning experience in a safe environment, improving patient care and outcomes. AI offers nursing education innovations, but educators must carefully negotiate difficulties to maximise its benefits. Nurses must embrace AI-enabled innovations and critical thinking to develop in the profession and lead in the digital future.[22]

Research Questions

This study is guided by the following research question: What is the current state of research on the use of chatbots and ChatGPT in the nursing field, as reflected in the scholarly literature from 2022 to 2024? This question is further broken down into the following sub questions:

1. What are the publication types and scholarly works of chatbots/ChatGPT and nursing over time?
2. Who are the prominent authors and most influential journals in the chatbot/ChatGPT and nursing field studies?
3. What are the institutions involved in the chatbot/ ChatGPT and nursing field studies?
4. What are the effects of chatbots/ChatGPT on the nursing field?

METHOD

A bibliometric analysis begins with defining the objective and scope of the study. The primary objectives included categorising the papers, identifying the most influential authors, delineating the prominent areas and institutions in the field, and examining the impact of ChatGPT on nursing education and practice using bibliometric methods. This involves analysing various research components and identifying the relationships among them.

According to Sjöstedt et al.,[28] a comprehensive bibliometric analysis should include at least 50 publications to ensure adequate depth and coverage. Accordingly, this study includes more than 50 scholarly articles, providing a broad base for meaningful bibliometric evaluation.

The literature was analysed using VOSviewer and quantitative approaches for domain-specific data. The software makes bibliometric graphs showing article co-authorship, citations, and bibliographic linkages from digital database data. This method outperforms quantitative methods in accuracy and efficiency. It reduces the reader's cognitive load and objectively identifies industry research needs and hot topics.

The main steps in the analysis are as follows:

1. Data Collection: Retrieve relevant publications from selected databases based on defined inclusion criteria.
2. Data Cleaning and Preprocessing: Standardise author names, keywords, and institutional affiliations to ensure consistency.
3. Data Analysis Using VOSviewer:
   - Citation Analysis: Explore how frequently articles are cited.
   - Co-citation Analysis: Examine how often two articles are cited together.
   - Co-occurrence Analysis: Identify key terms and topics that frequently appear together. The minimum number of keyword occurrences was set to 5.

Co-authorship Analysis: Map collaborative networks among authors and institutions. The clustering algorithm used was the VOS clustering technique, which maximises a quality function that is a weighted, resolution-parameterised variant of Newman's modularity; optimisation is done with the Smart Local Moving (SLM) algorithm.

Data Collection

Rather than relying solely on keyword searches, which may suffer from ambiguity due to inconsistent terminology, VOSviewer constructs networks based on bibliographic coupling and citation links between documents, allowing for more objective clustering of related publications.[29] Relationships were defined without relying on specific keywords, as it proved challenging to provide a more precise explanation of their meaning.[30] When applied in different contexts, keywords can be interpreted in various manners.[31] As a result, the categorisation of clusters can become ambiguous, leading to challenges in analysing the judgements made regarding clustering.[32,33] Therefore, VOSviewer categorises articles into various groups by analysing the connections between them. To circumvent any potential technical or analytical complications, we have categorised the specific articles included in this analysis into separate groups. This is the approach that was taken to gather data.

A Lens.org search was done on June 30, 2024. Search terms included "Chatbot" OR "ChatGPT" AND "nursing". We obtained 344 academic articles from our query and used VOSviewer for bibliometric analysis. The collection comprised journal articles, editorial notes, conference proceedings, book chapters, letters, and preprints. Specific criteria were used to evaluate studies for inclusion. These requirements included an emphasis on chatbots and ChatGPT in nursing research, sufficient study information, English writing, and persuasive outcomes. Manual screening or inter-rater agreement was applied during inclusion. Studies were excluded if they were

i. duplicates
ii. irrelevant
iii. not relevant to the research issue
iv. written in a different language,
v. not complete texts
vi. or not related to nursing

Procedure of Data Analysis

This paragraph details the sequential content analysis procedure. We initially used The Lens citation report. This report shows citation and publication trends. We used the citation report to analyse publishing trends for search topics. VOSviewer received 344 well-selected scholarly articles in the second phase. After some time, we used co-occurrence investigation to do a bibliometric study of publication kinds, academic works throughout time, famous authors, top journals, top countries/ regions, and institution names. Using co-occurrence data, the progress was analysed. A bibliometric assessment of the citation network was done with VOSviewer. The application received 344 articles in the third phase. VOSviewer provides author, title, and source information.

Following screening, the selected articles underwent data preprocessing to standardise author names, keywords, and institutional affiliations to ensure consistency. The pre-processed data were then imported into VOSviewer software for comprehensive bibliometric analysis. Four types of analyses were conducted:

1) Citation Analysis to explore how frequently articles were cited.
2) Co-citation Analysis to examine how often two articles were cited together.
3) Co-occurrence Analysis to identify key terms and topics that frequently appeared together (minimum of 5 keyword occurrences).
4) Co-authorship Analysis to map collaborative networks among authors and institutions.

The clustering algorithm used was the VOS clustering technique with Smart Local Moving (SLM) algorithm optimisation. The results from these analyses were visualised as network diagrams, which were subsequently interpreted and reported to address the research questions.

RESULTS

This section presents the findings of the bibliometric analysis of 344 publications on chatbots and ChatGPT in the nursing field from 2022 to 2024. The results are organised to address the four research questions systematically. First, we examine the publication types and temporal trends of scholarly works to understand the evolution of research output in this domain (RQ1). Second, we identify the prominent authors and most influential journals contributing to this field, highlighting key researchers and publication venues (RQ2). Third, we analyse the institutional landscape to reveal the geographic distribution and leading institutions engaged in chatbot and ChatGPT research within nursing (RQ3). Finally, we explore the effects and applications of chatbots and ChatGPT on nursing practice and education through citation network analysis (RQ4). Together, these findings provide a comprehensive overview of the current state of research and the impact of AI-powered conversational technologies in the nursing discipline.

RQ1: Publication Types and Scholarly Works Over Time

Since ChatGPT was initiated on November 30, 2022,[34] this analysis started from December 2022 until June 2024. The analysis results indicated the total number of

scholarly works, which includes journal articles, conference proceedings, letters, editorials, preprints, book chapters, and news articles. Throughout the years, the top scholarly work is the journal article with the highest number of publications (264 articles, 76.74%), followed by editorial (30 articles, 8.72%), letter (28 articles, 8.14%), preprint (17 articles, 4.94%) and news (2 articles, 0.58%), and the least published are book chapters (0.29%), conference proceedings (0.29%), and others (0.29%), with 1 article for each type of mentioned publication. For journal articles, the number of relevant studies significantly fluctuated until June 2024 (Figure 1). For other types of publications, for example, letters, preprints, and editorials, the numbers are relatively consistent (Figure 1). According to this analysis, we need more information beyond June 2024 to better observe the trend in the future.

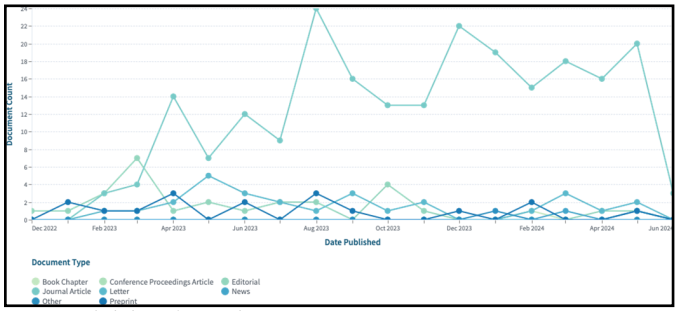


Figure 1. Scholarly works over time.

RQ2: Prominent Authors and Most Influential Journals

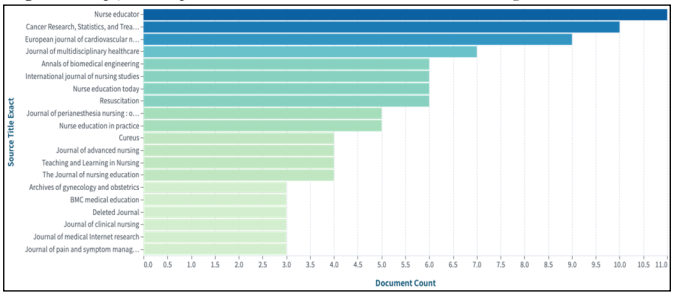
Geographically and institutionally, the top 10 nursing and chatbot/ChatGPT researchers are diverse (Table 1). Katholieke Universiteit Leuven's Academic Centre for Nursing and Midwifery's Liesbet Van Bulck and Philip Moons lead with seven articles apiece, highlighting their efforts. Five articles by Ahmed Lateef Alkhaqani from Kufa University in Iraq and Viroj Wiwanitkit from Chandigarh University in India indicate ongoing research in these places. Four articles by private academic consultant Amnuay Kleebayoon in Cambodia and Gregor Štiglic from the University of Maribor in Slovenia demonstrate the collaboration between private consultants and university institutions in generative AI research. Jialin Liu from West China Medical School, Siobhan O'Connor from King's College London, and Siru Liu from Vanderbilt University Medical Centre, each with four articles, emphasise China's, the UK's, and the US's contributions. Finally, Sirwan Khalid Ahmed, of the University of Raparin in Iraq, emphasises Middle Eastern research. This varied set of writers represents global interest and collaboration in nursing AI applications.

Figure 2 shows a concentrated but fragmented venue landscape: publications cluster most strongly in nursing-education journals (e.g., Nurse Education Today/in Practice/Nurse Educator), signalling that chatbot/ ChatGPT work in nursing is currently education-led (curriculum, assessment, academic integrity), while general nursing/practice outlets (e.g., International Journal of Nursing Studies, Journal of Advanced/Clinical Nursing) and clinical subspecialty titles (cardiovascular, oncology) carry a smaller but growing share that reflects use-case pilots and early practice evaluation. A visible long tail across many additional journals, including health -informatics/biomedical engineering venues, indicates a young field without a single "home" journal; methods and implementation pieces are being imported from cross -disciplinary outlets and cited by nursing papers to frame feasibility and risk. Overall, the pattern points to an area that is anchored in pedagogy, with select clinical niches beginning to adopt and test tools, and diffusion occurring across diverse, relatively low-count outlets.

Table I. Prominent Authors, Document Count, Affiliation, and ORCID ID.

Author Display Name	Document Count	Affiliation	ORCID iD
Liesbet Van Bulck	7	Academic Centre for Nursing and Midwifery, Katholieke Universiteit Leuven, Belgium	0000-0001-8975-4455
Philip Moons	7	Academic Centre for Nursing and Midwifery, Katholieke Universiteit Leuven, Belgium	0000-0002-8609-4516
Ahmed Lateef Alkhaqani	5	College of Nursing, Kufa University, Al -Najaf, Iraq	0000-0002-7694-7503
Viroj Wiwanitkit	5	Chandigarh University, Punjab, India	0000-0003-1039-3728
Amnuay Kleebayoon	4	Private Academic Consultant, Samraong, Cambodia	Not Available
Gregor Štiglic	4	Faculty of Health Sciences, University of Maribor, Slovenia	0000-0002-0183-8679
Jialin Liu	4	Department of Medical Informatics, West China Medical School/West China Hospital, Sichuan, China.	Not Available
Siobhan O'Connor	4	Faculty of Nursing, Midwifery and Palliative Care, King's College London, United Kingdom	0000-0001-8579-1718
Siru Liu	4	Vanderbilt University Medical Center, Nashville, United States	Not Available
Sirwan Khalid Ahmed	4	College of Nursing, University of Raparin, Rania, Iraq	0000-0002-8361-0546

Figure 2. Top journals published the chatbot/ChatGPT in the nursing field.



RQ3: Institutions Involved in Chatbot/ChatGPT Research

This section discusses how different countries contributed to chatbot/ChatGPT and nursing field research publications. Europe and North America publish more, concentrating their contributions. Also evident are Japanese, Singaporean, and Chinese influences. African, South American, and Middle Eastern countries' low document submissions might be addressed. According to Figure 3, Columbia University submitted the highest number, with 8 documents. Katholieke Universiteit Leuven and the National University of Singapore follow closely; 7 and 6 documents, respectively, show their engagement. The universities in Cape Town, Florida, and Gothenburg each provided five papers. The University of Cape Town's Department of Paediatrics and Child Health, Duke, Harvard, and the Institute of Health and Care Sciences University of Gothenburg upload 4 more documents, making it the top contributor. Research is worldwide, with European, North American, Asian, and African universities contributing. The data suggests that colleges with more documents have more research money, focused objectives, or big collaborative networks that increase productivity. Specialised departments like Cape Town Paediatrics and Child Health value targeted academic research. Document counts show that strategic focus, funding, and cooperation boost scholarly productivity and exposure.

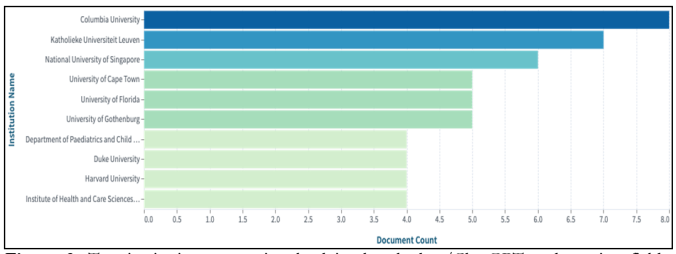


Figure 3. Top institution names involved in the chatbot/ChatGPT and nursing field studies.

RQ4: Effects of Chatbot/ChatGPT on the Nursing Field

To address RQ4, this study examined the publications and constructed an additional citation network based on VOSViewer (Figure 4). This citation network included a total of 344 publications. After excluding studies that did not reach seventeen citations and contained "nursing" as a keyword, our focus shifted to the ones conducted by several articles [24,34–40]. It was found that all eight articles explored the effects of incorporating chatbots in the nursing field. Dwivedi et al. discuss the broad applicability of AI tools like ChatGPT, which can generate human-like text and enhance productivity in various fields.[24]

Beyond counts, Figure 4 shows two small, weakly connected themes. One cluster gathers education-ethics/academic-integrity debates, O'Connor's "tools for academic progress or abuse?" [41] anchors a discussion that is extended by Choi et al. on "chatting or cheating?" [35] in nurse education and Abdulai & Hung on whether ChatGPT undermines ethical values [34]. The second cluster is practice/clinical enablement, where Moons & Van Bulck appraise value for cardiovascular nurses,[37] Scerri & Morin outline practice support,[39] and Gunawan surveys future uses in nursing.[36] Dwivedi et al. sits at the periphery as a cross-disciplinary opinion hub that multiple nursing papers cite to situate their arguments.[24] The long, sparse links, especially the bridging role of O'Connor, indicate conceptual cross-citation rather than tight co-authorship, suggesting leading authors are thematically aware of each other's work but largely operate in siloed teams across different journals/venues.

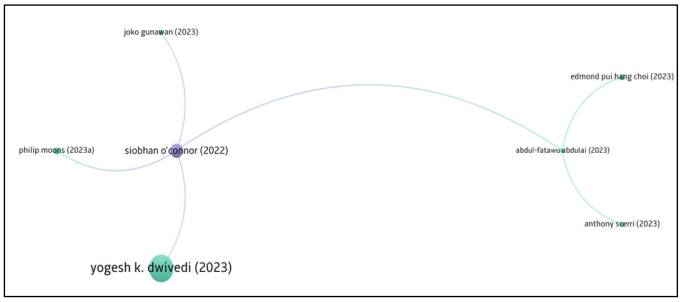


Figure 4. The visualisation of the citation network in VOSViewer.

DISCUSSION

ChatGPT has over 100 million users after two months of debut.[42] This chatbot is one of several with advanced AI. This technique has generated a lot of medical and health research publications.[43] However, nursing professionals and academics have little chatbot usage data. We did a bibliometric analysis of chatbot/ChatGPT technologies to better understand how the scientific and medical community has reacted to their use in both academic and clinical settings.

The discussion is organised around the four research questions that guided this study. We begin by interpreting the publication trends and scholarly output patterns observed over time, which reveal the rapid growth of interest in this domain (RQ1). Next, we discuss the contributions of prominent authors and influential journals, highlighting key thought leaders and publication venues that are shaping discourse in this field (RQ2). We then examine the geographic and institutional distribution of research activity, considering factors that may explain regional variations in engagement with chatbot and ChatGPT technologies (RQ3). Finally, we synthesise findings related to the effects and implications of these AI tools on nursing practice and education, addressing both opportunities and challenges identified in the literature (RQ4). Throughout this discussion, we contextualise our findings within the broader landscape of AI adoption in healthcare and nursing, while considering ethical, practical, and educational implications for the profession.

RQ1: Publication Types and Scholarly Works Over Time

RQ1 examined nursing chatbot/ChatGPT trends and technologies using bibliometrics. Analysis of journal article, editorial, letter, and preprint tendencies and scholarly activity might guide future study. Journal papers are the most common publications in our analysis, highlighting the rising popularity of chatbot/ChatGPT and nursing. Journal articles preserve study findings and provide dependable references for future studies.[44] Journals also foster collaboration and networking.[45] RQ1 showed the trend of research on chatbot/ChatGPT tools in nursing, which began in December 2022 due to internet users' ChatGPT usage in November 2022.[42] The dominance of journal articles as the primary publication type indicates that the research in this field is reaching a level of maturity where it is being disseminated through formal academic channels. The steady increase in the number of publications over the past two years suggests that this is a vibrant and active area of research that is likely to continue to grow in the coming years.

RQ2: Prominent Authors and Most Influential Journals

RQ2 identified the top 10 authors and journals. Results showed a considerable increase in nursing chatbot/ ChatGPT exposure and use. Liesbet Van Bulck and Philip Moons are the most prolific nursing journal authors. Both are from Katholieke Universiteit Leuven's Academic Centre for Nursing and Midwifery. Both authors found that ChatGPT can enhance patient information, but it needs more fine-tuning and cautious use to ensure reliability and safety.[46] The top journal is Nurse Educators with 11 publications. The current issues of this journal are focusing on AI, immersive learning, and big data in healthcare,[47] and the trends were consistent for the previous issues. Therefore, this might contribute to the high number of relevant journals in this theme. The identification of prominent authors and journals offers useful information about the key players in this field. The fact that the top authors are from a diverse range of countries and institutions suggests that this is a global area of research. The limited collaboration between research groups, as revealed by the co-authorship analysis, suggests that there is an opportunity for greater collaboration to advance the field more effectively. The prominence of journals focused on nursing education suggests that this is a key area of application for chatbots and ChatGPT in nursing.

RQ3: Institutions Involved in Chatbot/ChatGPT Research

US publications promote ChatGPT advancements the most based on RQ3 geography. Despite its restriction in China, nursing education researchers are interested in ChatGPT, an alternative AI chatbot.[48] Thus, this nation has conducted more chatbot research to boost learning. Investing in AI institutes and using premier university

research keeps the US ahead in AI. Certainly, both governments believe AI is essential for scientific and economic superiority.[49] The geographical distribution of research activity, with a concentration in Europe and North America, is consistent with broader trends in scientific research. The involvement of a diverse range of institutions, from universities to private consultants, suggests that the research in this field is being driven by a variety of stakeholders. The strong presence of universities in the top contributing institutions highlights the important role of academic research in advancing this field.

RQ4: Effects of Chatbot/ChatGPT on the Nursing Field

For the RQ4, experts from various disciplines contributed insights, noting both the technology's potential benefits and limitations. Opinions differ on whether ChatGPT should be restricted or legislated. Based on the culmination of the discussion, it was concluded that there is a dire need for further research in areas such as necessary skills for handling AI, biases in training datasets, optimal human-AI task combinations, text accuracy assessment, and ethical considerations. Although AI has the potential to aid in the process of drafting and editing, it is incapable of assuming moral, legal, and ethical obligations.[40] The citation network analysis reveals that the research in this field is organized around three main themes: patient education, nursing education, and ethical and professional implications. This suggests that the research is addressing a wide range of issues related to the use of chatbots and ChatGPT in nursing. The findings of the studies included in the citation network suggest that chatbots and ChatGPT have the potential to have a positive impact on the nursing field, but that there are also a number of challenges and ethical considerations that need to be addressed.

Utilising ChatGPT in the field of nursing presents ethical dilemmas that have the potential to compromise the fundamental principles of nursing.[35] However, incorporating artificial intelligence (AI) into nursing research, education, and practice also holds promise for progress. Given the expanding presence of AI technologies, it is crucial for nursing researchers and educators to actively participate in thoughtful discussions and philosophical analyses of the consequences, ethical considerations, and possible disadvantages related to the use of AI in nursing settings.[34] Hence, according to O'Connor,[38] it is important to educate nursing students on the importance of academic integrity and the value of gaining information and skills via extensive reading, analytical thinking, and scientific writing. These skills can be employed in a nurse's professional vocation to improve patient care and the delivery of healthcare services.

Due to the fact that the area of cardiovascular nursing and allied health is continuously undergoing development, it will be essential for healthcare workers to remain current with the most recent technologies and methods, including artificial intelligence (AI) language models like ChatGPT.[37] In a study,[36] the ChatGPT model may help nurses complete routine tasks, but it cannot replace the personal and emotional support they provide to patients and their vital role in patient assessment, treatment planning, and care coordination. Technology and robotics will likely be used in nursing to enhance patient outcomes, efficiency, and eliminate mistakes. Another study also noticed that the nurses must keep informed and adapt to new technology and innovations in the profession to benefit patients and improve their skills and expertise, making their work easier and more efficient.[36] Therefore, ChatGPT offers the potential to reduce the need for repetitive writing and administrative tasks, such as summarising extensive patient information lists.[39] Furthermore, it may encompass case summaries or care plans that outline nurse interventions specifically targeted to the unique needs of the patient. It has the capacity to enhance communication by providing cues for interaction between nurses and patients.

CONCLUSION

This bibliometric analysis provides a comprehensive overview of the current state of research on the use of chatbots and ChatGPT in the nursing field. The findings reveal a rapidly growing and dynamic field of research, with a diverse range of authors, institutions, and research

themes. The study highlights the potential of chatbots and ChatGPT to transform nursing education and practice, while also acknowledging the challenges and ethical considerations that need to be addressed.

Despite its thoroughness, this study has limitations. The conclusions may have been limited by using certain databases to omit relevant research from other sources. The omission of non-English articles may have missed important research in other languages. The study's concentration on publications with at least 17 citations may have missed promising but under-cited research. AI technology evolves quickly; therefore, some discoveries may become outdated.

The study's findings lead to the following recommendations for future research:

- Develop and evaluate frameworks for integrating chatbots and ChatGPT into nursing curriculum. Nursing curriculum should include AI literacy modules to equip students with the knowledge and skills to use these technologies effectively and ethically.
- Investigate the long-term impacts of chatbots and ChatGPT on patient care. Research is needed to assess the impact of these technologies on patient outcomes, patient safety, and the nurse-patient relationship.
- Establish guidelines for the ethical use of chatbots and ChatGPT in clinical simulations and practice. Clear guidelines are needed to ensure that these technologies are used in a way that is consistent with professional nursing standards and values.
- Promote interdisciplinary collaboration to advance research in this field. Collaboration between nurses, computer scientists, ethicists, and other stakeholders is essential to address the complex challenges and opportunities associated with the use of chatbots and ChatGPT in nursing.

In conclusion, this study contributes to the growing body of literature on the use of AI in nursing by providing a comprehensive overview of the emerging field of chatbot and ChatGPT research. The findings of this study can be used to inform future research, practice, and policy in this important area.

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REVIEW ARTICLE

Recent Updates on the Mechanism of Action of Spirulina as an Anticancer Agent Against Breast Cancer

Angie L[a], Subramaiam H[b*]

[a]School of Medicine, IMU University, Bukit Jalil, Kuala Lumpur

[B] Pathology and Pharmacology Department, School of Medicine, IMU University, Bukit Jalil, Kuala Lumpur

ABSTRACT

Spirulina, a small blue-green algae that lives in warm, alkaline seas, is one of the world's oldest life forms. With century-old history, this nutrient-rich organism has received a lot of interest in recent years for its possible health benefits and sustainable production practices. Studies have indicated its antioxidant, anti-cancer, and anti-inflammatory qualities are contributed by its bioactive compounds, mainly phycocyanin. Other compounds or elements include phycocyanobilin, carotenoids, unsaturated fatty acids, selenium, and amino acids. Breast cancer is one of the major causes of cancer related death in women. As some of the cancer therapies are highly associated with side effects, nutraceuticals such as *Spirulina* could be an alternative therapeutic intervention. Although some research has been conducted to investigate the anti-breast cancer effects of *Spirulina* in the past, its mechanism of action is not entirely understood. Previous studies suggest that it may trigger apoptosis and autophagy via modifying signalling pathways such as NF-ϰB and Bcl-2/Bax ratio. It also has anti-proliferative properties, inhibits cell migration, causes cell cycle arrest, and lowers cancer cells' capacity to form colonies. Phycocyanin has been shown to produce reactive oxygen species (ROS) and down-regulate anti-apoptotic molecules, which contribute to its anticancer capabilities. These findings show that *Spirulina* fights cancer by targeting a variety of cellular mechanisms involved in carcinogenesis. While these data imply potential benefits, more clinical trials and research into the exact mechanisms of *Spirulina* in cancer treatments are needed to fully demonstrate its efficacy in treating breast cancer in humans.

Keywords:
Spirulina, Breast Cancer, Phycocyanin, Ki-67, Apoptosis

Corresponding Author
Dr. Hemavathy Subramaiam
Pathology Department, School of Medicine, IMU University, 126, Jalan Jalil Perkasa 19, Bukit Jalil, 57000 Kuala Lumpur
E-mail: hemavathy@imu.edu.my

Received: 7th March 2025; Accepted: 3rd November 2025

Doi: https://doi.org/10.31436/imjm.v25i01.2877

INTRODUCTION

Breast cancer accounts for 1 in 8 (12.5%) of all new annual cancer cases worldwide, making it the world's most prevalent cancer type.[1] The American Cancer Society's estimated that in the US, 353,510 invasive and non-invasive (in situ) breast cancers will be diagnosed among women with a projected death of 43,700 in 2023.[2] Various breast cancer risk factors have been identified including inheritance of DNA defects or pro-cancerous genes such as BRCA1 or BRCA2, genetic mutations due to aging process, hormone replacement therapy, or obesity.[2,3] Some characteristics of cancer include inflammation and evasion of host immune response.[4] Immune cells such as CD4+ Th2 and CD4+ T-regulatory cells assist in tumour growth as it promotes immunosuppression. This is in contrast to T-helper-1 (Th1) cells (CD4+ T-cells that produce IFN-γ), CD8+ cytotoxic T-lymphocytes, and NK which inhibits immunosuppression. Among the cell proliferation markers, Ki-67 plays a crucial role as a marker for providing information regarding cell proliferation. It is widely used to differentiate luminal A and luminal B breast cancer types. Luminal B cancer has higher histologic grade, more aggressive, and worse prognosis than luminal A, possessing high expression of Ki-67 (>20%).[5,6] Ki-67 score reflects the cancer's aggressiveness in a human body and identifies the treatment and time for recurrence.[7] Expression of Ki-67 defines survival rate and contains important information regarding potential follow-ups for recurrence and picking the most suitable treatment therapy for breast cancer.[5] Higher Ki-67 index means that a large proportion of tumour cells are rapidly dividing, indicating a fast growing, aggressive tumour with

a higher potential to spread.

While treatment options such as surgery, radiation therapy, or endocrine therapy could be useful to reduce cancer, they are associated with various negative side effects such as hair loss, vomiting, depressed immunity, neutropenia, and nausea.[8] Therefore, treatments with lower cytotoxic effects would be more preferred. A combination therapy for treating cancer using plant-based chemicals, known as nutraceuticals, which includes *Spirulina* is becoming more recognized.[9] Previous study on immunohistochemical analysis indicated that supplementation of *Spirulina* reduced the expression of Ki-67, indicating tumour growth inhibition and downregulation of cell proliferation.[10] *Spirulina*, a filamentous cyanobacteria, besides containing rich nutritional content (such as proteins, essential fatty acids, phycobiliprotein C-phycocyanin, and vitamins) also possess anti-inflammatory, immune enhancing and anticancer properties.[11] The main bioactive compound in *Spirulina* includes phycocyanin, phycocyanobilin, carotenoids, unsaturated fatty acids and amino acids.[11] Despite growing examination, there are still unclear and insufficient studies assessing how *Spirulina* influences tumour reduction in breast cancer. This review is therefore designated to address the impact of *Spirulina* on tumorigenesis and its significance on breast cancer.

Ki-67 as a prognostic biomarker

Ki-67, a protein synthesized by the MK167 gene, is an established primary prognostic and predictive biomarker for assessing biopsies to determine cell proliferation in tissues, especially in suspected cancer cases. Classification of breast cancer lies on the presence of hormone receptors, clinically important for prognosis and response to treatment modalities. In addition, Ki-67 aims to aid therapeutic decision-making and create new personalized breast cancer treatment approaches.[7] Together with the expression of hormone receptors, Ki-67 is able to biologically classify luminal breast cancer. Breast tumours with ER+, PR+, and HER-2 negative status are referred to as luminal. Luminal type A has high ER expression, less aggressive, slow growing and has low Ki-67 expression. Comparatively, Luminal type B has high ER expression, more aggressive, fast growing and has high Ki-67 expression as there is high cell proliferation.[12] Previous study using 8 weeks old Sprague Dawley rats which is DMBA-induced mammary cancer model has indicated that supplementation of *Spirulina* reduced the expression of Ki-67 based on immunohistochemical analysis, indicating tumour growth inhibition and downregulation of cell proliferation.[10] Ki-67 also has other roles in breast cancer as it can serve as predictive marker for therapy response, predict recurrent risk, guides treatment decisions and acts as pharmacodynamics marker in clinical trials (Table 1).

Table 1. Role of Ki-67 in breast cancer

No.	Major Role of Ki67	Reference
1	Acts as a prognostic marker – High Ki-67 expression is associated with poor prognosis and increased tumour aggressiveness.	(13)
2	Serves as a predictive marker for therapy response – Reduction of Ki-67 after neoadjuvant endocrine or chemotherapy indicates good treatment response.	(14)
3	Used for molecular subtyping of breast cancer – Helps distinguish Luminal A (ER^+/PR^+, low Ki-67 <14%) from Luminal B (ER^+/PR^+, high Ki-67 ≥14%) subtypes.	(15)
4	Guides treatment decisions – Luminal B tumours with high Ki -67 may benefit more from chemotherapy in addition to endocrine therapy, unlike Luminal A with low Ki-67.	(16)
5	Predict recurrence risk – High Ki67 index correlates with shorter disease-free and overall survival, particularly in hormone receptor–positive cancers.	(17)
6	Acts as a pharmacodynamic marker in clinical trials – Used to assess biological efficacy of new agents by comparing Ki-67 before and after treatment.	(18)

Mechanism of action of *Spirulina* in cancer and the tumour microenvironment

Phycocyanin, which is an active component in *Spirulina*, promotes apoptosis via mitochondrial cytochrome c release independent of Bcl-2 expression.[19] This was demonstrated in a study that used *Spirulina* to decrease cell growth in DMBA-induced rat breast carcinogenesis.[9] In addition, *Spirulina* also enhances the expression of p53 and its downstream target gene, Cdkn1a/p21 and raised Bax and lowers Bcl-2 expression, confirming its potential application in cancer chemoprevention.[9] In addition, phycocyanin also targets the MAPK/ERK pathway to induce apoptosis, as it interacts with cell surface receptors to activate Ras and subsequently the MAPK pathway.[20] Another element of *Spirulina* that exhibited anti-cancer

activities is the selenium, which is a trace mineral.[21] The selenium-enriched *Spirulina* extract has been reported to inhibit the growth of human breast cancer cells by induction of G1 cell cycle arrest and also apoptosis mediated by mitochondria.[22] This activity has been associated with a decrease in the expression of cyclin D1 (CD1), cyclin D3, CDK4 and CDK6.[22] The anticancer effects were reported to be induced by mitochondrial dysfunction through upregulation of Bax (Bcl2-associated X-protein) and Bad (Bcl-2 related family member. The latter promotes cell death and its function is regulated by phosphorylation).[22] In another study, selenium-containing phycocyanin showed effective antiproliferative properties in human melanoma cells and human breast adenocarcinoma cells through induction of apoptosis, accumulation of sub-G1 cell populations, DNA fragmentation, and nuclear condensation. [23] In one of the first human studies, the chemopreventive activity of *Spirulina* has been reported to show complete regression of lesions in oral leucoplakia of tobacco chewers without toxicity association. [24]

Inhibition of VEGFR2-VEGFA pathway in breast cancer by phycocyanobilin

Breast cancer arises from the dysregulated signalling pathways within mammary epithelial cells. Among the receptors implicated in cancer signalling pathways is the vascular endothelial growth factor receptor (VEGFR), which responds to vascular endothelial growth factor (VEGF), a key player in this process.[25] Angiogenesis, the process of new blood vessel formation, serves as a central factor that promotes the proliferation of cancer cells.[26] Of the various isoforms of VEGF, VEGFA is the most active, and its signalling through VEGFR2 constitutes the primary pathway driving angiogenesis. This pathway induces endothelial cell (EC) proliferation, survival, sprouting, and migration, while also increasing endothelial permeability.[27] Previous report has shown that phycocyanin from *Spirulina* is able to exert anti-cancer effects in *in silico* study by inhibiting VEGFR-VEGF pathway through, inhibition of angiogenesis process in breast cancer progression.[28]

Induction of apoptosis by GR15 peptide in breast cancer cells by *Spirulina*

The antioxidant qualities of GR15, a peptide including an aliphatic amino acid sequence, have been recognized to be present in the cyanobacterium *Spirulina*.[29] Due to the presence of Arg and Lys amino acids in its sequence, GR15 may target the cell membrane and involved in cell membrane disruption. In addition, the positively charged amino acids arginine (Arg) and lysine (Lys) damage cell membrane integrity, allowing them to penetrate the cell and induce cytotoxicity in cancer cells.[30] Furthermore, GR15 demonstrates no toxicity in both *in vitro* (MDCK cells) and *in vivo* (zebrafish embryos) models, indicating its potential safety for therapeutic applications.[29] In a breast cancer cell line study (MCF-7), the GR15 peptide showed inhibition of cancer cell proliferation and reduction of ROS level in a dose-dependent manner. In addition, GR15 also significantly affects the cellular morphology and promotes apoptosis in the same study.[30]

Overall, GR15 from *Spirulina* has been a promising candidate for further investigation due to its capacity to inhibit cancer cell proliferation, notably in breast cancer, making it a potential anti-cancer agent. However, further research will have to be done to focus on understanding the pharmacodynamic aspect and drug delivery performance of GR15 in an in-vivo model since they will be necessary before the molecule can be used as a medication for anti-cancer therapeutic purposes.

Immune enhancing properties of *Spirulina in* breast cancer model

Spirulina has been reported to have numerous immune-boosting properties due to its distinctive proteins, sugars, and lipids.[31] However, the precise molecular mechanisms underlying these effects are yet to be understood. It is known that the T cell mediated immunity is an important arm of the adaptive immune response, especially in cancer microenvironement.[32] Previous study have shown that *Spirulina* supplementation has significantly ($p<0.05$) increased the $CD4^+/CD127^+$ T cell population compared to control group in a syngeneic mouse mammary cancer

model.[3] $CD4^+/CD127^+$ T cells could enhance tumour inhibitory effects as they play an important role in the development of lymphocytes and regulation of peripheral T-cell populations.[33] In the same study also, it was found that supplementation of *Spirulina* has significantly ($p<0.05$) reduced the population of $CD4^+/CD25^+$ T cells which are the T regulatory cells. The T regulatory cells can inhibit anti-tumour immunity and promote tumour growth because there is increased evidence to show that elevated proportions of these cells are present in various types of cancers,[34] including breast cancer.[35] Collectively, *Spirulina* is able to enhance anti-tumour immunity in the previously mentioned breast cancer study model by increasing $CD4^+/CD127^+$ T cells and decreasing CD4+/ CD25+ T cells.[3]

Immunomodulatory effects of *Spirulina* have been extensively studied in various models previously and it has been reported that *Spirulina* and its extract enhance immunity through the modulation of immune cell function, modulation of immune cell number and modulation of inflammatory mediators (Table 2).

Table 2: Immunomodulatory effects of *Spirulina* in different study models

Type of study	Effects	Reference
Arthritis mice	Significantly reduced β-Glucuronidase induced by zymosan.	(36)
Human peripheral blood mononuclear cells	Enhanced secretion of IL-1β, IL-4 and IFN-γ.	(37)
Male Human	The IFN-γ production from CD56 positive NK cells was significantly increased.	(38)
Mice	Increased number of splenic antibody producing cells in the primary immune response to sheep red blood cells.	(39)
In vitro	The percentage of phagocytic cells in peritoneal macrophages was significantly increased. The proliferation of spleen cells by either concavalin A or phytohemagglutinin was significantly increased.	(39)
In vitro	*Spirulina* treated chicken macrophages showed increased spreading and vacuolization with minimal cytotoxicity.	(40)

CONCLUSION

Tumour invasion and metastasis are the primary causes of breast cancer death. Ki-67 is a prognostic marker that is commonly used to diagnose and detect cancer severity. *Spirulina* is known as "the food of the improve" because of its numerous health benefits mainly contributed by its bioactive compounds such as phycocyanin, phycocyanobilin, carotenoids, unsaturated fatty acids, and amino acids. These bioactive compounds of *Spirulina* improve the body's immune function, promotes apoptosis in cancer cells, inhibits cancer cell proliferation and subsequently, aids in the fight against cancer.

Future prospective

Most investigations into *Spirulina* focused on its anti-inflammatory, antioxidant, anti-cancer, and immunomodulatory effects on various models. However, only a few studies have attempted to investigate the mechanisms underlying these effects on breast cancer models and our current understanding remains limited. Due to the complex chemical components of *Spirulina*, its molecular mechanisms remain unclear, and further studies are needed. Currently, most of the studies that show evidence of *Spirulina* having anti breast cancer effects are done *in vivo* and *in vitro*. As such, clinical trials would be a better option to develop new strategies of treatment.

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ORIGINAL ARTICLE

Prevalence of Erectile Dysfunction and Its Associated Factors among Non-Diabetic Overweight & Obese Patients Attending Government Health Clinics in Kuantan, Pahang

Che' Man M[a], Mohd Zainal AZAR[a], Yusof MZ[b]

[a] Department of Family Medicine, Kulliyyah of Medicine, International Islamic University Malaysia, Kuantan, Pahang
[b] Department of Community Medicine, Kulliyyah of Medicine, International Islamic University Malaysia, Kuantan, Pahang

ABSTRACT

INTRODUCTION: In the clinical setting, erectile dysfunction (ED) is a significant issue that should not be neglected, as it can adversely impact the quality of life of patients and their partners, especially among overweight and obese populations. This study aims to determine the prevalence of ED and its associated factors among non-diabetic, overweight, and obese patients who attend a government health clinic in Kuantan, Pahang, Malaysia. **MATERIALS AND METHODS:** A six-month cross-sectional study was conducted from February 2024 to August 2024 at twelve health clinics in Kuantan, Pahang. The selected respondents were married men over 18 years old, and those with diabetes mellitus, cardiovascular disease, psychiatric illness, or illiteracy were excluded. Data were collected using the validated Malay version of the International Index of Erectile Function (IIEF-5). ED was defined as an IIEF-5 score of less than 22. Descriptive analysis and simple and multiple logistic regression were performed using SPSS. **RESULTS:** All 221 eligible patients in the study responded (100% response rate). The prevalence of ED was 66.1% (n=146). Multiple logistic regression showed that ED was significantly associated with dyslipidemia [AOR (95% CI): 2.42 (1.06–5.52); p-value=0.036], anxiety [AOR (95% CI): 3.99 (1.44–11.01); p-value=0.008] and older age [AOR (95% CI): 1.07 (1.02–1.12); p-value=0.009]. **CONCLUSION**: The study revealed a high prevalence of ED among non-diabetic overweight and obese patients, potentially linked to increasing age, dyslipidemia, and anxiety. Increasing awareness among the public and healthcare providers could improve detection rates in primary care.

Keywords:
Overweight & Obese, Erectile Dysfunction, Dyslipidaemia, Anxiety

Corresponding Author
Dr. Abdul Zaki Ar Rasyid Mohd Zainal
Family Health Clinic, Department of Family Medicine, Kulliyyah of Medicine, International Islamic University Malaysia, Kuantan, Pahang, Malaysia
Email : abdulzakiarrasyid.moh@gmail.com

Received: 1st July 2025; Accepted: 19th November 2025

Doi: https://doi.org/10.31436/imjm.v25i02.2897

INTRODUCTION

As defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), erectile dysfunction (ED) is the inability to achieve and/or maintain an erection of sufficient quality for satisfactory sexual intercourse and performance. These symptoms must persist for at least six months and appear on nearly all occasions of sexual activity. Additionally, the condition must cause significant distress to the individual, and the dysfunction cannot be explained by another mental disorder, relationship issues, other stressors, or substances/ medications.[1]

It is estimated that in 1995 there were over 152 million men worldwide who experienced ED. The Massachusetts Male Aging Study reported a prevalence 52% in men aged 40 to 70.[2] In the Asian population, a recent meta-analysis reported an overall prevalence rate of 2.0%–81.8% throughout Asia. However, this study was limited by the fact that the included studies used different tools to evaluate the prevalence of ED.[3] In Malaysia, the Cross-National Prevalence Study on ED in 1998 showed that more than 16% of men aged 40 years and above had moderate to complete ED.[4] If the prevalence rates of ED in Malaysia were to include those with mild ED, more than 60% of Malaysian men aged 40 years and above would be said to have ED.[4] There are multiple factors associated with the development of ED. The disease

arises due to either local or central causes such as neurological factors, psychological factors, vascular diseases, endocrine, lifestyle, drugs related, and substances.[5]

A study done in January-March 2016 involving two major outpatient clinics in Johor Bahru and Segamat, Malaysia, found that the overall prevalence of ED among male outpatient clinic attendees was 81.5%, which was high.[6] This was significantly higher than the prevalence rates reported in other countries such as Singapore (2%–53%) and Thailand (29%–65%).[6] This may be due, in part, to the unexpectedly high rates of metabolic syndrome among Malaysians and the increasing epidemic of obesity. Indeed, Malaysia is currently described to have the highest obesity rate (45.3%) in Southeast Asia.[6] Various studies have investigated the prevalence of ED across different regions and populations in Malaysia. However, there is a lack of studies looking into the prevalence of ED among overweight and obese populations. Data from a host of clinical studies have indicated that there is an association between visceral obesity, androgen deficiency, endothelial dysfunction, and ED; however, the causal relationship between these variables remains unknown. Considerable evidence links obesity with reduced testosterone levels, resulting in a hypogonadal state, which is a risk factor for ED.[7]

In Malaysia, the overall prevalence of overweight and obesity in 2023 was 54.4 %, and it had increased by 10 % from 20-11-2023.[8] Obesity is a complex and chronic disease that has a heterogeneous presentation. Studies have shown that being overweight and obese reduces the quality of life and increase the risk of chronic health conditions, including type 2 diabetes mellitus (DM).[9] The presence of DM in a patient was a significant predictor of ED.[10] The risk of ED steadily increased with the duration of type 2 diabetes to a nearly two-fold greater risk compared with men without diabetes.[11]

ED is a significant sexual health concern among men that is frequently overlooked and insufficiently treated, particularly in outpatient settings. Therefore, this research aims to measure the prevalence of ED and its associated factors among non-diabetic overweight and obese patients attending government health clinics in Kuantan, Pahang, Malaysia.

MATERIALS AND METHODS

Study design and population

A six-month cross-sectional study was conducted from February 2024 to August 2024 at twelve health clinics in Kuantan, Pahang. The sample size was calculated based on the prevalence of ED among obese men in Denmark and added with a 20% non-response rate, and the final estimated sample size was 221.[12] Outpatient attendees aged 18 years old and above who could read Malay and married at least for the last six months were included in the study. Those who were illiterate, diagnosed with DM, had cardiovascular disease, or with any psychiatric illness or mental retardation were excluded. All male outpatients who attended the respective clinic on the day of data collection were selected through simple random sampling. Patients who met the inclusion criteria were recruited at the registration counter. The participating respondents were required to sign an informed consent form. All information were kept confidential.

Data collection

A self-administered questionnaire consisting of three sections. Section A: Sociodemographic and medical illness age, race, BMI, work status, education level, monthly income, alcohol status, caffeine and smoking status, dyslipidaemia, and hypertension. Section B assessed the psychological status by using the Depression Anxiety Stress Scale (DASS-21). The third section C is to screen for ED by using the International Index of Erectile Function (IIEF-5).

Malay version International Index of Erectile Function (IIEF-5)

The IIEF-5 questionnaire had a Cronbach's alpha coefficient of 0.86 for Bahasa Malaysia, demonstrating good test-retest reliability, high sensitivity, and specificity.[13] This instrument comprises five items across five domains. Classification of the Severity of ED based on total score: 1-7 (Severe), 8-11 (Moderate), 12-16 (Mild-

to-moderate), 17-21 (Mild), and 22-25 (No abnormality).

Malay version 21-item Depression Anxiety Stress Scale (DASS-21)

The DASS-21 Malay Version demonstrated satisfactory internal reliability with Cronbach's alpha coefficients of 0.75, 0.74, and 0.79 for depression, anxiety, and stress, respectively.[14] Responses were recorded on a 4-point scale, ranging from 0 (indicating the statement did not apply at all) to 3 (indicating the statement applied to the participant very much or most of the time). Subscale scores varied from 0 to 21 and were classified into normal, mild, moderate, severe, and extremely severe.

Data analysis

SPSS 29.0 software was used to analyse the data. The continuous data were not normally distributed; hence, median and interquartile ranges were used. Furthermore, descriptive statistics for categorical data employ frequency and percentage. The prevalence and severity of ED were calculated in percentages with a 95% confidence interval (CI). The relationship between ED and other variables, such as sociodemographic profile, medical illness, behavioural factors, and psychological factors, was analysed using simple logistic regression. A multiple logistic regression model using the Enter method was used to determine the factors associated with ED. All significant variables of known clinical relevance ($p < 0.25$) were included in the multivariate logistic regression.[15] The final model showed a significant value ($P < 0.05$), which was considered a statistically significant associated factor for ED.

RESULTS

Sociodemographic data

A total of 221 selected male patients responded, with a response rate of 100%. Table I shows the sociodemographic data of the subjects. The mean age was 45 years old, ranging from 18 to 59 years. The vast majority were Malays, accounting for 79.2% of the total, and the non-Malays 20.8%. Many respondents had a secondary education (43.0%), and 34.8% had university or college education. Most men were employed (90.5%), and about two-thirds were in the low-income category (B40) (78.2%). Non-smokers and smokers were nearly equal at 49.3% and 50.7%, respectively. The majority had a BMI category of overweight and obese class I, with each comprising 41.2% and 41.6%. A substantial proportion of respondents had dyslipidemia (45.7%) and hypertension (46.2%). Surprisingly, more than half of the people who participated in the survey did not experience any symptoms of stress (94.1%), anxiety (74.2%), or depression (92.3%).

Table I. Sociodemographic and Clinical Characteristics of Respondents

Variables	Characteristics	n	(%)	Median (IQ)
Age (years)		-	-	45.4 (16)
Ethnicity	Malay	175	79.2	
	Non-Malay	46	20.8	
Education Level	No Formal Education	5	2.3	
	Primary School	20	9.0	
	Secondary School	95	43.0	
	Vocational Institute	24	10.93	
	College/University	77	4.8	
Working Status	Unemployed	21	9.5	
	Employed	200	90.5	
Monthly Household Income	B40	173	78.2	
	M40/T20	48	21.8	
Body Mass Index	Overweight	91	41.2	
	Obese I	92	41.6	
	Obese II	25	11.3	
	Obese III	13	5.9	
Physical Activity	High	22	10.0	
	Moderate	58	26.2	
	Low	141	63.8	
Smoking Status	Yes	112	50.7	
	No	109	49.3	
Caffeine Status	Yes	127	57.5	
	No	94	42.5	
Dyslipidaemia	No	120	54.3	
	Yes	101	45.7	
Hypertension	No	119	53.8	
	Yes	102	46.2	
Stress	No	208	94.1	
	Yes	13	5.9	
Anxiety	No	164	74.2	
	Yes	57	25.8	
Alcohol Status	No	199	90.0	
	Yes	22	10.0	
Depression	No	204	92.3	
	Yes	17	7.7	

Prevalence of erectile dysfunction and severity

Figure I show that 66.1% of patients had ED. Looking into the severity domain, the results showed that 47% of patients reported having mild ED, 16.7% had mild to moderate ED, 1.8% had moderate ED, and 0.5% had a severe form of ED, as shown in Table II.

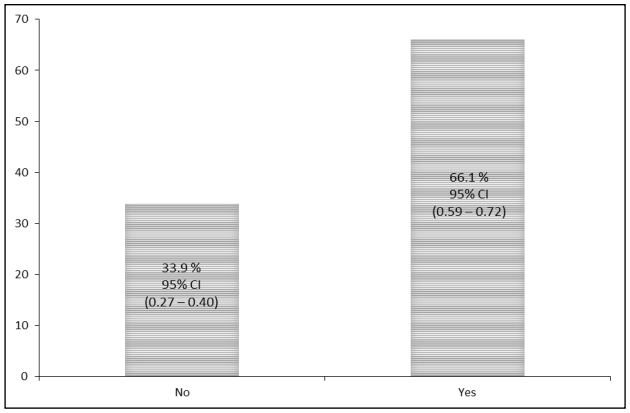

Figure I. Prevalence of Erectile Dysfunction

Table II. Severity of Erectile Dysfunction

Severity	n (%)	95% CI
Mild	104 (47.0)	0.40 – 0.54
Mild to Moderate	37 (16.7)	0.12 – 0.22
Moderate	4 (1.8)	0.01 – 0.05
Severe	1 (0.5)	0.11 – 0.19

Associated factors

Table III displays the results of simple and multiple logistic regression. From simple logistic regression, the associations with ED include age (OR=1.12, 95% CI 1.08–1.16), Malay ethnicity (OR=0.47, 95% CI 0.22–1.01), primary school (OR = 13.50, 95% CI 1.34–135.98), BMI obese III (OR=3.28, 95% CI 0.69–15.70), anxiety (OR=4.23, 95% CI 1.88–9.51), depression (OR=4.18, 95% CI 0.93–18.79), stress (OR=6.63, 95% CI 0.85–51.98), smoking (OR=0.52, 95% CI 0.29–0.92), employment (OR=0.085, 95% CI 0.011–0.647), hypertension (OR=6.611, 95% CI 3.39–12.90) and dyslipidaemia (OR=4.62, 95% CI 2.46–8.70). However, no significant correlation was found between ED and factors such as household income, physical activity, alcohol, and caffeine consumption.

According to Table III, certain factors significantly increase the likelihood of ED. Anxiety individuals were nearly four times more likely to report ED (AOR=3.99, 95% CI 1.44–11.02). Those individuals with increasing age (median age of 45) are more likely to report ED (AOR=1.07, 95% CI 1.02–1.13). Additionally, individuals with dyslipidaemia were twice as likely to develop ED (AOR=2.42, 95% CI 1.06–5.52). Although other factors were linked to an increased risk of ED, these associations were not statistically significant in this study.

Table III. Associated factors for erectile dysfunction

Variables	Simple Logistic Regression			Multiple Logistic Regression		
	Wald[a]	p-value[b]	Crude OR[c] (95% CI) [d]	Wald[a]	p-value[e]	Adjusted OR[f] (95% CI) [c]
Age	35.00	<0.001	1.12 (1.08 – 1.16)	6.77	0.009	1.070 (1.02 –1.13)
Ethnicity						
Non-Malay (ref.)						
Malay	3.74	0.053	0.47 (0.22 –1.01)	1.15	0.28	1.79 (0.62 – 5.18)
Physical Activity						
High (ref.)						
Moderate	0.01	0.919	1.05 (0.39-2.86)	-	-	-
Low	0.94	0.333	1.58 (0.63-3.96)	-	-	-
Employment						
No (ref.)						
Yes	5.66	0.017	0.09 (0.01-0.65)	2.05	0.153	0.20 (0.02-1.83)
Household Income						
B40 (ref.)						
M40/T20	0.35	0.56	0.82 (0.42-1.59)	-	-	-
Educations Level						
No Formal (ref.)						
Primary School	4.88	0.027	13.50 (1.34-135.98)	3.14	0.076	15.37 (0.75-316.0)
Secondary School	2.69	0.101	4.70 (0.74-29.89)	2.60	0.107	8.75 (0.63-22.24)
Institute Vocational	0.01	0.917	0.90 (0.13-6.46)	1.00	0.317	4.09 (0.26-64.22)
University/ College	0.63	0.428	2.11 (0.33-13.36)	2.08	0.150	6.81 (0.50 - 2.48)
Body Mass Index						
Overweight (ref.)						
Obese I	0.27	0.604	1.17 (0.64-2.15)	0.02	0.880	0.94 (0.43-2.05)
Obese II	0.24	0.622	1.27 (0.49-3.25)	0.09	0.764	0.82 (0.22-3.02)
Obese III	2.21	0.137	3.28 (0.69-15.69)	0.97	0.325	2.51 (0.40-15.69)
Alcohol Consumption						
No (ref.)						
Yes	0.48	0.488	1.41 (0.53-3.78)	-	-	-
Caffeine Consumption						
No (ref.)						
Yes	0.29	0.585	0.85 (0.48-1.50)	-	-	-
Smoking Status						
No (ref.)						
Yes	5.09	0.024	0.52 (0.29-0.92)	0.87	0.351	0.69 (0.33-1.49)
Dyslipidaemia						
No (ref.)						
Yes	22.51	<0.001*	4.62 (2.46-8.70)	4.38	0.036	2.42 (1.06-5.52)
Hypertension						
No (ref.)						
Yes	30.64	<0.001*	6.61 (3.39-12.90)	3.72	0.054	2.46 (0.98-6.15)
Stress						
No (ref.)						
Yes	3.24	0.072	6.63 (0.84-51.98)	1.78	0.183	4.86 (0.47-49.71)
Anxiety						
No (ref.)						
Yes	12.19	<0.001*	4.23 (1.88-9.51)	7.12	0.008*	3.99 (1.44-11.01)
Depression						
No (ref.)						
Yes	3.48	0.062	4.18 (0.93-18.79)	0.42	0.519	1.84 (0.29-11.79)

[a]Wald statistic; [b] p-value of Simple Logistic Regression; [c] Crude odd ratio; [d]Confidence Interval; [e]p-value of Multiple Logistic Regression; [f]Adjusted odd ratio; *significant at p value less than 0.05. The model of Nagelkerkr R square for this study was 0.459. This implies that only 46% of the variation in this study was explained in this model.

DISCUSSION

Prevalence of erectile dysfunction

Results in this study demonstrated that 66.1% of the participants reported experiencing ED, which closely matches the previous reported prevalence of ED in Malaysia.[16,17] However, the prevalence was slightly lower than the nationwide population study, with the overall prevalence of ED (78.7%).[18] However, the current study found a higher ED prevalence compared to primary care studies in other countries, highlighting significant variability. Reported ED rates include 55.1% in Nigeria and lower rates in Southeast Asia: Indonesia (11%), Singapore (2–53%), Thailand (29–65%), and the Philippines (33–65%).[3,19,20] The rise in ED appears to be linked to the growing burden of non-communicable diseases in the population over the past two decades.[18] There is a higher prevalence of metabolic syndrome among men.[21] The risk factors of metabolic syndrome are interconnected in contributing to the development of ED.[22,23]

Regarding obese populations, prevalence of ED in this study was also higher than the previous studies on obese men. For instance, the prevalence of ED in obese men varied by study and age group: 13% in men aged 20–45, 36.5% in men aged 26–70, and 22.3% in men over 20.[24] In addition, The European Male Ageing Study found that ED prevalence was higher in obese men (36.7%) compared to healthy weight men (24.8%).[24] Lastly, it was reported that 36% of men undergoing bariatric surgery experienced ED.[24]

Since our study focused on non-diabetic overweight and obese participants only, the other study with an almost similar population was a 5-year cohort regional study involving six primary care centres in Malaga, Spain, where they investigated the prevalence of ED in younger (age 18 – 49) non-diabetic obese men. The prevalence of ED in the whole cohort was 42.1%.[24] The findings were significantly lower than our study prevalence, even though our sample sizes were almost similar. This might be explained by the differences in the range of ages of participants included in the studies. In our study, we involved individuals beyond young ages which is those aged 18 to 59 years old. It was consistent with the Massachusetts Male Aging Studies revealed that the prevalence of ED increased with age, with complete ED rising from 5–15% between 40–70 years.[23] This was also supported by another local study that increasing age was associated with a higher prevalence of ED in the elderly (90.8%), followed by middle-aged (83.3%) and young (73.3%) men.[6]

Interestingly, we found this high ED prevalence despite the restrictive inclusion and exclusion criteria in our study: (i) Only participants under 60 were included to minimize the impact of age on ED prevalence; (ii) subjects with DM, cardiovascular diseases (conditions associated with increased prevalence of ED) were excluded; and (iii) Patients were recruited from primary care to avoid preselection bias from hospital or specialized care settings, as these patients could present more obesity-associated comorbidities (Berkson's bias).[25,26]

Severity of erectile dysfunction

In terms of ED severity, the study found that most ED cases (47%) were mild, aligning with Malaysian prevalence data showing 47.1% mild ED and 31.6% moderate to severe ED .[23] Aside from that, other studies reported comparable results, with 70% of men having ED and 48% experiencing mild severity.[24]

However, other Malaysian studies in the Johor Bahru and Segamat found 29.5% of respondents had severe ED, unlike our study, where only 0.5% had severe ED.[27] This can be explained by the recruitment age limit, wherein our study only limited up to 59 years old, whereas the other involved individuals were beyond 70 years old. Advanced age is significantly related to atherosclerosis due to impaired blood circulation to the sex organs.[22,27]

Associated factors

Three variables were shown to have a significant association with ED, which are anxiety, increasing age, and dyslipidaemia. Our study found that individuals with

anxiety were 4 times as likely to experience ED compared to those without anxiety. The present analysis demonstrates a robust correlation between anxiety and ED, which is consistent with a study in Kuantan, Malaysia, conducted in 2021, which found a similar association with ED, indicating a 2.85 likelihood of developing ED in men with anxiety.[28] Another study found that men with anxiety disorders faced a higher risk of ED, with resulting behavioural changes further fueling the vicious cycle between ED and anxiety.[29] This matter of distraction will to avoiding sexual situations or intimacy which in turn cause a poor relationship with the spouse. Consequently, men will have low self-confidence and even more anxiety. Spectrums of anxiety disorders include social anxiety disorder (SAD), panic disorder, obsessive-compulsive disorder (OCD), generalized anxiety disorder, and post-traumatic stress disorder (PTSD). The overall prevalence of ED in individuals with anxiety ranged from 0% to 85%, with rates varying by anxiety type: PTSD (3–85%), panic disorder (2–36.2%), and both SAD and OCD (0–20%).[29] The prevalence of anxiety and depression increases with the worsening severity of ED.[30] Most EDs are in the mild to moderate severity group.[29]

Increasing age has consistently been demonstrated as a significant predictor of ED.[31] Supporting evidence from both local and international studies has clearly established age as a significant, non-modifiable, and independent risk factor for ED.[32] Increasing age significantly raises ED risk due to physiological changes, including atherosclerosis, that limit blood flow to the sexual organs.[27] With increasing age, many acute and chronic conditions can emerge, acting as confounding factors that diminish sexual desire, lower self-esteem, and introduce medications that may worsen ED.[33] This was consistent with our study, which showed that on multivariate analysis, significant predictors for erectile dysfunction were age (odds ratio (OR) 1.070, 95% confidence interval (CI) 1.017–1.125, p=0.009). They had a median age of 45 years (IQR 16; range 18–59). More than one-third (39.4%, n=87) are in the age range from 50 to 59 years old. Our findings were supported by a study done in Singapore, which reported that age above 50 is the single most significant risk factor in multivariate analysis when adjusted for all confounding factors.[2] The fact that, the strong association between age and ED has also been highlighted in other studies, particularly the Massachusetts Male Aging Study, which found that the prevalence of complete ED tripled from 5% to 15% between the ages of 40 and 70.[2]

Our study also showed that those individuals with dyslipidaemia were at risk twice as likely to develop ED as compared to those without dyslipidaemia. The present analysis shows a strong correlation between dyslipidaemia and ED, consistent with findings from a cross-sectional study in Spain. That survey, involving 121 family physicians from 64 primary care centres of the Madrid Region Health Service (SERMAS), reported higher rates of lipid-lowering drug use among individuals with ED compared to those without (OR: 4.0 [CI: 3.3–4.9]). It also found a stronger association of hypercholesterolemia (OR: 2.3) and hypertriglyceridemia (OR: 1.2) with ED.[34]

Another study comparing the prevalence of hyperlipidemia between individuals with and without ED found that hypercholesterolemia (TC >200 mg/dl or 5.17 mmol/l) was present in 70.6% of the ED group versus 52% of the non-ED group (p=0.06). After adjusting for confounding factors, logistic regression analysis identified HDL-C and the TC/HDL-C ratio as significant predictors of ED (p=0.011 and p=0.000, respectively).[35]

Finally, both our crude and adjusted analyses did not show a positive correlation between overweight or obesity and ED risk after controlling for confounding factors. Therefore, we cannot conclude that overweight or obesity was associated with ED risk in our study. This differs from findings that reported a significant association between the degree of obesity and ED in younger non-diabetic men (AOR 2.02; CI 1.336–5.068; p=0.005).[24] In their study, degree of obesity referred specifically to morbid obesity (obesity class III, BMI ≥ 40). Since we are using an Asian population cut-off value in this study, according to the WHO BMI classification for the Asian population, morbid obesity is defined as BMI≥37.5. In our study, only 5.9% (n=13) of

participants were morbidly obese (obesity class III), and 11.3% (n=25) were in obesity class II, both representing a small proportion. The majority of participants were either overweight (41.2%, n=91) or in obesity class I (41.6%, n=92). This limited number of class II and III obese individuals may have reduced the statistical power of our analysis. Moreover, unlike previous studies that recruited only obese participants, our research included both overweight and obese individuals. Supporting evidence from another cross-sectional study found a higher ED prevalence among obese men (67.3%) compared to overweight men (50.8%), with an overall prevalence of 53.1%.[36]

STRENGTHS AND LIMITATIONS

The strengths of our study lie in the careful design (including only non-diabetic overweight and obese subjects without T2DM or CVD) as well as the assessment of sexual function with the IIEF-5 validated test. Despite the findings, the study has several limitations, including its self-reported data, which may cause recall bias. Additionally, this study is cross-sectional, which limits the ability to establish the causality of ED, potential unmeasured confounding variables, and cultural factors influencing the results. Future research should address these limitations by addressing more diverse populations and comprehensive assessments of comorbidity, psychological, and physiological factors, including hormonal evaluation. The findings are specific to the Kuantan area and may not represent the entire state of Pahang, Malaysia.

CONCLUSION

This study found that the prevalence of erectile dysfunctions was found to be high among non-diabetic overweight and obese patients attending government health clinics in Kuantan, Pahang. Anxiety, age, and dyslipidaemia were significantly associated with ED. Raising awareness among the public and healthcare providers can help improve detection rates among our overweight and obese patients in primary care. Therefore, utilizing screening tools such as IIEF-5 and DASS-21 can effectively identify patients with undisclosed sexual health problems. These measures would support early diagnosis and intervention. Notably, ED serves as a valuable early indicator of future cardiovascular events, as ED and cardiovascular disease share underlying mechanisms such as endothelial dysfunction and inflammation.

CONFLICT OF INTEREST

The author discloses that they do not have any conflicts of interest.

INSTITUTIONAL REVIEW BOARD (ETHICS COMMITTEE)

This study obtained approval from the Department of Family Medicine and Kulliyyah Research Committee (KRC) of Kulliyyah of Medicine, International Islamic University Malaysia (IIUM) on 12th April 2023 with Research ID: 987. Furthermore, this study was registered with the National Medical Research Register (NMRR) and obtained approval from the Medical Research and Ethics Committee (MREC) with ID: NMRR ID-23-02856-L2P (IIR).

ACKNOWLEDGEMENT

The researchers express their profound appreciation to the Director General of the Ministry of Health Malaysia for authorizing the publication of this manuscript. Special thanks to the Pahang State Health Department and Kuantan District Health Office for allowing me to use government health clinics for data collection. Thank you to the staff for their cooperation and assistance in ensuring smooth data collection.

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ORIGINAL ARTICLE

Factors Affecting Triple Elimination Testing Participation by the Pregnant Women During Their First Visit (K1) at *Harapan Baru* Health Center, East Kalimantan

Tuti Meihartati[a], Prita Maharani[a], Sumiati[a], Aries Abiyoga[b], Leny Suzana Suddin[c]

[a]Department of Midwifery, Institute of Health Technology and Science Wiyata Husada Samarinda, Indonesia
[b]Department of Nursing, Institute of Health Technology and Science Wiyata Husada Samarinda, Indonesia
[c]Department of Public Health Medicine, Faculty of Medicine, Universiti Teknologi MARA, Selangor, Malaysia

Keywords
Triple Elimination Screening, Pregnant women, Education, Knowledge, Health Worker Support

Corresponding Author
Dr. Tuti Meihartati
Department of Midwifery,
Institute of Health Technology and Science Wiyata Husada Samarinda, East Kalimantan, Indonesia
E-mail: tuti@itkeswhs.ac.id

Received: 5th January 2026; Accepted: 16th October 2025

Doi: https://doi.org/10.31436/imjm.v25i02/3073

ABSTRACT

INTRODUCTION: Mother-to-child-transmission of HIV, syphilis and hepatitis B is a significant public health issue in Indonesia. Triple elimination screening, which tests these three infections, is a crucial strategy for early detection and prevention, ideally conducted during the first antenatal visit (K1). However, the coverage of this screening remains suboptimal in several regions, including the Harapan Baru Health Center. This study aimed to test factors affecting participation in the triple elimination screening during the first antenatal visit among pregnant women in the service area of the Harapan Baru Health Center. **MATERIALS AND METHODS:** A cross-sectional study was conducted involving 50 pregnant women who attended their K1 visit in June 2025. Participants were selected using convenience sampling. Data were gathered through structured questionnaires and maternal and child health (MCH) books and analysed using the Pearson chi-square test. **RESULTS:** Respondents' knowledge (OR=5.4, p=0.023) and health worker support (OR=10.7, p=0.002;) were significantly associated with screening participation. However, the education level was not significantly associated. **CONCLUSION:** Good knowledge level and positive support from health workers could increase the likelihood of pregnant women undergoing triple elimination screening during their first antenatal visit.

INTRODUCTION

Mother-to-child transmission (MTCT) of infectious diseases remains a major challenge to maternal and child health across various countries, including Indonesia. The primary focus is on three diseases: Human Immunodeficiency Virus (HIV), syphilis, and hepatitis B. These diseases can be transmitted through sexual contact, blood transfusion, contact with contaminated blood, and vertically from mother to child during pregnancy, childbirth, or breastfeeding. Such transmission not only leads to short-term health issues, such as miscarriage, stillbirth, and childbirth complications, but also poses long-term risks, including congenital defects, chronic diseases, and even death in infants.[1,2]

As part of a global initiative, the World Health Organization (WHO) has set a target to eliminate MTCT of HIV, syphilis, and hepatitis B by 2030. Indonesia is committed to achieving this target by implementing a policy of triple elimination screening for all pregnant women, which includes testing for HIV, syphilis, and hepatitis B at least once during pregnancy, as follows. This screening is strongly recommended to be conducted during the first antenatal visit (K1) to enable early detection and prompt management if a pregnant woman is diagnosed with reactive results[3]. The screening is a crucial part of antenatal care and is often conducted at the first visit, known as K1. The goal is to detect these infections early so that treatment can be started to protect both the mother and the unborn child.[27,25]

The implementation screening adheres to the national protocol outlined by the Indonesian Ministry of Health, primarily targeting all pregnant women during their first Antenatal Care (ANC) visit (K1) at primary health centers (Puskesmas). This protocol integrates the testing of HIV, Syphilis, and Hepatitis B into the routine ANC service, adopting an 'opt-out' approach where testing is offered unless explicitly declined. Unlike protocols in some other countries that may focus solely on HIV, the Indonesian guideline emphasizes the simultaneous screening for the three diseases (Triple Elimination). This commitment to integrated and mandatory screening highlights the high level of governmental priority given to the program; however, its successful execution continues to be hampered by local implementation gaps.[3]

Furthermore, the Indonesian Ministry of Health mandates that the triple elimination screening for HIV, Syphilis, and Hepatitis B be provided free of charge and integrated into routine Antenatal Care (ANC) at public health facilities (Puskesmas). However, screening coverage in Indonesia remains suboptimal. According to the 2023 Indonesian Health Profile, the coverage of HIV screening in pregnant women is only 68.4%, while that of syphilis is only 36.5%. These figures fall far short of the national target of 100% coverage. A similar situation is observed in East Kalimantan, where the coverage of HIV and hepatitis B screenings in pregnant women which is 87%, while syphilis screening coverage is only 43%. In Samarinda City, the statistics for 2024 were 75% for HIV, 69% for hepatitis B, and 70% for syphilis. Even at the Harapan Baru Health Center, screening coverage decreased from 65% in 2023 to 57% in 2024. This consistent underachievement, despite the service being free, suggests that the primary challenges lie in systemic and operational failures (such as supply chain issues or differences between public and private service availability) and individual-level compliance factors (such as knowledge, acceptance, or indirect costs like transportation). This decline indicates complex challenges in the program's implementation, which, if not addressed promptly, could increase the risk of mother-to-child transmission.

The low coverage of triple elimination screening is an urgent issue, as pregnant women who do not undergo screening are at a high risk of transmitting infections to their babies. HIV infection can lead to babies being born with HIV-positive diagnosis, while congenital syphilis poses the risk of permanent disabilities or death. Perinatal hepatitis B can also develop into chronic liver disease and liver cancer in adulthood.[1] Therefore, triple elimination screening participation during the first antenatal care (ANC) visit is crucial to prevent this.

Several factors influence pregnant women's compliance with screening, including education, knowledge, and support from healthcare workers. Low education levels are often associated with a lack of understanding of the benefits of screening, while good knowledge has been proven to increase awareness of the risks of transmission.[4,17] Support from healthcare workers, such as providing information and motivation from midwives or doctors, plays a crucial role in encouraging pregnant women to undergo screening.[5,18]

Several previous studies have indicated a relationship between predispositional factors and the behaviour of the triple elimination screening. Knowledge and attitudes of pregnant women have been significantly associated with triple elimination screening participation in Pekanbaru[6]. A similar result was reported by Warliana and Solihah (2023), who found that women with good knowledge were 2.73 times more likely to undergo screening than those with low knowledge. Support for healthcare workers also plays a crucial role.[7,21] Adequate knowledge among healthcare workers was also crucial for shaping positive attitudes. Therefore, it is essential to periodically assess healthcare workers' knowledge to identify and address any gaps.[22] The active involvement of healthcare workers in providing information, education, and motivation can enhance pregnant women's compliance[5]. A study in Bandar Lampung has even shown a significant relationship between healthcare worker support and screening compliance.[7] Education, as a predispositional factor, cannot be overlooked; however, several studies have yielded varied results: some found a significant relationship, while others found no association between

education and triple elimination screening.[4]

Hence, this study is essential to thoroughly identify the factors associated with compliance in triple elimination (HIV, syphilis, and hepatitis B) screening participation among pregnant women in the X region. While similar studies have been conducted in Indonesia, previous studies had certain limitations. For instance, many focused on only one disease or utilized a less comprehensive methodological design (such as small sample sizes or limited geographical reach), which made generalization of the findings difficult. This study seeks to bridge that gap by applying a more robust methodology to obtain more accurate and representative data. The findings of this study are expected to provide valuable input for healthcare workers and policymakers to formulate targeted and context-specific intervention strategies and significantly improve screening coverage. This will support the effort to achieve the target of eliminating mother-to-child transmission of HIV, syphilis, and hepatitis B by 2030.

MATERIALS AND METHODS

This study employed a quantitative approach using a correlational analytic cross-sectional design to identify factors associated with triple elimination screening during the first antenatal visit (K1) among pregnant women in the working area of Harapan Baru Health Center, Samarinda. In June 2025, a total of 57 pregnant women attended their first antenatal care (K1) visit, both with and without triple elimination testing. Using a non-probability total sampling method, all members of the population were initially included. However, seven participants were excluded due to emergencies, incomplete questionnaires, or uncooperative responses. Thus, the final sample consisted of 50 respondents who met the study criteria.

Data were collected using structured questionnaires, including a characteristics questionnaire (education), a knowledge questionnaire, and a healthcare provider support questionnaire, all of which had undergone validity and reliability testing. Secondary data were obtained from the Maternal and Child Health (MCH) handbook to determine the status of triple elimination screening. Data collection was conducted through structured interviews and review of the MCH handbook after respondents provided written informed consent.

Operational definitions included education, healthcare provider support, and triple elimination screening (whether or not HIV, syphilis, and hepatitis B screening was performed during the K1 visit).

Table I. Operational Definition

Variable	Operational Definition	Instrument	Measurement Result	Scale
Education	The formal education level and the latest diploma obtained by pregnant women	Questionnaire	Low: (< Senior High School) High: (≥ Senior High School Reference: Wiyayanti & Sutarno, 2023	Ordinal
Knowledge	Pregnant women's knowledge of triple elimination, including definition, benefits, examinations, disease transmission from mother to child, and maternal management	Questionnaire	Poor: (< 50% correct answers) b. Good: (≥ 50% correct answers) Reference: Aristadewi, 2022	Ordinal
Health worker support	Health workers' support for pregnant women in the form of education & information, counseling & communication, and access & facilities	Questionnaire	Positive support: (score ≥ 3) Negative support: (score < 3) Reference: Andhini, 2023	Ordinal
Triple elimination test	Pregnant women's action in undergoing triple elimination test (HIV, syphilis, hepatitis B) during the first antenatal care visit (K1)	Maternal and Child Health Book (KIA)	Yes: underwent triple elimination test during K1 b. No: did not undergo triple elimination test during K1	Nominal

Data analysis consisted of univariate analysis to describe frequency distributions, followed by bivariate analysis using the chi square test for education and knowledge variables, and Fisher exact test for healthcare provider support, with a significance level of α=0.05. Odds ratios were calculated to determine the magnitude of association between variables.

Research ethics were upheld through the principles of confidentiality, justice, and voluntary participation. This study received ethical clearance from the Health Research Ethics Committee of Poltekkes Kemenkes Medan, under approval number No. 01.26.1027/KEPK/POLTEKKES KEMENKES MEDAN 2025. To ensure informed consent, all prospective respondents were thoroughly briefed on the study's purpose, procedures, potential risks, and their right to withdraw at any time without penalty. Following this explanation, respondents who agreed to participate provided written informed consent prior to data collection. Confidentiality was strictly

maintained by anonymizing all collected data, assigning unique numerical codes to replace personal identifiers, and storing the data securely in a password-protected file accessible only to the primary researcher.

RESULT

The results of this study describe the distribution of respondent characteristics, including education level, knowledge, healthcare worker support, and triple elimination screening during the first antenatal visit to the Harapan Baru Health Center, Samarinda City. Additionally, an analysis of the relationships between the studied variables is presented.

Table II. Respondents Characteristics (n=50)

Variable	Frequency (n)	Percentage (%)
Age		
<20 years	2	4
20-35 years	42	84
> 35 years	6	12
Occupation		
Unemployed	45	90
Employed	5	10
Education Level		
Basic	19	38
Higher	31	82
Knowledge level		
Good	18	36
Poor	32	64
Healthcare Worker Support		
Positive	38	76
Negative	12	24
Triple Elimination Screening Participation		
Yes	36	72
No	14	28

Based on Table 2, it can be observed that the majority of respondents are aged between 20 and 35 years (42/50, 84%), and were unemployed (45/50, 90%), have a higher education level (31/50, 62%) with good knowledge (32/50, 64%), had received positive healthcare worker support (38/50, 76%) and had undergone triple elimination screening (36/50, 72%).

Table III. Association between educational level, knowledge and healthcare worker support with Triple elimination screening participation

Variable	Triple Elimination Screening Category				OR (95%CI)	P value
	Yes		No			
	Frequency (n)	Percent (%)	Frequency (n)	Percent (%)		
Education Level					0.560 (0.147, - 2.129)	0.595
Basic	21	68	1	32		
Higher	15	79	4	21		
Missing						
Knowledge level					5.400 (1.431, 20.382)	0.023*
Good	27	84	5	16		
Poor	9	50	9	50		
Healthcare Worker Support					10.667 (2.420, 47.023)	0.002*
Positive	32	84	6	16		
Negative	4	33	8	67		

Based on Table 3, it was shown that among women with higher education, 68% had underwent triple elimination screening during K1, when compared to the one with basic education, 4 respondents (21%) did not undergo the screening with no significant relationship found between education level and triple elimination screening during the K1.

There was a significant relationship between knowledge level and triple elimination screening (p=0.023) during the K1 by pregnant women at Harapan Baru Health Center. The odds ratio (OR) was 5.4, indicating that respondents with good knowledge had 5.4 times odds to undergo triple elimination screening compared to those with poor knowledge.

Similarly, it was found that there was a significant relationship between healthcare worker support and triple elimination (p=0.002) screening during the K1. The odds ratio (OR) was 10.7, indicating that respondents with positive healthcare worker support had 10.7 odds to undergo triple elimination screening compared to those with negative healthcare worker support.

DISCUSSION

The results of this study indicate that most pregnant women respondents underwent triple elimination screening during their first antenatal visit (K1). Multiple studies have shown that while there has been an increase in the number of pregnant women undergoing triple elimination screening at their first antenatal care visit (K1), the coverage often remains below national and international targets[23]. Research, particularly in countries like Indonesia, reveals a mixed picture. While some studies show a high percentage of pregnant women getting screened, the results are often not uniform across all three diseases. For example, a study in Makassar City, Indonesia, found that in 2022, 99.4% of pregnant women had an HIV test, but only 87.3% were screened for syphilis and 56% for hepatitis B. This suggests that even when a woman goes for her K1 visit, she may not receive the full "triple" screening.[24]

The findings also emphasised the importance of

**p level of<0.05 taken as level of significance*

knowledge as a factor closely related to triple elimination screening participation. Pregnant women with good knowledge were more likely to be aware of the risks of HIV, syphilis, and hepatitis B transmission to the foetus, which motivated them to undergo screening. This finding is consistent with Dyna et al. (2023), who stated that maternal knowledge was significantly associated with triple elimination screening[10]. Similar research by Sinaga et al. (2022) found that the knowledge, attitudes, and actions of pregnant women were significantly related to triple elimination screening[11]. Good knowledge enables pregnant women to make informed health decisions, including screening in the early stages of pregnancy.

The results of this study further emphasise the critical role of healthcare worker support in enhancing pregnant women's compliance with triple elimination screening. Pregnant women who received positive support from healthcare workers were more likely to comply with screening. This finding aligns with the study by Veronika et al. (2023), who identified a significant relationship between healthcare worker involvement and triple elimination screening at the Palembang Health Center.[12] Similarly, Ellen, Sari, and Wulandari (2024) underscored the central role of healthcare workers in improving pregnant women's compliance through education, motivation, and counseling[5]. Rohani et al. (2022) emphasised that healthcare worker support goes beyond providing information and serves as emotional support that significantly influences pregnant women's decisions to undergo screening.[8]

Community-based approaches have also proven effective in enhancing pregnant women's knowledge and attitudes. Fatiah et al. (2024) demonstrated that health education at Posyandu (community health posts) significantly improved pregnant women's perceptions, attitudes, and knowledge regarding the importance of triple elimination services[13]. This finding underscores the importance of community-based interventions as a key strategy for reaching pregnant women, particularly those residing in areas with limited access to healthcare facilities.

In addition to individual factors and healthcare worker support, systemic factors play a significant role in the success of the triple elimination program. An evaluative study by Syaputri et al. (2023) in Rokan Hilir revealed that limited midwifery competencies, insufficient health promotion, and weak supportive policies are serious barriers to achieving national screening targets.[14] In line with this, Mramel et al. (2024) stated that opportunities to fully experience the breadth of midwifery skills were limited. Additionally, most midwifery students and recent graduates exhibit insufficient competence in handling high-risk situations and emergencies.[20] Limited resources in health facilities, such as a shortage of rapid test kits or trained staff was another influence factor.[25] These findings indicate that to improve the coverage of triple elimination screening, a comprehensive approach is needed, involving education, healthcare worker training, and regulatory and policy support.

Overall, this study reaffirms that knowledge and healthcare worker support play a significant role in enhancing triple elimination screening compared to formal education. This was consistent with Green's (1980) Health Belief Model, which posits that health behaviour is determined by predispositional factors (knowledge, attitudes), enabling factors (facilities, access to services), and reinforcing factors (support from healthcare workers, family, and the environment).[15] This indicates that a majority of pregnant women are not consistently receiving the full screening.[26] The practical implication of this study is the need to strengthen continuous health education programs for pregnant women, particularly regarding the risks of HIV, syphilis, and hepatitis B transmission, as well as the importance of early detection through triple elimination screening. Furthermore, the role of healthcare workers needs to be enhanced, not only as service providers but also as motivators and companions in the decision-making process for pregnant women.[16,19]

Finally, education level was not significantly associated with the triple elimination screening. This lack of a significant relationship could be explained by the health behaviour concept, which states that education is merely one predispositional factor and not the primary

determinant of behaviour (Notoatmodjo, 2014). Even though pregnant women may have higher education, it does not necessarily guarantee compliance with screening if their knowledge about triple elimination is low or if there is no support from their surroundings. This finding aligns with Marwini's (2023) study, which concluded that maternal education had no significant effect on the implementation of triple elimination screening.[4] This suggests that specific information plays a more crucial role in influencing behaviour than formal education.

Therefore, strategies to increase the coverage of triple elimination screening should focus on comprehensive education, community-based approaches, improving healthcare worker competency, and regulatory support. If these strategies are implemented effectively, the national target of eliminating mother-to-child transmission of HIV, syphilis, and hepatitis B by 2030, as directed by the WHO and the Ministry of Health of the Republic of Indonesia, will be achieved.

CONCLUSION

The findings of this study indicate that maternal knowledge and healthcare provider support are significantly associated with the uptake of triple elimination screening during the first antenatal visit (K1), with p=0.023 (OR=5.4) and p=0.002 (OR=10.667), respectively. Conversely, formal educational attainment demonstrates no significant relationship with screening participation (p=0.595). These results underscore that higher maternal education does not inherently ensure compliance with triple elimination screening in the absence of condition-specific knowledge and adequate professional support.

The discussion highlights that knowledge functions as a critical predisposing factor shaping health related behavior, wherein women with sufficient knowledge exhibit greater awareness of the risks of vertical transmission of HIV, syphilis, and hepatitis B. Healthcare provider support emerges as the most influential reinforcing factor, as providers contribute not only to the dissemination of information but also to the provision of motivational cues that facilitate early detection. The limited influence of formal education suggests that strategies to enhance screening uptake should prioritize structured, targeted health education interventions and more active engagement from healthcare professionals.

In conclusion, adequate maternal knowledge and strong healthcare provider support substantially increase the likelihood of pregnant women undergoing triple elimination screening at the initial antenatal visit. Strengthening maternal health education through ongoing counseling and evidence based educational media, both within primary care settings and community-based platforms, is recommended. Healthcare providers are further encouraged to adopt a more proactive role in delivering comprehensive informational and emotional support throughout antenatal care.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this study.

ACKNOWLEDGMENT

The authors would like to express their sincere gratitude to the pregnant women who participated in this study at *Harapan Baru* Health Center, East Kalimantan, for their cooperation and trust. Special thanks are extended to the healthcare providers, midwives, and traditional leaders who supported the research, offering invaluable insights and assistance during the data collection process.

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ORIGINAL ARTICLE

Development of Components for A Glaucoma Screening Programme in Malaysia: A Qualitative Study

Hui WX[a], Sharanjeet-Kaur S[b], Hairol MI[c], Abd Rahman MH[b], Nasaruddin RA[a], Md Isa Z[d], Ismail R[e], Che Hamzah J[a]

[a]Department of Ophthalmology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Wilayah Persekutuan Kuala Lumpur, Malaysia
[b]Centre for Rehabilitation & Special Needs Studies (iCaReRehab), Faculty of Health Sciences, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia
[c]Centre for Community Health Studies (ReaCH), Faculty of Health Sciences, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia
[d]Department of Public Health Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia, Wilayah Persekutuan Kuala Lumpur, Malaysia.
[e]Sentul Health Clinic, Wilayah Persekutuan Kuala Lumpur, Malaysia

ABSTRACT

INTRODUCTION: Glaucoma is a leading cause of permanent blindness, often going undetected in its early, asymptomatic stages, especially in older age groups. In Malaysia, glaucoma is a growing public health issue due to an increase in the ageing population. While screening is essential for early glaucoma detection, the most suitable strategy for Malaysia's healthcare system remains unclear. This study explored the perspectives of eye healthcare professionals on the most suitable glaucoma screening strategies for Malaysia. **MATERIAL AND METHODS:** This qualitative study used semi-structured interviews with 19 eye health professionals (ophthalmologists, optometrists, nurses, ophthalmic technicians, and assistant medical officers) practicing in the Klang Valley. The interviews were conducted face-to-face in their workplace or via a video conferencing platform. All interviews were recorded, transcribed, and analysed using thematic analysis. **RESULTS:** Six major themes were identified: types of glaucoma screening programmes, accessible screening locations, target screening population, instruments and use of digital technology, trained personnel, and referral criteria. Opportunistic case finding and population-based programmes were identified as the glaucoma screening programmes in which trained personnel conducted screening at accessible locations. Glaucoma screening for high-risk individuals was recommended, focusing on visual acuity testing, tonometry, anterior chamber angle assessment, funduscopy, perimetry, and retinal nerve fibre assessment. A lack of clear referral criteria due to low awareness and poor implementation of existing guidelines was observed. **CONCLUSION:** Further investigations are required to identify the best combination of components for glaucoma screening. This will enable policymakers to develop an effective glaucoma screening programme in Malaysia.

Keywords
glaucoma, screening, interviews, policy, Malaysia

Corresponding Author
Assoc. Prof. Dr. Jemaima Che-Hamzah
Department of Ophthalmology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Bandar Tun Razak, Wilayah Persekutuan Kuala Lumpur, Malaysia
Email: jemaima@ppukm.ukm.edu.my

Received: 24th February 2025; Accepted: 6th March 2026

Doi: https://doi.org/10.31436/imjm.v25i02/2875

INTRODUCTION

Glaucoma was reported as one of the leading causes of blindness following cataracts in 2020.[1] At least 3.6 million adults aged 50 years and above were estimated to be blind in 2020 because of glaucoma.[1] As Asia is the continent with the highest population density[2], with a growing ageing population, glaucoma cases were expected to increase from 51.32 million in 2013 to 80.87 million in 2040.[3] In Malaysia, according to the National Eye Survey 2014, glaucoma contributed to 6.6% of blindness in adults aged 50 years and older.[4]

Glaucoma is a chronic eye condition that impairs the patient's quality of life. [5] Glaucoma patients may experience significant financial burdens because glaucoma requires long-term and often expensive medical treatments.[5] The asymptomatic nature of glaucoma in its early stages makes it harder to detect.[6] Many people are unaware that they have glaucoma, which increases the risk of irreversible blindness.[7] Thus, early detection through screening is crucial in preventing blindness caused by glaucoma.

Access to eye care in Asia, especially in rural areas, is limited compared with developed countries.[8] Six out of ten countries in Southeast Asia have not achieved the target number of ophthalmologists-to-population ratio (1:100,000).[9] Additionally, most ophthalmologists are concentrated mainly in urban areas.[9] This limitation may contribute to undetected glaucoma cases in these nations.[10]

The United States Preventive Services Task Force has not found sufficient data to recommend glaucoma screening for adults who do not have vision problems.[11] However, several studies in Asia have found that community screening was more effective than opportunistic case finding in detecting glaucoma early.[12,13] Furthermore, model-based studies have found that population-based eye screening was cost-effective in China and India.[14,15] These disparities in results may lead to confusion about the appropriate strategies for glaucoma screening. In Malaysia, the detection of glaucoma was primarily conducted through opportunistic case screening and, less commonly, community-based screening. There is no national glaucoma screening programme.

As glaucoma screening may reduce the risk of blindness, it is essential to find effective screening strategies. A study in the United Kingdom had identified tonometry combined with either visual field tests or optic disc photography, performed by trained personnel in primary care settings, as the key components for glaucoma screening.[16] In India, similar findings were reported, with recommendations to use the Goldmann tonometer, slit lamp, and fundoscopy using an ophthalmoscope and Volk lenses in a primary care setting.[17] However, no similar study has been conducted in Malaysia. Therefore, this study aimed to seek the opinions of eye healthcare practitioners on the components of a glaucoma screening programme and to triangulate possible strategies that may be suitable in a Malaysian healthcare setting.

MATERIALS AND METHODS

Study Design and Setting

This study employed an exploratory qualitative design in which semi-structured interviews were carried out between 15 December 2020 and 14 February 2021 in Klang Valley. Klang Valley, a densely populated urban area encompassing Kuala Lumpur, Putrajaya, and six Selangor districts, was chosen for its high number of healthcare facilities.

Participants

Purposive sampling was used to recruit nineteen registered eye healthcare practitioners from both the government and private healthcare sectors, who were proficient in English or Malay and willing to participate in an interview. The study was conducted during the COVID-19 pandemic, when the national quarantine was implemented. A list of ophthalmologists and optometrists in Klang Valley was obtained from the National Specialist Register and the Malaysian Optical Council websites, respectively. Eligible ophthalmologists and optometrists were approached and agreed to participate in online interviews. However, recruitment of other eye healthcare practitioners was confined to two selected health facilities, as most participants preferred face-to-face interviews.

Eligible participants were approached via WhatsApp and informed about the study. Informed consent and permission for audio recording were obtained from the participants before they were enrolled in the study. Participants were invited to join the study until data saturation was reached, when no new information was obtained from subsequent interviews.

Data Collection and Analysis

A topic guide for the semi-structured interview was developed after reviewing the literature review on glaucoma screening by a panel comprising ophthalmologists and optometrists. The topic guide consisted of open-ended questions on perspectives on glaucoma screening, the screening population, suitable locations, appropriate instruments to be used on-site, and a strategies to reduce false positives in glaucoma screening. The topic guide was piloted among the potential target population, who judged that the questions did not require significant modification.

The first author conducted the interviews in either English (10) or Malay (9), depending on the participants' language proficiency. Ten interviews were conducted via the Zoom or Skype platforms, while nine were conducted face-to-face in a quiet room at their workplace. The interviews lasted between 25 and 50 minutes, with probing questions used until the participants did not offer any new information. Online interviews were video-recorded, while in-person interviews were audio-recorded. The researcher observed and recorded participants' facial expressions and body language. The audio recordings were transcribed verbatim. The Malay interview transcripts were translated into English and back-translated to ensure accuracy. The transcripts were repeatedly checked against the audio recordings, anonymised, and imported into NVivo 14. Two eye healthcare practitioners trained in qualitative research methodology analysed the data using an inductive thematic analysis.[18] Any disagreements about the themes were resolved through discussion. Member checking and an audit trail were conducted to ensure the trustworthiness of the study.

RESULTS

Nineteen eye healthcare practitioners participated in the study, including six optometrists, five nurses, four ophthalmologists, three ophthalmic technicians, and one assistant medical officer. There were twelve females and seven males, with the majority being Malay (16), two Chinese, and one Indian. The mean age was 41.47±10.62 years and ranged from 29 to 69 years old. Sixteen participants had five to ten years of work experience, while three had over a decade of experience.

The results from the semi-structured interviews were presented in six major themes: (1) types of glaucoma screening programmes, (2) accessible screening locations, (3) target screening population, (4) instruments and use of digital technology, (5) trained personnel, and (6) referral criteria.

Theme 1: Types of glaucoma screening programmes

Participants perceived that there were two types of glaucoma screening programmes in Malaysia: i) opportunistic case finding done by eye care providers and ii) population-based screening by non-profit organisations. Furthermore, the Ministry of Health utilised the existing diabetic retinopathy screening programme to screen patients for glaucoma.

'….. The first is we do it in-house in our practice and the second is through community vision screening.' (P19, optometrist)

'Ministry of Health has a diabetic screening programme. During the diabetic screening, cases with suspicious changes to the optic nerve head are often picked up.' (P5, ophthalmologist)

Theme 2: Accessible screening locations

Most participants preferred primary care facilities and optometrist practices as locations for glaucoma screening because of their accessibility to the public, availability of expertise and instruments.

"Usually, the first point of care happens at community level such as optometry practices and health clinics. Some health clinics have fundus camera and this can be used to not only diagnose diabetic retinopathy, but also glaucoma. You only need doctors to diagnose glaucoma" (P1,ophthalmologist)

Some participants proposed using hospitals as screening sites. As one ophthalmologist (P10) noted,

"*If you want a location, I think hospitals have more patients. Most people come for mild illnesses. So, we have the opportunity to screen them there.*"

This viewpoint highlights the potential of hospitals to screen an existing population who are attending for other medical reasons.

Several participants believed in conducting screenings in public places.

'…conducted near a shopping mall as it is convenient.' (P15, Nurse)

'…target areas such as places of worship … and community centres.' (P4, ophthalmologist)

Public places were thought to be suitable for screening due to their accessibility and the possibility of reaching a wider and diverse population.

Theme 3: Target screening population

Most participants perceived that targeted screening of individuals with glaucoma risk factors was a more appropriate approach:

"I think for a screening programme, perhaps you can try and narrow down the group of people that come for screening to increase the pick-up rate." (P4, ophthalmologist)

High-risk individuals identified by participants were individuals aged 40 and above who have a family history of glaucoma, systemic diseases like diabetes and hypertension, obstructive sleep apnoea, a history of eye surgery, high myopia, hyperopia, and taking steroid medication.

Some participants preferred that glaucoma screening be conducted at all ages:

'I believe that everyone should go for a yearly screening regardless. Some people do get glaucoma at an early age.' (P8, Optometrist)

Screening of all ages may prevent undiagnosed glaucoma, especially in high-risk young individuals, e.g. myopia, under steroid medication, and family history of glaucoma.

Theme 4: Instruments and use of digital technology

Most participants recommended using a variety of instruments, including the visual acuity chart, pen torch, ophthalmoscope, slit lamp, fundus camera, Volk lens, optical coherence tomography (OCT), Humphrey Field Analyser (HFA), pachymeter, gonioscope, and various types of tonometers.

However, ophthalmologists disagreed with other healthcare providers regarding the use of specific instruments for screening, such as the slit lamp, OCT, HFA, pachymeter, and gonioscope. They felt that these instruments were better suited for diagnostic purposes.

Some participants believed that portable instruments, especially those with artificial intelligence (AI) were ideal for screening.

'…portable fundus camera with AI is a more effective way.' (P8, Optometrist)

AI helps in improving the accuracy of screening without ophthalmologists on site and refers the suspected individuals to ophthalmologists in well-equipped hospitals for better management of cases.

Theme 5: Trained personnel

All participants agreed that eye healthcare practitioners should be involved in glaucoma screening. Most agreed that civilians should not be involved due to their lack of knowledge about glaucoma.

'I would say definitely no. Because when we are talking about the chronic type of glaucoma, the layman may not have adequate knowledge even to suspect that they have this disease.' (P5, ophthalmologist)

This indicates that screeners should be well-trained personnel with a fundamental understanding of eye disease.

Some participants suggested civilians could be trained for glaucoma screening:

'They can be involved in taking intraocular pressure. Nowadays, there are a lot of automated tonometer and fundus camera.' (P7, optometrist)

This perspective suggests that technological advancements have simplified glaucoma screening, making it feasible for civilians to perform.

Most participants believed that ophthalmologists and optometrists should interpret the clinical results.

'….. But when all the results come back, I suppose the ophthalmologists and optometrists will have to look at each result' (P8, optometrist)

The participants believed that, at the end of the screening, clinical data should be reviewed by personnel with certification from a professional body.

Some participants felt that assistant medical officers, nurses and ophthalmic technicians could be trained to detect glaucoma.

'I think paramedics should also be trained in detecting glaucoma, especially if they are doing fundus photograph screening for diabetes.' (P1, ophthalmologist)

This approach optimizes the use of assistant medical officers, nurses, and ophthalmic technicians to screen for glaucoma in addition to diabetic retinopathy.

Theme 6: Referral criteria

Most optometrists were unaware of the referral criteria guidelines:

'In order for you to reduce the false positive rate, you can make sure that the optometrist knows what the criteria are to refer for glaucoma.' (P2, optometrist)

Clear referral criteria would help the eye healthcare practitioners to filter the patients and improve the accuracy of referrals.

There are no specific guidelines for glaucoma screening in Malaysia, according to participants.

'We don't have a specific guideline for glaucoma screening. Some hospitals have implemented some guidelines, but I think not all hospitals in Malaysia.' (P6, ophthalmologist)

This highlights the need to develop clear referral criteria for glaucoma.

DISCUSSION

This study identified the components needed for a glaucoma screening programme in Malaysia. The components included the types of glaucoma screening programmes, the target population, potential screeners, instruments, locations, and referral criteria.

Participants identified opportunistic case finding and population-based screening as the common glaucoma screening programmes in Malaysia. Opportunistic case finding was mostly conducted in a developing countries as it is more cost-effective.[19] However, several population -based glaucoma screening programmes have been successful in screening high-risk individuals.[20,21]

Many participants recommended targeted screening as an effective strategy for early detection of glaucoma. The findings were similar to those of another UK study on the clinical components of glaucoma screening.[16] That study found that targeted glaucoma screening should be conducted in a primary care setting using funduscopy or perimetry combined with tonometry by trained eye care providers.[16] Several studies reported that targeted screening among high-risk individuals, such as those aged 40 and above or with a family history of glaucoma, can effectively detect glaucoma.[14,22] This finding is relevant for policymakers who must justify the allocation of resources for a screening programme.

Participants suggested that screening should be conducted at primary healthcare settings and public locations. Previous studies have found that screening at primary healthcare clinics or hospitals effectively detects glaucoma.[23,24] Tan et al.[10] recommended screening in community settings such as churches and community centres to reach individuals who may not attend clinic-based screenings.[10] However, tertiary healthcare facilities are not ideal for screening in Malaysia because they are less accessible to the public[25] and have high patient loads.[26] Additionally, patients often need a referral letter to get their eyes examined at public hospitals.[25]

Our participants recommended many instruments for visual acuity testing, funduscopy, tonometry, visual field assessment, anterior chamber angle assessment, and retinal nerve fibre layer assessment. This aligns with the International Agency for the Prevention of Blindness's recommendations for using the visual acuity chart, ophthalmoscope, and tonometer in a primary care setting.[27] While one study suggests combining tonometry with either funduscopy or perimetry[16], our study suggested using Optical Coherence Tomography (OCT) for retinal nerve fibre layer assessment. Although OCT can improve the diagnostic accuracy of glaucoma[28], it is not usually used in screening programmes due to its high cost, lack of portability, and the need for trained personnel.[29]

Ophthalmologists recommended instruments such as OCT and HFA for glaucoma diagnosis rather than screening. These findings were similar to those of a UK

study.[16] This is due to their cost, limited portability, and the need for specialised personnel.[28,29,30] Screening tools should ideally be inexpensive and user-friendly.[31] However, other eye healthcare practitioners viewed them as important for glaucoma detection, as the inclusion of these instruments improves the accuracy of glaucoma detection in a screening programme.[28]

All participants preferred using a non-mydriatic fundus camera for glaucoma screening. In Malaysia, fundus cameras are widely available in primary healthcare clinics, as they are used in the diabetic retinopathy screening programme.[22] Thus, this makes them suitable instruments for glaucoma screening and facilitates programme implementation.

Portable instruments are mostly used in community screening programmes because they are easily transported,[32] as shown in a Nepal screening programme which utilised portable tools such as Tonopen, portable slit lamps, direct ophthalmoscopes, and frequency-doubling technology.[33] Participants also suggested using AI-equipped instruments, as many studies have shown that AI can accurately identify probable glaucoma from fundus photographs.[34,35] As AI technology advances, it may enable more accurate identification of glaucoma which would allow eyecare providers to refer their patients more confidently to ophthalmologists.

Most participants recommended that trained eye healthcare practitioners conduct glaucoma screening. They perceived that members of the public have a low level of knowledge about glaucoma, which may lead to an inability to conduct glaucoma screening. Most studies use eye healthcare practitioners for glaucoma screening.[36,37] However, some participants proposed training laypersons to use automated instruments for glaucoma screening. Good agreement was found between laypersons and ophthalmologists when measuring the vertical cup-to-disc ratio with a fundus camera (intraclass correlation coefficient of 0.65).[38] This approach is similar to the World Health Organization's recommendation to use community health workers to address workforce shortages and improve access to care.[39]

There was a mixed view on the role of screeners in glaucoma screening. Ophthalmologists and optometrists largely preferred that either profession could interpret results and make a diagnosis. Burr et al.[16] reported that clinicians preferred ophthalmologists to interpret the results. However, due to a shortage of ophthalmologists in developing countries, it is difficult for them to conduct screening in the community settings. Optometrists may play a crucial role in both screening and result interpretation. A study in Malaysia found a high level of agreement (87%) between optometrists and ophthalmologists in diagnosing eye diseases.[40] Other studies also suggested that other healthcare providers can detect glaucoma if they are appropriately trained.[41,42] Therefore, eye care providers can detect glaucoma with an appropriate training programme.

Many participants in our study suggested the need for clear referral guidelines. In Malaysia, the Clinical Practice Guidelines (CPG) on the Management of Glaucoma were developed by the Ministry of Health Malaysia in 2017 to help eye healthcare practitioners manage glaucoma.[43] The referral criteria are outlined in the CPG,[43] but there is a lack of awareness among private optometrists and ophthalmologists. A workshop should be organised to introduce the CPG to these eye healthcare practitioners. Implementing guidelines has been shown to improve the accuracy of glaucoma referrals.[44] Thus, implementing clear referral criteria may reduce the number of false-positive referrals to the hospital.

Several factors in the Malaysian health system could influence glaucoma screening implementation. The high cost of specialised equipment[45,46] and the training of personnel[45,47] are significant barriers to the effective implementation of glaucoma screening. Furthermore, the high patient load[26] and the risk of false positives resulting from widespread screening[48] could strain resources at government hospitals. Therefore, a national screening strategy must balance resource allocation and workforce capacity to be feasible and sustainable.

This was the first qualitative study conducted in Malaysia to explore the perspectives of eye healthcare professionals

on glaucoma screening components. Most interviews were conducted online due to COVID-19 restrictions. Poor internet connectivity occasionally disrupted the interviews, which may have affected the participants' ability to fully express their opinions. This study also did not consider the perspective of glaucoma patients. Thus, future studies should consider their viewpoints.

CONCLUSION

In conclusion, this study provides a foundation for developing a glaucoma screening model in the Malaysian healthcare setting. These findings will inform policymakers in developing national glaucoma screening guidelines to reduce blindness in Malaysia. Further studies should include the development and validation of training modules for glaucoma screeners.

ACKNOWLEDGEMENT

We thank the Director General of Health Malaysia for permitting us to publish this article.

INSTITUTIONAL REVIEW BOARD (ETHIC COMMITTEE)

Ethical approval was received from the university's Research Ethics Committee (UKM/111/8/JEP-2020-127) and the Ministry of Health Malaysia's Medical Research Ethics Committee (NMRR-20-2418-56993).

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ORIGINAL ARTICLE

Gender Variations in Hypertension Prevalence and Associated Factors in Malaysia: National Health and Morbidity Survey 2019

Abd Hamid HA[a], Ab Majid NL[a], Hasani WSR[b], Mohd Yusoff MF[a]

[a]Center for Non-Communicable Diseases, Institute for Public Health, National Institutes of Health, Ministry of Health, Selangor, Malaysia.
[b]Department of Community Medicine, School of Medical Sciences, Universiti Sains Malaysia

ABSTRACT

INTRODUCTION: Hypertension represents a worldwide public health challenge related to chronic illnesses. This study set out to examine gender-based variations in prevalence and associated factors of hypertension in Malaysia. **MATERIALS AND METHODS:** We conducted a secondary data analysis based on the National Health and Morbidity Survey 2019, which was a nationwide cross-sectional study employing a two-stage stratified random sampling approach. Hypertension was defined as systolic BP≥ 140 or diastolic BP≥ 90 mm Hg, told to have hypertension by medical personal previously. Multiple logistic regression analysis was applied. **RESULTS:** The prevalence of hypertension among adults in Malaysia was 30.0% (95% CI: 28.57, 31.50), men 30.3% (95% CI: 28.2, 32.5), and women 29.7% (95% CI: 28.0, 31.5). For both genders, increasing age, adults with higher BMI, other Bumiputras, unemployed and those with diabetes and high cholesterol had higher odds of hypertension. Among men, alcohol consumption showed higher odds [AOR: 1.31 (95% CI: 1.02, 1.68)], meanwhile, active smokers [AOR: 0.74 (95% CI: 0.64, 0.86)] and married men [AOR: 0.74 (95% CI: 0.57, 0.94)] showed lower odds of hypertension. Among women, Chinese [AOR: 0.62 (95% CI: 0.49, 0.77)], Indian [AOR: 0.65 (95% CI: 0.49, 0.86)], and tertiary education [AOR: 0.49 (95% CI: 0.35, 0.69)] showed lower odds and physically inactive women [AOR: 1.31 (95% CI: 1.1, 1.55)] showed higher odds of hypertension. **CONCLUSION:** Prevalence and the factors associated with hypertension differ between the two genders. Intervention strategies related to hypertension should consider the gender differences particularly among young men and elderly women.

Keywords
Adult, Prevalence, Hypertension, Gender differences, Malaysia

Corresponding Author
Dr Hamizatul Akmal Abd Hamid
Centre of Non-Communicable Disease Research, Institute for Public Health, National Institute of Health, Ministry of Health Malaysia, Selangor, Malaysia.
Email: hamizatul_ah@moh.gov.my

Received: 14th May 2025; Accepted: 19th November 2025

Doi: https://doi.org/10.31436/imjm.v25i02/2784

INTRODUCTION

Globally, hypertension stands as the top preventable risk factor for cardiovascular disease (CVD) and death from all causes. Uncontrolled hypertension contributes to stroke, heart conditions, cognitive impairment, Chronic Kidney Diseases, and renal failure.[1]

Hypertension affected 1.38 billion adults globally in 2010, representing 31.1% of the adult population.[2] It caused around 9.4 million deaths annually and was linked to 10.7 million deaths in 2015. By 2025, the global number of hypertensive individuals is expected to reach 1.56 billion.[3]

In Malaysia, cardiovascular and circulatory diseases were the main contributors to mortality in 2014 (34.8%). For both men (33.9%) and women (36.2%), cardiovascular and circulatory diseases caused the highest number of deaths and contributed to more than a third of deaths.[4] Evidence from previous research indicates that blood pressure differs between genders from early life.[5,6]

Although higher hypertension prevalence is generally tied to increased cardiovascular disease risk, this association shows gender-related differences. Both biological and behavioural factors contribute to gender differences in hypertension. Biologically, sex hormones, chromosomal variations, and other sex-related characteristics provide some protection against hypertension in women. These protective effects become evident during adolescence and continue into adulthood until menopause. Behavioural risks for hypertension include high body mass index (BMI), smoking, and physical inactivity.[7]

The associations of hypertension between men and women in Malaysia are not clear and studies between the two genders are limited. This study seeks to identify gender variations in the prevalence and associated factors of hypertension in the adult population of Malaysia.

MATERIALS AND METHODS

This study utilised data from the National Health and Morbidity Survey (NHMS) in 2019, a nationwide cross-sectional survey that employed two-stage stratified random sampling. The sampling frame was obtained from the Department of Statistics Malaysia, and further methodological details are available in the survey report.[8] Respondents provided written informed consent before being interviewed face-to-face with the aid of a tablet. Questions were adapted from the WHO STEPS questionnaire. All household members aged ≥18 years were examined for blood pressure readings. Three readings of systolic and diastolic pressure taken 15 minutes apart using Omron Digital Automatic Blood Pressure Monitor Model HEM-907, which was already validated and calibrated.[9] Blood pressures and heights and weights of respondents were measured using a standard procedure by trained nurses. Those found to have hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg) were informed of their condition and referred to the nearest health facility or clinic for follow-up and management.

Definitions and Dependent variables

The average of the second and third readings of systolic and diastolic pressure were used to determine the blood pressure level in the study. Respondents were classified as having hypertension if their blood pressure was ≥140 mmHg systolic or ≥90 mmHg diastolic or told to have hypertension by medical personnel previously. Hypertension status was coded as "yes=1" and "no=0".

Independent variables

Independent variables included seven socio-demographic variables and six variables related to lifestyle factors, and other Non-Communicable Diseases (NCDs). Socio-demographic variables respondents included locality, age, ethnicity, marital status, educational level, employment status and household income group. Household income was categorized into B40 (lower income group, median RM 3000), M40 (middle income group, median RM 6,275), and T20 (high-income group, median RM 13,148).[10]

Lifestyle factors comprised of smoking and alcohol drinking status, BMI, and physical activity. For smoking (adapted from the GATS questionnaire) and drinking status (adapted from AUDIT questionnaire), an individual who was currently using any smoked tobacco products and drinking alcohol was considered as "current smoker" and "current drinker". Height was measured using SECA Stadiometer 213 and weight was measured using Tanita Personal Scale HD 319. BMI was calculated by dividing weight (kg) by height in metres squared (m^2) and classified according to WHO standards: <25 kg/m^2 as underweight or normal, 25.0–29.9 kg/m^2 as overweight, and ≥30 kg/m^2 as obese. Physical activity was self-reported using the International Physical Activity Questionnaire (IPAQ) and expressed in metabolic equivalent task minutes per week (MET-minutes/week). Participants were categorised as either "active" or "inactive" based on their activity levels.

A fasting blood glucose ≥7.0 mmol/L or a previous medical diagnosis was used to define diabetes, while high cholesterol was defined as serum total cholesterol ≥6.2 mmol/L or prior diagnosis.[11,12]

Statistical analysis

Data were analysed using IBM SPSS Statistics (Version

25). The complex samples procedure was applied, with analyses conducted at the 95% confidence interval (CI). Weighting was applied to adjust for unequal sampling probabilities, non-response, and post-stratification. This was done to ensure analysis can be estimated for the population in Malaysia. Descriptive statistics was used to summarize characteristics of the study population. Complex sample descriptive analysis and Rao – Scott chi square test was used to estimate the prevalence of hypertension.

The association between hypertension status and various independent variables was examined using univariable and multivariable logistic regression. Given established evidence that blood pressure and hypertension risk differ between men and women due to biological and behavioural factors, sex-stratified logistic regression models were employed to assess whether the associations between sociodemographic, lifestyle, and other NCDs and hypertension varied by sex. This approach ensured that potential gender-specific effects were not obscured in pooled analyses and aligns with recommendations for sex-disaggregated reporting in cardiovascular research. Findings were reported as adjusted odds ratios (AOR) with 95% confidence intervals. The logit model was developed through the Backward Likelihood Ratio (LR) approach. *Confounders were selected based on theoretical considerations, clinical relevance, and evidence from previous studies.* Diagnostic testing to assess the Goodness of Fit was conducted to ensure the fit of a logistic regression model for individual cases or covariates. Potential interactions among predictors were tested to assess their scientific relevance and impact on multicollinearity. The final model incorporated all predictors and interactions that were significantly associated at the $\rho < 0.05$ level.

RESULTS

A total of 10,463 respondents aged ≥18 years were included in the study. The demographic characteristics of the survey respondents are shown in Table I. More than half of the respondents were Malays, urban dwellers, married, currently working/employed and from the lower household income group (B40 or below 40). Nearly half of them had completed secondary education. There was almost equal distribution of respondents between the two genders and age group, with the highest among the age group of ≥60 years. The mean ± SD age for this study was 40.4±16.1 years.

Table I: Sociodemographic characteristics of the respondents

Variables		Frequency (n)	Percentage (%)
Sex	Male	4782	45.7
	Female	5681	54.3
Age group (Years)	18-29	2243	21.4
	30-39	2073	19.8
	40-49	1798	17.2
	50 - 59	1896	18.1
	60 & above	2453	23.4
Locality	Urban	6376	60.9
	Rural	4087	39.1
Ethnicity	Malay	6744	64.5
	Chinese	1326	12.7
	Indian	662	6.3
	Other Bumiputras[a]	1113	10.6
	Others[b]	618	5.9
Marital status	Single	2180	20.8
	Married	7151	68.3
	Widow(er)/Divorcee	1132	10.8
Education level	No formal education	644	6.2
	Primary education	2378	22.8
	Secondary education	4961	47.7
	Tertiary education	2425	23.3
Occupation	Employed	5941	56.8
	Unemployed[c]	4514	43.2
Household Income Group (State-DOSM 2016)	B40	6694	68.2
	M40	2324	23.7
	T20	795	8.1

[a] Other Bumiputras comprising more than 40 indigenous ethnicities that reside in both Peninsular and Borneo, Malaysia
[b] Other ethnicities comprising other Malaysian minorities such as Sikh, Baba, Chitty, Eurasian, and non-citizens
[c] Unemployed includes not working and old age

The overall prevalence of hypertension (Table II) among respondents ≥18 years was 30.0% (95%CI: 28.57, 31.50). It was estimated that nearly 6.4million people in Malaysia had hypertension (data not shown). The prevalence of hypertension among men and women ≥18 years was 30.3% (95% CI: 28.22, 32.50) and 29.7% (95% CI: 27.98, 31.46) respectively. The overall mean for systolic blood pressure (SBP) was 128.01 (95% CI: 127.45, 128.56) mmHg and mean for diastolic blood pressure (DBP) was 78.46 (95% CI: 78.05, 78.87) mmHg. The mean SBP and DBP among men was 129.97 (95% CI: 129.22, 130.71) mmHg and 79.35 (95% CI: 78.82, 79.88) mmHg respectively. Meanwhile the mean SBP and DBP among women was 125.96 (95% CI: 125.20, 126.72) mmHg and 77.54 (95% CI: 77.04, 78.04) mmHg respectively.

Table II: Prevalence of hypertension among adults aged ≥ 18 years by gender in Malaysia

Variables	Male (N= 4,782)	p-value	Female (N= 5,681)	p-value
	% (95% CI)		% (95% CI)	
Overall	30.3 (28.22, 32.50)		29.7 (27.98, 31.46)	
Locality				
Urban	30.3 (27.83, 32.94)	0.987	28.1 (26.11, 30.16)	<0.001[a]
Rural	30.3 (26.87, 33.95)		35.4 (32.28, 38.73)	
Age group (years)				
18-29	11.3 (8.63, 14.74)	<0.001[a]	3.9 (2.78, 5.37)	<0.001[a]
30-39	21.5 (18.02, 25.53)		15.9 (13.34, 18.95)	
40-49	33.8 (29.09, 38.86)		35.1 (31.04, 39.36)	
50-59	49.1 (44.37, 53.79)		52.5 (48, 56.9)	
60 and above	68.6 (64.38, 72.63)		75 (71.9, 77.95)	
Ethnicity				
Malay	31.9 (29.81, 34.04)	<0.001[a]	32.6 (30.59, 34.68)	<0.001[a]
Chinese	30.2 (24.31, 36.88)		25.8 (21.6, 30.6)	
Indian	32.2 (25.25, 40.1)		29.1 (23.65, 35.17)	
Other Bumiputras	40.6 (34.59, 46.8)		34 (28.71, 39.74)	
Others	15 (9.74, 22.36)		15.5 (11.41, 20.68)	
Marital status				
Single	16.8 (13.76, 20.26)	<0.001[a]	8.4 (6.66, 10.45)	<0.001[a]
Married	36.2 (33.56, 38.95)		31.1 (28.99, 33.28)	
Widow(er)/Divorcee	60 (49.06, 69.99)		63.2 (58.28, 67.92)	
Education level				
No formal education	33.4 (23.13, 45.47)	<0.001[a]	58 (49.58, 65.98)	<0.001[a]
Primary education	38.8 (33.37, 44.51)		50.7 (46.42, 55.02)	
Secondary education	29.6 (27.17, 32.16)		29.1 (26.75, 31.52)	
Tertiary education	24.5 (20.62, 28.92)		10.7 (8.86, 12.75)	
Occupation status				
Employed	25.6 (23.45, 27.95)	<0.001[a]	19.1 (17.22, 21.17)	<0.001[a]
Unemployed	48.5 (44.42, 52.69)		38.8 (36.23, 41.43)	
Household income group (State-DOSM 2016)				
B40	30.7 (28.26, 33.16)	0.265	32.2 (29.82, 34.6)	<0.001[a]
M40	26.3 (22.78, 30.16)		22 (19.19, 25.08)	
T20	26.6 (18.09, 37.34)		19.7 (14.59, 26.12)	
BMI				
Normal BMI	21.8 (19.33, 24.54)	<0.001[a]	18.2 (15.99, 20.61)	<0.001[a]
Overweight	37.8 (34.62, 40.99)		35.9 (32.92, 38.93)	
Obesity	45.5 (40.22, 50.8)		44.2 (40.32, 48.1)	
Physical activity				
Active	28.1 (25.68, 30.62)	<0.001[a]	29 (27.04, 30.94)	0.172
Inactive	38.1 (33.79, 42.54)		31.6 (28.28, 35.07)	
Current smokers				
Non-Smokers	33.9 (30.95, 37)	<0.001[a]	29.8 (28.11, 31.59)	0.225
Current Smokers	25.6 (22.79, 28.57)		20.4 (10.02, 37.01)	
Current drinker				
Past/Non drinker	30 (28.03, 32.07)	0.618	30.5 (28.76, 32.36)	<0.001[a]
Current drinker	31.8 (25.16, 39.35)		17.3 (12.95, 22.65)	
Diabetes				
Normal	24.5 (22.39, 26.69)	<0.001[a]	22.5 (20.91, 24.19)	<0.001[a]
Diabetes	56.6 (51.64, 61.35)		61.5 (57.87, 65.09)	
Cholesterol				
Normal	20.8 (18.62, 23.22)	<0.001[a]	17.5 (15.72, 19.49)	<0.001[a]
Raised Cholesterol	50.5 (46.99, 53.95)		44.9 (41.94, 47.84)	

[a] Significant at $\alpha = 0.05$

For both genders, the prevalence of hypertension was highest among the age group ≥60 years, widower/ divorcee, lower educational group, unemployed, B40 group, Other Bumiputras, physically inactive, non-smokers and among alcoholic drinkers.

The prevalence of hypertension increased with age and BMI. Hypertension prevalence was higher among men compared to women in the 18-29 age group. However, starting at the age of ≥40 years, women had higher prevalence than men. For both genders, the population with underlying diabetes and hypercholesterolaemia had more than two times higher prevalence compared to those without comorbidities when other factors were not considered. Single men had higher prevalence compared to single women. Meanwhile, women in higher educational group, particularly women with tertiary education showed lower prevalence of hypertension.

The multivariate analyses (Table III) demonstrated that age, BMI, other Bumiputras, unemployed, current drinker, having diabetes and hypercholesterolemia had higher odds of hypertension among men. Married men and current smokers showed lower odds of hypertension. Among women, age, BMI, other Bumiputras, unemployed, physically inactive, having diabetes and hypercholesterolemia had higher odds of hypertension. Chinese and Indian women, and women with tertiary educational group had lower odds of hypertension.

In both genders, age had the highest odds of hypertension and it increased significantly with age. The highest odds were seen among the women aged ≥60 years with AOR 33.15 (95% CI: 22.35, 49.17) (ρ<0.001) compared to those aged 18-29 years. Comparing to individuals aged 18-29 years, at the age of 40 years and above, the women has about two times higher odds of hypertension compared to the males in the same age group. Similarly, the odds of having hypertension increased with increasing BMI. The odds among the overweight and obese women increased proportionately. Meanwhile, the odds to have hypertension among obese men increased nearly two times compared to overweight men.

DISCUSSION

Although high blood pressure is the leading risk factor for death globally, it is also one of the most modifiable across the life course.[13] From this study, it can be stipulated that three in ten of the Malaysian population had hypertension and the overall prevalence was similar with Indonesia (33.4%)[14] and India (30.7%)[15], but higher than Laos (20.0%)[16] and Iran (17.3%)[17]. Hypertension prevalence in this study between men and women were

Table III: Factors associated with hypertension among adults aged ≥ 18 years in Malaysia

Variables		Male				Female			
		Crude OR (95%CI)	p-value	Adjusted OR (95%CI)	p-value	Crude OR (95% CI)	p-value	Adjusted OR (95%CI)	p-value
Locality	Urban	1		1		1		1	
	Rural	1.18(1.04,1.33)	0.008*	0.99(0.84,1.15)	0.858	1.41(1.27,1.57)	<0.001*	0.97(0.83,1.14)	0.737
Age group (years)	18-29	1		1		1		1	
	30-39	2.14(1.69,2.72)	<0.001*	2.07(1.55,2.78)	<0.001*	3.59(2.64,4.88)	<0.001*	3.06(2.13,4.39)	<0.001*
	40-49	4.14(3.27,5.24)	<0.001*	4.03(2.95,5.5)	<0.001*	10.63(7.94,14.22)	<0.001*	7.37(5.13,10.58)	<0.001*
	50-59	8.11(6.46,10.19)	<0.001*	6.88(5.02,9.43)	<0.001*	24.17(18.1,32.27)	<0.001*	13.35(9.24,19.29)	<0.001*
	60 and above	16.65(13.31,20.83)	<0.001*	14.6(10.48,20.33)	<0.001*	61.18(45.73,81.84)	<0.001*	33.15(22.35,49.17)	<0.001*
Ethnicity	Malay	1		1		1		1	
	Chinese	1.34(1.13,1.6)	0.001*	0.93(0.74,1.18)	0.570	0.84(0.71,0.99)	0.041*	0.62(0.49,0.77)	<0.001*
	Indian	1.13(0.89,1.44)	0.319	0.91(0.67,1.24)	0.551	0.92(0.74,1.15)	0.455	0.65(0.49,0.86)	0.003*
	Other Bumiputras	1.27(1.05,1.54)	0.014*	1.58(1.23,2.04)	<0.001*	1.02(0.86,1.21)	0.834	1.45(1.15,1.83)	0.002*
	Others	0.43(0.33,0.57)	<0.001*	0.93(0.67,1.29)	0.648	0.56(0.43,0.73)	<0.001*	0.97(0.7,1.35)	0.868
Marital status	Single	1		1		1		1	
	Married	3.35(2.86,3.93)	<0.001*	0.74(0.57,0.94)	0.015*	4.78(3.89,5.87)	<0.001*	0.9(0.67,1.2)	0.474
	Widow(er)/ Divorcee	7.03(5.11,9.67)	<0.001*	1.15(0.76,1.75)	0.510	16.33(12.86,20.73)	<0.001*	1.23(0.88,1.73)	0.221
Education level	No formal education	1		1	0.827	1		1	
	Primary education	1.14(0.82,1.56)	0.436	1.09(0.71,1.67)	0.709	0.71(0.57,0.89)	0.003*	0.83(0.63,1.11)	0.211
	Secondary education	0.55(0.41,0.75)	<0.001*	1.03(0.67,1.58)	0.893	0.26(0.21,0.33)	<0.001*	0.77(0.58,1.03)	0.081*
	Tertiary education	0.44(0.32,0.61)	<0.001*	0.96(0.61,1.53)	0.880	0.09(0.07,0.12)	<0.001*	0.49(0.35,0.69)	<0.001*
Occupation status	Employed	1		1		1		1	
	Unemployed	2.81(2.46,3.21)	<0.001*	1.37(1.12,1.67)	0.002*	2.98(2.66,3.34)	<0.001*	1.28(1.09,1.5)	0.002*
Household income group (State- DOSM 2016)	B40	1		1	0.275	1		1	0.990
	M40	0.75(0.65,0.86)	<0.001*	0.89(0.75,1.07)	0.208	0.65(0.56,0.75)	<0.001*	0.99(0.82,1.19)	0.888
	T20	0.77(0.62,0.96)	0.019*	0.85(0.65,1.1)	0.218	0.56(0.45,0.71)	<0.001*	0.99(0.73,1.34)	0.952
BMI	Normal BMI	1		1		1		1	
	Overweight	1.82(1.59,2.08)	<0.001*	1.77(1.51,2.09)	<0.001*	2.27(1.98,2.59)	<0.001*	2.23(1.87,2.65)	<0.001*
	Obesity	2.38(2.01,2.82)	<0.001*	3.09(2.51,3.8)	<0.001*	3.03(2.63,3.49)	<0.001*	3.55(2.94,4.27)	<0.001*
Physical activity	Active							1	
	Inactive	1.52(1.33,1.75)	<0.001*	1.15(0.97,1.37)	0.113	1.23(1.09,1.39)	0.001*	1.31(1.1,1.55)	0.002*
Current smokers	Non-smokers	1		1		1		1	
	Current smokers	0.57(0.51,0.65)	<0.001*	0.74(0.64,0.86)	<0.001*	0.47(0.25,0.88)	0.019*	0.57(0.26,1.24)	0.156
Current drinker	Past/Non drinker	1		1		1		1	
	Current drinker	1.02(0.85,1.22)	0.839	1.31(1.02,1.68)	0.035*	0.53(0.39,0.72)	<0.001*	0.98(0.65,1.48)	0.930
Diabetes	Normal	1		1		1		1	
	Diabetes	3.71(3.23,4.25)	<0.001*	1.78(1.5,2.1)	<0.001*	5.06(4.45,5.76)	<0.001*	2.18(1.85,2.56)	<0.001*
Cholesterol	Normal	1		1		1		1	
	Raised Cholesterol	3.37(2.98,3.81)	<0.001*	2.03(1.75,2.36)	<0.001*	3.85(3.43,4.32)	<0.001*	1.71(1.47,1.99)	<0.001*

Backward likelihood ratio multiple logistic regression was applied. Multicollinearity and interactions were checked and not found. For men: Hosmer–Lemeshow test ϱ=0.681. Classification table (overall correctly classified percentage =75.0%) and ROC curve =81.0%) were accepted to check model fitness. For women: Hosmer–Lemeshow test ϱ=0.348. classification table (overall correctly classified percentage =77.7%) and ROC curve =85.8%) were accepted to check model fitness.
*p <0.05

equivalent. Higher prevalence was seen in men compared to women in India (men 34.2%, women 23.7%) and Iran (men 18.9%, women 15.5%) but vice versa in Indonesia (men 31.0%, women 35.4%) and Laos (18.5% among men, 21.1% among women).

The overall prevalence of hypertension in Malaysia among ≥30 years was 40.3%, higher than Korea[18] with men 34.6% and women 30.8%. Our study also showed that men have significantly higher mean SBP and DBP than women. It was similar to many studies which showed higher mean among men compared to women[15-19] and the risk of cardiovascular disease was 1.1-fold higher in women than in men for each 10mmHg increase in SBP.[20]

Age is an established independent risk factor for hypertension.[21] Our study showed high association between increasing age and hypertension. Aging reduces the elasticity of blood vessels causing arterial stiffness leading to an increase in blood pressure. It was reported in many previous studies.[22,23,24] Our study found that men had higher prevalence and odds of hypertension than women at age ≤40 years, particularly in those aged 18-29. From age 40, women showed higher prevalence and odds than men. This pattern reflects the protective role of oestrogen in women before menopause, delaying the onset of hypertension.[3,25]

Our study found that Malaysian women developed hypertension at an earlier age compared to findings from Korea, India, and the United States of America [18,26], where hypertension in women typically became more common than in men only around the age of 60. This

suggests that women in Malaysia experience a steeper rise in blood pressure starting as early as their 30s and continuing across their lifespan compared to men.[27] One study attributed this pattern to vascular resistance, linked to the balance between vasodilating and vasoconstricting adrenergic receptor tone; present in men throughout life, absent in young women, but emerging in women after menopause.[28]

Physical inactivity and overweight or obesity, both modifiable factors, are strongly linked to hypertension.[21,29] The risk of hypertension is about five times greater in obese individuals compared to those with a normal weight.[30] In our study, overweight or obese women had slightly higher odds of developing hypertension than men. Higher BMI is commonly associated with metabolic and endocrine disturbances. It is linked to greater fat mass, increased salt retention, and insulin resistance, all of which contribute to elevated blood pressure.[3,22] Sympathetic activation is also considered a key mechanism in raising blood pressure, particularly given its role in obesity and weight-related blood pressure differences between men and women.[31]

Hypertension affects differently between ethnic groups. Compared to the Malays, Other Bumiputras had higher odds of hypertension for both men and women, meanwhile the Chinese and Indian women had lower odds of hypertension. Previous studies have reported the possibility of different factors influencing the blood pressure regulations on ethnicities such as genetics and environmental factors including diets and food intake.[32,33,34] Racial differences related to hypertension between the two genders should be explored further in future studies. However, our findings were similar to a study in Singapore which showed that differences among ethnicities was partly attributed to the variability in sociodemographic characteristics of each ethnic group.[35] This finding is contrary to a study among the elderly in Malaysia which found no relation between ethnicity and hypertension.[36]

Socio economic status (SES) includes income, education level, employment type, and measures of poverty and wealth. The relationship between SES and hypertension has been inconsistent in the literature, with some studies showing higher hypertension rates in wealthier groups, while others report greater prevalence among the poor.[29] In our study, unemployment among both genders showed higher odds for hypertension, and women with tertiary education showed lower odds of getting hypertension. Research in France and Korea[18] showed that women with the highest levels of education had a lower likelihood of hypertension compared to those with the lowest levels. The studies also noted that inequalities related to education, income, and deprivation were greater in women than in men.[37] Women with low SES, especially in education, lead to the development of hypertension and were related with lower awareness, less access and contact to healthcare services and having a higher number of risk factors such as stress, poor dietary habits, poor working conditions and psychosocial exposure, less social support and health beneficial effects.[38,39,14]

An association between marital status and hypertension was also observed, with our study showing that married men had lower odds of hypertension. Single individuals may experience greater stress and lower levels of social support, while marriage could provide stability and reduce stress exposure. This supports our finding that marriage may protect men against hypertension, possibly as unmarried individuals tend to eat out more frequently and have less control over their diet.[22] Findings from Nepal showed that ever married had higher odds of hypertension for both genders.[40] Meanwhile, study in Ghana showed contrary findings with married or cohabiting women had higher odds for hypertension.[41] The study suggested that demands and stress in the marriage were the cause for hypertension among married/cohabiting women.

Evidence has indicated that cigarette smoking and drinking alcohol increases the risk of hypertension. In this study, smoking and drinking were associated with hypertension only for men. The apparent protective association for current smokers is more difficult to interpret since it contradicts extensive evidence of

smoking as a vascular stressor. One recent investigation in Saudi Arabia reported a paradoxical 22% lower risk of uncontrolled hypertension among current smokers compared to non-smokers. However, the authors cautioned that residual confounding or reverse causation may explain this counterintuitive result.[42] Another Korean epidemiological study observed an inverse relationship between current smoking and measured blood pressure after adjusting for obesity, suggesting that smokers' typically lower BMI might partly mediate the association.[43] Still, longitudinal evidence argues against a truly protective role: a Japanese cohort found that persistent smoking was associated with increased risk of incident hypertension over time (adjusted HR ~1.34), while smoking cessation attenuated this risk.[44] Thus, the cross-sectional "protective" finding in our sample is more plausibly explained by selection biases, for example, those who develop hypertension after quitting smoking, survivor bias, or underdiagnosis among long-term smokers, rather than a real protective effect.

Unlike smoking, alcohol drinking among men showed higher odds for hypertension. And it is consistent with other studies which associate current alcoholic drinking habit with hypertension.[45,46,47] Earlier studies in Malaysia found that men had a higher prevalence and greater odds of current alcohol consumption compared to women.[48,49] Infrequent or moderate alcohol intake was linked to lower systolic and diastolic blood pressure, whereas frequent consumption was associated with higher levels of both.[13] Alcohol may raise blood pressure through various mechanisms, including direct effects on the heart and vascular smooth muscle, and by stimulating the sympathetic nervous system or the renin-angiotensin-aldosterone system.

Diabetes and hyperlipidaemia are the most common comorbidities seen in individuals with hypertension. Coronary heart disease (CHD), diabetes, and arteriosclerosis become significant risks in hypertensive patients over the age of 40.[50] The presence of multiple comorbidities increases the likelihood of end-organ damage, contributing to greater morbidity and mortality. The strong link between diabetes and hypertension is believed to stem from underlying obesity, insulin resistance, and/or hyperinsulinaemia. These comorbidities appear to affect both genders similarly.

Strengths and Limitations

This study has both strengths and limitations. Its cross-sectional design limits the ability to infer causal relationships between the associated factors and hypertension. The temporal direction of associations, particularly for lifestyle-related variables such as smoking, alcohol consumption, and physical activity, cannot be determined. For example, individuals with hypertension may have modified their behaviours following diagnosis, which could lead to reverse causation. Longitudinal or prospective studies are therefore needed to establish temporality and better understand how lifestyle changes influence hypertension risk over time. Nonetheless, it is a large, population-based study that used the standard, pretested STEPS questionnaire, widely applied in other large-scale surveys, enabling comparison with similar studies.

In addition, we did not collect data on some important factors linked to hypertension, such as family history and salt intake. The absence of these data may have limited our ability to fully capture relevant risk factors. Hypertension was defined based on blood pressure measurements taken in the field rather than in a clinical setting. However, all measurements were conducted by trained nurses to maintain accuracy during data collection.

CONCLUSION

This study identified distinct gender-specific factors associated with hypertension among Malaysian adults. For both men and women, increasing age, higher BMI, being from other Bumiputra ethnicity, unemployment, and the presence of diabetes or hypercholesterolemia were associated with elevated odds of hypertension. Among women, Chinese and Indian ethnicity, as well as tertiary education, were associated with lower odds, while physical inactivity increased the odds of hypertension. Among men, current alcohol consumption was associated

with higher odds of hypertension, whereas being a current smoker or married was associated with lower odds. Although our findings suggest lower odds of hypertension among married men and current smokers, these associations should be interpreted with caution. The protective effect of marriage may be mediated by psychosocial support and healthier behaviours, whereas the inverse association with smoking likely reflects bias or confounding rather than a true physiological benefit. Longitudinal studies or causal inference methods are needed to clarify these complex relationships. The findings of this study highlight gaps in the determinants of hypertension between genders, largely influenced by biological, genetic, and environmental factors. The results underscore the need for sex-specific approaches to hypertension screening and management, particularly targeting young men and middle-aged women. Public health initiatives should address behavioural risk factors predominant among men while strengthening education, screening, and access to care for women, especially around the menopausal transition. Integrating gender considerations into prevention frameworks and clinical guidelines can promote health equity and enhance the effectiveness of hypertension and cardiovascular disease prevention efforts. Further research should examine gender-related mechanisms and guide the development of evidence-based, sex-sensitive blood pressure management strategies.

FUNDING

The research grant was funded by the Ministry of Health Malaysia.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

ACKNOWLEDGEMENT

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

INSTITUTSIONAL REVIEW BOARD (ETHIC COMMITTEE)

The Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia (NMRR-18-3085-44207) approved the study. Access to the NHMS 2019 dataset was granted by the Director General of Health Malaysia, and all data were anonymised prior to analysis.

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ORIGINAL ARTICLE

Judicial Medicine: How the Ivermectin Ruling Redefined Doctors' Responsibilities in Drug Governance

Muuti, M[a], Zainal Abidin, H[b], Razali HYH[a]

[a]Faculty of Medicine, University Teknologi MARA, Sungai Buloh Campus, Selangor.
[b]Faculty of Medicine and Health Sciences, Universiti Sains Islam Malaysia (USIM), Negeri Sembilan, Malaysia

ABSTRACT

INTRODUCTION: Ivermectin, a tropical medicine recognised with the 2015 Nobel Prize, is safe at approved doses but in Malaysia remains registered solely for veterinary use under the Poisons Act, raising complex legal and regulatory issues when dispensed to humans. This paper critically analyses the Federal Court decision in Dr Vijaendreh a/l Subramaniam, situating it within Malaysia's drug dispensing framework and assessing implications for medication safety and patient protection. **MATERIALS & METHODS:** Using a doctrinal legal research approach, statutory interpretation and case law analysis were applied to the Poisons Act, Sale of Drugs Act, Control of Drugs and Cosmetics Regulations, and appellate decisions, highlighting tensions between medical practice and pharmaceutical governance. **RESULTS:** The Federal Court affirmed that section 19 of the Poisons Act grants registered doctors' statutory authority to dispense Group B poisons, including ivermectin, regardless of whether products are registered for human or veterinary use, and that this right cannot be curtailed by subsidiary legislation under the Sale of Drugs Act. The Poisons Act was deemed a complete code for practitioners, while the Sale of Drugs Act governs commercial trade. This interpretation exposes regulatory gaps: the Poisons List lacks human–veterinary distinction, NPRA's product control may be undermined, and safeguards remain reactive, leaving no proactive mechanism to prevent unsafe prescribing. **CONCLUSION:** Legislative reform is urgently needed to distinguish human and veterinary medicines, ensuring safe prescribing, protecting patients, and modernising Malaysia's regulatory framework for public trust.

Keywords
Ivermectin, Drug Control, Pharmaceutical Policy, Legal Case, Poisons

Corresponding Author
Dr Hazdalila Yais Haji Razali,
Department of Medical Ethics & Law,
Faculty of Medicine, Universiti Teknologi MARA (UiTM), Selangor, Malaysia.
Email: hazdalila@uitm.edu.my

Received: 21st November 2025; Accepted: 30th January 2026

Doi: https://doi.org/10.31436/imjm.v25i02/3122

INTRODUCTION

Ivermectin, a macrocyclic lactone derived from *Streptomyces avermitilis*, was first discovered in Japan in the late 1970s[1] and later commercialised by Merck & Co.[2] as a broad-spectrum antiparasitic drug. It revolutionised the treatment of parasitic diseases such as onchocerciasis, strongyloidiasis, and scabies, earning its discoverers the 2015 Nobel Prize in Physiology or Medicine. Pharmacologically, Ivermectin acts on glutamate-gated chloride channels in invertebrate nerve and muscle cells, leading to paralysis and death of the parasite while maintaining a wide safety margin in humans at approved doses. Adverse effects are usually mild, though misuse or overdose may cause hypotension, neurotoxicity, or hepatotoxicity.[3] In Malaysia, Ivermectin is registered solely for veterinary use under the Poisons Act 1952 and has never been authorised for human consumption.[4]

The COVID-19 pandemic brought Ivermectin into controversy. An early in vitro study suggested inhibition of SARS-CoV-2 replication within 48 hours,[5] generating significant public and professional interest. However, subsequent pharmacokinetic data showed that effective antiviral concentrations in humans would require toxic dosing,[6] yet global misinformation and advocacy groups

promoted ivermectin as a "miracle cure".[7] During Malaysia's 2021 Delta wave, public pressure led the Ministry of Health to convene the Drug Expert Task Force for Ivermectin (DETF-Ivermectin)[8] and to initiate the I-TECH randomised clinical trial,[9] which found no significant benefit in preventing COVID-19 progression or death. By 2022, the Ministry reaffirmed that ivermectin should not be used for COVID-19 treatment outside clinical trials,[10] but unregulated sales and off-label prescribing persisted, prompting enforcement under the Poisons Act 1952 (Act 366) and Sale of Drugs Act 1952 (Act 368).

These tensions culminated in *Kerajaan Malaysia & Anor v Dr Vijaendreh a/l Subramaniam & Anor* [2025] 2 MLJ 209. Following the seizure of ivermectin from the second appellant's clinic in June 2021, the appellants sought judicial declarations on whether registered medical practitioners were legally entitled to dispense ivermectin under the Poisons Act and its regulations. The High Court dismissed the application, but the Court of Appeal (2024) allowed the appeal, holding that both appellants had a statutory right to supply Group B poisons, including Ivermectin, in accordance with section 19 of Act 366. Crucially, the Court held that this right could not be curtailed by subsidiary legislation such as the Control of Drugs and Cosmetics Regulations 1984. The Federal Court upheld this reasoning in 2025, affirming that declaratory relief was appropriate and that Act 366 constitutes a complete code governing the handling, sale, and dispensation of poisons by medical practitioners. Because Ivermectin is listed as a Group B poison, section 19(1)(a) expressly authorises registered medical practitioners to dispense it for treatment. The Court further clarified that Act 368 governs the commercial trade of drugs and does not override the clinical dispensing rights conferred by Act 366.

Malaysia's regulation of the manufacture, sale, distribution, and use of medicines are grounded in four principal statutes: the Poisons Act 1952 (Act 366), the Sale of Drugs Act 1952 (Act 368), the Dangerous Drugs Act 1952 (Act 234), and the Medicine (Advertisement and Sale) Act 1956 (Act 290). Together, they form an interdependent regulation that is central in controlling hazardous substances. Under First Schedule of the Poison Act, the Poisons List, classifies substances into Groups A to F based on their level of restriction. Group A poisons, often highly toxic or narcotic, may only be supplied by licensed wholesalers to pharmacists or authorised dealers. Group B poisons, which include most therapeutic agents such as antibiotics and Ivermectin, may be dispensed by registered medical practitioners, dentists, veterinary officers, or licensed pharmacists under sections 19 and 21. Groups C to F encompass substances with progressively fewer controls. Section 6 empowers the Minister of Health to amend the Poisons List via Gazette order, ensuring regulatory adaptability. Importantly, the Act does not distinguish between human and veterinary formulations of the same active ingredient. The Sale of Drugs Act 1952 (Act 368) regulates the commercial sale of pharmaceutical products and forms the basis of the Control of Drugs and Cosmetics Regulations 1984, under which the Drug Control Authority (DCA) and National Pharmaceutical Regulation Authority (NPRA) require all human medicines to be registered for safety, efficacy, and quality. The Dangerous Drugs Act 1952 (Act 234) criminalises the manufacture, possession, and trafficking of narcotics and psychotropic substances, while still permitting limited medical use under strict controls. The Medicine (Advertisement and Sale) Act 1956 (Act 290) governs public advertising of medicines, prohibiting misleading claims and requiring Ministry of Health approval for treatment claims involving serious diseases.

MATERIALS & METHODS

This article adopts a doctrinal legal research methodology, supported by socio-legal and regulatory analysis, to examine the implications of the ivermectin litigation for Malaysia's drug control framework. No empirical data were collected; instead, the study relied on systematic examination of legislation, case law, regulatory instruments, and policy documents. Primary statutes, including the Poisons Act 1952, Sale of Drugs Act 1952, Dangerous Drugs Act 1952, and Medicine (Advertisement and Sale) Act 1956, were analysed alongside the Control of Drugs and Cosmetics Regulations 1984, with attention to statutory definitions,

ministerial powers, classification mechanisms such as the Poisons List, and enforcement provisions. The Federal Court decision in *Kerajaan Malaysia & Anor v Dr Vijaendreh a/l Subramaniam & Anor* [2025] 2 MLJ 209 was examined through close reading of the judgment particularly on the Court's reasoning on statutory interpretation and the relationship between primary and subsidiary legislation. Professional regulatory sources, including the Medical Act 1971 and the Malaysian Medical Council Code of Professional Conduct (2019), were reviewed to situate the ruling within the broader framework of medical accountability. Policy documents, such as Ministry of Health advisories, the DETF-Ivermectin report, and the I-TECH trial findings, were consulted to contextualise regulatory intent. The analysis adopts a purposive, harmonising approach to assess the implications for regulatory oversight, practitioner autonomy, and patient safety.

RESULTS

When the Federal Court affirmed that registered medical practitioners possess a statutory right under section 19 of the Poisons Act to dispense Group B poisons, including Ivermectin, the decision was widely perceived as a significant challenge on the Ministry of Health's regulatory authority in matters of public health. Despite the findings of the Drug Expert Task Force for Ivermectin (DETF-Ivermectin) advising against its use for COVID-19, Chief Justice Tengku Maimun Tuan Mat clarified that the Court's focus was not on Ivermectin's clinical efficacy, but solely on the substantive right of medical practitioners to dispense Group B poisons for patient treatment in compliance with the Act. The judgment also effectively invalidated the reliance on Regulations 7 and 15 of the Control of Drugs and Cosmetics Regulations 1984, which stipulate that no person shall manufacture, sell, supply, import, possess, or administer any product unless it is a registered product and the person holds the appropriate licence issued under the Regulations. The court held that interpreting these provisions as a regulatory prohibition on the use of ivermectin was misconceived, since the subsidiary legislation could not override or remove a vested statutory right expressly granted under the Poisons Act 1952. In simple terms, the ruling means that once a drug is classified as a Group B poison, any registered doctor is legally entitled to prescribe or dispense it, even if the product was originally approved for veterinary rather than human use and did not go through the safety monitoring by NPRA.

DISCUSSION

This legal development raises important regulatory questions, particularly whether a medical doctor may lawfully prescribe or dispense a drug approved only for veterinary use. Medicines for human use in Malaysia fall under the Sale of Drugs Act 1952 (Act 368) and the Control of Drugs and Cosmetics Regulations (CDCR) 1984, which establish the Drug Control Authority (DCA) and its operational arm, the National Pharmaceutical Regulatory Agency (NPRA). Regulation 7(1) of the CDCR 1984 prohibits the manufacture, sale, supply, import, possession, or administration of any product unless it is registered with the DCA and the person holds the appropriate licence. This ensures that only authorised, quality-assured medicines reach human patients. However, both human- and veterinary-approved substances appear collectively in the Poisons List under the Poisons Act 1952 (Act 366), which classifies active ingredients into Groups A–F without distinguishing between human, dental, or veterinary applications. Traditionally, Regulation 7 would prevent doctors from dispensing unregistered products. However, the court in the case of *Dr Vijaendreh a/l Subramaniam* held that Act 368 governs commercial trade, not clinical dispensation by registered medical practitioners. The Court affirmed that section 19 of Act 366 grants doctors a statutory right to dispense Group B poisons, regardless of whether the formulation is registered for human or veterinary use, and that subsidiary legislation cannot override this primary statutory right. Thus, a medical practitioner may lawfully dispense a veterinary-approved substance classified as a Group B poison regardless of its registration. However, this legal entitlement sits within a narrow statutory framework and does not shield practitioners from civil or professional liability should harm occur.

A doctor who prescribes a substance irresponsibly or

outside accepted medical standards remains answerable under tort law and professional ethics. In civil jurisprudence, liability would still arise through the doctrine of medical negligence, guided by the Bolam principle (*Bolam v Friern Hospital Management Committee*, 1957) and refined by the Bolitho test (*Bolitho v City and Hackney Health Authority*, 1998). These principles hold that a practitioner is not negligent if the treatment adopted is supported by a responsible body of medical opinion, provided that such opinion is logically defensible and scientifically sound. Thus, if the prevailing consensus among competent Malaysian or international experts maintains that ivermectin lacks proven efficacy against COVID-19, a doctor prescribing it could be found negligent. Conversely, if a substantial body of qualified professionals reasonably supports its use based on credible scientific evidence, the doctor may rely on Bolam protection. Yet, under Bolitho, courts retain the discretion to reject any medical opinion that is illogical, outdated, or contrary to established science. Applied to Ivermectin, judicial scrutiny would likely assess whether medical advocacy for its use during the pandemic was grounded in rigorous empirical evidence rather than conjecture or anecdote. In Malaysia, professional opinion on ivermectin remains divided, some clinicians endorse its use while others firmly reject it.

This divergence presents a judicial challenge in determining what constitutes an *accepted standard of care.* In such cases, courts may refer to authoritative sources, such as the Drug Expert Task Force for Ivermectin (DETF-Ivermectin) technical report, as persuasive (though not binding) guidance on medical consensus. Ultimately, the court must exercise judicial realism by evaluating not only the law in theory but also the realities of medical practice, social context, and evolving scientific understanding. From a sociological jurisprudence perspective, such adjudication reflects the law's adaptive function, balancing the professional autonomy of physicians with the broader societal duty to protect patients from harm. Hence, a doctor's liability depends not merely on peer agreement but on whether that consensus is rational, evidence-based, and aligned with the community's legitimate expectation of safe and ethical medical practice.

Outside the courtroom, the conduct of medical practitioners continues to fall under the regulatory supervision of the Malaysian Medical Council (MMC) and related statutory bodies. The Medical Act 1971 and the Malaysian Medical Council (MMC) Code of Professional Conduct (2019) empower the Council to initiate action against any practitioner who prescribes unregistered, unsafe, or veterinary-only products to human patients. Under Section 1.1 of the Code, it constitutes professional misconduct when a practitioner "endangers the welfare of a patient by persisting in independent practice of a branch of medicine in which he does not have the appropriate knowledge and skill and has not acquired the experience which is necessary." In this context, prescribing veterinary formulations or unapproved medicines for human use could be construed as practising beyond one's competence and, consequently, a breach of professional standards. Disciplinary sanctions under the Medical Act 1971 may include formal censure, suspension, or removal from the medical register, even in the absence of a civil negligence claim. However, as the MMC functions on a complaint-driven process, an inquiry can only be initiated once a formal complaint has been lodged. Although the complainant need not be limited to the patient concerned, any individual, including a colleague, member of the public, or regulatory authority, who becomes aware of such professional misconduct may file a report with the MMC to trigger an investigation, the complaint can only arise after harm or damage has already occurred.

Second, if a drug approved for animals falls within Group B poisons, must it still undergo human clinical trials before being used in patients? In current practice, any attempt to repurpose a veterinary drug for human treatment must involve toxicological studies, Phase I–III clinical trials, and registration with the NPRA. These steps ensure compliance with international standards of Good Clinical Practice (GCP) and pharmacovigilance, protecting patients from untested or unsafe therapies. However, following this case, pharmaceutical companies may exploit this ambiguity, seeking approval solely for animal use while allowing practitioners to rely on section 19 of the Poisons Act to administer the drug to humans.

Although the Federal Court clarified that Act 368 governs commercial sale rather than clinical dispensation, and that subsidiary legislation cannot override rights conferred under the Poisons Act, this interpretation should not negate the need for scientific validation when a substance transitions from animal to human use.

Third, while the NPRA still retains its regulatory role, the problem stems from a structural conflict in the law. Ivermectin is *not approved by the NPRA for human use*, yet it appears in the Poisons List under the Poisons Act 1952, a principal Act. Since the NPRA's authority comes from subsidiary legislation, it cannot override what is permitted under the principal Act. As a result, doctors may rely on the Poisons List to justify dispensing a substance that the NPRA has not authorised for human consumption. By reinforcing broad dispensing rights, the court's interpretation of section 19 further exposes this gap and weakens the practical effectiveness of NPRA oversight. Hence, while the Federal Court affirmed the legal rights of medical practitioners, the decision also exposes significant regulatory gaps that require urgent legislative clarification. The Poisons Act 1952 should be improvised to include distinct, clearly defined schedules that differentiate medicines authorised for human use from those approved for veterinary purposes. Such differentiation is crucial not only to guide prescribers but also to support enforcement authorities in monitoring and controlling the circulation of regulated substances.

In addition, amendments should aim to harmonise professional prescribing rights with robust regulatory safeguards, ensuring that statutory protection for doctors does not inadvertently create loopholes that undermine patient safety. This includes establishing clearer prescribing boundaries, defining cross-species prescribing exceptions, and ensuring that any expanded clinical discretion is matched by appropriate accountability measures. Strengthening the Poisons Act in this manner would help maintain the integrity of Malaysia's drug control system, prevent misuse or inappropriate access to veterinary medications, and reinforce public trust in clinical and regulatory institutions. Ultimately, a balanced and updated legislative framework is essential to safeguard both the professional autonomy of medical practitioners and the safety and wellbeing of the patients they serve. Because the Poisons List determines which substances are controlled and who may handle them, regular regulatory oversight is essential to keep the list scientifically current and aligned with therapeutic practice. Section 6 of the Act empowers the Minister of Health, after consultation with the Poisons Board, to amend the list dynamically in response to new pharmaceutical developments, emerging safety data, or public-health threats. Yet, in practice, updates have lagged behind rapid advances in pharmacology, leaving outdated classifications and gaps that create uncertainty for enforcement officers and healthcare practitioners alike.

Alternatively, the Ministry of Health could restrict the use of ivermectin in private healthcare settings by issuing a directive or guideline under section 76 of the Private Healthcare Facilities and Services Act 1998 (Act 586), which empowers the Director General to prescribe any quality or standards requirements for private healthcare facilities as he considers necessary. Such a guideline would automatically bind all private facilities, and non-compliance may trigger enforcement action. Under section 43, read together with section 44(d) of Act 586, the Director General may issue a show-cause notice with the intention to suspend, cancel, or refuse renewal of a facility's licence where any directive, order, or guideline issued by the Minister or Director General is not complied with. Yet, this mechanism may still create uncertainty, as ivermectin remains listed under the Poisons List, which could further obscure its lawful use. This reflects a deeper structural gap in Malaysia's regulatory ecosystem: a haphazard mosaic of overlapping laws and authorities.

CONCLUSION

The ivermectin litigation culminating in the Federal Court's 2025 decision revealed a critical tension in Malaysia's regulatory framework: broad statutory dispensing rights under the Poisons Act 1952 coexist uneasily with product-based controls under the Sale of Drugs Act 1952 and the Control of Drugs and Cosmetics Regulations 1984. While the Court clarified that

registered medical practitioners may dispense any Group B poison, including ivermectin, this interpretation exposed structural gaps in a system designed for a different era. Outdated statutory language, the absence of human–veterinary differentiation in the Poisons List, and limitations of subsidiary legislation have created ambiguity over safe and defensible prescribing.

The ruling should not diminish the need for rigorous scientific evaluation, NPRA registration, or adherence to Good Clinical Practice when medicines transition from animal to human use. Nor does it shield practitioners from civil liability or disciplinary scrutiny. Instead, it highlights the haphazard mosaic of Malaysia's healthcare regulatory system, characterised by overlapping laws and authorities that urgently require reform. Legislative reform of the Poisons Act is urgently required. Introducing distinct schedules, clarifying cross-species prescribing boundaries, and aligning statutory rights with regulatory safeguards would restore coherence, protect patients, and preserve public trust. Modernisation is essential to balance professional autonomy with robust oversight in an evolving clinical landscape.

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ORIGINAL ARTICLE

An Investigation on Body Composition, Bone Parameters, Physiological Function, Quality of Life, And Cancer-Related Fatigue in Malaysian Breast Cancer Survivors

Rahman ANA[a,b], Ooi FK[a], Justine M[b], Jawis MN[a], Yahya M[c]

[a]Exercise and Sport Science Programme, School of Health Sciences, Universiti Sains Malaysia, Kelantan, Malaysia
[b]Centre for Physiotherapy Studies, Faculty of Health Sciences, Universiti Teknologi MARA Selangor, Malaysia
[c]Department of Surgery, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, Kelantan, Malaysia

ABSTRACT

INTRODUCTION: The aim of the study is to determine the correlation of body composition, bone parameters, physiological functions, with the quality of life (QoL) and cancer-related fatigue (CRF) among Malaysian breast cancer survivors. **MATERIALS AND METHODS:** Eighty-three female breast cancer survivors participated. Assessments of body composition, bone speed of sound (SOS), and T-score. Physiological functions consisted of handgrip strength, shoulder and lower body flexibility, and peak expiratory flow rate (PEFR) were performed on the participants. The Breast Cancer Functional Assessment of Cancer Therapy questionnaire was used for determining their QoL, while the Brief Fatigue Inventory scale questionnaire was used for assessing the CRF.Descriptive statistics and Pearson correlation were performed for statistical analysis. **RESULTS:** The mean T-score value for the right and left radius and tibia of the participants ranged between -1 and -2.5 SD, i.e., under the osteopenia category. There was no significant correlation between the percentage of body fat and fat-free mass with components of QoL and CRF, respectively. In addition, statistically significant positive correlations of bone SOS with components of QoL were not evidenced. A significant negative correlation was found between left handgrip strength and CRF ($r=-0.240$, $p=0.032$). However, no statistically significant correlations were observed between shoulder and lower body flexibility or PEFR with components of QoL and CRF, respectively. **CONCLUSION:** Higher handgrip strength of participants was related to lower CRF. Thus, the aspect of improvement of muscular strength of the arm should be emphasized while designing interventions for rehabilitation among breast cancer survivors.

Keywords
Body composition, bone health, physiological function, cancer-related fatigue, quality of life

Corresponding Author
Assoc. Prof. Dr. Ooi Foong Kiew
Exercise and Sport Science Programme, School of Health Sciences, Universiti Sains Malaysia, Kelantan, Malaysia
E-mail: fkooi@usm.my

Received: 27th March 2025; Accepted: 24th December 2025

Doi: https://doi.org/10.31436/imjm.v25i02/2919

INTRODUCTION

Breast cancer is a major health problem worldwide, including Malaysia, with a rising incidence rate. The incidence rate of breast cancer in Malaysia shows an increasing rate from 34.1 to 38.9 per 100,000 population.[1,2] With the advancement of cancer treatment, breast cancer survivors who had undergone primary cancer treatments are expected to return to their daily life and work at their levels like before the cancer diagnosis.[3] However, it is important to be aware that the treatments received by cancer patients also lead to prolonged side effects and complications that hinder them from returning to their normal daily life. It has been reported that cancer and its treatments lead to physical and psychosocial health problems.[4]

Poor body composition, such as the presence of visceral adipose tissue and skeletal muscle density, are associated with body function, which can affect treatment tolerability

and cancer outcomes.[5] In addition, it has been reported that higher abdominal body fat may be associated with a higher risk of breast cancer recurrence and death.[6]

Breast cancer treatment can have negative effects on bone health.[7] In breast cancer patients, treatment-associated bone loss can be caused by adjuvant endocrine therapy such as aromatase inhibitors (AIs), surgery, or chemotherapy.[8] One of the challenging comorbidities faced by cancer survivors is osteoporosis, which can increase the risk of bone fracture.[9]

Secondary to cancer illness, cancer survivors face changes in physiological functions which negatively affect their quality of life (QoL). It has been reported that cancer survivors may experience physiological side effects such as muscular atrophy, weight changes, reduced aerobic capacity, decreased muscular strength, and flexibility loss.[10]

Cancer-related fatigue (CRF) is one of the major problems among cancer survivors[11], which is described as a distressing, permanent feeling of tiredness or exhaustion related to cancer.[12] It is multifactorial and can be influenced by various demographic, medical, psychosocial, behavioural, and biological factors.[13] Additionally, it is partly induced by cancer treatments such as chemotherapy, radiation, and endocrine therapy, which can be further exacerbated by physically inactive lifestyle.[14]

QoL refers to a person's perception and satisfaction with life and their general appraisal of their level of functional well-being.[15] Given the evolving norms, values, lifestyle, and changing conceptualization of QoL over time, studies on QoL in the breast cancer population are warranted.[16]

Breast cancer survivors are at high risk of developing comorbid conditions such as osteoporosis, sarcopenia, and cardiovascular disease, which lead to a decline in bone health, muscular strength, cardiorespiratory fitness, and QoL.[17] To date, there are limited studies, especially on the association of bone health, QoL and CRF among breast cancer survivors in Malaysia. A previous study showed inconclusive results on CRF due to several factors such as homogeneity of the participants and strict inclusion criteria.[18]

Therefore, the present study was carried out to explore body compositions, bone speed of sound, physiological functions and their correlation with QoL and CRF among breast cancer survivors among Malaysian.

MATERIALS AND METHODS

Study Participants and Experimental Design

This study applied a cross-sectional study design. A total of 83 participants were selected by purposive sampling. The inclusion criteria for the participants were: Malaysian females diagnosed with breast cancer (stage 1-4) more than one year prior to the study and who had completed primary treatment, were between 25 and 70 years old, and possessed normal cognitive function and communication abilities. Those with a history of other types of cancer were excluded.

Participants were recruited from two hospitals and one primary clinic in Malaysia. Data collection procedures were conducted by the researcher at the above-mentioned hospitals and primary clinic. During the visit, participants were required to fill up a basic information form. Brief Fatigue Inventory (BFI) scale questionnaire and Breast Cancer Functional Assessment of Cancer Therapy (FACT-B) questionnaire were answered by the participants to assess their basic information, level of CRF and QoL, respectively. The participants also performed physical tests: 1. Anthropometric and body composition measurements, 2. Bone speed of sound and T-score assessment for bilateral radius and tibia bones of arms and legs, 3. Physiological function tests consisted of a handgrip strength test for both upper limbs, shoulder and lower body flexibility tests, and a peak expiratory flow rate test.

Basic information of the participants

All participants basic information, such as age, ethnicity, category of breast cancer stages and breast cancer affected side were obtained.

Body weight, body height, and body composition measurements

Body height of participants was assessed by using a stadiometer (Seca 220, Hamburg, Germany) and their body weight and body composition, comprised of percent body fat and fat-free mass were measured by using a body composition analyser (Tanita model TBF-140, Japan).

Bone speed of sound (SOS) and T-score assessment

The bone SOS and T-scores of both upper and lower limbs were assessed at the mid-shaft of the tibia and radius using a bone sonometer (Sunlight Mini Omni™, Petah Tikva, Israel) as described in previous studies.[19, 20]

Physiological function assessments

Handgrip strength test

Handgrip strength was assessed using a handgrip dynamometer (Jamar J00105, USA). Participants were instructed to squeeze the dynamometer as forcefully as possible for approximately 5 seconds. Three attempts were conducted for each hand, and the highest value was recorded

Back scratch test for assessing shoulder flexibility

Back scratch test was conducted to reflect the overall shoulder range of motion by measuring the distance between (or overlap of) the middle fingers of both hands as they moved towards each other behind the back. The test was conducted three times for both arms and the final score in centimetres (cm) was calculated as the mean value of the best attempt for both arms.

Sit and reach test for assessing lower body flexibility

The flexibility of participants was tested via the sit and reach test. They were instructed to sit with their feet placed against the sit-and-reach testing box, then reach forward as far as possible by pushing the marker on top of the box. The highest score from three attempts was recorded as the final score.

Peak expiratory flow rate (PEFR) test

A Wright handheld peak flow meter was used to measure the participants' PEFR. The participants were instructed to take a deep breath and blow into the peak flow meter as fast, powerfully, and fully as possible in a single exhalation. This test was repeated three times for each participant, and the highest recorded value was used for analysis.

Quality of life (QoL) assessment

QoL was assessed using the Breast Cancer Functional Assessment of Cancer Therapy (FACT-B) questionnaire. The FACT-B was developed by the Functional Assessment of Chronic Illness Therapy authority (FACIT.org) to measure the QoL of breast cancer survivors. The tool consisted of five sub-dimensions, which are: physical well-being, social/family well-being, emotional well-being, functional well-being, and a subscale on additional concerns for breast cancer survivors. A higher score indicates a better QoL.

Cancer-related fatigue (CRF) assessment

The Brief Fatigue Inventory (BFI) scale questionnaire was used to determine the CRF levels among the participants in this study.[21] The validity and reliability of BFI has been established with internal consistency reported at 0.96.[22] The higher score of CRF obtained from the BFI scale questionnaire reflects higher severity of the CRF.

Data Analysis

Statistical Package for Social Science (SPSS) version 24.0 was used for the statistical analysis. Data are presented in percentage (%) and mean (standard deviation) (SD). Correlation analysis was conducted to evaluate the magnitude and direction of the relationship between the variables by using Pearson correlation. A 'p' value of <0.05 was considered statistically significant.

RESULTS

Basic information of the participants

A total of 83 breast cancer survivors diagnosed with either of cancer stages 1, 2, 3, or 4 completed this study. The age of the participants ranged from 35 to 72 years, with a mean of 52.8 (8.7) years. Participants consisted of

90.4% (n=75) Malays, 7.2% (n=6) Chinese, and 2.4% (n=2) Indians. It was found that 39.8% (n=33) of participants were diagnosed with breast cancer stage 2, followed by 34.9% (n=29) with stage 3, 15.7% (n=13) with stage 1, and 9.6% (n=8) diagnosed with stage 4. A total of 60.2% (n=50) participants had breast cancer on the left side of the breast, 36.2% (n=30) on the right side of the breast, whereas 3.6% (n=3) were affected on both breasts.

Body composition, bone speed of sound, physiological functions, components of quality of life (QoL) and cancer-related fatigue (CRF) of the participants

Table I shows the results of body composition, i.e., percentage of body fat and fat-free mass, bone speed of sound, bone T score value, and physiological functions. It was found that the mean bone T-scores of the participants were ranged between -1 and -2.5 SD, i.e., under the osteopenia category. It was also found that the mean total score of QoL was 110.44 (2.68). The mean subscale total scores of physical, social, emotional, functional well-being, and additional concerns were 20.55 (0.83), 23.84 (0.68), 18.15 (0.67), 23.2 (0.67), and 25.11 (0.79), respectively. The mean CRF score was 3.20(2.69).

Table I: Body composition, bone speed of sound, bone T scores, and physiological functions of breast cancer survivors in Malaysia.

Variables		Mean (SD)
Body height (cm)		154.0 (0.68)
Body weight (kg)		67.2 (1.61)
Body Mass Index (kg/m²)		28.15 (0.62)
Body composition:		
Percent of Body Fat (%)		39.8. (0.75)
Fat Free Mass (kg)		37.2 (0.48)
Bone Parameters:		
Bone Speed of Sound (m/s) :	Right radius bone	3750.7 (975.8)
	Left radius bone	3750.0(960.5)
	Right tibia bone	3768.2 (163.5)
	Left tibia bone	3720.5 (309.1)
Bone T score value	Right radius bone	-1.84 (1.56)
	Left radius bone	-1.80 (1.95)
	Right tibia bone	-1.98 (1.48)
	Left tibia bone	-1.82 (1.75)
Physiological Functions:		
Handgrip strength (kg)		
Right side		26.25 (5.11)
Left side		24.71 (5.05)
Shoulder flexibility (cm)		
Right side		7.02 (7.32)
Left side		13.47(9.90)
Lower body flexibility (cm)		29.12 (6.70)
Pulmonary function, PEFR (L/min)		350.36 (74.5)

Abbreviations:
PEFR: Peak expiratory flow rate which indicates pulmonary function Note: A lower value obtained from the back scratch test indicates higher shoulder flexibility

Correlations of body weight, percentage of body fat, fat-free mass, and bone speed of sound (SOS) with quality of life (QoL) and cancer-related fatigue (CRF)

As presented in Table II, there was no significant correlation between percentage of body fat, fat-free mass, with total QoL score and CRF score, respectively. There were also no statistically significant positive correlations of bone SOS of right and left arms and legs with components of QoL of the participants. Meanwhile, statistically significant negative correlation of all the bone SOS values with CRF was also not observed.

Table II Correlation of body weight, percentage of body fat, fat-free mass, and bone speed of sound with QoL and CRF (B)

Variables	Total QoL score				CRF Score		
Body weight	r=0.046 p=0.68				r=0.107 p=0.33		
Percent body fat	r=0.110 p=0.33				r=-0.02 p=0.881		
Fat free mass	r=-0.017 p=0.88				r=0.077 p=0.49		
	Components of QoL						CRF score
	Physical wellbeing	Social wellbeing	Emotional wellbeing	Functional wellbeing	BCS	Total QOL score	
Bone SOS							
R arm	r=-0.199 p=0.101	r=0.051 p=0.679	r=-0.331** p=0.005	r=-0.101 p=0.409	r=-0.107 p=0.381	r=-0.189 p=0.120	r=0.083 p=0.496
L arm	r=-0.026 p=0.847	r=0.080 p=0.542	r=-0.235 p=0.071	r=-0.066 p=0.617	r=-0.061 p=0.642	r=-0.090 p=0.493	r=-0.084 p=0.522
R leg	r=-0.140 p=0.229	r=0.058 p=0.616	r=-0.064 p=0.582	r=-0.196 p=0.091	r=-0.092 p=0.427	r=-0.135 p=0.244	r=0.137 p=0.238
L leg	r=-0.139 p=0.236	r=0.157 p=0.178	r=-0.099 p=0.398	r=-0.195 p=0.094	r=-0.122 p=0.298	r=-0.126 p=0.282	r=0.105 p=0.371

Abbreviations:
Bone SOS; Bone speed of sound, R arm: Right arm, L arm: Left am, R leg: Right leg, L leg: Left leg, BCS: Additional concern for breast cancer survivors; QoL: Quality of life; CRF: cancer-related fatigue
*Pearson correlations (r) were performed to explore the correlation between measured parameters. P<0.05 was considered as statistically significant. Bold numbers and ** indicate statistically significant at p<0.001.*

Correlations of handgrip strength with quality of life (QoL) and cancer-related fatigue (CRF)

As shown in Figure 1, there was a significant negative correlation between the handgrip strength of the left hand and CRF score (r=-0.240, p=0.032). As shown in Table III, statistically significant positive correlations between right-handgrip strength and left handgrip strength with components of QoL were not evidenced.

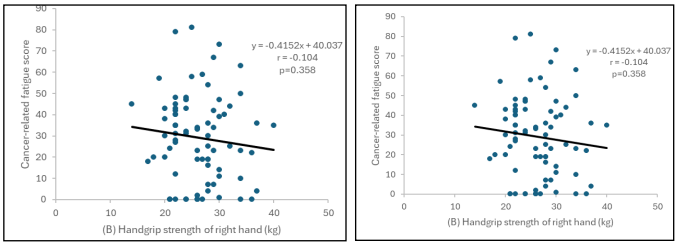

Figure 1: Correlations of handgrip strength (A) of left hand and (B) right hand with cancer -related fatigue

Table III Correlation matrix of handgrip strength with QoL

Variables	Components of QoL					
	Physical wellbeing	Social wellbeing	Emotional wellbeing	Functional wellbeing	BCS	Total QoL score
Right handgrip strength (kg)	r=-0.107 p=0.346	r=0.107 p=0.344	r=-0.234* p=0.037	r=0.063 p=0.582	r=-0.062 p=0.582	r=-0.103 p=0.365
Left handgrip strength (kg)	r=-0.110 p=0.331	r=0.093 p=0.413	r=-0.132 p=0.243	r=0.077 p=0.500	r=-0.108 p=0.339	r=-0.093 p=0.409

Abbreviations:
BCS: additional concern for breast cancer survivors; QoL: Quality of life

Correlation of shoulder and lower body flexibility and peak expiratory flow rate (PEFR) with quality of life (QoL) and cancer-related fatigue (CRF)

The correlations of right and left shoulder flexibility, lower body flexibility, and pulmonary function reflected by PEFR values with components of QoL and CRF are shown in **Table IV**. Results showed that there were no statistically significant correlations of the above-mentioned physiological function parameters with QoL and CRF.

Table IV: Correlations of shoulder and lower body flexibility and pulmonary function with QoL and CRF

Variables	Components of QoL,						CRF score
	Physical wellbeing	Social wellbeing	Emotional wellbeing	Functional wellbeing	BCS	Total QoL score	
R Sh flexibility (cm)	r=0.195 p=0.108	r=-0.038 p=0.758	r=0.136 p=0.266	r=0.092 p=0.450	r=0.131 p=0.282	r=0.159 p=0.191	r=-0.115 p=0.345
L Sh flexibility (cm)	r=0.114 p=0.360	r=0.086 p=0.491	r=0.230 p=0.061	r=0.142 p=0.252	r=0.013 p=0.915	r=0.163 p=0.188	r=0.003 p=0.983
SRT	r=-0.029 p=0.795	r=0.061 p=0.586	r=-0.074 p=0.507	r=-0.087 p=0.433	r=-0.153 p=0.167	r=-0.137 p=0.218	r=-0.029 p=0.795
PEFR (L/min)	r=-0.154 p=0.182	r=-0.060 p=0.606	r=-0.173 p=0.133	r=0.088 p=0.447	r=-0.140 p=0.224	r=-0.142 p=0.217	r=0.100 p=0.389

Abbreviations:
R Sh flexibility: Right shoulder flexibility; L Sh flexibility: Left shoulder flexibility; SRT: Lower body flexibility; PEFR: Peak expiratory flow rate indicates the pulmonary function; BCS: Additional concern for breast cancer survivors; QoL: Quality of life

DISCUSSION

Breast cancer patients experience weight gain and changes in body composition during and after breast cancer treatment. This weight gain occurs due to several factors, including side effects of treatment, hormonal changes, as well as a reduction in physical activity.[23] Higher abdominal body fat may be associated with a higher risk of breast cancer recurrence and death.[24] The average percentage of body fat of the participants in this study was 39.8% (0.75), and fat-free mass was 37.2 (0.48) kg. The BMI and body composition data indicate that the participants in the study are generally overweight, with high body fat percentage and substantial fat-free mass. A recent JAMA study reported that obesity was associated with an increased risk of breast cancer recurrence among postmenopausal patients with HR+ early-stage breast cancer treated with aromatase inhibitors.[25]

The present study shows that there was no significant correlation between the percentage of body fat and fat-free mass with CRF and QoL, respectively. These findings are inconsistent with a study that reported that higher fat mass and lower muscle mass were associated with worse CRF, and physical domain of QoL.[26] Thus, we would like to speculate that the discrepancy between the findings of these previous studies and the present study could be due to differences in the general physical conditions of the breast cancer survivors, variability in clinical characteristics of the breast cancer, age, and stages of cancer.

Regarding bone health and cancer treatments, previous studies found that cancer treatment, such as chemotherapy, can negatively affect bone health and lead to osteoporosis, and hence affecting their physical activity and increasing the level of fatigue.[27,28] The bone health status of the participants identified in this study was categorised under the osteopenia category. This finding implies that breast cancer survivors are at the borderline of osteoporosis and may have a risk of having osteoporosis in the future. Unexpectedly, the current finding indicates that there was no statistically significant positive correlation between bone SOS and components of QoL. In addition, a statistically significant negative linear correlation between bone SOS and CRF was also not evidenced. To date, there is a lack of studies on the relationship between bone health status, QoL, and CRF. Therefore, direct comparison could not be performed.

Regarding muscular strength, the present study found that the right handgrip strength of the participants was higher, with 26.25(5.11) kg compared to the left side, with 24.71(5.05) kg. This finding was supported by the fact that majority of the participants were diagnosed with breast cancer at the left side of breast (60.2%) compared to right side of breast (36.2%), hence, it is not surprising to observe higher handgrip strength at the right side compared to the left side. Besides, 92.8% of the participants were right-handed compared only 7.2% who were left-handed; this may contribute to the fact that the right hand is stronger compared to the left hand among the participants. In contrast to a study conducted in Malaysia[29] with findings on handgrip strength among breast cancer patients was very much lower, i.e., 9.60 (4.89) kg compared to the findings of the present study. This indicates good handgrip strength with reference to 27.6(6.58) kg as reported in a previous study[30]. In this study, we found a weak negative linear correlation between right handgrip strength and emotional well-being among breast cancer survivors. One possible explanation could be that breast cancer survivors with stronger physical capabilities may have higher expectations for their recovery. Unmet expectations could lead to emotional distress.

The most notable finding in the present study is that there was a significant negative relationship between left handgrip strength and CRF score (r=-0.240, p=0.032), which reflects that higher muscular strength of the upper limb could be related to lower level of CRF **(**Figure 1A). Previous study reported that higher CRF was linked to reduced physical function including the handgrip strength[31]. In addition, it was also reported that higher handgrip strength was associated with better cognitive function, indicating a potential inverse relationship between muscular strength and CRF, as cognitive function can be a component of overall fitness.[32] Nevertheless, another study found that CRF levels were not significantly related to muscular strength or fatigability, suggesting that cancer patients can benefit from following standard exercise guidelines regardless of their self-reported fatigue levels.[33]

Shoulder muscle activity is significantly affected by breast cancer surgery through altered muscle activation patterns due to muscular inactivity and muscle tightness, and different surgical techniques, such as axillary surgery, which leads to muscle dysfunction.[34] The alterations in muscular activity lead to functional impairments such as pain, weakness, and limitation in range of motion, impacting daily activity and overall QoL of the breast cancer survivors.

The normal value for shoulder flexibility measured via the back scratch test, regardless of right and left side and age, is −2.3 (8.5) cm in the healthy female population.[35] The present study observed that there was low shoulder flexibility on both sides compared to the healthy female population. Comparison between right and left side shoulder flexibility of the participants in this study showed that the participants had higher shoulder flexibility at the right side compared to the left side. This finding is also supported by the fact that the majority of the participants' affected side was on the left side of the breasts compared to the right side. The current study also found that participants exhibited good lower body flexibility, with a mean score of 29.12 cm (SD = 6.70), compared to the healthy population, where a score of 24.3 cm (SD=13.2) is considered indicative of good lower body flexibility.[35]

PEFR is the reflection of the functioning of the larger airways, and the normative value of PEFR for females was reported as 320-470 L/min in adults.[36] The mean PEFR value of the participants in this study was 350.36 (74.5) L/min, which can be categorised as normal pulmonary function. Conventional radiotherapy causes a restrictive pattern of the lungs, causing inability to fully expand hence resulting in an abnormal pattern of breathing which can impact the pulmonary function.[37]

The present study showed that there were no significant correlations between shoulder and lower body flexibility and pulmonary function with QoL and CRF, respectively. This might be due to the participants of this study were relatively healthy breast cancer survivors, with minimal physical impairment. As a result, the variability in

flexibility and pulmonary function may not have been substantial enough to demonstrate a significant association with QoL and CRF.

CONCLUSION

Bone health status of the participants in this study is categorized as osteopenia. It was also evidenced that body composition, flexibility, and pulmonary function showed no significant correlations with QoL nor CRF in breast cancer survivors of this study. Notably, there was a significant negative relationship between the handgrip strength of the left hand and CRF among the participants, implying that higher handgrip strength was linked to lower fatigue levels. These findings have practical implications, as they may assist healthcare providers and breast cancer survivors in addressing the importance of bone health, and the relationship between muscular strength with CRF. Furthermore, it is hoped that this study provides evidence-based insights that may strengthen the theoretical framework for cancer rehabilitation in Malaysia.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

INSTITUTIONAL REVIEW BOARD (ETHIC COMMITTEE)

This study was approved by Human Research Ethics Committee of Universiti Sains Malaysia (USM) (JEPeM code: USM/JEPeM/20040233) and Medical Research and Ethics Committee (MREC) of Malaysia Ministry of Health (NMRR ID: NMRR ID-21-02047-QRK(IRR).

ACKNOWLEDGEMENTS

The authors would like to thank the breast cancer survivors who participated in this study. Special gratitude is also extended to the staff of Breast Cancer Awareness & Research (BesTARI) Unit of Hospital Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia; Institut Kanser Negara, Putrajaya and Klinik Hayat, Jasin Bestari, Melaka for the technical support.

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ORIGINAL ARTICLE

Exploring Transferrin Gene Expression as A Biomarker of Ineffective Erythropoiesis and Iron Overload in HbE/β-Thalassaemia and β-Thalassaemia Trait

M. Saad HK[a], Wan Taib WR[a], Ab Ghani AS[b], Al-Rawashde FA[d], Ilsmail I[a], Johan MF[c], Nagi Al-Jamal HA[a]

[a]School of Biomedicine, Faculty of Health Sciences, Universiti Sultan Zainal Abidin, Terengganu, Malaysia
[b]Department of Pathology, Hospital Sultanah Nur Zahirah, Terengganu, Malaysia
[c]Department of Haematology, School of Medical Sciences, Universiti Sains Malaysia, Kelantan, Malaysia
[d]Department of Medical Laboratory Sciences, Faculty of Allied Medical Sciences, Al-Balqa Applied University, Jordan

ABSTRACT

INTRODUCTION: Iron overload is a major concern in transfusion-dependent thalassaemia patients, with soluble transferrin receptors (sTfR) playing a key role in iron regulation. This study aimed to evaluate the gene expression of *TfR1* and *TfR2* and their association with ineffective erythropoiesis (IE) and iron overload in HbE/β-thalassaemia patients. **MATERIALS AND METHODS:** A total of 2 ml whole peripheral blood was extracted for RNA from 6 subjects recruited from each HbE/β-thalassaemia patient, β-thalassaemia trait carriers, and healthy controls. TfR levels were measured using ELISA, while *TfR1* and *TfR2* gene expression were assessed using RT-qPCR. Data were analysed using ANOVA, Student's t-test, Kruskal–Wallis, and Mann–Whitney U tests with Bonferroni correction. **RESULTS:** Gene expression analysis revealed a significant downregulation of *TfR2* in HbE/β-thalassaemia patients and β-thalassaemia carriers *(P<0.001)* compared to healthy controls, while *TfR1* expression was significantly upregulated *(P<0.001)*. Additionally, sTfR levels were statistically higher in HbE/β-thalassaemia patients and parents compared to healthy controls (P<0.001). **CONCLUSION:** These findings suggest that *TfR1* and *TfR2* expression patterns may serve as potential biomarkers for assessing IE and iron overload in β-thalassaemia. Furthermore, elevated *sTfR* levels indicated that the transfusion regimen was insufficient to suppress ineffective erythropoiesis. In β-thalassaemia intermedia patients, haemoglobin levels may not be the most reliable marker for monitoring transfusion therapy, whereas *sTfR* could help in tailoring individualised transfusion regimens.

Keywords
Soluble Transferrin Receptor (sTfR), Iron-overload, Ineffective erythropoiesis, β-thalassaemia trait, HbE/β-thalassaemia patients.

Corresponding Author
Assoc. Prof. Dr. Wan Rohani Wan Taib
Faculty of Health Sciences,
Universiti Sultan Zainal Abidin, Gong Badak Campus, Terengganu, Malaysia.
E-mail: wanrohani@unisza.edu.my
Phone:+6016-9712549

Received: 23rd September 2025; Accepted: 27th November 2025

Doi: https://doi.org/10.31436/imjm.v25i02/3077

INTRODUCTION

The World Health Organisation (WHO) recognises thalassaemia as a major public health concern, particularly in tropical countries such as Malaysia, highlighting the need for systematic data collection and analysis to monitor disease prevalence, treatment outcomes, and related complications, including iron overload. Despite being the most common hereditary haematological disorder in Malaysia, comprehensive nationwide data on the geographical distribution of patients, as well as socioeconomic, clinical, and treatment outcome information, remain limited. The total cumulative number of registered thalassaemia patients increased by 9.0%, from 8,767 in 2020 to 9,554 in 2023, largely due to improved overall survival and enhanced data collection and cleaning efforts. HbE/β-thalassaemia is most prevalent among Malays, accounting for 3,101 patients (49.0%), whereas β-thalassaemia major occurs more frequently among Chinese, Indian, and Kadazan Dusun populations, comprising 353 (36.1%), 16 (25.4%), and 835 (83.9%) patients, respectively, based on the Annual Report of The Malaysia Thalassaemia Registry 2023.[1]

β-thalassaemia is an inherited autosomal recessive disorder characterised by reduced production of β-globin chains in haemoglobin A (HbA), which normally consists of two α- and two β-globin chains. HbE/β-thalassaemia results from the inheritance of a β-globin gene mutation alongside the HbE variant, leading to a spectrum of anaemia severity, ranging from mild to transfusion-dependent cases.[2] The imbalance in globin chain synthesis causes unpaired α-globin chains, resulting in ineffective erythropoiesis (IE) due to the premature destruction of erythroblasts at the polychromatic normoblast stage and the haemolysis of mature red blood cells.[3] This process contributes to erythroid expansion, extramedullary erythropoiesis, and bone deformities.[4] While disease severity can be influenced by additional genetic factors, such as α-hemoglobinopathies, HbE/β-thalassaemia remains highly variable in its clinical presentation.[5]

Chronic iron overload represents one of the most serious and challenging complications arising from long-term blood transfusions. Patients with Transfusion-Dependent Thalassaemia (TDT) inevitably develop clinical manifestations of iron overload over time unless timely and effective iron chelation therapy is administered. Transferrin receptors (TfRs) are critical for iron uptake and are predominantly expressed in erythroid precursor cells, with around 80% located in the erythroid marrow of adults. During erythroid maturation, truncated forms of TfR are released into circulation as soluble transferrin receptors (sTfR). Iron deficiency triggers an increase in TfR synthesis [6], leading to elevated sTfR levels, making them reliable indicators of iron deficiency anaemia (IDA).[7] Moreover, sTfR levels correlate with erythroid activity, serving as a useful marker of increased erythropoiesis.[8] Elevated sTfR levels have been observed in various haematologic disorders, including autoimmune haemolytic anaemia, hereditary spherocytosis, and β-thalassaemia major, all of which involve heightened erythropoietic demand. Therefore, the sTfR level may serve as a valuable adjunct marker for improving monitoring in non–transfusion-dependent thalassaemia (NTDT), where serum ferritin alone does not adequately reflect erythroid activity or the balance of iron metabolism in the management of β-thalassaemia.

Based on our current understanding of TfR regulation at the cellular level and the minimal biological and analytical variability observed in sTfR assays [9], this study aimed to assess the expression level of TfR and its association with iron overload and IE in patients with HbE/β-thalassaemia and β-thalassaemia trait. Additionally, the study explored the diagnostic and potential therapeutic significance of TfR in managing these conditions.

MATERIALS AND METHODS

Sample recruitment and ethical considerations

This study was conducted in accordance with the ethical standards outlined in the Declaration of Helsinki. All participants were provided with a Participant Information Sheet (PIS) and an Informed Consent Form (ICF) prior to their inclusion in the study upon approval from Universiti Sultan Zainal Abidin (UniSZA) Human Research Ethics Committee [(approval no. UniSZA.C/2/UHREC/628-2 J1d.2) (73)] and the Medical Research and Ethics Committee [(approval no. NMRR-19-855-45851 (IIR)].

A total of 6 subjects were selected from each group, HbE/β-thalassaemia patients and β-thalassaemia trait carriers, based on the severity of the disease. The patient samples were collected from the Haematology Department at Hospital Sultanah Nur Zahirah (HSNZ), while 6 healthy control samples were obtained from postgraduate students at Universiti Sultan Zainal Abidin (UniSZA), Gong Badak Campus, Terengganu, Malaysia.

Participants were included in the study if they met the following criteria: (i) transfusion-dependent HbE/β-thalassaemia patients and their biological parents (HbE trait and β-thalassaemia trait); and (ii) healthy individuals with normal haematological profiles, iron levels, and haemoglobin electrophoresis results. Exclusion criteria included: (i) presence of iron deficiency anaemia (IDA) or alpha-thalassaemia trait, confirmed by DNA analysis of the alpha-globin gene; and (ii) healthy participants with low haemoglobin levels, abnormal red cell indices, or the

presence of haemoglobin variants. The demographic data were obtained from patient's folder from the respective hospital.

Laboratory investigations

Biochemical assays

Serum soluble transferrin receptor (sTfR) level was quantitatively measured using ELISA employing monoclonal antibodies specific to sTfR. The assay was performed using a commercial kit (BioVendor Research and Diagnostic Products, Heidelberg, Germany), following the manufacturer's protocol. The reference range for sTfR was 1.0–2.9 μg/mL. Optical density (OD) readings were recorded at a wavelength of 450 nm using an ELISA reader, within 5–10 minutes of reaction completion. All samples were run as triplicate.

Quantitative RT-PCR

Total RNA was extracted from peripheral blood samples using the GeneJET RNA Purification Kit (Thermo Scientific, USA), following the manufacturer's instructions. RNA purity and concentration were determined using a NanoPhotometer® NP80 (Implen GmbH, Germany). Complementary DNA (cDNA) synthesis was performed using the GoTaq® 2-Step RT-qPCR Kit (Promega Corporation, USA).

Gene expression analysis of *TfR1* and *TfR2* was conducted using the SYBR Green-based GoTaq® 2-Step RT-qPCR System (Promega, Madison, WI, USA), adhering to the manufacturer's guidelines. Each 20 μL reaction mixture contained 10 μL of GoTaq® qPCR Master Mix (2X), 0.2 μL of CXR reference dye, 1 μL each of forward and reverse primers (20X), 6.8 μL of nuclease-free water, and 2 μL of cDNA template. A no-template control (NTC) was included, replacing the cDNA template with nuclease-free water. The analysis was conducted in technical triplicate for six biological samples for each group.

Amplification was performed using a StepOnePlus™ Real-Time PCR System (Applied Biosystems, Foster City, CA, USA) with the following thermal cycling conditions: initial activation of GoTaq® DNA polymerase at 95°C for 2 minutes, followed by 40 cycles of denaturation at 95°C for 15 seconds, and annealing/extension at 60°C for 1 minute.

Gene expression levels were normalised to the endogenous control β-actin, and relative expression was calculated using the $2^{-}\Delta\Delta Cq$ method. Results were expressed as fold changes. The primer sequences used for amplification are detailed in Table I.

Table I. The primer sequences utilized for reverse transcription-quantitative PCR analysis

Gene name	Forward primer	Reverse primer
TfR 1	5′-GGCAAGTAGATGGCGATA -3′	5′-GCCCAAGTAGCCAATCTAA-3′
TfR 2	5′-GTGCGGAGACTCTGTGTT-3′	5′-GTTCCCGAAGGCTGGTTT -3′
β-actin	5′-GAGCGCGGCTACAGCTT-3′	5′-TCCTTAATGTCACGCACGATTT-3′

Statistical Analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS) version 20 (IBM Corp., Armonk, NY, USA). Group comparisons were performed using the Kruskal-Wallis test, with statistical significance set at $P<0.05$. For pairwise comparisons, the Mann-Whitney U test with Bonferroni correction was applied, adjusting the significance threshold to $P<0.017$. One-way analysis of variance (ANOVA) was used for comparisons involving multiple groups, while Student's t-test was employed to assess differences in sTfR levels between two groups.

RESULTS

Demographic data

Table 1 summarises the demographic, clinical, and biochemical characteristics of healthy controls, carrier parents, and HbE/β-thalassaemia patients. The gender distribution was balanced across groups. Patients exhibited markedly lower haemoglobin and BMI, with substantial increases in ferritin and sTfR levels, indicating anaemia with enhanced erythropoietic activity and iron overload. Hepcidin concentrations were significantly decreased in both patients and parents compared with controls, consistent with erythroid-driven hepcidin suppression. Splenomegaly was universally present in the patient group but absent in controls. Regular transfusion

and iron chelation therapy were reported only in patients. These results underscore the interplay between erythropoietic drive, iron dysregulation, and clinical severity across the thalassaemia spectrum.

Table II. Demographic, clinical, and biochemical characteristics of study participants (Mean ± SD).

Characteristics	Healthy Controls (n = 6)	Parents (n = 6)	HbE/β-thalassaemia Patients (n = 6)
Gender (M/F ratio)	3 / 3	3 / 3	3 / 3
Age (years)	25.3 ± 2.4	39.3 ± 2.1	12.5 ± 1.7
BMI (kg/m²)	22.8 ± 1.6	22.1 ± 1.5	17.9 ± 1.3
Hb (g/dL)	13.9 ± 0.3	11.9 ± 0.4	8.0 ± 0.3
Hepcidin (ng/mL)	20.2 ± 1.2	14.8 ± 1.5	8.9 ± 1.1
Ferritin (ng/mL)	92.7 ± 4.2	212.0 ± 15.6	686.0 ± 30.4
Serum Iron (µg/dL)	107.5 ± 4.1	115.5 ± 5.2	155.7 ± 6.1
sTfR (mg/L)	2.7 ± 0.2	4.1 ± 0.3	7.9 ± 0.4
Splenomegaly (mean size, cm)	None	Mild (1.5 ± 0.4)	Present (13.2 ± 1.6)
Transfusion status	None	None	Regular
Chelation therapy	No	No	Yes

Increased serum sTfR in HbE/β-thalassaemia patients

The analysis of the iron profile revealed a significant elevation in serum soluble transferrin receptor (sTfR) levels among HbE/β-thalassaemia patients and their parents compared to healthy controls *(P<0.001)* (Figure 1). Additionally, pairwise comparisons showed significant differences in sTfR levels between HbE/β-thalassaemia patients and their parents *(P<0.001)*, between patients and healthy controls *(P<0.001)*, and between parents and healthy controls *(P<0.001)*.

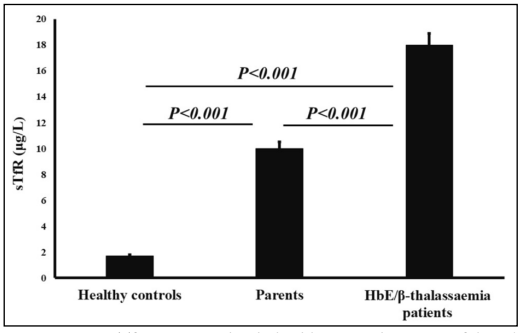

Figure 1. Serum sTfR concentration in healthy control, parents of the HbE/β-thalassaemia patients and HbE/β-thalassaemia patients.

Upregulated TfR1 in HbE/β-thalassaemia patients and their parents.

A significant increase in *TfR1* expression was observed, with levels more than five-fold higher in HbE/β-thalassaemia patients and over three-fold higher in their parents compared to healthy controls *(P=0.001)*. Furthermore, *TfR1* expression was significantly higher in HbE/β-thalassaemia patients than in their parents *(P=0.006)*. However, a significant decrease in TfR1 expression was observed in the parents (p=0.006) compared to the HbE/β-thalassaemia patients. (Figure 2).

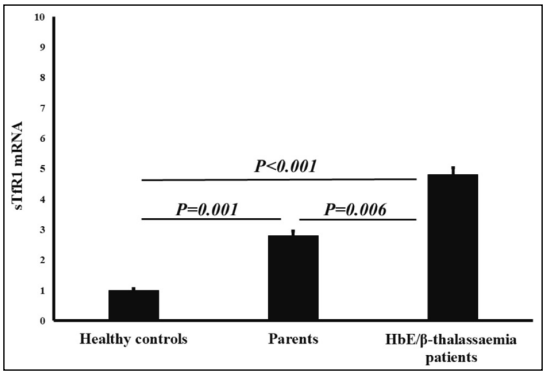

Figure 2. Gene expression analysis of sTfR1 in healthy control, parents of the HbE/β-thalassaemia patients and HbE/β-thalassaemia patients.

Downregulated sTfR2 in HbE/β-thalassaemia patients and their parents

The expression of *TfR2* was markedly reduced in both HbE/β-thalassaemia patients and their parents. Specifically, *TfR2* expression was 25-fold lower in patients and 11.5-fold lower in parents compared to healthy controls *(P<0.001)*. However, no statistically significant difference in *TfR2* expression was found between HbE/β-thalassaemia patients and their parents

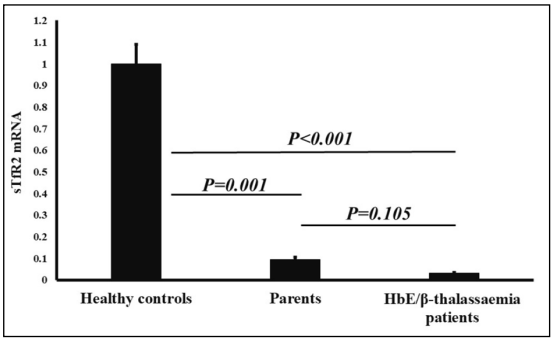

Figure 3. Gene expression analysis of *TfR2* in healthy control, parents of the HbE/β-thalassaemia patients and HbE/β-thalassaemia patients.

DISCUSSION

This study highlights the role of sTfR as a biomarker for IE, predominantly secreted by erythroid progenitor cells. Elevated sTfR levels are associated with erythrocyte hyperplasia and depleted iron reserves.[10] These findings underscore the importance of sTfR as a reliable marker for assessing the severity of IE in HbE/β-thalassaemia

patients. Additionally, understanding how sTfR levels reflect iron demand in erythropoiesis can further guide clinical decisions in managing thalassaemia patients, particularly in determining the need for transfusions.

sTfR2, a type II transmembrane glycoprotein, binds diferric-transferrin (holo-TF) with lower affinity than TfR1[11] and plays a regulatory role in iron homeostasis.[12] Unlike TfR1, which facilitates iron uptake, TfR2 is primarily involved in *hepcidin (HEPC)* regulation. Mutations in *TfR2* can lead to iron overload disorders, and its expression, predominantly in the liver, is essential for systemic iron sensing and erythropoiesis regulation.[13] Exploring the regulation of *TfR2* at the molecular level in the context of thalassaemia could provide valuable insights into how its downregulation contributes to the iron dysregulation observed in these patients. Given its potential to serve as a therapeutic target, further research on modulating *TfR2* expression could offer new avenues for iron overload management in thalassaemia.

TfR2 is stabilised on hepatic and erythroid cell membranes through differential TF binding, acting as a circulating iron sensor that modulates HEPC synthesis and red blood cell (RBC) production.[14] Aforementioned above, TfR2 plays a significant role in erythropoiesis, and its therapeutic modulation could help correct iron homeostasis in thalassaemia. Further studies should investigate the clinical implications of targeting TfR2 in thalassaemia patients, particularly in managing anaemia and iron overload.

Our findings revealed a significant elevation in serum sTfR levels *($p<0.001$)* in HbE/β-thalassaemia patients compared to their parents and healthy controls. These results align with previous studies that reported increased serum sTfR levels in individuals with β-thalassaemia trait (βTT), reinforcing its role in ineffective erythropoiesis. While haemoglobin levels alone may not be reliable indicators for guiding transfusion therapy in β-thalassaemia [15], sTfR offers valuable insights into transfusion needs. Elevated sTfR levels in βTT patients underscore ongoing erythropoietic stress, even in the absence of overt anaemia. Previous research has consistently reported higher sTfR levels in thalassaemia major compared to thalassaemia intermedia.[16] The use of sTfR as a clinical tool to predict transfusion requirements in thalassaemia patients is particularly promising, as it allows for better management of anaemia while avoiding unnecessary transfusions. This can improve the quality of life for patients and potentially reduce transfusion-associated complications.

Based on our previous study, HbE/β-thalassaemia patients and β-thalassaemia carriers showed increased serum ferritin, iron levels and transferrin saturation together with reduced serum hepcidin antimicrobial peptide (HAMP) and haemoglobin concentration levels compared to healthy controls ($P<0.001$).[17] In addition, we observed significantly higher reticulocyte counts in both groups compared with healthy controls ($P<0.001$), reflecting enhanced erythropoietic activity. This finding was consistent with elevated serum sTfR levels, further supporting the presence of ineffective erythropoiesis in thalassaemia.

In an integrative mechanism of thalassaemia, erythropoietin (EPO) is produced due to chronic anaemia and tissue hypoxia. This elevated EPO promotes massive expansion of erythroid precursors, which express abundant transferrin receptors (TfR1) to acquire iron for haemoglobin synthesis. Shedding of these receptors into circulation increases serum soluble transferrin receptor (sTfR) levels - a biomarker reflecting the magnitude of erythropoietic activity. Reticulocyte counts may also increase, reflecting heightened erythroid turnover, although many reticulocytes are prematurely destroyed due to ineffective maturation. The hyperactive yet ineffective erythropoietic marrow releases erythroferrone (ERFE) and growth differentiation factor-15 (GDF15), which suppresses hepatic HAMP expression. As a result, serum hepcidin levels (HAMP) become inappropriately low, even in the presence of iron overload. Reduced hepcidin removes its inhibitory effect on ferroportin, allowing continuous iron efflux from enterocytes and macrophages into plasma. Although total body iron is high, functional iron utilization is inefficient, as most erythroid precursors undergo apoptosis before producing

mature red cells. Consequently, haemoglobin (Hb) concentration remains low, and the anaemia persists, further stimulating EPO and worsening ineffective erythropoiesis.[18,19, 20]

Additionally, our study demonstrated a significant downregulation of *TfR2* expression in HbE/β-thalassaemia patients and their parents *(p<0.001)* compared to healthy controls, indicating altered iron regulatory signalling associated with ineffective erythropoiesis. The observed downregulation of *TfR2* expression in HbE/β-thalassaemia may reflect a disruption of the hepatic iron-sensing pathway, as TfR2 plays a critical role in mediating hepcidin (HAMP) induction in response to circulating holotransferrin. Reduced *TfR2* expression could therefore contribute to inappropriately low hepcidin levels, enhancing intestinal iron absorption and exacerbating systemic iron overload.[21] Understanding these regulatory mechanisms could lead to more targeted therapeutic approaches that address the underlying iron homeostasis issues in thalassaemia.

Furthermore, our results revealed significant upregulation of *TfR1* expression in HbE/β-thalassaemia patients and their parents *(p<0.001)* compared to healthy controls. These findings are consistent with previous studies demonstrating increased *sTfR1* expression in murine models of β-thalassaemia major and intermedia.[22] Elevated *TfR1* levels were particularly pronounced in patients requiring frequent transfusions and splenectomy, reinforcing its association with severe disease phenotypes.[23] However, some studies have reported reduced *TfR1* expression in specific β-thalassaemia models, highlighting potential context-dependent regulatory differences.[24]. This discrepancy in *TfR1* expression suggests that the regulation of *TfR1* might vary depending on disease stage, iron status, and treatment interventions. Future studies could explore how modifying TfR1 levels in different clinical settings could optimise patient management, especially in transfusion-dependent patients.

TfR1 is widely regarded as the "cellular iron gate" due to its role in iron uptake via ferric-transferrin internalisation. It is highly expressed in mammalian tissues and is critical for erythropoiesis, though its role in hematopoietic stem and progenitor cells remains unclear.[22] Prior research has shown that iron regulatory protein 2 (IRP2) binding at the 3' untranslated region enhances TfR1 translation during iron deficiency anaemia (IDA), leading to increased *TfR1* expression.[25] These findings suggest that *TfR1* plays a crucial role in erythroid precursor iron metabolism and iron transfer from erythroid cells to macrophages in the bone marrow. Consequently, targeting *TfR1* has been explored as a potential therapeutic approach to modulating iron metabolism and IE in thalassaemia.[26] Therapeutic strategies targeting *TfR1* could not only help control iron uptake but also improve erythropoiesis in thalassaemia patients, especially those with iron overload or transfusion dependency. Further clinical trials could explore the safety and efficacy of *TfR1* modulation in managing these conditions.

Excess iron disrupts IRP1 binding to iron-responsive elements, leading to TfR1 degradation and reduced cellular levels.[27] In contrast, *TfR1* expression is upregulated in conditions associated with increased erythropoiesis, such as β-thalassaemia major and IDA.[28] However, inconsistent patterns of *TfR1* expression have been observed in HepG2 cells treated with sera from β-thalassaemia major patients, underscoring the complexity of *TfR1* regulation in different cellular contexts.[22]

Taken together, our findings indicate significant upregulation of *TfR1 (p<0.001)* and marked downregulation of *TfR2 (p<0.001)* in HbE/β-thalassaemia patients and their parents compared to healthy controls. The altered expression of these genes correlated with increased serum sTfR concentrations, highlighting their role in erythropoiesis and iron metabolism. These results suggest that TfR1 may be a viable therapeutic target for managing thalassaemia. Given that *TfR* expression is tightly regulated by iron availability, its modulation could offer new treatment strategies to reduce red blood cell transfusion dependence and prevent iron overload in these patients. Future studies could investigate how modulating TfR1

levels can alleviate iron overload while promoting IE in transfusion-dependent thalassaemia patients.

The use of sTfR as a biomarker for assessing IE and iron overload in β-thalassaemia patients is further supported by these findings. Targeting TfR1 could provide a novel therapeutic avenue for reducing transfusion burden and mitigating systemic iron accumulation, ultimately improving patient outcomes. Moreover, longitudinal studies could track sTfR levels over time to evaluate disease progression and monitor therapeutic responses in patients undergoing treatment.

However, the sample size was considerably small (n= 6 per group) for sTfR level measurement due to COVID pandemic and lockdown was implemented during the time of subject recruitment. This limitation substantially limits the statistical power and may not be sufficiently robust to account for biological variability. The other limitation due to the same reason was the normal control group among the university students which might provide a selection bias who may not accurately represent the general population when comparing to the age, socioeconomic background or baseline health status.

CONCLUSIONS

In conclusion, this study provides suggestive evidence that the sTfR is a valuable biomarker for assessing IE and iron overload in patients with HbE/β-thalassemia. Elevated levels of sTfR were found to correlate with increased erythropoietic activity and iron demand, highlighting its significance in understanding the pathophysiology of thalassaemia. Our results also revealed a marked dysregulation in the expression of transferrin receptor isoforms, with upregulation of *TfR1* and downregulation of *TfR2*, which further emphasises their roles in erythropoiesis and iron metabolism in thalassaemia patients.

These findings suggest that sTfR could serve as a diagnostic tool to better assess the severity of IE and iron overload in thalassaemia patients. Moreover, the differential expression of *TfR1* and *TfR2* presents potential therapeutic targets. Modulating *TfR1* could help improve erythropoiesis and reduce transfusion dependency, while targeting *TfR2* could be key to managing iron overload, a common complication in thalassemia. Targeted therapies designed to regulate *TfR1* and *TfR2* expression hold promise for optimising iron homeostasis and alleviating the clinical burden of this disease.

Further research in a larger sample size is needed to better understand the complex regulatory mechanisms governing TfR expression, particularly in the context of varying disease states, and to evaluate the clinical efficacy of modulating sTfR levels in therapeutic interventions. Longitudinal studies are also crucial to track TfR levels as potential biomarkers for disease progression and response to treatment. Ultimately, the findings of this study open new avenues for improving patient outcomes in HbE/β-thalassaemia by enhancing our ability to manage IE and iron overload through targeted interventions.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest related to this manuscript.

FUNDING

This work was supported by the University Research Fund UniSZA/2022/DPU2.0/26 (R0425).

INSTITUTIONAL REVIEW BOARD (ETHICS COMMITTEE)

The study was approved by Universiti Sultan Zainal Abidin (UniSZA) Human Research Ethics Committee [(approval no. UniSZA.C/2/UHREC/628-2 J1d.2) (73)] and the Medical Research and Ethics Committee [(approval no. NMRR-19-855-45851 (IIR)].

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ORIGINAL ARTICLE

The Efficacy of Orthokeratology in Controlling Myopia Progression in Primary School Children in Kuala Lumpur

Mohd-Ali B[a], Low YC[a], Mizhanim MS[a], Norlaili A[a], Mohidin N[a]

[a]Optometry and Vision Science Program, Research Centre for Community Health (REACH), Faculty of Health Sciences, Universiti Kebangsaan Malaysia, Kuala Lumpur

ABSTRACT

INTRODUCTION: Myopia is a global public health issue. Advanced myopia can lead to potentially serious ocular pathologies such as glaucoma and maculopathy, thus controlling progression of myopia is essential. Orthokeratology (Ortho-K) has been shown to be effective in controlling the progression of myopia in children. However, limited data is available on this from the East Asian populations. This study investigated the efficacy of Ortho -K in controlling the progression of myopia in children in Kuala Lumpur. The results were compared with those for single vision spectacles (SVS). **MATERIALS AND METHODS:** Children aged 8-9 years, with myopia of -0.50 to -4.00D and astigmatism of ≤1.00D, were invited to participate. Cycloplegic refraction at the central and peripheral retina, visual acuity (VA), corneal topography, and axial length (AL) measurements were taken at baseline (BL) and every 6 months over a 1-year period. **RESULTS:** In all, 70 children (35 males and 35 females), with a mean age of 8.31±0.47 years, participated. Forty -five children were fitted with Ortho-K lenses and 25 with SVS. Significant changes in the refraction, corneal curvature, and AL were found over the study period and between the groups ($p<0.05$). Significant myopic shifts in the relative peripheral refraction (RPR) ($p<0.01$) were noted in the Ortho-K wearers, while hyperopic shifts ($p<0.01$) were found in the SVS group. Myopia progression and AL elongation were slowed by around 50% and 44%, respectively. **CONCLUSION:** Wearing the Ortho-K lenses for 12M is effective in controlling myopia progression children and can be recommended when managing myopic children.

Keywords
Myopia, Children, Orthokeratology, Axial length, Refraction

Corresponding Author
Prof. Dr. Bariah Mohd-Ali
Optometry and Vision Science Program, Research Centre for Community Health (REACH), Faculty of Health Sciences, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia
Email: bariah@ukm.edu.my

Received: 19th April 2024; Accepted: 5th January 2026

Doi: https://doi.org/10.31436/imjm.v25i02/2601

INTRODUCTION

The prevalence of myopia is increasing worldwide, especially in East Asia regions.[1-3] It has been reported that the prevalence of myopia in East Asian countries to be as high as 90% in young adults.[1] Holden et al.[3] estimates that almost half of the world's population will be myopic by 2050. In addition, myopia now is being diagnosed at a younger age and tends to progress more rapidly to become high myopia.[3] Hence, there are concerns that advanced myopia will become more common in the future.[4] High myopia is associated with sight-threatening eye diseases such as myopic macular degeneration, retinal detachment, and glaucoma, due to axial length elongation.[5]

Several interventions have been shown to be effective in slowing down the progression of myopia, and one of them is orthokeratology (Ortho-K).[6] The Ortho-K is a specialized clinical technique of overnight wear of high-DK gas-permeable rigid contact lenses for the correction of myopia through corneal reshaping.[7] The first clinical study on the Ortho-K was reported in Hong Kong, that involved 35 children aged 7-12 years wearing Ortho-K lenses and 35 children in a single vision spectacles (SVS) control group.[8] The results demonstrated a reduction rate of 46% in the progression of myopia induced by wearing the Ortho-K lenses. Walline et al. fitted 40 children, aged 8 to 11 years with myopia (-0.75D to -4.00D), with the

Ortho-K lenses and measured the axial length (AL) changes annually for 2 years.[9] The subjects were age-matched to soft contact lens wearers from another myopia control study, and the results showed that wearing the Ortho-K lenses reduced 55% of AL elongation over the period of 2 years, with a significantly lower annual rate of change than the control group. In a study, Retardation of Myopia in Ortho-K (ROMIO), Cho and Cheung randomly assigned 102 myopic children aged 6-10 years with myopia of -0.50 to -4.00D to wear the Ortho-K lenses and SVS for a period of 2 years. [10] The authors concluded that children wearing Ortho-K lenses had a slower increase in AL elongation by 43% than the SVS group; and that younger children tended to have faster axial elongation and may benefit from early Ortho-K treatment.

It is hypothesized that the Ortho-K lenses control the progression myopia by flattening the central cornea and forming a junction wherein the oblate part of the cornea returns to its original curvature, which effectively results in images focusing centrally on the fovea, while the peripheral light focuses anterior to the peripheral retina, thus creating myopic defocus.[11] The simultaneous creation of peripheral myopic defocuses while still providing clear foveal vision has been assumed to be the reason why the Ortho-K lenses have been reported to slow the progression of myopia. Queiros et al measured peripheral refraction along the horizontal meridian of 28 myopic subjects before and after one month of wearing the Ortho-K lenses.[12] Their study reported a hyperopic change in the central refractive error, which indicated the elimination of uncorrected myopia within the central ±20° of retinal eccentricity (a significant myopia reduction at the central 40) and a myopic shift in the peripheral beyond 25°.

To date, there is no published report about the long-term impact of wearing the Ortho-K lenses on refraction and AL elongation in myopic children in Malaysia. Previous reports focused on the short-term impact (1 week and 6M) of wearing the Ortho-K lenses in children and young adults but not on the progression of myopia. [14,15] Given the significant increase in myopia prevalence specifically in the East Asian region and the growing interest in Ortho-K treatment, it is essential for optometrists to have reference data from the Malaysian population specifically on the efficacy of the Ortho-K in controlling progression of myopia. Thus, this study was conducted to investigate changes in the refraction and axial length (AL) elongation in myopic school children after 12 months of wearing the Ortho-K lenses. The results were compared with single vision spectacles (SVS).

MATERIALS AND METHODS

This was a prospective longitudinal clinical study involving myopic school children, aged 8 to 9 years old from Kuala Lumpur. The inclusion criteria were spherical equivalent refractive error (SER) of -0.75<SER<-4D, astigmatism less than ≤1.50D in both eyes and demonstrated myopia progression of at least -0.75D in the 12 months or at least -0.50D in the 6 months prior to enrollment, based on past records. They were further required to have a best corrected visual acuity (VA) 0.0 log of the minimal angle of resolution (logMAR) in each eye, a birth weight of ≥ 2000g, and no history of ocular or systemic disease, myopia treatment, or contact lens use.

Subjects were allocated to either the Ortho-K group or the SVS group based on the decisions of the children and their guardians. They were given a balanced account of the advantages and disadvantages of the two vision correction modalities offered in this study (SVS or Ortho -K lens). Care was taken not to suggest that one modality might perform better than the other or provide better control over the progression of myopia. This study was approved by the Ethics Committee of the Universiti Kebangsaan Malaysia (UKM PPI-800-1/1/5 JEP-2017-422) and was conducted in accordance with the tenets of the Declaration of Helsinki. Written consent was obtained from the parents or guardians of all participants prior to data collection.

Based on the results from previous studies [16], the sample size calculation using the statistical power of 95%, type 1 error probability of 0.05, and the two-tailed paired t test showed that the minimum sample size for the treatment group was estimated to be 8, and it was 6 for the control

group. To account for the possibility of subjects dropping out during the 12 months, as well as the higher accuracy in parametric statistical tests, the minimum sample size was estimated to be at least 20 for each group.

Subjects in the control group were prescribed distance SVS with a spherical design and made of plastic material with a refractive index of 1.56 (Integrated lens technology, ILT, Singapore) having the most plus power with optimum VA, and they were asked to wear the spectacles all the time. The prescription was updated when the monocular aided vision was 0.18 (logMAR) or worse or when the change in SER was -0.50D or greater. Subjects in the Ortho-K group were fitted with Menicon Z night Ortho-K lenses (NKL Contactlenzen, The Netherlands) made of gas-permeable material (Menicon ZÔ) to be worn overnight. The lenses were made of siloxanylstyrene fluoromethacrylate (Tisifilcon A) material (DK 163 ISO, central thickness 0.24mm). The total lens diameter was 10.60 mm with a 6.0mm diameter optic zone. The initial lens parameters were determined using the computer software provided by the manufacturer (Easyfit Software, Menicon Ltd, Nagoya, Japan). Corneal topography and cycloplegic refraction data for both eyes were input into the software, which automatically calculated the specifications of the trial lens to allow the Ortho-K lens fitting. The Ortho-K lenses were ordered and dispensed to subjects approximately 3 weeks after the baseline (BL) examination.

Examination and measurement

Cycloplegic refraction was performed at BL and every 6 months on all subjects, after the commencement of the study. Following the instillation of topical anesthetic (Proxymetacaine hydrochloride 0.5%, Alcaine, Alcon), cycloplegia was induced using two drops of (Cyclopentolate hydrochloride 1%, Cyclogel, Alcon) separated by 5-minute intervals. Objective refraction measurements were taken with the WAM-5500 autorefractor (Grand Seiko Co. Ltd., Hiroshima, Japan) when the pupil size was larger than 5mm and were refined using subjective refraction.

The eye rotation technique was used to obtain the peripheral refraction (PR) in this study. All subjects were instructed to stabilize their heads while facing straight ahead and to rotate their eyes to fixate on high-contrast letter targets with the sizes of 6/12 (20/40, 0.3 logMAR) that were mounted on the wall at 4 m. These targets were separated by 10° intervals over the central ±30° interval across the horizontal eccentricities in the nasal and temporal visual fields (VFs, 30° N, 20° N, 10° N, center 10° T, 20° T, 30° T). As the eye rotated, the axis of the autorefractometer was aligned with the pupil's center and the corneal reflex. When measuring the right eye, the left eye was occluded, and *vice versa*. Five consistent measurements were taken at each point of the target, and the mean was obtained. If an error or fixation loss was found, the reading was discarded and repeated. The results were recorded as visual field (VF) eccentricities, where the nasal VF represented the temporal retina, and the temporal VF represented the nasal retina. Refractive error readings were obtained in the form of sphere (S), cylinder (C), and axis (θ).

The results were then calculated by converting the spherocylindrical refractive error into power vector components—M, J180, and J45—as recommended by Thibos et al below:

$$M = S + C/2,$$
$$J180 = -(C/2)\cos(2\theta),$$
$$J45 = -(C/2)\sin(2\theta),$$

where M represents the mean spherical equivalent, J180 represents the horizontal component, and J45 represents the oblique cross-cylindrical component.[17] However, only M was analyzed in this report.

An ultrasound direct contact A-Scan (PacScan Plus, Sonomed Escalon, NY) was used to measure the AL. One drop of local topical anesthetic (proxymetacaine hydrochloride 0.5%, Alcaine, Alcon, 15mL) was administered to the subject's eye before starting the measurement. When taking the measurements, the transducer hand-held probe was brought into contact

perpendicularly with the cornea to its center, with minimal possible compression. The outcome was calculated by a single continuous beep, which automatically recorded the mean of five measurements with a standard deviation of <0.30 mm. AL evaluation was carried out at the BL and 6 and 12-month follow-ups. Visual acuity (VA) was determined using a logMAR chart at 6 meters. The contact lens fitting and anterior segment health were examined using a slit lamp biomicroscope (Righton MW50D LED, Tokyo, Japan).

Statistical analysis

The data obtained in this study were analyzed using the statistical software Statistical Package for the Social Sciences (SPSS, version 21.0), and only data for the right eye were included in the analysis to avoid the confounding effect from intercorrelation. All data were normally distributed. The paired t test was used to compare the results at BL, 6 months, and 12 months of wearing Ortho-K and SVS. Repeated measures ANOVA was used to compare variables within the same subject at BL, 6 months, and 12 months of wearing Ortho-K and SVS.

RESULTS

In total, 80 children were initially selected to participate, but only 70 of them (45 Ortho-K and 25 SVS) completed the study. Of the five children in the Ortho-K group who did not proceed, one (1) child was unable to control his frequent eye rubbing habit, two children showed poor compliance to contact lens wear, and another two children dropped out due to COVID-19 infection. A total of five children from the SVS group were dismissed due to non-compliance during follow-up visits. There were no statistically significant differences in the BL data between both groups (p>0.05). The demographic and BL data of the participants are described in Table I.

The measurements at BL, 6M, and 12M for both groups are shown in Table 2. The central refraction was reported in spherical equivalent (SE). At BL, the SE in the Ortho-K group was -2.92 ± 1.07D (range -0.75D to -4.59), while the SE in the SVS group was -2.51 ± 1.12D (range -0.75 to -4.41D). No significant differences were shown in the SE between both groups at BL (p=0.127). In the Ortho-K group, the SE decreased significantly from -2.92 ± 1.07D at BL to -0.15 ± 0.13D at 6M and -0.06 ± 0.12D at 12M (p<0.05), respectively. In the SVS group, the SE increased significantly -2.51 ± 1.12D at BL to -3.15 ± 1.08D and 3.77 ± 1.23D at 6 and 12M (p<0.05), respectively.

Table I. Clinical demographics and baseline measurements of both study groups

Parameters		Ortho-K	SVS	p value
Age (y)		8.38 ± 0.49	8.20 ± 0.41	0.110
Male/Female*		21/24	15/10	0.289
Refractive error (D)		-2.92 ± 1.07	-2.51 ± 1.12	0.127
VA (unaided)		1.21 ± 0.65	1.12 ± 0.62	0.577
Axial length (mm)		23.85 ± 0.71	23.49 ± 0.95	0.081
Cornea FK (D)		43.6 ± 1.27	43.12 ± 1.03	0.116
Central corneal thickness (CCT) (um)		537.6 ± 28	528.44 ± 22.1	0.065
Peripheral refraction (D)	N30	-1.92 ± 1.01	-1.89 ± 0.93	0.906
	N20	-2.45 ± 1.06	-2.30 ± 1.16	0.588
	N10	-2.95 ± 1.06	-2.72 ± 1.35	0.44
	C	-3.22 ± 1.11	-3.03 ± 1.35	0.529
	T10	-2.92 ± 1.11	-2.76 ± 1.30	0.592
	T20	-2.50 ± 1.08	-2.47 ± 1.21	0.899
	T30	-2.02 ± 1.11	-1.95 ± 1.18	0.781

Ortho-K= orthokeratology, SVS= single vision spectacles, D= diopter, VA = visual acuity, PR= peripheral refraction, CCT= central corneal thickness, FK= flat keratometry, N= nasal retina, T= temporal retina

Table II. Measurements at baseline and 12 months for both study groups

Parameters	BL		p value	12 months		p value
	SVS	Ortho-K		SVS	Ortho-K	
Refraction (D)	-2.51 ± 1.12	-3.22 ± 1.11	0.529	-3.77 ± 1.23	-0.06 ± 0.12	0.000 *
VA (unaided)	± 0.62	1.21 ± 0.65	0.577	1.73 ± 0.95	-0.03 ± 0.09	0.000 *
Cornea FK (D)	43.12 ± 1.03	43.6 ± 1.27	0.116	43.28 ± 0.96	40.69 ± 2.54	0.000 *
AL (mm)	23.45 ± 0.97	23.85 ± 0.71	0.082	23.97 ± 1.02	23.64 ± 0.75	0.002 *
CCT (um)	537.6 ± 28	528.44 ± 22.1	0.065	538.28 ± 28.22	524.22 ± 22.25	0.018 *

*p<0.05 significant value. Ortho-K= orthokeratology, SVS= single vision spectacles, HCVA = high-contrast visual acuity, LCVA = low-contrast visual acuity, D = diopter, CCT= central corneal thickness, FK= flat keratometry.

The mean difference in the SE at 6 and 12M was significantly lower in the Ortho-K group when compared to the BL. The mean SE reduced to 2.78 ± 1.07D and 2.86 ± 1.11D at 6 and 12M, respectively (p<0.05). In the SVS group, the mean difference in SE progression was significantly higher than that at BL (p<0.05). At 6 and 12M, subjects in the SVS group presented an increase in the mean SE of -0.65 ± 0.54D and -1.26 ± 1.01D. Regarding VA, the unaided VA improved significantly in the Ortho-K group from 1.21 ± 0.65 at BL to -0.03 ± 0.08 at 6M and -0.03 ± 0.09 at 12M post treatment (p<0.05); however, the VA deteriorated significantly from 1.12 ± 0.62 at BL to 1.43 ± 0.78 and 1.73 ± 0.95 at 6 and 12M, respectively (p<0.05), in the SVS group. A significant negative correlation was noted between the

change in the SE and the unaided VA (r=-0.752, p<0.05) in the Ortho-K group.

The AL decreased significantly from 23.85 ± 0.71mm (BL) to 23.75 ± 0.49 (6M) and 23.64 ± 0.59mm (12M) in the Ortho-K group (p<0.05); however, it increased significantly from 23.49 ± 0.95mm (BL) to 23.73 ± 0.54mm (6M) and 23.97 ± 0.59mm (12M) (p<0.05) in the SVS group. When comparing between groups, no significant differences were shown in the AL between both groups during the first 6M, (p>0.05); however, a significant difference was noted at 12M (p<0.05). Regarding the progression of AL, the mean difference in AL progression was significantly lower in the Ortho-K group compared to the SVS group. At 6 and 12M, the subjects in the Ortho-K group showed a reduction in the mean AL to -0.10 ± 0.24mm (6M) (p<0.05) and -0.18 ± 0.38mm(12M) (p<0.05). In the SVS group, the mean difference in the AL progression was significantly higher when compared to the BL. At 6 and 12 M, the subjects in the SVS group showed an increase in the mean AL of 0.24 ± 0.45mm (6M) (p<0.05) and 0.48 ± 0.47mm (12M) (p<0.05). A significant negative correlation was shown between the change in AL and SE within 12M of wearing Ortho-K lenses (r=-0.238, p<0.05).

Wearing the Ortho-K lenses flattens and thins the central cornea. The FK decreased significantly from 43.6 ± 1.27D at BL to 42.17 ± 1.52D at 6M and 40.69 ± 2.54D at 12M after treatment (p<0.05). In the SVS group, the FK increased significantly from 43.12±1.03D at BL to 43.3±1D and 43.47 ± 1.1D at the 6M and 12M follow-ups (p<0.05). The mean difference in FK was significantly lower in the Ortho-K group as compared to BL. At 6 and 12M, the mean FK reduced to -1.43 ± 1.27D and-2.91 ± 2.58D, respectively, both (p<0.05). In the SVS group, the mean difference in FK was statistically significantly higher when compared to the BL. At 6 and 12M, the mean FK in the SVS group increased to 0.18 ± 0.33 and 0.35 ± 0.7mm, respectively.

The CCT in the Ortho-K group decreased from 528.53 ± 22.26 at BL to 526.89 ± 21.81um at 6M and 524.87 ± 23.15 at 12M after treatment (p<0.05). No significant change was noted in the CCT of the SVS group (p>0.05). When comparing between groups, no significant differences were shown in both groups during the first 6M, (p>0.05), but significant differences were noted between both groups at 12M (p<0.05). The mean difference in CCT showed a statistically significant reduction in the Ortho-K when compared to the BL. At 6M and 12M, the subjects in the Ortho-K group showed a reduction in the mean CCT; -1.64 ± 6.08um (p>0.05) and -3.67 ± 11.12um (p<0.05), respectively. No significant difference was noted in the SVS group.

Relative peripheral refraction (RPR)

The M-value from the RPR measurements (N10°, N20°, N30° and T10°, T20° and T30°) at the BL and 12M is shown in Table 3. All subjects in both groups showed hyperopic RPR at the BL, and it did not significantly vary between the Ortho-K and SVS groups (p > 0.05). However, the RPR at all eccentricities in the Ortho-K group was significantly more myopic at 12M than at the BL (p < 0.05) and was evident with a myopia increment beyond 20° of the visual field. By contrast, in the SVS group, the RPR at 12M was significantly more hyperopic than that at the BL, thus increasing the hyperopic defocus (p < 0.05) (Table 3, Figures 1 and 2). The difference in the RPR measurements between the nasal and temporal parts of the retina in both groups was also analyzed and was found to be insignificant (p > 0.05).

Table III. Mean RPR (M-value) in both the Ortho-K and SVS groups at the BL and 12 months

	Ortho-K (n=45)			SVS (n=25)		
Eccentricities	BL	12M	p value	BL	12M	p value
RPR-30N	1.3 ± 0.55	-1.38 ± 0.64	0.000*	1.14 ± 0.92	2.58 ± 1.33	0.001*
RPR-20N	0.76 ± 0.45	-0.71 ± 0.54	0.000*	0.72 ± 0.57	1.94 ± 1.06	0.000*
RPR-10N	0.27 ± 0.30	-0.19 ± 0.53	0.000*	0.31 ± 0.33	0.76 ± 0.75	0.013*
RPR-10T	0.3 ± 0.24	-0.20 ± 0.46	0.000*	0.27 ± 0.33	0.72 ± 0.60	0.003*
RPR-20T	0.72 ± 0.42	-0.80 ± 0.44	0.000*	0.56 ± 0.74	1.73 ± 0.99	0.000*
RPR-30T	1.19 ± 0.49	-1.40 ± 0.58	0.000*	1.08 ± 1.02	2.25 ± 0.94	0.000*

*p<0.05 significant value
Ortho-K= orthokeratology, SVS= single vision spectacles, RPR = relative peripheral refraction, N = nasal, T=temporal.

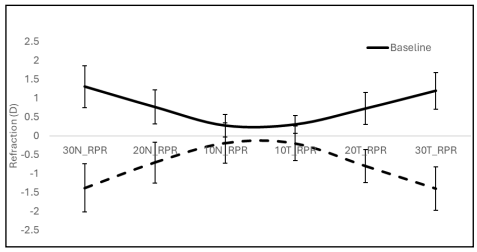

Figure 1. Mean relative peripheral refraction (RPR) at baseline and 12 months in orthokeratology lens wearers.

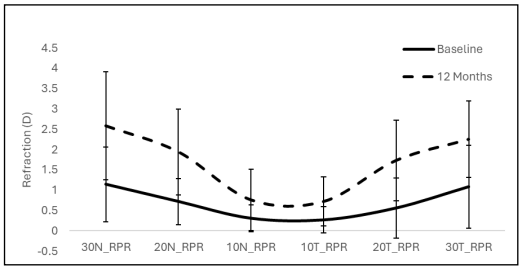

Figure 2. Mean relative peripheral refraction (RPR) at baseline and 12 months in single vision spectacle wearers

DISCUSSION

The efficacy of orthokeratology in reducing the myopic refractive error and thereby providing an improved unaided VA has been well documented by several investigators.[8-10] Nevertheless, to our knowledge this is the first reported study about the efficacy of the Ortho-K lenses in controlling progression of myopia in Malaysian children. Overall, the results of this study demonstrated that wearing the Ortho-K lenses for 12M successfully reduced myopia progression and improved unaided VA in Malaysian children. The unaided VA improvement in this study was consistent with the reduction in the refractive error, where more than 90% of refractive correction was achieved after 6M of wearing the Ortho-K lenses. Chen et al reported that the Ortho-K lenses successfully corrected and reduced myopia from -2.46D at BL to 0.18D at 6M and with no subsequent change at 12M. [18] As for the control group, the amount of myopia increased gradually from -2.04±1.09D to -3.17±1.22D at 12M, which is similar to the findings of this study. In a meta-analysis review study, Lee et al reported that children in the Ortho-K group had a significantly lower trend ($p<0.001$) of refractive error change during the follow-up periods.[19] The authors concluded that wearing overnight of the Ortho-K lens was effective in slowing the progression of myopia and improved unaided VA, over a 12-year follow-up period.[19]

Regarding AL elongation, the results of this study showed that wearing the Ortho-K lenses successfully reduced AL progression by 47% within the period of study. The results are consistent with the outcomes of previous investigations.[8, 10] In the LORIC study in Hong Kong, the authors reported that AL elongation was reduced by 46% after 2 years of wearing the Ortho-K lenses, compared to spectacle-wearing historical controls.[8] In a study conducted in Spain, Santodomingo-Rubido et al reported that the AL in children wearing the Ortho-K lenses was shorter than that in those wearing the SVS lenses (0.22m vs. 0.37mm) over a 12M period.[20] Nevertheless, the results of this study also demonstrated an AL shortening of -0.18±0.38mm after 12M of wearing the Ortho-K lenses. Swarbrick et al revealed a significant shortening of the AL -0.02±0.05mm and -0.04±0.08 at 6 and 12M, respectively, in subjects who were assigned to wear the Ortho-K treatment in their study. [21] Wang et al also reported an AL shortening of -0.08 ± 0.04 mm and -0.28 ± 0.19 at 1 and 20M post Ortho-K lens wear.[22] The authors suggested that the apparent shortening of AL among the Ortho-K lens wearers may reflect the contribution of Ortho-K-induced central corneal thinning, combined with choroidal thickening or recovery due to a reduction or neutralization in the myogenic stimulus to eye growth in these myopic children.[22] The thinning of the CCT was observed among Ortho-K wearers in this study, which may indirectly contribute to the AL shortening. However, choroidal thickness was not measured in this study; therefore, its contribution cannot be confirmed and warrants further investigation.

The results of this study also demonstrated that wearing the Ortho-K lenses for 12M caused significant hyperopic shifts within 20 degrees of central refraction and myopic defocus beyond 30 degrees along the horizontal meridian, which support previous studies. Queiros et al measured the PR along the horizontal meridian of 28 subjects with mean age 24.6±6.3 years and myopia between -0.88 and -5.25D before and after wearing the Ortho-K lenses for 1M.[12] The authors concluded that the Ortho-K lenses invert the pattern of peripheral refraction in SE, creating a treatment area within the central 25 degrees of the visual field and a myopic shift beyond 25 degrees.[2] Yoo et al compared the impact of wearing the Ortho-K lenses and SVS on PR and progression of myopia in a population of South Korean children.[23] Their results also showed peripheral myopia across the horizontal meridian of the retina, at 30T, 20T, 10T, 10N, 20N, and 30N from the fovea. The authors also reported that the central AL elongation in children who wore the Ortho-K lenses was shorter than those who wore SVS after 12M of treatment.[23]

Overall, this study demonstrates that wearing the Ortho-K lenses for 12M alters refraction, creates myopic defocus at the peripheral retina, and reduces AL elongation and progression of myopia in children. It is hypothesized that Ortho-K lenses correct central myopia by flattening the central cornea and increasing the steepness of the mid-peripheral cornea, which indirectly leads to the increase in the myopic defocus and ocular higher-order aberrations on the peripheral retina, which maybe the stimulus for slowing eye growth, thereby reducing the visual feedback for AL elongation. [18, 23] The outcomes of this study concurred with the hypothesis.

Nevertheless, there are several limitations of this study that must be acknowledged. The first is the short follow-up period, which makes it difficult to determine whether the change in PR was the stimulus for AL elongation or the resultant effect of the AL growth. A longer follow-up period is recommended so that the impact of the magnitude of RPR myopic shifts on the progression of myopia can be monitored. Second, the PR on the vertical meridian was not measured in this study. Mutti et al reported that myopic subjects demonstrated myopic defocus in the vertical meridian relative to the fovea. [24]

CONCLUSION

This study concludes that the Ortho-K lenses are effective in controlling the progression of myopia in Malaysian children. More eye care practitioners should consider prescribing Ortho-K lenses when managing myopic children in the local population.

ACKNOWLEDGEMENT

This research was funded by Menicon Ltd, Japan (NN2022-019).

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ORIGINAL ARTICLE

A Qualitative Exploration of Diabetes Self-Management among Young People with Type 2 Diabetes Mellitus in Malaysia

Othman N[a,b], Lean QY[b,c], Neoh CF[a,d], Abd Wahab MS[a,e], Mohd Noor N[f,g], Lim SL[h], Wong YY[a,d]

[a]Faculty of Pharmacy, Universiti Teknologi MARA (UiTM), Cawangan Selangor, Kampus Puncak Alam, Selangor Darul Ehsan, Malaysia
[b]Faculty of Pharmacy, Universiti Teknologi MARA (UiTM), Cawangan Pulau Pinang, Kampus Bertam, Pulau Pinang, Malaysia
[c]Vector-Borne Diseases Research Group (VERDI), Pharmaceutical and Life Sciences CoRe, Universiti Teknologi MARA, Selangor, Malaysia
[d]Collaborative Drug Discovery Research (CDDR) Group, Pharmaceutical & Life Sciences Community of Research, Universiti Teknologi MARA, Selangor, Malaysia
[e]Non-Destructive Biomedical and Pharmaceutical Research Centre, Universiti Teknologi MARA (UiTM), Selangor, Malaysia
[f]Endocrine Unit, Hospital Putrajaya, Precint 7, Malaysia
[g]Clinical Research Centre, Hospital Putrajaya, Precint 7, Malaysia
[h]Department of Medicine, Division of Endocrinology, Penang General Hospital, Pulau Pinang, Malaysia

ABSTRACT

INTRODUCTION: Diabetes self-management, an essential part of diabetes care, involves complex cognitive abilities such as performing medical, physical, and emotional management tasks. Nonetheless, little knowledge is available on how the young population with type 2 diabetes mellitus (T2DM) in Malaysia engages in self-management, despite the growing prevalence of T2DM in this group. Therefore, this study aimed to explore self-management behaviours among young people with T2DM. **MATERIALS AND METHODS:** In-depth interviews were conducted with sixteen young people aged between 10 and 24 years old at two tertiary hospitals in Malaysia, and data were analysed thematically. **RESULTS:** The themes that emerged revealed that young people demonstrated different levels of activation in self-managing their T2DM, which can be grouped into proactive, adaptive, inadequate, and negligent. **CONCLUSION:** The young people in this study recognised the importance of diabetes self-management; however, they needed the support from caregivers, friends, and healthcare professionals to maintain emotional well-being and sustain daily diabetes self-management.

Keywords
Diabetes self-management; Type 2 diabetes mellitus, young people, qualitative study

Corresponding Author
Dr. Yuet Yen Wong
Faculty of Pharmacy, Universiti Teknologi MARA (UiTM), Cawangan Pulau Pinang, Kampus Bertam,, Pulau Pinang, Malaysia.
Email: yuetyen@yahoo.com

Received: 28th June 2023; Accepted: 11th February 2026

Doi: https://doi.org/10.31436/imjm.v25i02/2405

INTRODUCTION

Type 2 diabetes mellitus (T2DM) has become a major public health concern among young people (aged 10 to 24 years) worldwide, including in Malaysia.[1] This phenomenon has been associated with urbanisation and industrialisation, the general transition to a sedentary lifestyle, globalisation, and the commercialisation of fast food products and consumption. [2,3] As young people with T2DM are at higher risk of developing diabetes-related micro- and macrovascular complications, diabetes self-management is the foundation of better T2DM health outcomes.[4]

Whilst several studies have explored diabetes self-management among adults with T2DM, the self-management behaviours of young people and adults may differ because the former might be less mature[5] and display lower self-efficacy in executing diabetes self-management tasks.[6,7] In addition, the management and treatment among young people is challenging since most of them have poorer illness control, behavioural problems, or risk-taking behaviours as compared to other groups of persons without chronic illness.[8,9] Previous studies of adolescents with T2DM have focused mainly on Western settings and generally aimed to identify the factors that influence diabetes self-management among young people. [10] There is also a lack of studies on the

patterns of diabetes self-management practices among young people from a multi-racial country such as Malaysia. Such information could aid in the development of interventions for young people at various stages of diabetes self-management. Therefore, this study aimed to explore the practices and self-management styles among young people with T2DM in Malaysia.

MATERIALS AND METHODS

Study design

Using descriptive phenomenology to explore the authentic experiences of individuals living with a common phenomenon, a qualitative study was conducted in the endocrine clinics of two Malaysian tertiary hospitals from November 2019 to September 2020. The purposive sampling method was used to recruit the informants, who were young people aged 10 to 24 years old [11], with a T2DM diagnosis for at least six months, and who could communicate in Malay or English. Potential informants were first identified by endocrinologists and nurses based on their medical records. Next, potential informants waiting for a doctor's consultation during their routine medical follow-ups were approached by the first author (NO) for an interview after obtaining informed consent.

Data collection

The informants were interviewed either in a secluded corner near the clinic or *via* telephone. As all the investigators were proficient in English or Malay, the interviews were conducted in either language, depending on the informants' preferences. The interviews were conducted using a semi-structured interview guide, which had been developed based on the literature review and the findings from a previous meta-synthesis conducted by the investigating team.[10] The interview sessions were audiotaped and lasted approximately 20-40 minutes.

In-depth interviews were conducted until saturation.[12] The informants' sociodemographic data, types of treatment, and anthropometric data were obtained from their medical records.

Data analysis

The data was first familiarised by iteratively listening to the audio recordings before transcription. For the interviews conducted in Malay, the transcripts employed the same language to maintain the exact meaning of the original conversations. Analysis was conducted in Malay and English to maintain contextual validity, and the selected participants' quotes were translated into English. The transcripts were read and verified by the informants and the other investigators (YYW and QYL) to ensure the accuracy of information.[13]

Thematic analysis was used to analyse and report themes within the data.[14] All the transcripts were line-by-line coded by NO to generate as many open codings as possible.[15] Then, NO held regular meetings with the team (YYW and QYL) to review, arrange, or collapse similar codings into sub-themes and finally generate the overarching themes.[16] The final themes were subsequently cross-checked and agreed upon by all the authors. The informants were identified and categorised into "pro-active", "adaptive", "inadequate", or "negligent", based on their diabetes self-management practices that emerged during the analysis process.[17,18]

All the qualitative data were managed using NVivo (QSR NVivo version 12, QSR International), whilst the informants' sociodemographic and anthropometric data were managed using Microsoft Excel® (Microsoft Corp, Redmond, WA, USA) and analysed using IBM® SPSS® version 20. The continuous data were presented as the median and interquartile range (IQR).

RESULTS

Characteristics of the young people

Sixteen young people with T2DM participated in this study. The majority were female (n=12) with a median (IQR) age of 19 (16.8-21.0) years old. Only one informant was diagnosed with nephropathy, whilst others did not suffer diabetes-related complications at the time of data collection. Table I summarises the clinical characteristics and the management of T2DM among the informants.

Table I: Young informants' sociodemographic characteristics (n = 16)

Characteristics	Median (IQR)	n (%)
Age (years)	19 (16.8-21.0)	
Gender		
Female		12 (75)
Male		4 (25)
Anthropometry		
BMI (kg/m²)	28.9 (22.9-34.0)	
BMI category*		
Normal		5 (31)
Pre-obese		4 (26)
Obese I		3 (19)
Obese II		3 (19)
Obese III		1 (6)
Age at diagnosis (years)	13 (10.8-16.5)	
Duration of diagnosis (years)	3 (1-8.5)	
HbA_{1c} (%)**		
≤7.0%	9.9 (6.7-11.5)	5 (31)
>7.0%		11 (69)
Physical activity***		
Yes		12 (75)
No		4 (25)
Management of T2DM		
Therapeutic lifestyle changes		2 (13)
Metformin		6 (38)
Insulin		2 (13)
Metformin and insulin		6 (38)
Types of insulin regimens		
Basal only		3(37.5)
Basal-bolus		1(12.5)
Pre-mixed		4 (50)

IQR, Interquartile range; T2DM, type 2 diabetes mellitus; BMI, Body Mass Index; HbA_{1c}, Glycated haemoglobin *Classification of weight by BMI (kg/m2); Underweight = <18.5; Normal range = 18.5-22.9: Pre-obese = 23.0-27.4; Obese I =27.5-34.9; Obese II =35.0-39.9; Obese III = >40 [19] **The most recent HbA_{1c} obtained from the informant's medical record at the point of interview ***Physical activity is defined as engagement in at least 150 minutes per week of moderate-intensity activity. For the answer "Yes", it indicated the respondents were able to complete physical activity for 150 minutes per week, while the answer "No", it indicated the respondents were unable to complete physical activity for 150 minutes per week.

Themes

Theme 1: Diabetes self-management activities

All the informants expressed the view that lifestyle modification is imperative for achieving optimal health outcomes. The diabetes self-management behaviours frequently practised by the informants were dietary changes, medication taking, physical activity, symptom monitoring, risk reduction, and healthy coping.

Dietary Changes

Almost all the informants attempted to eat healthily, for instance, by avoiding foods with high sugar content, reducing rice portion sizes, intermittent fasting, starting to consume brown rice, and monitoring their calorie intake.

"I tried to reduce my glucose intake by reducing sweet foods and drinking lots of water." (P#10)

However, the young people were sometimes unable to resist the temptation of certain foods or drinks, such as when going out with friends or seeing advertisements on social media.

"I still ate fast food and sweet drinks, once a month, when I am going out with my friends." (P#14)

"… Of course, I have the desire to eat, especially viral food [food that had been advertised on social media]. So that was the hardest part." (P#08)

Medication taking

Most informants acknowledged that taking medications was crucial for optimal glycaemic control. The subjects of the study practised medication adherence strategies, such as punctual post-meal medication taking or keeping medication close to hand. Informants with long-standing (11 years) T2DM claimed that medication taking had become part of their daily rituals.

"I took medicine as usual, to manage, I will make sure I take medicine right after a meal." (P#12)

However, some informants expressed concern about the side effects of medications, such as headache, fatigue, and weight gain. Moreover, some of them neglected their medication routine as they felt overwhelmed by the daily demands of diabetes self-management. Another reason might be attributed to the overwhelming daily demands of multiple insulin injections.

"Because of the medicine, sometimes I become easily tired and sleepy. At work, I kept drinking water to keep fresh, because I am afraid that anything might happen to me." (P#01)

"Sometimes I am too lazy even to look at my medicines. I just look at the medicine; sometimes, I do not inject at all." (P#14)

Physical activity

Physical activity tended to be performed by the school-age informants, as sport is on the school syllabus. However, in general, the involvement of young people in sports activities was minimal, especially among females. Common reasons for their lack of physical activity included time constraints, low self-esteem, feeling uncomfortable when exercising alone in public, living in a

rural area, and feeling too tired to exercise.

"For me, the difficult part is exercise, as it will take my time and energy." (P#01)

Self-monitoring blood glucose (SMBG)

SMBG was frequently performed by young people using insulin, but rarely by those treated only with metformin or therapeutic lifestyle changes.

"I did glucose monitoring at home. Previously, 7 times per day, 7 times, before and after a meal. But now, the doctor asked me to do it just once daily. From there, I know my blood glucose level, and I control my meals based on the glucose reading." (P#08)

Meanwhile, not having a glucometer or glucose strips, fear of finger pricking, and not knowing how to use a glucometer were the reasons given by the informants for not performing SMBG.

"… My mother has her glucometer, but I don't know how to use it, so I rarely check my glucose at home." (P#10)

Risk reduction

To resolve hypoglycaemia, several informants who had experienced this acute event mentioned their strategies, such as keeping sweets nearby, adjusting insulin doses, and taking medications punctually.

"I have experienced hypoglycaemia before, I took sweet, 3 sweets, I took sweet anywhere I go." (P#04)

Healthy Coping

The young people encountered stress due to the disease and its management, yet they found ways to cope. For example, the female informants preferred to talk and seek advice from their friends during their T2DM journey.

"Sometimes I feel I want to rebel, then I always call my friend, tell her my problem about this [T2DM management], then she gives me advice." (P#14)

Theme 2: Diabetes self-management styles

Although the activities mentioned above are essential to controlling the disease and delaying its advancement, not all the self-management behaviours were collectively practised by the young patients. The data obtained suggests that the informants could be grouped into four diabetes self-management styles: proactive, adaptive, inadequate, and negligent, based on their levels of effort in diabetes self-management. Table II summarises the diabetes self-management styles adopted by the young people with T2DM in this study.

Table II: Diabetes self-management styles among the young people with type 2 diabetes mellitus

Self-management styles	Pro-active	Adaptive	Inadequate	Negligent
Young informants' diabetes self-management behaviours	They were strict in their diet, medication taking, and SMBG.	Maintained a healthy diet and performed physical activity, but the people around them might influence their diabetes self-management behaviours.	Performed certain self-management tasks, but they tended to make excuses to avoid practising the behaviours.	Not performing any diabetes self-management due to diagnosis denial.
Caregiver's involvement	No caregiver involvement due to independence.	Need involvement from caregivers.	Improper guidance from caregivers or rejection by informants.	Little to no caregiver involvement.
Informant(s)	P#03, 23 years old, duration 1 year, HbA1c=8.6% P#08, 21 years old, duration 1 year, HbA1c=6.5% P#09, 21 years old, duration 1 year, HbA1c=6.0% P#12, 21 years old, duration 11 years, HbA1c=6.1%	P#02, 18 years old, duration 8 years, HbA1c=12.6% P#04, 18 years old, duration 2 years, HbA1c= 12.6% P#13, 22 years old, duration 12 years, HbA1c= 11.0% P#14, 19 years old, duration 10 years, HbA1c=12.0% P#15, 19 years old, duration 8 years, HbA1c=11.3% P#16, 15 years old, duration 2 years, HbA1c=6.0%	P#01, 19 years old, duration 1 year, HbA1c=9.2% P#06, 17 years old, duration 4 years, HbA1c=16.4% P#07, 21 years old, duration 10 years, HbA1c=11% P#10, 16 years old, duration 3 years, HbA1c=7.7% P#11, 13 years old, duration 0.5 years, HbA1c=13.5%	P#05, 14 years old, duration 1 year, HbA1c=6.7%

SMBG = Self-monitoring blood glucose, HbA1c= glycated haemoglobin

Pro-active: The pro-active informants tended to accept responsibility for self-managing the disease and were committed to change by adhering to a healthy diet, medication taking, and SMBG. The proactive informants were older, and the majority had achieved good glycaemic control (Table II).

"I really take care [of my T2DM]. Even when I get pregnant, I can reduce [my HbA1c] to 6.5% as compared to before, 8.4%." (P#08)

Adaptive: Those who demonstrated the adaptive style recognised the importance of diabetes self-management;

however, they were not prepared for the autonomy of behavioural change. Most informants in this category were younger than those in the proactive category and had been diagnosed with T2DM for over 2-12 years. and had relatively poor glycaemic control, with most falling into the HbA_{1c} range of 11%-12.6%. The informants indicated that the involvement of parents is essential in their daily diabetes self-management, especially in ensuring healthy eating and medication taking, as narrated by one of the informants:

"I reduced my carbohydrate, fat, and sweet foods. My mum always cooks for me, fish and vegetables. She cooks either curry or steamed dishes." (P#04)

Moreover, support from friends was crucial in sustaining diabetes self-management, especially in out-of-home settings.

"… they [friends] are helpful. They will ask me whether I have already taken my medicines or not." (P#15)

Inadequate: The young people with inadequate diabetes self-management tended to manage their T2DM without proper guidance from their caregivers.

"My mother is also diabetic; she eats as usual. So, I just eat whatever I want as well." (P#07)

Some informants even exhibited rebellious behaviour and rejected their caregivers' instructions.

"Sometimes after school they ask me to take medicine. I am stressed. So, I told them to keep quiet and go. I know what to do." (P#06)

Negligent: Only one informant, having been categorised as negligent, was in denial about his diabetes status, as his HBA1c was low and therefore, he made no progress in learning and practising disease self-management. Moreover, the patient mistakenly thought that his HbA1c was 3.3%, given that he was in denial mode.

"… I am fine. My glucose level (HbA1c) is just 3.3% [correct value was 6.7%]. I ate 3 plates of rice and chicken for each mealtime. I ate 3-4 pieces of chicken or fish. I ate rice and chicken three times, morning, evening, and for dinner." (P#05)

Due to his condition, he had been mocked by his friends.

"…. I frequently need to go to pee [at school], and my friends make fun of me. I don't want to go to school, I want to change to another school, but my teacher said I had been dismissed from school." (P#05)

DISCUSSION

This study aimed to explore the diabetes self-management practices and styles of young people with T2DM in Malaysia. The current study findings echoed those of previous research, with healthy eating, medication taking, and physical activity identified as the most frequently performed diabetes self-management tasks among young people.[20,21] Meanwhile, a few young people who performed SMBG had an awareness of hypoglycaemia and displayed effective coping with T2DM, which are indispensable for patient empowerment.[22]

Previous meta-synthesis identified that individual knowledge, coping skills, and health status might influence diabetes self-management among young people with T2DM.[10] Our current findings suggested that the age of the informants and the duration of diagnosis may affect the style of diabetes self-management. The older informants tend to proactively self-manage their own illness. This is also confirmed in previous qualitative studies that the older young people are more mature than the younger group, thus having more understanding, better skills, and a willingness to take responsibility in managing their own illness.[23,24] Having said that, our findings speculated that individuals with longer duration of T2DM and suboptimal HbA_{1c} readings are found to have poorer diabetes self-management, which is in agreement with previous studies.[25–27] This study also clearly demonstrated that the patient's treatment modalities influence diabetes self-management style, particularly when combining insulin injections and oral medication. Most young people in the proactive group were managed by a single therapy, whereas the majority

of individuals in the adaptive and inadequate group were treated by a combination therapy including insulin injection. This situation suggests that young people with T2DM face challenges in self-management, especially those with complex insulin regimen therefore, future studies may seek to fill this gap.[28,29]

In addition, the young people from the pro-active group exhibited more discipline and autonomy in diabetes self-management, so they were the most likely to demonstrate controlled HbA_{1c}. The characteristics of the pro-active informants in this study resembled the attitudes of young people with pre-diabetes and T2DM reported in a previous study: those displaying highly disciplined, autonomous, and strategised diabetes self-management tended to achieve better HbA_{1c} control. [17] Furthermore, pro-active adults with T2DM were reported to be active in knowledge seeking and peer support groups.[18] Importantly, most informants in this group also had a shorter duration of T2DM, which may have contributed to better glycaemic control compared with the adaptive group, who generally had a longer disease duration and poorer HbA1c outcomes. Early in the disease trajectory, compensatory insulin secretion and fewer cumulative metabolic complications may facilitate glycaemic stability, thereby reinforcing the effects of proactive self-management behaviours.

Although the "adaptive" young people were shown to understand the importance of diabetes self-management, social support could influence the long-term sustainability of their diabetes self-management, as mentioned in the meta-synthesis.[10] In contrast, those classified as 'inadequate' were at the contemplation stage because they understood diabetes self-management but lacked motivation and action. This was possibly due to the influence of caregivers with diabetes, who tended to be poor role models for their children. The caregiver must be a positive role model in promoting self-management.[21] On the other hand, one patient was categorised as negligent despite having an HbA1c level of 6.7%. The relatively favourable HbA1c observed in this patient may be attributable to the short duration since disease diagnosis (approximately one year). During the early phase of diabetes, residual pancreatic b-cell function and endogenous insulin secretion may be partially preserved, permitting a transient compensatory response to hyperglycaemia and consequently contributing to lower HbA1c levels.[30] The "negligent" young patient, however, denied his diabetes status and was unmotivated in performing daily diabetes self-management tasks, which could potentially deter him from sustaining good glycaemic control. This corresponded with other study findings identifying that individuals who denied their diabetes diagnosis were less likely to assume responsibility for adopting lifestyle changes and diabetes self-management, which consequently jeopardised their health outcomes. [18,31]

The current findings revealed that the 'pro-active' group of young people, who possessed diabetes self-management discipline, awareness, and abilities, could serve as role models for effective diabetes self-management behaviour. Continuous support from family and friends is likely required by young people in the 'adaptive', 'inadequate', and 'negligent' groups. More enforcement by healthcare professionals is needed for those in the 'inadequate' and 'negligent' groups. These include frequent discussions with the young people and caregivers to identify the issues and to provide support in their self-management activities.[23,32,33] In addition, young patients need to accept responsibility for making lifestyle changes and cultivate a sense of empowerment to control their disease,[23,] and intervention in diabetes self-management education should include the participation of caregivers and peers to allow young people with T2DM to cope with external environments.[17]

This stratification of the young population based on their diabetes self-management styles might help healthcare professionals to identify which forms of support and services are needed to enable more proactive diabetes self -management among young people. The trustworthiness of this study was determined by employing four-dimensional criteria, namely credibility, transferability, dependability, and confirmability.[34] Accordingly, the credibility of the study was enhanced, whereby the researcher employed member checking by continually engaging authors who had rich experience in diabetes management to ensure the results reflected the

informants' perspectives. Furthermore, data triangulation was performed as the informants' clinical data were extracted from their medical records. The information about the study design and the data collection method was succinctly described in the method section of this manuscript for transferability. A maximal variation sampling strategy from two different hospitals was used in this study to maximise the range of relevant information and diversity of participants. For dependability and confirmability, the themes were generated based on the coding by three authors and further confirmed by all authors. Furthermore, the themes obtained were derived and supported by direct informants' quotations. An additional qualitative and quantitative study using a large sample size from various settings would be useful to confirm the influences on the different types of self-management practices and styles employed by young people with T2DM.

CONCLUSION

Most of the young people performed diabetes self-management, especially in terms of healthy eating, medication taking, and physical activity, exhibiting four identified categories of diabetes self-management style: proactive, adaptive, inadequate, and negligent. An understanding of the strengths and weaknesses of each diabetes self-management style would enable healthcare professionals to channel the appropriate support and services to enhance young people's ability to self-manage their T2DM.

INSTITUTIONAL REVIEW BOARD (ETHIC COMMITTEE)

The study was approved prior to its commencement by the Medical Research and Ethics Committee, Ministry of Health, Malaysia [NMRR-18-3476-44989 (IIR)] and the Universiti Teknologi MARA Research Ethics Committee [UiTM_600-IRMI (5/1/6)].

ACKNOWLEDGEMENTS

The authors would like to thank the Director General of Health for approving the publication of this manuscript. All the authors also would like to thank the healthcare professionals for their assistance in recruiting the participants. The cooperation of the informants and their caregivers is highly appreciated. The authors would like to thank the Faculty of Pharmacy, Universiti Teknologi MARA and the Ministry of Higher Education, Malaysia for supporting this study. A PhD scholarship awarded to NO by Universiti Teknologi MARA and the Ministry of Higher Education, Malaysia is gratefully acknowledged.

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ORIGINAL ARTICLE

Tualang Honey Ameliorates The Cholesterol Diet-Induced Non-Alcoholic Steatohepatitis in an Animal Model

Abdul Ghani AS[a], Abdul Rahim R[a], Muhammad N[b], Abdullah NZ[b]

[a]Department of Basic Medical Science, Kulliyyah of Medicine, IIUM
[b]Department of Pathology and Laboratory Medicine, Kulliyyah of Medicine, IIUM

ABSTRACT

INTRODUCTION: Non-alcoholic steatohepatitis (NASH) is the progressive form of non-alcoholic fatty liver disease (NAFLD) with potential progression to cirrhosis. Currently, no definitive treatment is available. This study evaluated the protective effects of Tualang honey (TH), which possesses antioxidant and anti-inflammatory properties, against a high cholesterol diet-induced NASH in an animal model. **MATERIALS AND METHODS:** Thirty-six male Sprague–Dawley rats were fed a 1% cholesterol diet (CD) for 14 weeks, followed by a 12% CD for 6 weeks to induce mild to moderate NASH. At week 20, rats were randomised into groups that continued the CD, with three groups receiving TH at doses of 0.2, 1.2, or 2.4g/kg/day for 4 weeks. Liver function tests, fasting insulin, HOMA-IR, and lipid profiles were assessed. After 24 weeks, livers of the rats were harvested for histological evaluation. Data were analysed using one-way ANOVA with Duncan's and Tukey's post hoc tests; $p < 0.05$ was considered significant. **RESULTS:** TH significantly reduced serum ALT (77.25±16.32 to 50.25 ± 10.56 U/L; p=0.025) and AST (193.25±43.95 to 106.75 ± 24.46 U/L; p<0.01). The 1.2 g/kg/day group showed marked improvement in insulin resistance, with reductions in fasting insulin (4.61 ± 1.38 to 0.18 ± 0.18 mIU/L) and HOMA-IR (1.14 ± 0.38 to 0.03 ± 0.03; both p=0.001). LDL-c decreased while HDL-c increased significantly. Histological analysis of the liver demonstrated improved NAFLD activity scores across treated groups. **CONCLUSION:** Tualang honey improved liver function, insulin resistance, dyslipidaemia, and hepatic histology in a mild–moderate NASH rat model.

Keywords
High Cholesterol Diet, NASH, Tualang Honey

Corresponding Author
Assoc. Prof. Dr. Roslina Abdul Rahim,
Department of Basic Medical Science,
Kulliyyah of Medicine,
International Islamic University Malaysia,
Email: roslinaar@iium.edu.my

Received: 19th September 2025; Accepted: 26th January 2026

Doi: https://doi.org/10.31436/imjm.v25i02/3062

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a chronic liver condition that arises without evident infection or substantial alcohol consumption. It's progressive form called non-alcoholic steatohepatitis (NASH), is defined by hepatic fat accumulation accompanied by inflammation in the periportal and lobular regions.[1] The development of the disease is multifactorial and strongly associated with obesity, type 2 diabetes mellitus, and insulin resistance.[2,3] NASH may advance to cirrhosis, which can subsequently result in complications including hepatocellular carcinoma and liver failure.[4,5,6]

Animal models are crucial for understanding the pathogenesis and progression of diseases, as well as for developing therapeutic strategies.[7] The methionine-choline deficiency (MCD) diet rapidly induces liver injury, with significant inflammation and fibrosis appearing within two to four weeks. It has a significant impact on the expression of genes related to fibrogenesis, oxidative stress, and inflammation pathways. Despite its effectiveness in mimicking the histological aspects of NASH, the MCD model lacks key features of metabolic dysfunction commonly observed in humans, including obesity and insulin resistance. In comparison, the high-fat

diet (HFD) mouse model better represents the metabolic disturbances linked to NAFLD, such as obesity, insulin resistance, and dyslipidaemia. Nevertheless, the development of liver fibrosis in this model occurs more gradually, usually taking 24 weeks or longer, and the disease is generally less pronounced. Additionally, the HFD influences the expression of genes and proteins related to lipid metabolism, inflammation, and oxidative stress, though the pattern differs from that seen with the MCD diet.[8]

Our pilot study demonstrated that administering a 1% high-cholesterol diet (HCD) for 14 weeks, followed by a 12% HCD for an additional 6 weeks, successfully induced mild NASH in the rat model. This was evidenced by elevated serum alanine aminotransferase levels, increased homeostatic model assessment of insulin resistance (HOMA-IR), and an altered lipid profile.[9]

Tualang honey (TH), a multifloral wild honey produced by the rock bee (*Apis dorsata*), is well known in Malaysia for its diverse medicinal benefits, including antimicrobial, antioxidant, anti-inflammatory, and wound-healing properties.[10] Harvested from hives built high on the giant *Koompassia excelsa*, also known as the "*Tualang* tree," found in the rainforests of Kedah, Malaysia, it has long been used in traditional therapies. The collection of TH is carried out by licensed bee hunters under the supervision of the Malaysian Federal Agricultural Marketing Authority (FAMA). Rich in antioxidant and anti-inflammatory properties, TH shows potential in supporting the management of NASH.[10]

This study aims to evaluate the effects of Tualang honey at varying concentrations in our established NASH animal model.[9]

MATERIALS AND METHODS

Animals

A total of thirty-six male Sprague-Dawley rats (6–8 weeks old, weighing 200–250 g) were obtained from A-Sapphire Enterprise, Seri Kembangan, Selangor, for this study. The rats were housed in pairs under controlled conditions of 60 ± 5% relative humidity and 20 ± 2ºC, with a 12-hour light/dark cycle. Prior to the experiment, all animals were given free access to water and standard rat pellets for two weeks to allow acclimatisation to the new environment.

Cholesterol diet

Analytical-grade cholesterol powder (Nacalai-Tesque, Kyoto, Japan) was incorporated into powdered commercial rat pellets to prepare the experimental diets. For the 1% cholesterol diet (CD) mixture, 1 kg of powdered rat pellets was blended with 10 g of cholesterol and 0.2 g of cholic acid. For the 12% CD mixture, 1 kg of powdered pellets was combined with 120 g of cholesterol and 2 g of cholic acid. To minimize oxidative modification of cholesterol, all diet preparations were freshly prepared daily.

Tualang honey

Tualang honey (TH) (AgroMas, Malaysia) was obtained from the FAMA, Kedah, Malaysia. Its nutritional composition and specifications are summarized in Table I. TH was given once daily to the experimental groups by oral gavage, with the dosage adjusted according to each body weight of the rats. The selected doses (0.2, 1.2, and 2.4 g/kg/day) were based on average local human consumption and converted to rat-equivalent doses using the Km factor.[11] On average, a healthy adult human weighing 60 kg consumes about one teaspoon of honey per day, equivalent to approximately 12 g. This corresponds to 0.2 g of honey per kilogram of body weight (0.2 g/kg). The equivalent rat dose was then calculated using the Km factor as shown below:

Table I: Nutritional composition and specifications of Tualang honey

Parameter, Unit	Result	Standard (Food Reg 1985,Reg. 130)
Reducing Sugar, g/100g:		>60.0
-Fructose	38.0	
-Glucose	36.9	
Sucrose, g/100g	Not detected (<0.01)	<10.0
Ash, g/100g	0.02	<1.0
Moisture, g/100g	23.1	<20.0

Experimental design

Twenty-four male Sprague-Dawley rats were initially fed a 1% cholesterol diet (CD) mixture for 14 weeks. From week 14 onward, all rats received a 12% CD mixture for an additional 6 weeks to establish a mild-to-moderate NASH model. At week 20, once NASH was confirmed

histologically, the rats were randomly allocated into four groups. All groups continued on the CD, while three groups additionally received TH supplementation at doses of 0.2, 1.2, and 2.4 g/kg body weight per day, respectively, for a duration of 4 weeks.

Biochemical study

After 24 weeks, all rats were fasted overnight, weighed, and fully anesthetised with diethyl ether. Blood samples were then collected from the orbital sinus of the mice at the medial canthus of the eye using a haematocrit tube. The samples were analysed for liver enzymes, glucose, insulin, and lipid profile (Roche Cobas, INTEGRA 400 plus). All biochemical assays were performed in triplicate by a certified diagnostic laboratory to ensure analytical precision.

Homeostatic model assessment of insulin resistance

The homeostatic model assessment of insulin resistance (HOMA-IR) is applied as a physiological indicator of insulin resistance. It is calculated using the following formula:

HOMA-IR=[Fasting Glucose (mmol/L)×Fasting Insulin (mIU/L)]/22.5

Histological study

At the end of 24 weeks, the rats were euthanised, and their livers were collected, weighed, and examined macroscopically before being fixed in 10% neutral buffered formalin for histological analysis. Liver tissues were processed using an automated tissue processor (Leica TP 1020) and embedded in paraffin blocks (Leica EG1160). Sections were then cut at a thickness of 3 μm and stained with haematoxylin and eosin (H&E) as well as Masson's trichrome for histological evaluation. The histological grading and staging of NASH were performed based on the Brunt Schema.[12] Brunt schema for NASH grading considers four parameters (steatosis, hepatocytes ballooning degeneration, lobular and portal inflammation) and based on these, NASH is graded into Grade 1 (mild), Grade 2 (moderate), and Grade 3 (severe). As for staging, it ranges from Stage 0 to Stage 4 (absence of fibrosis to peri-sinusoidal fibrosis, periportal fibrosis, bridging fibrosis, and cirrhosis). The NAFLD activity scoring was also performed using a scoring system developed by the Nonalcoholic Steatohepatitis Clinical Research Network.[13] The scoring systems take into account three parameters: steatosis (0-3); lobular inflammation (1-3), and ballooning (1-2).

Statistical analysis

Data analysis was carried out using SPSS statistical software version 18.0. A significance level was set at a 95% confidence interval ($p < 0.05$). Mean comparisons were assessed using analysis of variance (ANOVA), and differences between group pairs were further determined using Duncan's and Tukey's post hoc tests.

RESULTS

Biochemistry results

Liver enzymes

All animal groups with TH supplementation (T1, T2, and T3) showed lower mean serum alanine aminotransferase (ALT) and serum aspartate aminotransferase (AST) levels as compared to the 12% CD group. However, only the T2 group ($p=0.025$) exhibited a significant reduction in the ALT level. As for the AST, both groups T2 ($p=0.002$) and T3 ($p=0.010$) showed significant differences with that of the 12% CD group. The mean serum ALP levels between the groups were not statistically significant (Table II).

Fasting blood glucose level

Table II shows the fasting blood glucose level in each of the experimental groups. The mean fasting blood glucose levels were lower in the TH-supplemented groups compared to the 12% CD group. The T2 ($p=0.018$) group exhibited a significantly lower mean fasting blood glucose level.

Fasting insulin level

The mean serum fasting insulin levels were also lower in the T1, T2, and T3 groups as compared to the 12% CD group. The differences were statistically significant in T2 ($p=0.001$) and T3 ($p=0.001$) groups (Table II).

Homeostatic model assessment of insulin resistance

The mean HOMA-IR index for each of the TH groups was lower than that of the 12% CD group. The differences were statistically significant when comparing the 12% CD group with T2 (p=0.001) and T3 groups (p=0.001) (Table II).

Lipid Profile

There was no significant difference in both serum total cholesterol (TC) and triglycerides (TG) throughout the groups. Although all the TH supplemented groups had lower LDL-c levels than the 12% CD group, only groups T1 (p=0.006) and T3 (p=0.013) exhibited a significant difference in the level, respectively. The serum high-density lipoprotein (HDL-c) level showed a significant increment in all groups compared to the 12% CD group (T1 group p=0.001; T2 group p=0.001; T3 group p=0.001) (Table II).

Table II: Blood biochemical parameters of 12% CD and TH-supplemented groups of the NASH animal model.

Group/ Parameter	12% CD (n=4)	T1 (n=4)	T2 (n=4)	T3 (n=4)	Significance
Liver enzymes					
ALT (U/L)	77.25± 16.32	58.75± 6.08	50.25± 10.56	57.00± 12.14	$p<0.05^{b}$
AST (U/L)	193.25± 43.95	140.00± 17.38	106.75± 24.46	122.75± 15.65	$p<0.05^{b,c}$
ALP (U/L)	94.00± 19.20	94.00± 18.57	89.75± 17.23	84.50± 11.27	NS
Glucose, Insulin & HOMA-IR					
Fasting glucose (mmol/L)	5.55± 0.71	4.03± 0.34	3.65± 0.91	4.63± 0.74	$p<0.05^{b}$
Fasting insulin (mU/L)	4.61± 1.38	2.83± 1.38	0.18± 0.18	0.30± 0.40	$p<0.05^{b,c}$
HOMA-IR	1.14± 0.38	0.53± 0.44	0.03± 0.03	0.09± 0.08	$p<0.05^{b,c}$
Lipid profile					
TC (mmol/L)	3.53±0.40	2.58±0.88	3.20±1.14	2.60±0.29	NS
TG (mmol/L)	0.64±0.18	0.73±0.26	0.68±0.21	0.43±0.19	NS
LDL-c (mmol/L)	2.71±0.75	1.10±0.70	1.54±0.68	1.23±0.21	$p<0.05^{a,c}$
HDL-c (mmol/L)	0.27±0.06	1.15±0.24	1.35±0.41	1.18±0.13	$p<0.05^{a,b,c}$

CD = cholesterol diet; TH= Tualang honey; T1 = 0.2g/kg/day TH; T2 = 1.2g/kg/day TH; T3 = 2.4g/kg/day TH; HOMA-IR = homeostatic model assessment of insulin resistance; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ALP = alkaline phosphatise; TC = total cholesterol; TG = triglycerides; LDL – c = low-density lipoprotein cholesterol; HDL – c = high-density lipoprotein cholesterol. a: 12% CD vs T1; b: 12% vs T2; c: 12% vs T3 ; NS: Not significant.

Pathology results

Gross morphology of the livers

The livers of rats in the 12% CD group appeared enlarged, with a yellow and greasy surface, consistent with hepatic steatosis. In contrast, the livers of TH-treated groups appeared less yellow, less greasy, and more reddish in colour (refer to Figure 1).

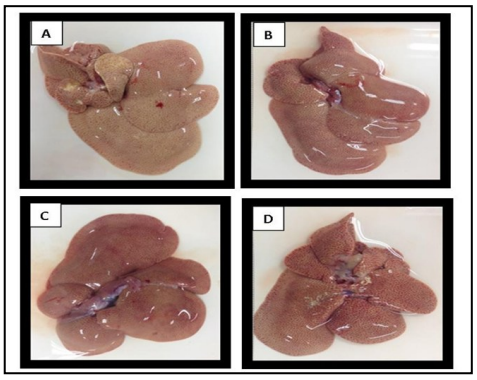

Figure 1: Gross morphology features of livers from (A) 12% cholesterol diet, (B) T1 = treatment dose (0.2g/kg/day); (C) T2 = treatment dose (1.2g/kg/day); (D) T3 = treatment dose (2.4g/kg/day)

The relative liver weights were lower in the T1, T2, and T3 groups compared to the 12% CD group, although there were no significant statistically (Table III).

Table III: Relative liver weight, NASH grading, staging, and NAFLD activity scores in experimental groups.

Group/ Parameter	12% CD (n=4)	T1 (n=4)	T2 (n=4)	T3 (n=4)	Significance
Relative liver weight	3.67±0.30	3.29±0.68	3.09±0.29	3.34±0.47	NS
NASH grading	2.25±0.50	1.25±0.50	1.25±0.50	1.25±0.50	$p<0.05^{a,b,c}$
NASH staging	1.50±0.58	1.00±0.00	0.50±0.58	0.50±0.58	NS
NAFLD activity score	7.50±0.58	4.25±0.96	3.50±1.00	4.50±2.08	$p<0.05^{a,b,c}$

CD = cholesterol diet; TH= Tualang honey; T1 = 0.2g/kg/day TH; T2 = 1.2g/kg/day TH;
T3 = 2.4g/kg/day TH. a: 12% CD vs T1; b: 12% vs T2; c: 12% vs T3 ; NS: Not significant.

Non-alcoholic steatohepatitis grading, staging, and activity scores

The mean grading of each of the TH groups was significantly lower than the 12% CD group (Group T1 p=0.044; Group T2 p=0.044; Group T3 p=0.044). The staging did not significantly differ between the non-TH supplemented group (12% CD group) and the supplemented groups (T1, T2and T3). As for the mean NAFLD activity scores, they were significantly lower in the TH groups (Group T1 p=0.010; T2 p=0.002; Group T3

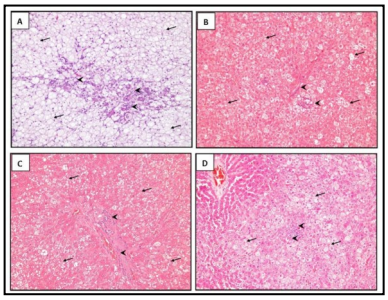

Figure 2: Pictomicrograph of liver sections stained with Haematoxylin and Eosin with x20 objective. A: (12% CD group); B: T1 group; C: T2 group; D: T3 group. The section showed areas of steatosis with portal inflammation. Arrow = steatosis, arrow head = inflammation.

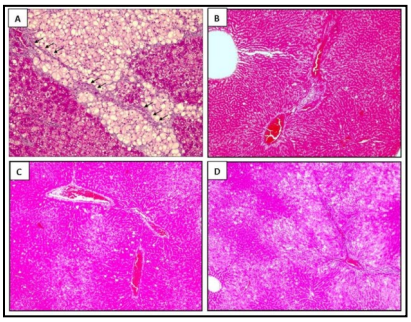

Figure 3: Pictomicrograph of liver sections stained with Mason trichrome. A: 12% CD group (x20 objective). The arrows indicate fibrosis. B: T1 group (x10 objective). C: T2 group (x10 objective). No area of fibrosis is seen in T1, T2, and T3.

Liver histology of the 12% cholesterol diet group

The liver sections exhibited extensive micro vesicular and macro vesicular steatosis affecting nearly the entire hepatic tissue. Occasional ballooning degeneration of hepatocytes was observed. Lobular inflammation was characterized by infiltration of neutrophils and mononuclear cells. Moderate portal inflammation was evident [Figure 2(A)], along with regions of perisinusoidal and periportal fibrosis identified through Masson Trichrome staining [Figure 3 (A)].

Liver histology of 12% cholesterol diet with 0.2 g/kg/ day Tualang honey group (T1)

The sections of the liver showed mixed areas of steatosis, predominantly of the micro vesicular type. Occasional hepatocyte ballooning degeneration was seen. There were areas of mild lobular and portal inflammation [Figure 2 (B)].

Liver histology of 12% cholesterol diet with 1.2 g/kg/ day Tualang honey group (T2)

The liver sections showed patchy areas of steatosis, predominantly of the micro vesicular type. Very occasional hepatocytes with ballooning degeneration were observed. Mild areas of portal and lobular inflammation were seen [Figure 2 (C)].

Liver histology of 12% cholesterol diet (12% CD) with 2.4 g/kg/day Tualang honey group (T3)

The sections of the liver showed patchy areas of steatosis with very occasional hepatocyte ballooning. The liver exhibited mild portal and lobular inflammation [Figure 2 (D)].

DISCUSSION

In our previous study, we demonstrated that a 12% cholesterol diet successfully induced mild to moderate NASH in the rat model.[9] With this established NASH animal model, we further investigated the effects of TH on this animal model. NASH development is believed to be "multiple–hit" in nature, and insulin resistance is proposed to be the first hit that subsequently sensitizes the liver to oxidative stress, inflammation, fibrosis, and cirrhosis.[14] Based on this pathogenesis, TH is seen to have potential benefits in improving NASH because honey has been shown to have antioxidant, anti-inflammatory, antidiabetic, as well as hepatoprotective properties and is known to improve lipid profile.[15–18]

In this study, we have demonstrated that TH supplementation in the NASH animal model improved the liver function profile, HOMA-IR, lipid profile, and histology of the liver. The improvement in liver function was indicated by the significant reduction in both serum ALT and AST levels in the TH-supplemented groups. Our results are consistent with the study by Onochie et al. (2018), which reported that honey exerts hepatoprotective effects, as evidenced by significant reductions in ALT, AST, and ALP levels in male Wistar rats treated with honey. Additionally, several other studies in the literature have also highlighted the hepatoprotective properties of natural honey.[19–22]

In our NASH animal model (CD 12%), the elevation of the AST and ALT is deemed to be related to the underlying pathogenesis of NASH, in which there is destruction to the hepatocytes. Hepatocyte injury in this condition has been associated with oxidative stress. According to Takaki et al. (2017), excessive accumulation of long-chain fatty acids activates the mitochondrial β-oxidation pathway in NASH, resulting in increased production of reactive oxygen species and subsequent cellular damage.[23] TH has been shown to have higher antioxidant activity than other local and commercially available honeys, and this is attributable to the high phenolic and flavonoid content, which may explain the reduction in the liver enzymes seen in this study.[15]

The rats that received TH supplementation showed improved insulin sensitivity, as indicated by decreased fasting insulin levels and lower HOMA-IR values. Insulin resistance is considered a key factor in the progression of NAFLD to NASH. Hepatic steatosis triggers the activation of liver macrophages, including Kupffer cells, which aggravates insulin resistance through the release of inflammatory mediators such as tumour necrosis factor (TNF)-α and interleukin (IL)-1β. These pro-inflammatory cytokines impair hepatic insulin sensitivity by activating inflammatory signalling pathways and suppressing insulin receptor signaling.[3]

Hence, honey most likely modulates insulin resistance in these NASH animal models through its hypoglycaemic effect, attributed to its fructose constituent.[24] Fructose stimulates glucokinase activity, which facilitates the conversion of glucose into glucose-6-phosphate, thereby lowering blood glucose levels.[25] Fructose has also been shown to stimulate insulin from the pancreas,[26] which leads to a decrease in blood glucose. TH has been shown to suppress the activity of protein tyrosine phosphatase 1B (PTP1B), an enzyme that negatively regulates insulin receptor signalling. This inhibition enhances the expression of insulin receptors and stimulates glucose uptake in liver cells, thereby improving glycaemic control.[27]

One of the approaches to the management of NASH involved addressing the dyslipidemia condition, which is one of the criteria of metabolic syndrome known to be closely associated with NASH.[28] We have demonstrated in our animal study that TH supplementation leads to improvement in the lipid profile. Our results are in agreement with those of El-Shafey et al. (2015), who reported that animals supplemented with natural honey exhibited increased HDL-c levels and decreased LDL-c levels.[29] Other studies have also reported that rats given natural honey showed elevated HDL-c levels.[30] Overall, it has been shown that honey supplementation improves lipid abnormalities in both animals and humans, and therefore, it has the potential to improve the lipid profile in NASH patients with metabolic syndrome.[16,17,31–33] Evidence suggests that TH regulates genes associated with lipid metabolism. It decreases the expression of fatty acid binding protein 1 (FABP1) and increases the expression of hepatic lipase (HL) and apolipoprotein A1 (APOA1), thereby supporting better lipid profile outcomes.[34]

In this study, notable improvements in histological grading and NAFLD activity scores were observed across all three groups of animals treated with varying doses of honey compared to the 12% CD group. Both the extent of steatosis and the levels of lobular and portal inflammation showed improvement relative to the 12% CD group. The anti-inflammatory activities of the honey have been linked to its ability to lower the prostaglandin E2 level and the inhibitory effect on nitric oxide, and hence may partly explain the findings in the TH supplemented groups.[35] These histologic changes parallel the changes observed in the biochemical parameters, the effects of TH, which cause a reduction in the liver enzymes and improvement in the insulin resistance and lipid profile.

CONCLUSION

Our study reveals that TH supplement improves the liver function tests, insulin resistance, and the abnormal lipid profile of the NASH animal models. This is further supported by the changes observed in the histological characteristics of the liver of the NASH animal model supplemented with TH. These findings pave the path for further research to be undertaken, one of which is to study the molecular mechanisms by which TH improves NASH biochemically and histologically in the NASH animal model.

INSTITUTIONAL REVIEW BOARD (ETHIC COMMITTEE)

All procedures related to animal handling, treatment, and experimental protocols were approved by the Institutional Animal Care and Use Committee of the International Islamic University Malaysia (IACUC-IIUM), Kuantan Campus (Approval No.: IIUM/IACUC Approval/2014/(4)(17)), and were conducted in accordance with the Malaysian Code of Practice for the Care and Use of Animals for Scientific Purposes.

ACKNOWLEDGEMENT

We would like to thank the Research Management Centre, International Islamic University Malaysia (IIUM), for providing us with the Endowment B grant (EDW B14-206-1091) and Research Initiative Grant Scheme (RIGS15-078-0078).

CONFLICT OF INTEREST:

No

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ORIGINAL ARTICLE

In-Silico and In-Vitro Assessment of Selected Fatty Acids against Vibrio Spp..

Nordin B[a], Liew HJ[b], Rozaini MZH[a], Ikhwanuddin M[b], Musa N[a,c], Sheikh HI[a,c]

[a]Faculty of Fisheries and Aquaculture Sciences (FSPA), Universiti Malaysia Terengganu, Terengganu, Malaysia
[b]Higher Institution Centre of Excellent (HICoE), Institute of Tropical Aquaculture and Fisheries, Universiti Malaysia Terengganu, Terengganu, Malaysia
[c]Aquatic Health and Disease (AHAD), Research Interest Group, Universiti Malaysia Terengganu, Malaysia

ABSTRACT

INTRODUCTION: *Vibrio* spp. is a zoonotic pathogen that can cause mild or fatal infection in human and animals. The overuse of antibiotics has led to increasing antimicrobial resistance (AMR). Fatty acids (FAs) offer a potential alternative due to their broad-spectrum antibacterial activity. Hence, this study aimed to investigate the anti-Vibrio effects of oleic acid (OA), lauric acid (LA), palmitic acid (PA), and stearic acid (SA) through in-vitro and in-silico approaches. **MATERIALS AND METHODS:** Molecular docking was performed using PyRx against 21 receptors belonging to *Vibrio* spp. retrieved from the Protein Data Bank (PDB) for in-silico investigation. To validate the findings, LA, OA, PA and SA were experimentally tested. Minimum Inhibitory Concentration (MIC) and Minimum Bactericidal Concentration (MBC) assays were conducted in-vitro against *Vibrio alginolyticus* and *Vibrio parahaemolyticus*. **RESULTS:** Molecular docking results revealed that OA exhibited the lowest binding energy (min=-7.2, mean=-4.8). OA also showed the second-highest number of hydrogen bond interactions and ranked third in van der Waals interactions. FAs demonstrated significantly stronger affinity ($p<0.05$) to proteins related to toxin production, nutrient acquisition, and quorum sensing. In-vitro assays aligned with in-silico where OA had the lowest MIC (125 µg/mL) against both *V. alginolyticus* and *V. parahaemolyticus* and exhibited bactericidal activity against *V. alginolyticus* at 500 µg/mL. **CONCLUSION:** Therefore, OA is a promising anti-Vibrio agent that might regulate environmental sensing and interaction with small molecules. The receptors 3MRU, 3WPW, 3A57 and 3X0T, matched in-vitro results and could be used in the design of new treatments for vibriosis.

Keywords
Vibriosis, Vibrio alginolyticus, Vibrio parahaemolyticus, Lauric acid, Oleic acid

Corresponding Author
Asst. Prof. Dr. Hassan I. Sheikh
Faculty of Fisheries and Aquaculture Sciences,
Universiti Malaysia Terengganu, Malaysia
Email: Sheikhinho@gmail.com

Received: 30th June 2025; Accepted: 22nd February 2026

Doi: https://doi.org/10.31436/imjm.v25i02/3014

INTRODUCTION

Vibrio spp. are gram-negative, rod-shaped bacteria that inhabit freshwater, estuary, and marine environments.[1] It is a zoonotic pathogen causing severe infection in human and animals.[2] Most *Vibrio* species are known to cause waterborne and foodborne diseases that spread through contaminated water and the consumption of raw and undercooked seafood, causing significant human health hazards.[3] According to WHO, there are up to 4.0 million cases reported annually of *Vibrio cholera* infection, causing mild to acute watery diarrhoea leading to severe dehydration.[4] *Vibrio harveyi* could infect human through an open wound coming in contact with contaminated water, which will cause severe inflammation and necrosis on the wound.[5] Meanwhile, *Vibrio vulnificus* is primarily linked to septicaemia on the skin through direct contact with contaminated seafood or water, which will trigger the immune system.[6] In terms of *Vibrio parahaemolyticus* and *Vibrio alginolyticus*, both species commonly infect farmed animals and lead to mass mortality in aquaculture industry.

The consumption of infected animals could cause serious gastroenteritis, fever, nausea, abdominal cramps, and bloody diarrhea.[7]

The primary medical treatment of these vibriosis through antibiotics has led to multiple antibiotic resistance (MAR) in numerous *Vibrio* species.[8] In a study, 67.2% of *Vibrio* spp. isolated from Malaysian seafood had high antimicrobial resistance (AMR).[9] According to another study on *Vibrio* spp. isolates from water samples, only some were susceptible to clinically relevant antibiotics, including tetracycline-class drugs used in current treatment regimens by the Centres for Disease Control and Prevention (CDC).[10,3] Thus, the adverse effects of the MAR on human and animal risk control have necessitated the development of an improved and more effective option for antimicrobial treatments with the least hazardous risk.

Over the years, fatty acids (FAs) properties have been studied as a potential substitute for conventional antibiotics to combat AMR problems. FAs are crucial for the immune system of organisms to protect against several diseases, including infection with antibiotic resistant bacteria.[11] FAs may function as biofilm inhibitors at low concentrations and exhibit antimicrobial activity at higher concentrations; however, bacterial responses can vary depending on the specific type of FA.[12] Long-chain fatty acids (LCFAs), including oleic, palmitic, and stearic acids, are naturally present in plants and animals via acetyl-CoA, and their carbon chain length varies between 12 to 24 carbons.[13] Meanwhile, lauric acid with a 12-carbon chain is known as a saturated medium chain fatty acid (MCFA) and can be rapidly absorbed and transported.[14] These medium to long-chain fatty acids are known to have antibacterial, antiviral, and antifungal properties. However, several studies reported that FAs are more effective against gram-positive bacteria than gram-negative bacteria.[11] For example, lauric acid demonstrate strong antimicrobial activity against gram-positive bacteria but have limited efficacy against gram-negative bacteria.[15,16]

The amphipathic nature FAs might play an important role in their antibacterial activity, which induces the disruption of the lipid packing leading to increased membrane permeability and leakage of cellular components.[17] Recent studies reported that unsaturated fatty acids are able to inhibit the growth of both gram-negative and gram-positive bacteria.[18] Unsaturated fatty acids, such as oleic and linoleic acid, have shown potential in treating *Helicobacter pylori*, *Staphylococcus aureus*, and *Escherichia coli* by disrupting the cellular membrane, leading to cell lysis.[19] Hence, this study aims to determine the antibacterial activity of selected fatty acids (FAs) against *Vibrio* spp..

MATERIALS AND METHODS

In-silico screening

Molecular docking simulations were done on 21 protein receptors identified from *Vibrio* spp. against 4 fatty acids (FAs), namely, lauric acid (LA) ($C_{12}H_{24}O_2$), oleic acid (OA) ($C_{18}H_{34}O_2$), palmitic acid (PA) ($C_{16}H_{32}O_2$), and stearic acid (SA) ($C_{18}H_{36}O_2$).

Ligand Preparation

The structure of the four different FAs, namely, lauric acid (LA), oleic acid (OA), palmitic acid (PA), and stearic acid (SA) were downloaded from the PubChem database. The ligands were prepared and optimized using Avogadro (v1.2.0), with polar hydrogens added to the 3D conformers. The ligands' geometry was optimized until convergence was reached. The prepared ligands were then saved in PDB format.[20]

Receptor Preparation

A total of 21 protein receptors belonging to *Vibrio* spp. were obtained from the Protein Data Bank (https://www.rcsb.org/) in PDB format.[21] The selected protein receptors were from various functional systems as well as functional classes as showed in Table I. All the water molecules, heteroatoms, and any co-crystallized ligands were removed from the protein structure using the Discovery Studio Version 21.1.0.20298. Finally, polar hydrogen atoms were added, and the protein structures were saved as a PDB file.[20] The active sites for all proteins were determined from previous publications linked to Protein Data Bank database. The grid box for

each receptor was established and the XYZ coordinates are provided in Table I.

Molecular Docking

The docking process was done by loading 1 receptor at a time, together with all 4 FAs into the PyRx software Version 0.8. Universal Forcefield (UFF) was applied due to its flexibility and viability for simulations in various systems which is needed considering the diversity of the 21 receptors used in this study.[22] The active site of the protein receptor was determined based on published research and data provided in the protein data bank database.

Molecular Docking Data Analysis

Molecular docking data was collected in triplicates to facilitate statistical analysis rather than reporting only the lowest free energy of binding (ΔG) or highest number of hydrogen bond. Statistical analyses were then carried out using SPSS software Version 20 to determine significant differences between FAs and protein receptors of *Vibrio* spp.. Univariate Analysis of Variance (ANOVA) and Tukey post hoc test ($p<0.05$) were used to compared FA, receptor's functional system and receptor's functional class in terms of binding energy, while chi-square test was used to compared number of hydrogen bonds and van der Waals interactions at $p<0.05$. Spearman's rho test was also applied to identify correlations between binding energy, number of hydrogen bonds and van der Waals interactions at $p<0.05$.

In-vitro screening

Compound preparation

Lauric acid (LA) ($C_{12}H_{24}O_2$), oleic acid (OA) ($C_{18}H_{34}O_2$), palmitic acid (PA) ($C_{16}H_{32}O_2$), and stearic acid (SA) ($C_{18}H_{36}O_2$) were purchased from Evachem (Malaysia) and were of analytical grade and used without further purification. A stock solution of 10 mg/ml of the 4 different FAs were prepared in 50% Dimethyl sulfoxide (DMSO).

Minimum Inhibitory Concentration (MIC) and Minimum Bactericidal Concentration (MBC)

MIC and MBC were determined using sterile 96-well microtiter plates according to CLSI (2012) and previously described methods.[23,25] Two pathogenic *Vibrio* spp. maintained in our laboratory collection, namely *V. alginolyticus* (GenBank accession number: PQ044564.1)

Table I. List of selected protein receptor of Vibrio spp. from PDB website

PDB ID	Name	Functional System	Functional Class	*Source species*	Coordinates of binding site
6JV4	VMB-1	Antimicrobial resistance & survival	Hydrolase	*Vibrio alginolyticus*	X:23.12, Y:-10.66, Z:29.14
7CUS	VbrK	Antimicrobial resistance & survival	Signalling protein	*Vibrio parahaemolyticus*	X:3.46, Y:-7.89, Z:-6.27
3VCY	MurA	Antimicrobial resistance & survival	Transferase	*Vibrio fischeri* MJ11	X:-10.91, Y:1.14, Z:22.37
6PXA	Chlo-resist	Antimicrobial resistance & survival	Transferase	*Vibrio fischeri* ES114	X:-4.99, Y:5.37, Z:23.05
3MRU	PepD	Biofilm formation	Hydrolase	*Vibrio alginolyticus*	X:-32.79, Y:13.63, Z:-10.00
4BE5	RbmA	Biofilm formation	Cell adhesion	*Vibrio cholerae* MJ-1236	X:44.31, Y:31.74, Z:13.15
7AGZ	BsrV	Biofilm formation	Peptide-binding protein	*Vibrio cholerae* O1 biovar El Tor str. N 16961	X:8.81, Y:52.59, Z:1.71
2ZF8	MotY	Motility & flagellar assembly	Structural protein	*Vibrio alginolyticus*	X:50.85, Y:9.47, Z:63.36
3W1E	FlgT	Motility & flagellar assembly	Motor protein	*Vibrio alginolyticus*	X:24.1, Y:3.4, Z:32.6
3WPW	PomB	Motility & flagellar assembly	Membrane protein	*Vibrio alginolyticus*	X:16.27, Y:35.28, Z:45.28
6IF6	SflA	Motility & flagellar assembly	Membrane protein	*Vibrio alginolyticus*	X:32.19, Y:23.12, Z:33.09
3CK6	ZntB	Nutrient acquisition	Structural protein	*Vibrio parahaemolyticus* RIMD 2210633	X:15.25, Y:-65.24, Z:53.56
3R5T	ViuP	Nutrient acquisition	Metal transport	*Vibrio cholerae*	X:22.44, Y:14.43, Z:15.09
3LJL	LuxT	Quorum sensing & signalling	Transcription regulator	*Vibrio parahaemolyticus* RIMD 2210633	X:7.03, Y:52.63, Z:36.05
2HJ9	LuxP-LuxQ complex	Quorum sensing & signalling	Signalling protein	*Vibrio harveyi*	LuxP domain (X:13.07, Y:-1.77, Z:59.36)
2WK8	CqsA	Quorum sensing & signalling	Transferase	*Vibrio cholerae*	X:62.44, Y:59.94, Z:-2.65
1ZHH	LuxP	Quorum sensing & signalling	Signalling protein	*Vibrio harveyi*	X:-27.13, Y:82.43, Z:12.23
3A57	TDH	Toxins & toxin-associated regulators	Toxin	*Vibrio parahaemolyticus*	X:26.93, Y:20.79, Z:35.20
3X0T	PirA	Toxins & toxin-associated regulators	Toxin	*Vibrio parahaemolyticus* M0605	X:31.04, Y:41.10, Z:9.08
3X0U	PirB	Toxins & toxin-associated regulators	Toxin	*Vibrio parahaemolyticus* M0605	X:28.35, Y:-11.036, Z:23.77
5KEV	VtrA/VtrC	Toxins & toxin-associated regulators	Signalling protein	*Vibrio parahaemolyticus* RIMD 2210633	X:210.70, Y:50.70, Z:32.58

and *V. parahaemolyticus* (GenBank accession number: PX462024), were used in this study ensuring biological relevance and public health significance. The bacteria were sub-cultured on tryptic soy broth (TSB) supplemented with 1.5% NaCl for 24 hours at 37°C. The inoculum was adjusted to a final concentration of 5×10^5 CFU mL^{-1} based on optical density measured at 600 nm.[24]

Muller Hilton Broth (MHB) with 1% NaCl was used as test media, and two-fold serial dilutions were prepared, yielding a concentration range of 1000-7.8 µg/mL. Tetracycline was used as a positive control, while the negative control was 50% DMSO (5% inside well). The MIC was determined qualitatively by adding 0.01% resazurin dye prepared in sterile distilled water, and the results were then reported in µg/mL.[25]

The wells that showed MIC were then streaked on Muller -Hinton Agar (MHA) with 1% NaCl and incubated at 37° C for 24 hours. Plates yielding no visible growth were taken as the MBC, and the results were reported in µg/ mL.[25] A fatty acid was interpreted as bactericidal if the MBC/MIC ratio was ≤4 and bacteriostatic if otherwise.[27]

RESULTS

In-silico screening of anti-vibrio activity of selected fatty acids

In-silico screening showed that oleic acid (OA) exhibited the lowest binding energy, followed by stearic acid (SA), palmitic acid (PA), and lauric acid (LA), respectively (Figure 1a), indicating potential high binding affinity. In terms of functional system, the FAs showed higher binding affinity to toxin-associated proteins, followed by nutrient acquisition and quorum sensing & signalling. In contrast, lower binding affinities were observed against motility, biofilm formation and antibiotic resistance protein receptors indicated by the higher binding energies. In terms of functional class, the FA had lower binding energy and potentially higher binding affinity towards peptide-binding proteins, metal transporters, toxins, and transferase related receptors.

This preliminary pattern identification was followed by statistical analysis to determine significant differences. Univariate ANOVA was used to determine main factors affecting binding energy showed that FA ($p<0.001$), functional system ($p<0.001$) and functional classes ($p<0.001$) significantly affected binding energy. With regards to FAs, OA and SA showed significantly lower binding energy than LA and PA ($p<0.05$), while OA and SA had similar binding energy ($p>0.05$) (Figure 1a). Functional system also differed significantly where toxin and toxin-associated regulatory proteins were significantly lower that all other system ($p<0.001$) (Figure 1b). This was followed by nutrient acquisition which had similar binding energy to quorum sensing and signalling receptors ($p>0.05$). Motility and flagellar assembly associated receptors showed the highest binding energy, which indicates a significantly lower binding affinity ($p<0.05$).

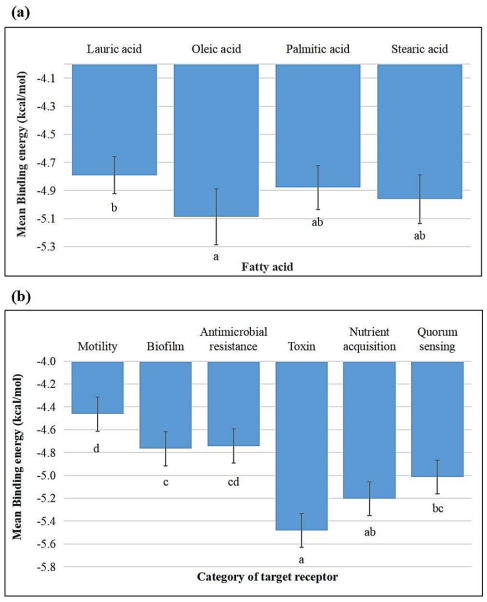

Figure 1 Mean binding energy (kcal/mol) of different fatty acids **(a)** and **(b)** across functional system of target receptors. Significant differences were determined using Univariate ANOVA and Tukey's post hoc test. Different letters (a, b, c, d) indicate statistically significant differences ($p<0.05$).

In terms of protein functional class, significant differences were observed between functional classes and post-hoc analysis showed that peptide-binding proteins, metal transporters, toxins, and transferase related receptors showed lower binding energies ($p<0.05$), which indicated potentially higher affinity to tested FAs (Table II). In contrast, hydrolase related receptors showed significantly higher binding energy compared to all other classes ($p<0.01$), followed by transcription regulators,

membrane proteins, cell adhesion and motor protein, indicating potentially a very poor binding affinity to those classes.

Overall, these results suggest that the selected FAs have potentially high binding affinity to proteins commonly involved in ligand recognition, environmental sensing, and interaction with small molecules. Hence, these FAs might have the potential as modulators of signalling or virulence pathways. In contrast, the FAs showed poor potential in binding catalytic enzyme (e.g. hydrolase) and structural protein.

Table II. Mean binding energy (kcal/mol) of different fatty acids across functional classes of target receptors

Functional Class	Binding Energy (kcal/mol, mean ± SD)
Cell adhesion	-4.68±0.39^{d}
Hydrolase	-4.22±0.21^{e}
Membrane protein	-4.63±0.31^{d}
Metal transport	-5.33±0.36^{ab}
Motor protein	-4.71±0.24^{d}
Peptide-binding protein	-5.39±0.28^{a}
Signalling protein	-5.01±1.03^{bc}
Structural protein	-5.08±0.37^{bc}
Toxin	-5.11±0.47^{abc}
Transcription regulator	-4.54±0.17^{d}
Transferase	-5.24±0.33^{abc}

*Values are presented as mean ± SD. Means sharing different superscript letters are significantly different (Univariate ANOVA followed by Tukey's HSD test, $p<0.05$).

The number of hydrogen bonds and van der Waals interactions exhibited similar patterns across all FAs ($p>0.05$) (Table III). LA exhibited the highest number of hydrogen bonds, followed by OA, whereas stearic acid demonstrated the strongest van der Waals interactions, followed by PA. This indicated that longer chain fatty acids showed more hydrophobic interactions, where shorter chain (LA) and unsaturation (OA) increased hydrophilic interactions. Spearman's rho test showed a weak but significant negative correlation between binding energy and van der Waals interaction energy (ρ=-0.297, $p<0.001$), while number of hydrogen bonds did not correlate with binding energy (ρ=-0.018, $p>0.05$). This indicated that van der Waals interactions were the main factor influencing binding affinity.

Table III. Hydrogen bond and van der Waals interactions of different fatty acids across all tested receptors

Fatty Acid	Hydrogen Bonds			van der Waals interactions		
	Median (IQR)	χ^2	*p*-value	Median (IQR)	χ^2	*p*-value
Lauric Acid (LA)	2 (1)	13.993	0.301	7 (4)	43.410	0.411
Oleic Acid (OA)	2 (1)			8 (4)		
Palmitic Acid (PA)	1 (1)			8 (4)		
Stearic Acid (SA)	1 (1)			9 (4)		

BIOVIA Discovery Studio Visualizer was used to visualize binding pocket of the FAs against selected receptor. The fatty acids produced the lowest binding energy when docked against PDB 5KVE. Superimposition analysis showed that the optimal docking poses of all four FAs occupied the same binding pocket in 5KVE (Figure 2), indicating a shared binding site preference.

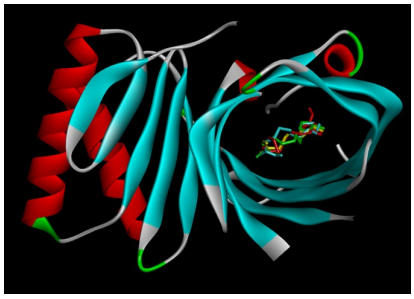

Figure 2 Superimposed structures of lauric acid (yellow), oleic acids (red), palmitic acid (cyan) and stearic acid (green) within the binding site of 5KVE showing similar binding pocket

Despite occupying the same binding site, the molecular interactions between the four FAs and 5KVE differed (Figure 3). LA was limited to alkyl and π–alkyl interactions, whereas PA and SA were limited to van der Waals interactions. In contrast, OAs demonstrated all three interaction types, indicating a comparatively broader interaction profile and supporting its intermediate binding behaviour among the tested fatty acids.

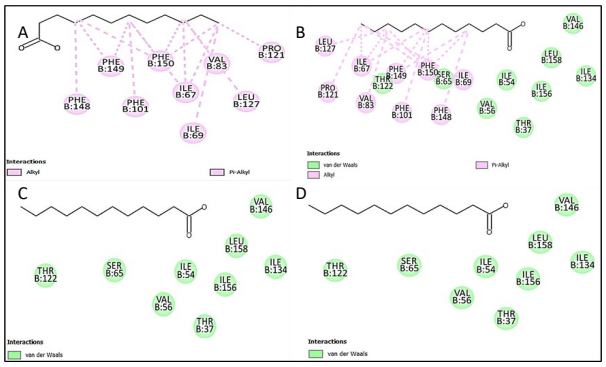

Figure 3 Interactions of lauric acid (a), oleic acids (b), palmitic acid (c) and stearic acid (d) within the binding site of 5KVE showing different interactions within the same binding pocket

In-vitro screening of anti-vibrio activity of selected fatty acids:

In-vitro screening was used to validate *in-silico* predictions based on MIC and MBC. OA and LA were the most effective in inhibiting the tested *Vibrio* spp.., with MIC values of 125 µg/ml and 500 µg/ml, respectively (Table IV). Meanwhile, the lowest MIC for PA and SA were

1000 µg/ml (Figure 4a). The MBC analysis indicates that OA was the most effective compound in killing *V. alginolyticus*, with the lowest observed MBC at 500 µg/mL. Meanwhile, no MBC was obtained against *V. parahaemolyticus* at the highest tested concentration of 1000 µg/mL (Figure 4b). This highlights OA's strong bactericidal activity, making it the most potent among the tested FAs. LA and PA also demonstrated bactericidal properties, effectively killing the *V. alginolyticus* strain, though at a higher concentration than OA.

Table IV. MIC and MBC assay, screened on different concentrations of selected fatty acids against *Vibrio* spp.

Species	Fatty acid	MIC (µg/mL)	MBC (µg/mL)	Category
Vibrio alginolyticus	Lauric acid	500	1000	Bactericidal
	Oleic acid	125	500	Bactericidal
	Palmitic acid	1000	1000	Bactericidal
	Stearic acid	1000	-	Bacteriostatic
	Tetracycline (control +)	<.7.8	<7.8	Bactericidal
Vibrio parahaemolyticus	Lauric acid	500	-	Bacteriostatic
	Oleic acid	125	-	Bacteriostatic
	Palmitic acid	1000	-	Bacteriostatic
	Stearic acid	1000	-	Bacteriostatic
	Tetracycline (control +)	<7.8	<7.8	Bactericidal

(-): No inhibition.

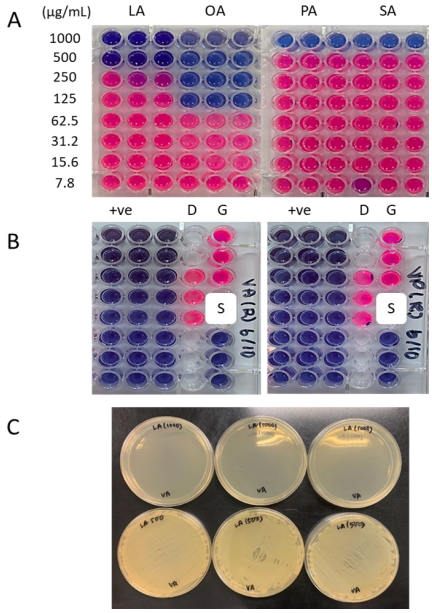

Figure 4, (A) MIC determination of Lauric acid, Oleic acid, Palmitic acid, and Stearic acid against *Vibrio alginolyticus* and *Vibrio parahaemolyticus* using a 96-well plate. (B) MIC determination of control samples where +ve: Positive control (Tetracycline), D: Negative control 50%DMSO, G: Growth control, S: Sterility control. Colour change from blue to pink indicates bacterial growth, while wells that remain blue indicate inhibition. Representative agar plates showing MBC results of Lauric acid against *V. alginolyticus* where 1000 µg/mL showed no growth, indicating bactericidal, while 500 µg/mL shows bacteria regrowth

DISCUSSION

Fatty acids (FAs) are well known for their antimicrobial properties against viruses, fungi, parasitic hosts, and bacterial infection.[11,26] However, research suggests that their antibacterial efficacy is limited to gram-positive bacteria, while they are less effective against gram-negative bacteria due to the presence of the outer membrane.[28] Few studies showed that FAs can be effective against gram-negative bacteria, including *Pseudomonas aeruginosa*, *Helicobacter pylori*, *Escherichia coli,* and *Vibrio* spp..[11]

The efficacy of FAs against gram-negative bacteria was previously linked to several factors, including carbon chain length, degree of saturation, and solubility.[29] In this study, the effect of carbon chain length and saturation on the efficacy of selected FAs against *Vibrio* spp. was investigated. The selected FAs chain length (12 to 18 carbons) was generally classified as long-chain FAs (LCFA) with carbon atoms between 12-26.[30] *In-silico* screening showed that OA had the lowest binding energy, followed by PA and LA (Figure 1). There was also a lack of conventional hydrogen bonds that usually promote stabilization. This was not according to the expected as the presence of several hydrophobic interactions in molecular docking might interfere with the hydrogen bond that improves the binding affinity and reduces the binding energy.[31] LCFA might have produced lower binding energy compared to LA due to the length of their carbon chain that favours hydrophobic interactions which are abundant in tested receptors. OA exhibited the highest affinity among molecules with the same hydrocarbon chain length. This can be linked to the presence of double bonds, which affect the orientation (cis- or trans-), which leads to different conformations and formation of new interactions with receptors.[17] Vaidyanathan et al. (2023) reported similar results where phenolic acid derivatives were tested against human serum albumin and reported that stability of molecular complexes was affected the both hydrogen bonding and hydrophobic interactions.[32] However, hydrophobicity is also critical factor that limits FAs' ability to access bacterial cells in an aqueous environment.[33] Hence, LCFA were expected to perform poorly *in-vitro* by

yielding weak antibacterial activity compared to LA.

The use of Universal Force Field (UFF) in this study was important due to the large number of receptors and their diversity. Despite Merck Molecular Force Field (MMFF94) being more suitable for organic compounds, UFF is computationally less intensive. A key disadvantage of UFF its ability to accurately predict hydrogen bonds[34], however hydrogen bonds were not expected to play major role in the docked fatty acids. UFF are also commonly applied when using PyRx,[35] which were used in this study.

In-vitro screening showed that among saturated FAs, OA (C18:1) exhibited the lowest MIC of 125 µg/mL, followed by LA (C12:0) with MIC of 500 µg/mL. PA (C16:0) and SA (C18:0) had an MIC of 1000 µg/mL (Table IV). Generally, MIC values below 100 µg/mL are considered "good" antibacterial agents, however, none of the fatty acids tested reached this effectivity. An MIC ranging from 100-500 µg/mL they are considered "moderate". MIC values between 500 and 1000 µg/mL are generally regarded as weak, while above 1000 µg/mL are considered inactive.[36] In terms of MBC, OA also had the best MBC 500 µg/mL, LA and PA gave best MBC 1000 µg/mL, while SA did not yield an MBC against either *Vibrio* spp.. LA, PA, and SA behaved as expected *in-vitro* (MIC and MBC) where the increase in carbon chain length has drastically reduced the antibacterial activity of the FAs, with the exception of OA. This could be due to the decreased solubility and therefore fewer interactions with the bacterial cell wall.[29] The primary antibacterial mechanism of FAs is known to involve the integration of the hydrophobic fatty acid alkyl chain into the bacterial lipid membrane causing cell lysis and death of bacteria.[35]

OA showed the strongest antimicrobial properties both *in -silico* and *in-vitro* studies against *Vibrio* spp., which may be attributed to its amphiphilic nature and optimal balance between hydrophobic and hydrophilic characteristics. Although OA contains a long hydrophobic C18 chain, the presence of a polar carboxyl group and a cis double bond enhances molecular flexibility and slightly increase hydrophilicity which improves access to the bacterial cell membrane.[29,36] This might have contributed to OA being more effective than the other FAs through the distinct combination of hydrophilic and hydrophobic properties that facilitate its interaction with the membranes of the microbial cell.[30] The presence of double bonds in the structure might indirectly affect bacterial cell membrane by introducing a kink and disrupting lipid packing. Such physicochemical changes ultimately to increased membrane permeability, leakage of intracellular components, and eventually leads to cell death.[24]

Long-chain saturated fatty acids like PA and SA, demonstrated strong performance in *in-silico* studies but exhibited limited efficacy in *in-vitro* experiments. This discrepancy highlights the necessity of validating theoretical drug candidates through experimental *in-vitro* tests because of various external factors, including solubility.[37] OA and LA were able to form hydrogen bonds *in-silico,* which correlated with enhanced performance in *in-vitro* assays. This finding supports previous research that highlights the critical role of hydrophilic interactions in modulating the solubility, membrane affinity, and overall antimicrobial effectiveness.[17] While OA has a cis double bond that can disrupt tight hydrophobic packing, reduce aggregation and improve dispersion in aqueous environments, LA has significantly shorter carbon chain which reduces its the hydrophobicity. A higher number of hydrogen bonds can also facilitate stronger interactions with microbial cell membranes, potentially leading to membrane destabilization and increased permeability. Additionally, improved solubility of the FAs can increase the interaction with bacterial cells, which will enhance the penetration of FAs and accordingly disrupting the essential cellular processes such as enzyme function and nutrient transport.[15]

In terms of species, the *in-vitro* test on the FAs demonstrated greater effectiveness against *V. alginolyticus* than *V. parahaemolyticus*. LA, OA, and PA all showed bactericidal activity against *V. alginolyticus*, while none of the 4 FAs showed bactericidal activity against *V. parahaemolyticus*. This might be a limitation of following

CLSI guideline on using 1% MHA, which might not be suitable for highly halophilic bacteria like *V. alginolyticus*.[38] It is hypothesized that *V. alginolyticus* might have encountered osmotic stress besides the FAs effect which could have led to it being more susceptible towards the FAs.

In terms of possible applications of selected FAs, *in-silico* analysis showed that FAs have preferential binding to proteins commonly involved in ligand or small-molecule binding, such as signalling proteins, transferase enzymes, peptide-binding proteins and metal transport. Li et al. (2022) summarized that disrupting signalling pathways such as N-acyl-homoserine lactone (AHL) results in increased susceptibility to antibiotics, inhibit biofilm formation and deactivation of efflux pumps.[39] The four FAs showed the highest binding affinity to PDB 5KEV, a key signalling protein involved in toxin production *V. parahaemolyticus*. This is particularly important because toxin production is a key in the pathogenicity of *V. parahaemolyticus*. They are used to regulate type III secretion system (T3SS) proteins, which are responsible for diseases such as Acute Hepatopancreatic Necrosis Disease (AHPND) and Early Mortality Syndrome (EMS) in shrimp aquaculture. These characteristics could also be transferred to human through ingestion of the infected shrimp which could led to gastroenteritis and sepsis.[40,41] The infected human could experience bloody diarrhoea, stomach cramps, nausea, and vomiting.[41,42] Besides that, the FAs also showed high affinity to PDB 7AGZ, a key peptide-binding protein involved in biofilm formation of *V. cholerae*. High inhibition potential was also observed against 6PXA, 2HJ9 and 3R5T. PDB 2HJ9 is quorum sensing & signalling protein in LuxP-LuxQ complex from *V. harveyi*.[43] Quorum sensing is a primary mechanism of intercellular communication in bacteria that enables a population of pathogenic bacteria to synchronize their gene expression.[44] It helps facilitate the collective behaviour of the bacteria to evade host immune responses while producing harmful virulence factors, as well as establish antibiotic-resistant biofilms.[45] The PDB 6PXA from *V. fischeri* is a transferase that aid in chloramphenicol resistance,[46,47] while 3R5T is a metal transporter involved in nutrient acquisition of ferric ion in *V. cholerae*.[48] Interfering with iron (Fe) acquisition via siderophores by *Vibrio* spp. is also a promising finding. Metal ions regulate the expression of various genes in *V. parahaemolyticus,* such as swarming and toxin secretion systems (e.g., T3SS).[49] Hence, the tested fatty acids might have various mechanism to potentially inhibit *Vibrio* spp., that could be developed into targeted drugs for prevention and treatment of Vibrio infections.

CONCLUSION

This study investigates the antibacterial activity of lauric acid (LA), oleic acid (OA), palmitic acid (PA), and stearic acid (SA) against *Vibrio* spp. using both *in-silico* and *in-vitro* approaches. Molecular docking predicted that OA exhibited the lowest binding energy, indicating the highest binding affinity with selected *Vibrio* protein receptors. This is despite OA being second-highest in the number of hydrogen bond interactions and third in terms of van der Waals interactions. These results suggest that its binding affinity is linked to the amphipathic nature, which is attributed to its long hydrophobic carbon chain and a hydrophilic carboxyl head. This is further coupled a single degree of unsaturation which give the structure conformational flexibility, making more chemical interactions and enhancing its binding affinity. *In-vitro* validation through MIC and MBC assays supported the *in-silico* predictions. OA demonstrated the lowest MIC of 125 μg/mL against both *Vibrio alginolyticus* and *Vibrio parahaemolyticus*, as well as bactericidal activity against *V. alginolyticus* at 500 μg/mL. Hence, molecular docking using selected receptors, particularly 3MRU, 3WPW, 3A57 and 3X0T, matched *in-vitro* results can be used to screen lead compounds in the future. Further research is recommended to explore its mechanism of action *in-vitro* and its effectiveness *in-vivo*. A positive outcome in future studies could establish an effective and safe alternative to antibiotics for the treatment of vibriosis.

ACKNOWLEDGEMENT

The authors wish to thank the Ministry of Higher Education (MOHE) Malaysia for the research funding

under the Fundamental Research Grant Scheme (FRGS) Fasa 1 2023 (FRGS/1/2023/WAB04/UMT/02/6, Vote No. 59757).

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ORIGINAL ARTICLE

Reproducible GC–MS Profiling of Urinary Metabolites as Biomarker Candidates for Dengue Infection: Seasonal Analysis Among Outpatients

Abd Rahman IZ[a], Wan Omar WFN[b], Abdullah A[b], Ahmad HF[c], Amid A[d]

[a]Department of Physiology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Cheras, Kuala Lumpur.
[b]Department of Basic Medical Sciences, Kulliyyah of Medicine, International Islamic University Malaysia, Kuantan, Pahang.
[c]Faculty of Industrial Sciences and Technology, University Malaysia Pahang Al-Sultan Abdullah, Gambang, Pahang.
[d]Department of Biotechnology Engineering, Kulliyyah of Engineering, International Islamic University Malaysia

ABSTRACT

INTRODUCTION: Dengue diagnosis remains a clinical challenge as early symptoms might overlap with other febrile illnesses. Urine-based metabolic profiling offers a promising, non-invasive approach for detecting dengue infection biomarkers. In our earlier study among warded patients, gas chromatography mass spectrometry (GC-MS) identified nine urinary metabolites associated with dengue infection. This study assesses the consistency of these metabolites in non-warded outpatients. **MATERIALS AND METHODS:** A cross-sectional study was conducted at outpatient clinics in Kuantan involving 30 dengue-confirmed patients and 30 healthy volunteers. Midstream urine samples were collected prior to treatment, and dengue infection was confirmed through serological testing. The nine targeted metabolites were analysed using GC-MS method described in our previous study. **RESULTS:** Two metabolites (hexadecane and pentadecane) were consistently detected in dengue-positive patients but absent in controls. Hexadecane eluted at a retention time (RT) of 20.95 ± 2.23 min, with a spectral similarity index (SI) of 85.50 ± 5.00 % and a peak area of 1360566.25 ± 1066618.37 a.u. Pentadecane eluted at RT of 24.07 ± 3.35 min, with an SI of 86.00 ± 4.55 % and peak area of 853458.25 ± 523318.12 a.u. Hexadecane exhibited a stronger signal, approximately 1.6 times higher than pentadecane with 100% specificity and sensitivity of 8%. **CONCLUSION:** These findings confirm that the presence of urinary hexadecane and pentadecane remain consistent across different patient subgroups. These results provide preliminary evidence that urinary hexadecane and pentadecane are reproducibly detected in a subset of dengue patients and warrant further large-scale studies to confirm their diagnostic utility.

Keywords
Urinary, Biomarker, Dengue, Screening, Diagnostic

Corresponding Author
Dr. Aszrin Abdullah
Department of Basic Medical Sciences, Kulliyyah of Medicine, International Islamic University Malaysia, Kuantan, Pahang.
Email: draszrin@iium.edu.my

Received: 6th November 2025; Accepted: 16th February 2026

Doi: https://doi.org/10.31436/imjm.v25i02/3113

INTRODUCTION

Dengue infection remains a significant public health concern in tropical and subtropical regions.[1] To date, no specific antiviral treatment exists for dengue fever; management remains primarily supportive, focusing on adequate hydration, rest, and relief of pain.[2] Its periodic outbreaks highlight the need for rapid, non-invasive diagnostic approaches. Laboratory diagnostic method for dengue virus infection is essential to support clinical diagnosis.[3] In the current clinical practice, several diagnostic approaches have been employed to confirm dengue infection including non-structural protein 1 (NS1) antigen detection, serological tests, molecular tests, and DENV subtype isolation by polymerase chain reaction (PCR).[4] Nonetheless, there is no single diagnostic method for dengue that fulfils the ideal criteria of sensitivity, specificity, speed, and affordability, and conventional tests often require venipuncture, trained personnel, and centralised facilities.[5] These limitations restrict their use in community or resource-limited settings. Moreover, only a limited number of studies have explored urinary

metabolites associated with this condition.[6–8] Urinary metabolic profiling with gas-chromatography mass spectrometry (GC-MS) has emerged as a promising alternative.[9] To our knowledge, this is among the first targeted reproducibility assessments to apply GC–MS analysis to previously identified urinary dengue-associated metabolites in outpatient dengue populations, with the goal of establishing a patient-friendly and non-invasive platform for identifying disease biomarker.

In our preliminary study, using an untargeted metabolomic approach via GC-MS among 10 hospitalised individuals diagnosed with dengue infection, we identified nine urinary metabolites associated with dengue infection namely, heptacosane, hexadecane, 2-bromooctane, tetradecane, pentadecane, 2,9-dimethyldecane, 2,4-bis (1,1-dimethylethyl) phenol, hexyl octyl ester sulphuric acid, and 2-benzoyl methyl ester benzoic acid.[10] Building on this, the present study evaluates the consistency and significance of these nine targeted urinary metabolites among non-warded patients and across multiple seasons. This approach aims to assess the robustness of these nine targeted urinary metabolites at different clinical settings and under natural temporal variations typical of tropical environments.

MATERIALS AND METHODS

Study Design and Participants

A cross-sectional study was conducted at outpatient clinics in Kuantan, from June 2022 to October 2023. Majority of the samples were collected between June to October each year, corresponding to non-monsoon season. Seasonal stratification was data-driven based on recorded sample collection dates rather than predetermined seasonal comparison. Inclusion criteria for the dengue-infected group comprised adults aged 18-60 years old with no known medical illness, newly diagnosed dengue infection confirmed by NS1 antigen and IgM/IgG serology, and ability to provide written informed consent. Exclusion criteria included individuals with chronic medical conditions (e.g., diabetes, hypertension, renal or hepatic disease), pregnant women, patients on long-term medication that could alter metabolic profiles, and patients with severe dengue (defined as dengue with any of the following clinical manifestations: severe plasma leakage causing shock or fluid accumulation with respiratory distress, severe bleeding, or severe organ impairment, including elevated transaminases ≥1,000 IU/L, impaired consciousness, or cardiac dysfunction). The control group consisted of adults aged 18–60 years with no known medical illness and capable of providing informed consent. Individuals with chronic diseases, pregnant or menstruating women were excluded.

Sample Collection

Midstream urine samples (15-30 mL) were collected in a sterile urine container and stored immediately at 4°C to preserve its integrity. Within 2 hours of collection, samples were centrifuged at 2000 rpm for 10 minutes to remove sediments. Post-centrifugation, 2 mL of the supernatant was carefully transferred into 1.5 mL microcentrifuge tubes (Eppendorf, Germany) and subsequently stored at -80°C, as described previously.[10] Urine of patients with suspected dengue infection were collected prior to treatment and dengue diagnosis was confirmed through serological test. The renal profile and liver function test were also performed to exclude underlying impairment and severe dengue.

The reproducibility of nine targeted urinary metabolites associated with dengue infection were analysed using GC-MS methods described in our initial study based on the retention time (RT) and similarity index (SI). Briefly, 1 µL of derivatized urine mixture was injected into a Shimadzu QP2010 Ultra GC-MS system (Kyoto, Japan) at an inlet temperature of 270°C using a 1:10 split ratio. Helium carrier gas was set at 1.2 mL/min. Separation was performed on an HP-5MS capillary column (30 m × 0.25 mm internal diameter, 0.25 µm film thickness) with the oven programme at 80°C for 2 minutes, ramped to 240°C at 5°C/min (held for 5 minutes), then to 300°C at 3°C/min (held for 5 minutes). The transfer line was maintained at 300°C. Electron ionisation was set at 70 eV with a mass range of 50–550 m/z. Metabolites were identified using the NIST 2017 library with similarity matches ≥80%. The levels of metabolites are quantified based on the peak area.[10]

Statistical Analysis

For each participant, GC-MS analysis was performed in three replicates, and the mean peak area of these replicates was used for all subsequent statistical comparisons. Data were analysed using IBM SPSS Statistics for Windows, Version 29.0 (IBM Corp., Armonk, NY, USA). Statistical significance was set at $p < 0.05$ with a 95% confidence interval. Categorical variables were expressed as frequencies and percentages, and comparisons were made using the Chi-square or Fisher's Exact test. Continuous variables with normal distribution were presented as mean ± standard deviation and analysed using the independent Student's t-test. Non-normally distributed data were expressed as median (interquartile range) and compared using the Mann–Whitney U test. Logistic regression was applied for multivariate analyses to adjust for covariates that might affect the production of urinary metabolites.

RESULTS

Sample Characteristics

30 dengue-confirmed patients and 30 healthy volunteers' urine samples were collected. There was no significant difference in the age, gender and ethnicity between dengue-infected subjects and healthy control group (p=0.523, 0.604 and 0.706 respectively) as shown in Table I.

Table I: Sociodemographic Characteristics of the Study Subjects (N=60)

Sociodemographic Characteristics		Overall (N = 60) n (%)	Dengue-infected subjects (n = 30) n (%)	Control group (n = 30) n (%)	p-value
Age group (years)	18-29	20 (33.3)	12 (40.0)	8 (26.7)	0.412*
	30-60	40 (66.7)	18 (60.0)	22 (73.3)	
Age (year)^		35.9 (12.6)	34.8 (11.6)	36.9 (13.6)	0.523**
Gender	Male	33 (55.0)	15 (50.0)	18 (60.0)	0.604*
	Female	27 (45.0)	15 (50.0)	12 (40.0)	
Ethnicity	Malay	52 (86.7)	27 (90.0)	25 (83.3)	0.706*
	Others	8 (13.3)	3 (10.0)	5 (16.7)	

^mean (SD), *Analysed using Chi-squared/Fisher's exact test, **Analysed using Independent Student's t-test

Both groups recorded a normothermic median temperature during the recruitment process. Dengue-infected subjects typically experienced fever for 4 days. The mean systolic blood pressure in dengue-infected subjects was significantly lower than controls (p=0.03). Nevertheless, they were within normotensive range. Other cardiovascular parameters such as pulse pressure, mean arterial pressure (MAP) and heart rate were similar in both groups as shown in Table II.

Table II: Clinical Parameters of the Study Subjects (N=60)

Clinical parameter	Overall (N= 60)	Dengue-infected subjects (n= 30)	Control group (n = 30)	p-value
Temperature (°C)#	36.7 (36.4 -37.1)	36.7 (36.5-37.2)	36.7 (36.4-37.0)	0.558*
Duration of fever (days)#		4 (3-6)	No fever	
Systolic blood pressure (mmHg)^	121 (17)	115 (14)	128 (17)	0.030**
Diastolic blood pressure (mmHg)^	77 (12)	75 (13)	79 (11)	0.254**
Pulse pressure (mmHg)^	45 (11)	48 (12)	41 (10)	0.201**
MAP (mmHg)^	92 (13)	95 (13)	89 (12)	0.076**
Heart rate (bpm)^	88 (16)	86 (16)	88 (15)	0.504**

#Median (IQR), ^mean (SD), IQR = interquartile range; MAP = mean arterial pressure; *Analysed using Mann-Whitney U/non-parametric test, **Analysed using Independent Student's t-test

Urinary Metabolites Detection

In the present study, five samples from the dengue-infected subjects and three from the control group were excluded in the GC-MS analyses due to compromised sample integrity, which resulted in error of the GC-MS analysis. From the remaining 52 samples, we found that two out of the nine targeted metabolites namely hexadecane and pentadecane (alkane group) were present in two samples (two to three replicates) of dengue-infected subjects. Hexadecane was characterised by a RT of 20.95 ± 2.23 min, a SI of 85.50 ± 5.00 %, and a mean peak area of 1360566.25 ± 1066618.37 a.u. Similarly, pentadecane exhibited a RT of 24.07 ± 3.35 min, a SI of 86.00 ± 4.55 %, and a mean peak area of 853458.25 ± 523318.12 a.u. The other targeted metabolites in this study were not detected in dengue-infected subjects. After evaluating the dataset comprising both positive and negative samples, it was observed that hexadecane and pentadecane demonstrated a sensitivity (true positive rate) of 8% and a specificity (true negative rate) of 100%.

Table III shows the statistical analysis of targeted metabolites identified in the study. The univariate analysis revealed presence of hexadecane and pentadecane in dengue-infected subjects (p=0.001 and p=0.024 respectively). Multivariate analysis further demonstrated the significant presence of hexadecane and pentadecane in dengue-infected subjects (p<0.01 and p<0.01) respectively.

Table III: Statistical Analysis of the Identified Targeted Metabolites (N=52)

Metabolite	Univariate analysis	Multivariate analysis	
	n = 156 (52 total subjects x 3 replicates)	n = 156 (52 total subjects x 3 replicates)	n = 75, (25 dengue-infected subjects x 3 replicates)
	p-value	p-value	p-value
Hexadecane	0.001*	<0.01**	<0.01**
Pentadecane	0.024*	<0.01**	<0.01**

*Analysed using Chi-squared/Fisher's exact test, **Analysed using Logistic Regression test
ϕAfter adjusting to presence of dengue infection, age, gender, ethnicity, day of fever, temperature, mean arterial pressure, heart rate, derangement of renal profile and liver function test

The two dengue patients with detectable urinary hexadecane and pentadecane were Malay females aged 22 and 43 years, recruited during the convalescent (recovery) phase, with normal renal function. One subject exhibited mildly elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, while the second subject exhibited liver parameters within normal ranges.

DISCUSSION

Subjects Socio-Demographics

Our study found no significant differences in age, gender, or ethnicity between dengue-infected subjects and the healthy control group. Approximately 60% of dengue-infected participants were aged 30–60 years, consistent with previous local reports showing higher susceptibility in this age group, likely due to increased outdoor exposure related to occupational and recreational activities.[11]

Our dengue-infected subjects were represented by a relatively equal number of males and females. In contrast, dengue infections are reported to be more prevalent among males, attributed to differences in gender-related behaviours and activities that increase exposure to the virus.[12,13] However, our observation may not accurately reflect the actual population, as the number of participants from both genders at the time of recruitment was roughly equal. Furthermore, our data showed that 90% of dengue-infected participants were Malays, reflecting the predominantly Malay demographic composition of the study area. It is important to note, however, that dengue infection does not demonstrate ethnic selectivity, as it affects Malay, Chinese, and Indian populations equally.[14]

Clinical Parameters

The present study revealed no significant difference in both groups of study subjects' body temperature, heart rates, and renal profile. The mean systolic blood pressure in dengue-infected subjects was within normal range despite significantly lower than controls.[15] Our study findings indicated that the dengue infected subjects were in the later stage of dengue infection as evidenced by positive IgM and IgG detected at their first presentation at healthcare facility, and were experiencing a non-severe dengue infection, which did not significantly impact the renal profile when compared to the controls. Furthermore, all exhibited no fever and maintained normal clinical parameters. The derangement of liver function test (raised ALT and AST) of one dengue-infected subjects could be explained by findings of other studies that hepatocellular injury is prevalent in more than half of the dengue-infected individuals.[16] This further highlights the necessity of liver enzymes serial monitoring throughout the course of the disease.

Detection of Targeted Urinary Metabolites

Both urinary metabolites *viz* pentadecane and hexadecane detected in serologically confirmed dengue-infected patients, belong to the alkane group. Dengue virus lacks metabolic enzymes capable of catalysing alkane oxidation.[17] Other studies found that dengue infection induces activation of immune and endothelial cells, leading to excessive generation of reactive oxygen and nitrogen species (ROS/RNS). These oxidants trigger lipid peroxidation of cell membranes, reflected by elevated markers such as malondialdehyde (MDA), 4-hydroxynonenal (4-HNE), and protein carbonyls, and result in the release of volatile hydrocarbons including alkanes, aldehydes, and ketones.[18–20]

Notably, positive detections of both urinary metabolites occurred in patients sampled during the convalescent phase. One plausible explanation is that urinary excretion of volatile hydrocarbons related to oxidative membrane injury may be detectable in time-dependent manner after the peak febrile period, when viraemia and acute systemic symptoms are subsiding. In addition, outpatient presentation in later illness may have limited our ability to

capture acute-phase metabolic markers. In contrast, humans do not utilise alkanes as energy substrates. Instead, cytochrome P450-mediated oxidation, can act on hydrocarbon substrates and occupational alkanes, producing alcohol, aldehyde, and acid intermediates that are subsequently excreted.[21] Together, these oxidative and detoxification mechanisms provide a plausible explanation for the urinary detection of hexadecane and pentadecane in dengue patients, reflecting host-derived oxidative membrane injury.

In comparison, bacterial species such as *Pseudomonas aeruginosa, Mycobacterium tuberculosis* and *Acinetobacter spp.* can produce similar alkanes through alkane monooxygenase (AlkB)-mediated oxidation.[22] In this study, however, the absence of bacterial growth and the temporal association with viremia suggest that these urinary alkanes are endogenously generated by the host. Collectively, our findings indicate that urinary pentadecane and hexadecane are host-derived oxidation products reflecting intense oxidative stress and membrane lipid breakdown triggered by dengue virus infection. These metabolites may therefore serve as non-invasive biomarkers of oxidative injury, potentially correlating with disease severity and tissue damage. Future metabolomic investigations should correlate urinary alkane profiles with clinical outcomes, hepatic function, and oxidative biomarkers to enhance their diagnostic and prognostic relevance.

CONCLUSION

This study suggests that urinary hexadecane and pentadecane levels remain consistent in a subset of dengue outpatients and are in-line with an intrinsic oxidative host response, reflecting a plausible mechanistic link between dengue-associated lipid peroxidation and urinary volatile alkane excretion. Importantly, these findings demonstrate the feasibility of targeted urinary metabolite detection using GC–MS in an outpatient setting. However, given the low detection rate observed, these metabolites should be regarded as exploratory biomarker candidates requiring further phase-stratified and larger-scale validation before any diagnostic application.

LIMITATIONS AND FUTURE DIRECTIONS

Nonetheless, several limitations should be acknowledged. The low sensitivity of urinary hexadecane and pentadecane detection despite high specificity suggests that most dengue-confirmed outpatients did not exhibit detectable levels of these metabolites under current sampling and analytical conditions, limiting their immediate utility as standalone diagnostic biomarkers. In addition, both detections occurred during the convalescent phase indicate that metabolite detectability may differ across stages of illness and that the optimal diagnostic window has yet to be established. The sample size was modest, and recruitment was limited to a single geographic region further limit generalisability. Quantitative validation using targeted metabolomics and controlled comparisons with other viral or bacterial infections are needed to confirm the specificity of hexadecane and pentadecane as dengue-related oxidative markers.

Future studies should integrate phase-stratified (acute, critical, and recovery phases), clinical severity grading and larger multicentre cohorts to clarify specificity, temporal dynamics and prognostic value of these metabolites in dengue infection. By addressing these areas, we aim to strengthen the evidence base for non-invasive urinary metabolite profiling as a feasible approach for dengue biomarker development.

INSTITUTIONAL REVIEW BOARD (ETHICS COMMITTEE)

This study was approved by the institutional, IIUM Research Ethics Committee (IREC) [IREC 2019-187]. Written informed consent was obtained from all participants.

ACKNOWLEDGEMENTS

The authors would like to thank all staff involved in data collection and sample analysis. This study was supported by IUMP-SRCG22-009-0009 grant.

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ORIGINAL ARTICLE

Two-Dimensional Radiological Analysis of Tibial Malalignment After Intramedullary Nailing: Prevalence, Associated Factors, and Outcomes

Che Mat Nasir MA[a], Ab Rahman S[a], Sharifudin MA[a,b,c], Ahmad MR[a], Ahmad NF[d]

[a]Department of Orthopaedics, School of Medical Sciences, Universiti Sains Malaysia, Malaysia
[b]Department of Orthopaedics and Rehabilitation, Faculty of Medicine, Universiti Sultan Zainal Abidin, Medical Campus, JalTerengganu, Malaysia
[c]Medical and Healthcare Research Cluster, Office of The Deputy Vice-Chancellor (Research and Innovation), Universiti Sultan Zainal Abidin, Terengganu, Malaysia
[d]Department of Radiology, Faculty of Medicine, Universiti Sultan Zainal Abidin, Medical Campus, Jalan Sultan Mahmud, Terengganu, Malaysia

ABSTRACT

INTRODUCTION: Tibial fractures are common long-bone fractures treated by orthopaedic surgeons. Intramedullary nailing (IMN) is the preferred standard treatment for tibial diaphysis fractures. This study aimed to evaluate the prevalence of tibial malalignment, its associated factors, and the outcomes following IMN. **MATERIALS AND METHODS:** A retrospective cross-sectional study was conducted on skeletally mature patients aged over 18 years who underwent IMN for tibial diaphysis fractures at a single academic trauma centre from January 2015 to December 2023. Data were extracted from the hospital database, including plain radiographs, medical records, and intraoperative notes. The Pearson chi-square test was used to examine the outcomes of malalignment, followed by logistic regression analyses to identify factors associated with tibial malalignment. **RESULTS:** A total of 163 patients were analysed. The prevalence of tibial malalignment following IMN was 66.0% in the proximal third, 58.8% in the distal third, and 25.0% in the middle third. The degree of comminution, specifically in Type 42C fractures, and lateral nail entry point were significantly associated with malalignment (p=0.02 and 0.011, respectively). However, no significant correlation was found between malalignment and bone union. **CONCLUSION:** Tibial malalignment is most common in the proximal third following IMN, with the degree of comminution being a significant factor. Despite the high prevalence of malalignment, it did not adversely affect bone union. These insights can guide preoperative planning and intraoperative techniques to optimize patient outcomes in tibial diaphysis fractures.

Keywords
tibial diaphyseal fractures, bone union, comminuted fractures, malalignment of tibia, intramedullary nailing.

Corresponding Author
Assoc. Prof. Dr Shaifuzain Ab Rahman
Department of Orthopaedics, School of Medical Sciences, Universiti Sains Malaysia
Email: shaifuzain@usm.my

Received: 3rd May 2025; Accepted: 5th January 2026

Doi: https://doi.org/10.31436/imjm.v25i02/2949

INTRODUCTION

Tibia diaphysis fractures are among the most prevalent long bone injuries encountered by orthopaedic surgeons, often resulting from high-impact trauma such as road traffic accidents or direct blows.[1,2] These fractures are classified into three segments: proximal, middle, and distal thirds. Diagnosis generally involves plain radiographs of the tibia and adjacent joints. Treatment options vary based on fracture configuration, soft tissue condition, and surgeon preference, including braces, external fixation, plate fixation, and intramedullary nailing (IMN). Each technique has specific indications, complications, and varying union rates.[1,3,4]

IMN is often the preferred method for managing tibial diaphysis fractures due to its load-sharing properties, high union rates, reduced soft tissue damage, lower infection risks, and shorter immobilization periods that facilitate early weight-bearing.[2,3,5-8] The primary goals of IMN are

to achieve a stable construction, ensure good fracture reduction, and maintain proper sagittal and coronal alignment, as well as restore rotation and length.[9] Despite these advantages, optimizing alignment and stability during IMN remains contentious.[2-4,10,11]

A significant complication of IMN is malalignment, which can lead to angular deformities such as varus, valgus, recurvatum, and procurvatum. Malalignment is defined as an angular deformity exceeding 5 degrees in any plane.[11,12] Malalignment in the tibia is defined by varus-valgus angulation exceeding 5 degrees, anterior/posterior angulation or rotational malalignment exceeding 10 degrees, less than 50% cortical apposition, or more than 1 cm of shortening.[7] Studies have reported its prevalence after IMN to range from 30% to 80%, with earlier literature cautioning against IMN for proximal third diaphyseal fractures due to the increased risk of deformity.[2] Contributing factors include deforming forces from surrounding musculature and inadequate endosteal fit of the nail.[4,6,13]

Despite the known prevalence of tibial malalignment, comprehensive data on its incidence across different tibial segments and the factors influencing these outcomes are lacking. This study aims to evaluate the prevalence of tibial malalignment in the proximal, middle, and distal thirds of the tibia, identify factors leading to angular deformities, and assess their impact on bone union. By providing this data, the research seeks to assist surgeons in preoperative planning and intraoperative decision-making, minimizing complications and enhancing patient quality of life.

MATERIALS AND METHODS

This single-centre, retrospective cross-sectional study was conducted at an academic trauma centre and commenced after obtaining ethical approval from the institution's Human Research Ethics Committee (Ref.: USM/JEPeM/KK/23060435). The study included patients over 18 years of age or those who had reached skeletal maturity, all of whom were admitted for tibial diaphysis fractures requiring surgical fixation with IMN between January 2015 and December 2023. Patients who were treated non-operatively, had received fixations other than IMN, had intra-articular fractures, congenital anomalies such as fibular hemimelia, or had poor-quality preoperative or postoperative radiographs that did not yield helpful information were excluded from the study. Data was collected from the centre's electronic database, medical records, and intraoperative notes. No patients were directly recruited for participation in this study.

Demographic, injury, and treatment data were extracted from medical records and intraoperative notes. Numerical and radiological findings (plain radiographs) in both coronal and sagittal views were measured using the Universal Viewer Zero Footprint Client (PACSZFP3 system). Tibial diaphysis fractures were classified based on their location into proximal, middle, and distal thirds (Figure 1). The longitudinal length of the tibia was measured using PACSZFP3 software, dividing it into three equal segments to determine the precise fracture location.

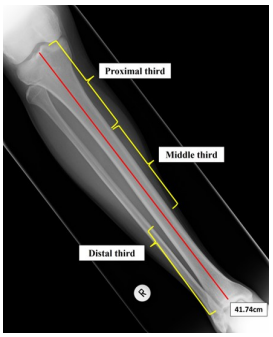

Figure 1: Location of fracture site along the tibial diaphysis, categorized into the proximal, middle, and distal thirds. The total length of the tibial diaphysis is measured (indicated by the red longitudinal line: 41.74 cm) and equally divided into three segments to determine the fracture location.

In the anteroposterior (AP) view, malalignment was evaluated using the anatomical axis as a reference point. A vertical line was drawn from the midpoint of the tibial spines to the distal end of the tibia, just above the tibiotalar joint (Figure 2). Any deviation from this line was categorized as malalignment, either in varus or valgus, and the angle of deviation was measured using the PACSZFP3 system. For the lateral radiograph, the anatomical axis was defined as a line passing through the medullary canal, positioned 7 cm from the plateau and 7 cm from the plafond (Figure 3).[14] Deviations from this axis were categorized as malalignment, either in procurvatum or recurvatum, with angles also measured

using the PACSZFP3 system. Significant malalignment was defined as any deviation exceeding 5 degrees on the AP radiograph and any deviation exceeding 10 degrees on the lateral radiograph.

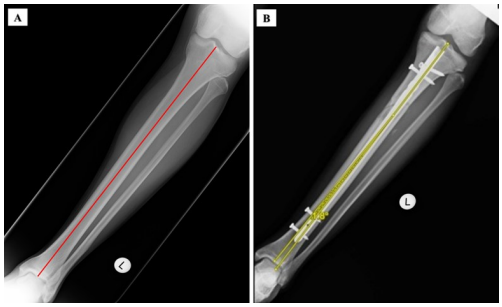

Figure 2: Anatomical axis of the tibia on anteroposterior view plain radiographs. The axis is drawn from the midpoint of the tibial spines to the distal end of the tibia, as depicted by **(A)** the red line on a normal tibia and **(B)** the yellow line on a tibia with a post-intramedullary nail (IMN), indicating a minimal valgus malalignment of 1.8 degrees.

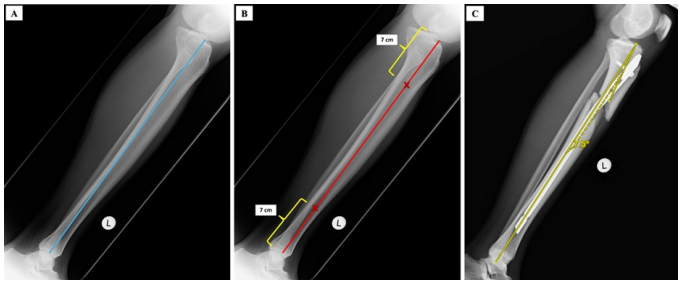

Figure 3: Lateral view plain radiographs of the tibia. **(A)** Represents the mechanical axis (blue longitudinal line), **(B)** shows the anatomical axis (red longitudinal line), determined by a line passing through the medullary canal, positioned 7 cm from the plateau and 7 cm from the plafond, and **(C)** depicts a 7.5-degree procurvatum malalignment of a proximal third tibial fracture post-intramedullary nail (IMN), as indicated by the yellow line.

The degree of comminution in tibial diaphysis fractures was evaluated using plain radiographs based on the Arbeitsgemeinschaft für Osteosynthesefragen/ Orthopaedic Trauma Association (AO/ OTA) classification system. Type 42A includes simple fractures with no significant comminution, which may be transverse, oblique, or spiral in nature. Type 42B is characterized by moderate comminution, where multiple fragments are present, but the fracture still maintains some degree of stability. Type 42C represents highly comminuted fractures with multiple fragments and instability, typically resulting from high-energy trauma.

Information regarding the size and type of nail used, as well as the grade of open fractures according to the Gustilo-Anderson classification, was retrieved from intraoperative notes. The presence and location of fibular fractures were analysed using both plain radiographs and intraoperative records. Any discrepancies identified in the radiological findings, intraoperative notes, or medical records were addressed based on current concepts and literature related to the management of tibial diaphysis fractures.

Outcomes related to tibial malalignment were assessed using plain radiographs obtained during the postoperative follow-up period. Radiographic images were reviewed to evaluate the progress of bone union within six months following the surgical procedure. The absence of at least three cortical bridges beyond this timeframe indicated non-union or delayed union.

The collected data was analysed using IBM SPSS version 27. Descriptive statistics summarized the sociodemographic characteristics of the patients, with numerical data presented as mean and standard deviation (SD) or median and interquartile range (IQR). Categorical data were reported as frequency and percentage. Factors associated with tibial malalignment were determined using logistic regression analysis, while crosstabulation (Pearson chi-square) was utilized to examine the outcomes of malalignment, followed by simple and multiple logistic regression analyses to assess associated factors following IMN.

RESULTS

A total of 163 patients were identified and analysed. The mean age of the entire cohort was 32.61 years (SD=16.57), with 122 patients (74.8%) being male. Most patients (n=142, 87.1%) sustained their injuries from motor vehicle accidents (MVA), while 21 patients (12.9%) experienced injuries due to non-MVA trauma. Table I shows the distribution of coronal and sagittal alignment based on the location of the tibial diaphysis. Regarding coronal alignment, the most significant malalignment cases were found in the proximal third of the tibial diaphysis, affecting six patients (66.7%). This was followed by malalignment in the distal third, which affected 40 patients (58.8%), and in the middle third, which affected 22 patients (25.6%). The analysis of sagittal alignment revealed that 44.4% of proximal third fractures (n = 4) exhibited malalignment, while the distal third showed a malalignment rate of 13.2% (n=9), and the middle third had a rate of 1.2% (n=1).

Table I: Prevalence and degree of malalignment by tibial diaphyseal location.

Degree of malalignment	Proximal third n (%)	Middle third n (%)	Distal third n (%)
Coronal plane			
< 5° varus	2 (22.2)	28 (32.6)	15 (22.1)
> 5° varus	3 (33.3)	11 (12.8)	17 (25.0)
< 5° valgus	1 (11.1)	36 (41.9)	13 (19.1)
> 5° valgus	3 (33.3)	11 (12.8)	23 (33.8)
Total cases of significant coronal malalignment	6 (66.7)	22 (25.6)	40 (58.8)
Sagittal plane			
< 5° procurvatum	3 (33.3)	45 (52.3)	22 (32.4)
> 5° procurvatum	4 (44.4)	0 (0.0)	2 (2.9)
< 5° recurvatum	2 (22.2)	40 (46.5)	37 (54.4)
> 5° recurvatum	0 (0.0)	1 (1.2)	7 (10.3)
Total cases of significant sagittal malalignment	4 (44.4)	1 (1.2)	9 (13.2)

Table II shows the association between tibial alignment and bone union among the 163 patients with tibial diaphysis fractures. There was no significant association between alignment groups and bone union (p>0.05). Specifically, 55 patients (72.4%) with varus malalignment achieved bone union, compared to 72 (82.8%) with valgus malalignment. For sagittal malalignment, 57 patients (75.0%) with procurvatum and 70 patients (80.5%) with recurvatum experienced bone union.

Table II: Association of tibial alignment and bone union outcomes (n = 163)

Tibial alignment		Bone union n (%)	Non-union/ Delayed union n (%)	p value*
Coronal plane				0.111
	Varus	55 (72.4)	21 (27.6)	
	Valgus	72 (82.8)	15 (17.2)	
	Total	127 (77.9)	36 (22.1)	
Sagittal plane				0.402
	Procurvatum	57 (75.0)	19 (25.0)	
	Recurvatum	70 (80.5)	17 (19.5)	
	Total	127 (77.9)	36 (22.1)	

*Pearson chi-square applied

Table III presents descriptive statistics related to tibial malalignment. The highest percentage of malalignment was observed among patients with Type 42C fractures, with 12 out of 14 patients (85.7%) affected. Nearly half of the patients with Grade 1 and Grade 2 open fractures also exhibited tibial malalignment. Similarly, almost half of the patients with concomitant fibular fractures (46.0%) had tibial malalignment, with the highest prevalence found in proximal fibular fractures, affecting 18 out of 30 patients (60%). This was followed by the same-level fibular fractures at 43.4% and distal fibular fractures at 38.7%. Among the nail entry points, lateral entry had the highest malalignment rate, with 10 out of 12 patients (83.3%) affected. The analysis of nail size revealed that sizes 9 to 11 were the most used, showing nearly equal prevalence of tibial malalignment among patients with sizes 9 and 10. Although the highest percentage of malalignment was observed in patients with nail size 8 (100.0%) and size 12 (66.7%), these groups had the fewest patients, indicating a potential skew in the results.

Table III: Descriptive statistics of factors associated with tibial malalignment

Variable	Total, n	Presence of tibial malalignment	
		YES, n (%)	NO, n (%)
Degree of comminution (OA/OTA Classification)			
Type 42A	94	32 (34.0)	62 (66.0)
Type 42B	55	28 (50.9)	27 (49.1)
Type 42C	14	12 (85.7)	2 (14.3)
Open fracture (Gustilo Anderson Classification)			
Grade 1	96	46 (47.9)	50 (52.1)
Grade 2	12	6 (50.0)	6 (50.0)
Grade 3	18	3 (16.6)	15 (83.3)
Concomitant fibular fracture			
Yes	137	63 (46.0)	74 (54.0)
No	26	9 (34.6)	17 (65.4)
Location of concomitant fibular fracture			
Proximal	30	18 (60.0)	12 (40.0)
Same level	76	33 (43.4)	43 (56.6)
Distal	31	12 (38.7)	19 (16.3)
Site of nail entry			
Medial	8	5 (62.5)	3 (37.5)
Center	143	57 (39.9)	86 (60.1)
Lateral	12	10 (83.3)	2 (16.7)
Size of nail (mm)			
8	1	1 (100.0)	0 (0.0)
9	16	8 (50.0)	8 (50.0)
10	74	35 (47.3)	39 (52.7)
11	69	26 (37.7)	43 (62.3)
12	3	2 (66.7)	1 (33.3)

The results of simple logistic regression, shown in Table IV, identified factors associated with tibial malalignment, including the degree of comminution, Gustilo-Anderson classification, presence of fibular fractures, location of fibular fractures, entry point of the nail, and nail size. The degree of comminution (Type 42C fractures) and lateral nail entry point showed statistically significant associations with malalignment (p=0.02 and p=0.011, respectively). A multiple logistic regression analysis included all variables with a p<0.25 and those deemed clinically important from simple logistic regression. The final model indicated that the degree of comminution, classified by AO/OTA, was significantly associated with tibial malalignment. Specifically, patients with Type 42C fractures were 17 times more likely to experience malalignment compared to those with Type 42A fractures (Adjusted OR=2.730; 95% CI:1.832, 159.802; p=0.013).

DISCUSSION:

Tibial diaphysis fractures are common in orthopaedic practice, and this study aimed to evaluate tibial malalignment following IMN, along with its contributing factors and effect on bone union. Despite IMN's high union rates and clinical efficacy, managing fractures,

particularly in the proximal and distal thirds, remains challenging.[3,4,13] Our findings align with previous studies, indicating that malalignment was most prevalent in the proximal third of the tibia (66%), observed in both sagittal and coronal planes, within the reported range of 44% to 84%.[7,11]

Table IV: Simple and multiple logistic regression analysis of factors associated with tibial malalignment

Variables	SLR[a]		MLR[b]	
	Crude OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Degree of comminution (OA/OTA)				
Type 42A	1		1	
Type 42B	2.009 (1.019, 3.963)	0.044	1.222 (0.387, 3.859)	0.732
Type 42C	11.625 (2.451, 55.131)	0.002	17.111 (1.832, 159.802)	0.013
Open fracture (Gustilo Anderson)				
Grade 1	1			
Grade 2	0.200 (0.037, 1.071)	0.060		
Grade 3	0.850 (0.231, 3.129)	0.807		
Concomitant fibular fracture				
No	1			
Yes	1.608 (0.670, 3.858)	0.287		
Location of concomitant fibular fracture				
Distal	1			
Proximal	2.375 (0.850, 6.636)	0.099		
Same level	1.215 (0.518, 2.852)	0.654		
Site of nail entry				
Centre	1			
Medial	2.515 (0.578, 10.936)	0.219		
Lateral	7.544 (1.594, 35.708)	0.011		
Size of nail	0.771 (0.496, 1.199)	0.249		

[a]Simple logistic regression applied.
[b]Forward stepwise multiple logistic regression model applied. The model's overall fit was checked and reported to be the Hosmer and Lemeshow Test (p>0.95), overall, correctly classified percentage = 71.4%, and the area under the curve (63.9%) was applied to check the model's fitness.
CI: confidence interval, MLR: multiple logistic regression, OR: odds ratio, SLR: simple logistic regression.

Managing proximal tibial fractures with IMN is challenging due to the tibia's voluminous shape and its proximity to the knee joint, which complicates nail insertion and increases the bending moment on the proximal fragment.[13,15] The distal Herzog bend in standard IMNs can cause displacement of the distal segment during insertion, contributing to malalignment.[16] Studies have linked proximal third fractures to higher incidences of malalignment in both sagittal and coronal planes.[8,11,15,16] Although modern IMNs feature a more proximally positioned Herzog bend to improve interlocking, correct nail positioning remains crucial to prevent malalignment.

Proper nail positioning is crucial for distal tibial fractures,[3,4,15] where malalignment was more common in the coronal plane (58.8%) than in the sagittal plane (13.2%). Studies show that distal nail placement, lateral to the talus and plafond or along the tibial mechanical axis, reduces coronal plane malalignment compared to medial placement, with malalignment rates of 2.9% versus 27.5%, respectively.[17] In the sagittal plane, malalignment reached 48%, with the highest incidence occurring in the anterior quadrant (100%).

The study found that the degree of comminution significantly affected tibial malalignment, with Type 42C fractures showing a 17-fold higher risk than Type 42A fractures. Previous studies have also linked comminuted fractures to malalignment following IMN,[2,10] 58% of tibial malalignments following IMN were associated with segmental or comminuted fractures, emphasising the importance of employing pre-reduction techniques to achieve proper alignment before nail insertion.[11] Previous studies have also linked comminuted fractures to malalignment following IMN, with 58% of tibial malalignments associated with segmental or comminuted fractures. This emphasises the importance of pre-reduction techniques,[4,15] such as large distractors, external fixators, or direct reduction methods, to realign bone fragments and optimize fracture healing before nail insertion.[9]

The tibial anatomy and nail curvature influence the entry point for IMN. For proximal tibial fractures, the ideal entry is behind the patellar tendon, either via a flexed knee or suprapatellar approach.[9,18] This central alignment with the tibial spine and medullary canal reduces pressure on the fracture, aiding reduction and minimizing fluoroscopy time. The optimal starting point should be central, in line with the medial to lateral tibial spine and the medullary canal.[19] Using the suprapatellar approach allows for nail insertion without exerting pressure on the reduced fracture fragments, facilitating easier reduction and minimizing the duration of intraoperative fluoroscopy.[18] Although some studies report no significant differences in outcomes between suprapatellar, infrapatellar, or lateral approaches, proper alignment with the medullary canal remains crucial to prevent malalignment.[20] Additionally, proximal locking improves

implant stability.[5]

The study did not reach statistical significance due to the small sample size; however, other research suggests that the nail entry point influences the degree of malalignment. Lateral entry points often cause varus deformity, while medial entry points lead to valgus malalignment.[21] Our study supports this, showing a significant correlation between the entry point and posterior alignment, with over 80% of lateral entries resulting in malalignment. Another study suggested that the ideal entry point for IMN should be centrally located, noting that 25% of fractures with a medial entry point showed no deviation, while all fractures with a lateral entry point exhibited some degree of misalignment.[14]

Open fractures classified by the Gustilo-Anderson system present challenges due to soft tissue injuries and infection risks. However, our study found no significant correlation between injury grade and malalignment prevalence, suggesting that this classification primarily assesses soft tissue severity and may not fully capture the complexities of malalignment in tibial fractures.

Fibular fractures often accompany tibial fractures due to their anatomical proximity. In this study, we found no significant correlation between fibular fractures and tibial malalignment. Previous research has shown mixed results regarding the impact of fibular fixation on malalignment rates.[1,9] Some studies reported minimal occurrences of malunion and malalignment without fibular fixation.[12,22] In contrast, others indicated that fixing the fibula alongside IMN reduces tibial malalignment and ankle malrotation in distal third fractures.[10] One study indicated that malalignment prevalence is higher in cases of fibular fractures, with rates of 8.3% in intact fibulas compared to 21.8% in fractured fibulas.[23] However, recent studies have found no significant relationship between fibular fixation and tibial non-union rates.[1,24,25] Our findings suggest that the presence of a fibular fracture does not inherently increase the risk of malalignment in tibial diaphysis fractures treated with IMN.

Our study found no significant correlation between nail size and malalignment incidence, supporting literature that suggests nail size should be determined by the intramedullary canal dimensions. Over-reaming can facilitate insertion and reduce hoop stress. Current research indicates no differences in union rates based on nail size, and larger nails may pose additional risks. Conversely, smaller nails simplify procedures, reduce costs, and minimize blood loss.[26] Some studies recommend reserving larger diameter IMN for revision surgeries.[27] Ultimately, factors influencing nail insertion may be more critical than nail size itself, with the choice of nail size prioritizing optimal surgical outcomes and minimized risks.

Tibial malalignment can significantly impact bone union and healing, potentially leading to complications like delayed union or non-union due to improper load distribution and inadequate stabilization. Malalignment disrupts optimal healing conditions, including fracture stabilization and mechanical loading. However, our study found no significant impact on non-union or delayed union rates, likely due to effective fracture stabilization and sufficient intraosseous stimulation through IMN.[28] Similar findings have been reported in previous studies, indicating that malalignment is not independently associated with non-union.[29]

LIMITATIONS

This study has several limitations. The retrospective cross-sectional design and relatively small sample size limit causal inference and reduce statistical power, making it difficult to detect subtle differences among fracture subgroups. Reliance on existing radiographs and medical records led to inconsistent or incomplete clinical outcome data, particularly regarding functional impairment and rotational malalignment. Additionally, rotational deformities were not assessed due to the inherent limitations of two-dimensional radiographs, which are less accurate than advanced imaging or clinical evaluation for detecting such deformities. Variability in IMN implant types and the limited representation of medial and lateral nail entry points further constrain the generalisability of our findings, as different surgical approaches may influence outcomes differently.

FUTURE RECOMMENDATIONS

Future research should focus on prospective, multicentre studies with larger cohorts to improve statistical power and reduce bias. Standardised surgical protocols combined with advanced imaging techniques, such as computed tomography, and thorough clinical rotational assessments will enable a more comprehensive evaluation of tibial malalignment, including rotational deformities that significantly impact patient function. Incorporating systematic collection of patient-reported outcomes and functional assessments is essential to link radiographic findings with clinical relevance. Further investigation of intraoperative techniques, including optimal nail entry point selection, use of blocking screws, and effective pre-reduction methods, could enhance surgical precision and reduce malalignment risk. These efforts will contribute to evidence-based protocols that optimise alignment and improve patient outcomes following IMN of tibial diaphysis fractures.

CONCLUSION

This study confirms the effectiveness of IMN as the preferred treatment for tibial diaphysis fractures, demonstrating favourable outcomes in bone union and minimal complications. Although malalignment remains a common issue, particularly in proximal and comminuted fractures, careful preoperative planning and precise surgical techniques can enhance patient outcomes. Key strategies to minimize angular deformity include adequate imaging, optimal entry point selection, and maintaining proper reduction throughout the procedure. By prioritizing these practices, surgeons can improve the success of IMN treatment for tibial diaphysis fractures.

INSTITUTIONAL REVIEW BOARD (ETHICS COMMITTEE)

This single-centre, retrospective cross-sectional study was conducted at an academic trauma centre and commenced after obtaining ethical approval from the institution's Human Research Ethics Committee (Ref.: USM/JEPeM/KK/23060435).

ACKNOWLEDGEMENT

The authors would like to express their gratitude to the Medical and Healthcare Research Cluster, Office of the Deputy Vice-Chancellor of Research and Innovation, Universiti Sultan Zainal Abidin, for the invaluable support and assistance that greatly facilitated the successful completion of this research and its publication.

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ORIGINAL ARTICLE

Functional and Radiological Outcomes of Plate Osteosynthesis in Closed Displaced Intraarticular Calcaneal Fractures

Ariffin MA[a,b], Ayeop MAS[a], Sharifudin MA[a,c,d], Che Ahmad A[a], Mohd Rashid Z[a,c], A.Rahman LM[a,c]

[a]Department of Orthopaedics, Rehabilitation and Traumatology, Kulliyyah of Medicine, International Islamic University Malaysia, Malaysia
[b]Department of Orthopaedics, Hospital Segamat, Johor, Malaysia
[c]Department of Orthopaedics and Rehabilitation, Faculty of Medicine, Universiti Sultan Zainal Abidin, Medical Campus, Terengganu, Malaysia
[d]Medical and Healthcare Research Cluster, Office of The Deputy Vice-Chancellor (Research and Innovation), Universiti Sultan Zainal Abidin, Malaysia

ABSTRACT

INTRODUCTION: Calcaneum fractures, particularly closed, displaced intraarticular fractures, are uncommon yet cause significant morbidity and impair quality of life (QOL). While open reduction and internal fixation a standard treatment, debate on optimal management continues. This study evaluated functional outcomes of plate osteosynthesis for these fractures, focusing on QOL and radiological measures. **MATERIALS AND METHODS:** This retrospective study reviewed records of patients with closed displaced intraarticular calcaneal fractures treated with plate osteosynthesis (January 2015-December 2020) at a single tertiary centre. Surgery involved open reduction and internal fixation using a locking calcaneal plate, performed on average 11 days post-trauma. Follow-up assessments were conducted for a minimum of one year, utilising the SF-36 for QOL and measuring Böhler's angle. **RESULTS:** Twenty-six patients (25 males, 1 female; mean age 42.8 years) were included. Fractures were primarily caused by motor vehicle accidents (65.4%). The mean QOL score was 55.9, and the mean post-operative Böhler's angle was 22°. Fracture type (Sanders' classification) was significantly associated with Böhler's angle. Correlation analysis revealed a weak, non-significant positive correlation between Böhler's angle and SF-36 scores ($r = 0.187$, $r^2 = 0.035$, $p = 0.360$). Superficial infections occurred in 7.6% of cases, all resolving without further surgery. **CONCLUSION:** Plate osteosynthesis for closed, displaced intraarticular calcaneum fractures provides favourable functional outcomes and restores anatomical alignment. The weak correlation between radiological restoration and patient-reported function suggests that additional factors may influence overall recovery.

Keywords
Böhler's angle, calcaneal fractures, plate fixation, quality of life, surgical outcomes.

Corresponding Author
Assoc. Prof. Dr Mohd Ariff Sharifudin
Faculty of Medicine, Universiti Sultan Zainal Abidin, Medical Campus, Jalan Sultan Mahmud, Terengganu, Malaysia
E-mail: ariffsharifudin@unisza.edu.my

Received: 8th May 2025; Accepted: 1st December 2025

Doi: https://doi.org/10.31436/imjm.v25i02/2951

INTRODUCTION

Calcaneum fractures, particularly closed, displaced intraarticular fractures, represent a significant clinical challenge due to their relatively low incidence yet substantial impact on patients' quality of life.[1-3] These fractures, accounting for approximately 2% of all fractures,[4-6] primarily result from high-energy trauma, including motor vehicle accidents and falls from heights.[1,7] The calcaneus, the largest tarsal bone, is crucial in foot mechanics and overall mobility. Therefore, injuries to this bone can lead to long-term functional impairment and increased healthcare costs,[5,8] highlighting the need for effective treatment strategies.

Despite advancements in surgical techniques, the optimal management of displaced intraarticular calcaneal fractures remains contentious.[9-11] Open reduction and internal fixation (ORIF) has been established as a standard treatment;[1] however, the outcomes can vary significantly

among patients. Factors such as the fracture's complexity, the timing of surgical intervention, and the surgical approach can influence recovery and functional outcomes. Current literature indicates that while ORIF may improve anatomical alignment, the correlation between radiological outcomes and functional recovery is not well-defined, leaving a gap in understanding the overall effectiveness of these interventions.

Previous studies have emphasised restoring Böhler's angle, a radiological measurement that evaluates calcaneal alignment, to improve functional outcomes.[12-15] However, there is a lack of consensus on the relationship between radiological measures and patient-reported quality of life (QOL). Many existing studies focus on short-term outcomes, with limited follow-up periods, which may not capture the full spectrum of recovery and long-term implications of these fractures. This gap in the literature emphasises the need for comprehensive evaluations that assess both clinical and radiological outcomes over extended periods.

The primary objective of this study is to evaluate the functional outcomes and quality of life in patients with closed displaced intraarticular calcaneum fractures treated with plate fixation. By examining the correlation between post-operative Böhler's angle and quality of life scores, this research aims to provide insights into the effectiveness of surgical interventions and identify factors that contribute to optimal recovery. The findings of this study will contribute to the existing body of knowledge and inform clinical practice in the management of calcaneal fractures.

MATERIALS AND METHODS

Inclusion and Exclusion Criteria

The inclusion criteria for this study included patients aged 18 to 75 years who presented with either open or closed displaced intra-articular fractures involving the posterior facet of the calcaneus, including fracture dislocations. All included patients underwent fixation with a locking calcaneal plate and had a minimum follow-up of one-year post-operatively. Patients with open fractures were included only if the degree of contamination, as documented by the attending surgeon based on intraoperative clinical judgment, was deemed suitable for immediate internal fixation, similar to closed fractures. Conversely, patients were excluded if they had grossly contaminated open fractures requiring initial debridement and infection control with delayed fixation, nondisplaced or minimally displaced extra-articular fractures, peripheral vascular disease, neuropathic foot conditions, pathological fractures, or if they declined participation in the study.

Patient Recruitment and Data Collection

Eligible patients were identified through the elective surgery list and subsequently approached for participation in the study. Informed consent was obtained from all participants, and data collection was conducted during follow-up visits at the Orthopaedic Clinic. Each patient was administered the SF-36 health survey questionnaire to assess their functional outcomes and quality of life. Additionally, radiological imaging of the ankle in lateral view was performed to measure the Böhler's angle, which serves as a key indicator of anatomical restoration.

Fracture Types According to Sanders' Classification

Sanders' classification is a widely used system for categorizing calcaneum fractures in clinical practice.[6,16] It is based on coronal and axial computed tomography (CT) cross-sections, using the widest undersurface of the posterior facet of the talus as a reference. The CT scans are organized in two planes: the semi-coronal or oblique coronal plane, which is perpendicular to the normal position of the posterior facet, and the axial plane, which runs parallel to the sole. This classification divides the articular surface of the talus into three equal columns and further segments the posterior facet of the calcaneus into four possible fracture fragments: lateral, central, medial, and sustentaculum.[17] Table I summarises the description for the classification. Sanders' classification not only aids in treatment planning but also provides prognostic insights regarding fracture healing.

Surgical Technique

All surgical procedures were performed by foot and ankle-trained surgeons using an open reduction and internal fixation approach via the extended lateral approach (Seattle approach). The patient was positioned laterally on a radiolucent operative table, and a full-thickness skin flap was created through an L-shaped incision over the lateral aspect of the heel. After achieving adequate exposure of the calcaneus and subtalar joint, anatomical reduction was performed, followed by applying a locking calcaneal plate to stabilize the fracture. Post-operatively, patients received third-generation cephalosporin for five days, and daily wound inspections were performed to monitor for complications.

Table I: Sanders' classification for calcaneum fractures.

Classification type	Description
Type I	Nondisplaced fractures; no significant separation of the fracture fragments.
Type II	Two articular pieces involving the posterior facet, further divided into: Type IIA: Lateral fragment displaced Type IIB: Medial fragment displaced Type IIC: Central fragment displaced
Type III	Three articular pieces, including an additional depressed middle fragment, are further divided into: Type IIIA: Lateral and central fragments displaced Type IIIB: Medial and central fragments displaced Type IIIC: Lateral and medial fragments displaced
Type IV	Highly comminuted fractures with four or more fragments, making anatomical restoration complex.

Post-operative Care and Follow-Up

Following surgery, patients were initially immobilised in a below-knee back slab positioned neutrally for two weeks, until suture removal at week two. During this period, elevation of the lower limb combined with ice pack therapy was employed to facilitate soft tissue recovery. After removal of the back slab, active and passive range of motion exercises were encouraged to prevent ankle stiffness. Non-weight-bearing ambulation using crutches or a wheelchair was permitted for the first six weeks. Partial weight-bearing was then gradually introduced, based on fracture healing progress and patient compliance, with full weight-bearing typically allowed after twelve weeks. Patients were scheduled for regular clinical and radiological follow-up appointments at the Orthopaedic Clinic, ensuring a minimum follow-up duration of one year.

Assessment Tools

The SF-36 questionnaire was utilized to assess the functional outcomes and quality of life of patients in this study. Developed for use in clinical practice, research, and health policy evaluation, the SF-36 is designed to be completed in approximately 10 minutes while effectively measuring a wide range of health concepts.[1,18] It includes eight multi-item scales that evaluate: limitations in physical activities due to health problems, limitations in social activities due to physical or emotional issues, role limitations due to physical health, bodily pain, general mental health, role limitations due to emotional problems, vitality (energy and fatigue), and general health perceptions. Each component is scored from 0 to 100, with higher scores indicating better functional status.

Radiological outcomes were assessed by measuring Böhler's angle, which is defined by two intersecting lines: one drawn from the anterior process of the calcaneus to the highest point of the posterior articular surface, and the other from that point to the most superior point of the tuberosity (Figure 1). In our population, a normal Böhler's angle ranges from 20 to 40 degrees.[19] This angle is a critical prognostic factor in determining treatment outcomes, as its restoration is associated with improved recovery.[13,20,21] To ensure the accuracy of measurements, all requests for post-operative radiographs for calcaneal fractures included the specific purpose of measuring Böhler's angle, adhering to the standards set by our radiological colleagues. Measurements were taken three times by experienced foot and ankle surgeons, and the mean of these measurements was used as the final value.

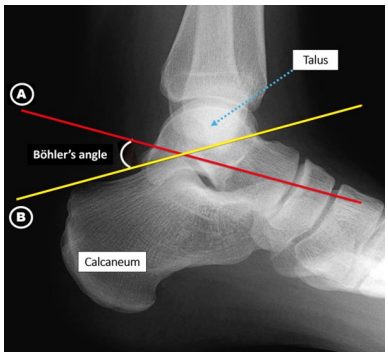

Figure 1: Measurement of the Böhler's angle. The angle is defined by the intersection of two lines: Line A (red), which extends from the anterior process of the calcaneus to the highest point of the posterior articular surface, and Line B (yellow), which runs from the posterior articular surface to the most superior point of the calcaneal tuberosity.

Sample Size Calculation

To assess the adequacy of our sample size, we conducted a post-hoc power analysis using G*Power software. For

this analysis, we utilised a Pearson correlation coefficient to evaluate the relationship between post-operative Böhler's angle and SF-36 scores. Based on preliminary data and similar studies in the literature,[4] we estimated a small to medium effect size (Cohen's r = 0.2). With an alpha level set at 0.05 and a desired power level of 0.80, the G*Power analysis indicated that a minimum sample size of 30 participants would be required to achieve adequate power for detecting a significant correlation. This calculation accounted for an anticipated dropout rate of approximately 15-20%, which is commonly accepted in clinical studies.

Data Analysis

Data collected from the SF-36 questionnaire and radiological measurements were analysed using SPSS version 27. Descriptive statistics were employed to summarize demographic data, functional outcomes, and radiological results. Pearson correlation coefficients were utilized to assess the relationship between post-operative Böhler's angle and SF-36 scores. Additionally, chi-square tests (with Yates' continuity correction applied for 2x2 comparisons) were conducted to evaluate the association between fracture type and radiological outcomes. Statistical significance was set at a p-value of less than 0.05.

RESULTS

A total of 30 patients with closed displaced intra-articular fractures of the calcaneus were identified; however, only 26 patients were included in the final analysis. Of the four patients excluded after recruitment, all declined to proceed with participation in the study. This rate of declined participation falls within the expected attrition range considered during sample size calculation. The demographic characteristics of the study population are summarised in Table II.

The majority of patients were male (96.2%), with a mean age of 42.8 years (± 13.97). Most patients in this cohort had type III fractures (69.2%), whereas type IV fractures were the least common, represented by a single patient. The mechanism of injury was predominantly due to motor vehicle accidents (65.4%), while falls accounted for 34.6% of cases. The average time from injury to surgery was 11.12 days (± 1.75). Two patients (7.6%) experienced superficial infections at the incision site, both of which healed with extended intravenous antibiotics and did not require further surgery. There were no cases of deep infection, compartment syndrome, peroneal tendinitis, reflex sympathetic disorder, or implant failure. Fracture union was achieved in all cases, and none of the patients required bone grafting.

Table II: Demographic distribution of study participants (n = 26).

Variables	n (%)
Age (years)	42.81 + 13.97*
Gender	
Male	25 (96.2)
Female	1 (3.8)
Mechanism of injury	
Motor-vehicle accident	17 (65.4)
Fall	9 (34.6)
Sanders' Classification	
II	7 (26.9)
III	18 (69.2)
IV	1 (3.8)
Days to surgical intervention	11.12 + 1.75*
Post-operative Böhler's angle	
Normal (20°-40°)	24 (92.3)
Abnormal (<20°)	2 (7.7)
Mean + SD	22.69° + 3.39*
Duration of follow-up (months)	
12	9 (34.6)
18	2 (7.7)
24	14 (53.8)
36	1 (3.8)
Mean + SD	24.31 + 3.59*
Complication	
Superficial infection	2 (7.6)

*Data presented in mean ± SD

Table III: Assessment of functional outcome and QOL by using SF-36 (n=26).

Domain/ Scale	Mean + SD
Overall SF-36 score	55.9 + 14.27
Physical functionality	60.8 + 16.11
Role limit due to physical health	51.9 + 28.22
Role limit due to emotional problems	57.7 + 33.42
Energy fatigue	51.9 + 11.58
Emotional well-being	63.2 + 11.32
Social functionality	74.0 + 20.29
Physical pain	67.4 + 15.34
General health	38.1 + 11.50
Health change	38.5 + 12.71

Functional Outcome and QOL Assessment

The functional outcomes were evaluated using the SF-36 questionnaire, with the results presented in Table III. The overall mean SF-36 score was 55.9 (± 14.27). The highest scores were recorded for social functionality (74.0 ± 20.29) and physical pain (67.4 ± 15.34), while general health had the lowest score (38.1 ± 11.50). Other dimensions of the SF-36, including physical functionality (60.8 ± 16.11) and emotional well-being (63.2 ± 11.32), also indicated moderate functional recovery among patients.

Radiological Outcomes

Post-operative measurements of the Böhler's angle were performed, with the mean angle recorded at 22.69 degrees (± 3.39). As shown in Table II, 24 out of 26 patients (92.3%) achieved a normal Böhler's angle (20°-40°), while 2 patients (7.7%) had an abnormal Böhler's angle (<20°). The correlation between the post-operative Böhler's angle and SF-36 scores was assessed, revealing a weak positive correlation of 18.7%, indicating that while anatomical restoration was achieved, it did not strongly correlate with functional outcomes.

Correlation Between Post-operative Böhler's Angle and SF-36 Score

Figure 2 presents the scatter plot illustrating the relationship between post-operative Böhler's angle and SF-36 scores. The correlation analysis using Pearson's correlation coefficient revealed a weak positive correlation (r=0.187, r^2=0.035), which was not statistically significant (p=0.360).

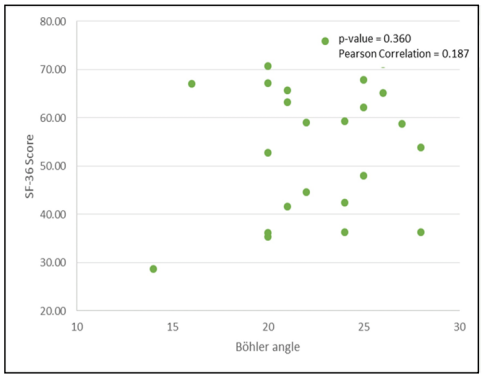

Figure 2: Scatter plot showing the correlation between post-operative Böhler's angle and SF-36 scores.

Association Between Fracture Type and Böhler's Angle

The association between fracture type (according to Sanders' classification) and post-operative Böhler's angle was statistically significant (p=0.002), as shown in Table IV. Among patients with type 2 fractures, all (100%) maintained a normal Böhler's angle, while 94.4% of type 3 fractures were within the normal range. Conversely, the patient with a type 4 fracture exhibited an abnormal Böhler's angle, highlighting the complexity associated with more severe fracture patterns.

Table IV: Association between post-operative Böhler's angle and types of fracture (according to the Sanders' Classification).

Types of Fracture	Post-operative Böhler's angle		Total	p-value*
	Normal (20°-40°)	Abnormal (<20°)		
II	7 (100%)	0 (0%)	7	0.002
III	17 (94.4%)	1 (5.6%)	18	
IV	0 (0%)	1 (100%)	1	
Total	24	2	26	

*Chi-square test with Yates' correction

Of the three fracture types classified according to Sanders', the majority were type III fractures (69.2%, or 18 patients). Among these, 94.4% maintained a normal Böhler's angle (20-40°), with only one patient unable to achieve this range (<20°). Type II fractures had the second highest representation, with all seven patients maintaining a normal Böhler's angle. Conversely, only one patient with a type IV fracture, characterised by a highly comminuted pattern, exhibited an abnormal post-operative Böhler's angle. The statistical analysis confirms a significant association between fracture type and post-operative Böhler's angle (p = 0.002). Figure 3 presents a histogram comparing Böhler's angles across different fracture types according to Sanders' classification.

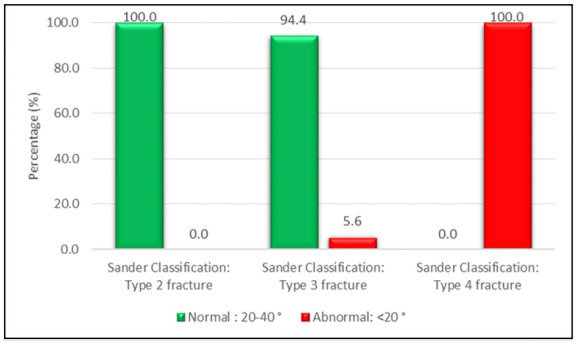

Figure 3: Association between post-operative Böhler's angle and types of fracture (according to the Sanders' Classification) (n = 26).

DISCUSSION

This study provides valuable insights into patients' functional and radiological outcomes with closed displaced intraarticular calcaneum fractures treated with plate fixation. The demographic data indicate a predominance of male patients, with a mean age of 42.8 years, consistent with literature showing that calcaneal fractures often occur in younger, active males engaged in high-risk activities.[10,18,22] Motor vehicle accidents were the leading cause, accounting for 65.4% of cases, highlighting the need for improved road safety measures.

Functional outcomes, measured by the SF-36 questionnaire, revealed a mean score of 55.9, indicating

moderate quality of life post-surgery. The highest scores were in social functionality and physical pain, suggesting that while physical limitations exist, social interactions remain relatively intact. This aligns with previous studies that have reported varying degrees of recovery in different dimensions of QOL following calcaneal fractures.[18,23] However, the lowest score was in general health, reflecting the significant impact of injury on overall well-being due to psychological and physical challenges.

Radiologically, the mean post-operative Böhler's angle was 22.69 degrees, with most patients maintaining a normal range. This restoration of anatomical alignment is crucial,[12,13,15] as deviations can lead to poor functional recovery and increased complications. Our findings underscore the importance of meticulous surgical techniques and careful patient selection, particularly in complex fractures. Restoring the post-operative Böhler's angle to a normal value is one of the most important prognostic factors for obtaining satisfactory results,[13,14] with our study showing a significant association between post-operative Böhler's angle and Sanders' classification.

In addition to Böhler's angle, maintaining the height, length, and width of the calcaneus is equally important.[12,15] In our series, all patients except two with highly comminuted fractures maintained a normal Böhler's angle (20 to 40 degrees). A previous study reported a strong association between Böhler's angle and Sanders' classification based on an analysis of 80 patients.[7] Similarly, our study identified a significant association between post-operative Böhler's angle and Sanders' classification among the 26 patients analysed. Technically, restoring Böhler's angle to the normal range is more challenging in cases of multifragmentary fractures compared to less severe injuries, suggesting that those with severe comminution are more likely to experience poor outcomes.[13] The results of our study align with previously reported outcomes for ORIF with plate osteosynthesis, demonstrating superiority over conservative treatment methods.[6,24]

Despite successfully restoring the Böhler's angle in most patients, the weak correlation with SF-36 scores (18.7%) indicates that anatomical alignment alone may not ensure optimal functional recovery. Previous studies suggest that post-treatment outcomes for calcaneus fractures are worse than those for knee and hip arthroplasties, likely due to the acute nature of the injury, which leaves little time for adaptation compared to chronic conditions.[18] Patients with displaced intraarticular calcaneus fractures often experience greater impairment and pain compared to those recovering from total knee or hip arthroplasties. Factors such as pre-existing health conditions, psychological well-being, and rehabilitation protocols are crucial in influencing functional outcomes, necessitating a comprehensive approach to recovery.

Osteosynthesis with locking plates provides superior outcomes in maintaining Böhler's angle and accommodating the calcaneus's complex shape. A biomechanical study demonstrated that locking plates offer greater stability during cyclic loading than non-locking plates.[25] They effectively manage multifragmentary fractures, preventing unstable displacement, especially in osteoporotic bones. Postoperative splinting is unnecessary, enabling early range of motion exercises that reduce stiffness and improve mobility.[26,27] Additionally, the use of locking plates reduces the need for bone grafting, as they do not yield superior results compared to fixation alone,[13,28-31] thereby minimising patient morbidity.

While ORIF is effective for anatomic reduction, it can lead to complications.[32-34] Our study reported a low complication rate, with only 7.6% of patients experiencing superficial infections, all resolving without further surgery. This suggests that locking calcaneal plates and the extended lateral approach may effectively manage soft tissue integrity. However, vigilance for complications is essential, as infection rates can vary based on surgical technique and patient factors. Continuous monitoring and early intervention are critical for minimising complications and improving recovery. Similar findings

were found in a survey of German orthopaedic surgeons.[35] Other studies have reported that the infection rate for ORIF ranges from 5% to 31%, with a reoperation rate due to infection at approximately 5%.[1,36-39]

Moreover, developing standardised rehabilitation protocols could enhance patient outcomes in this challenging area of orthopaedic practice.[1] The post-operative care protocol used in this study emphasised early mobilisation and gradual weight-bearing, which likely contributed to the positive functional outcomes observed. Early range of motion exercises are crucial for preventing stiffness and improving joint mobility, significantly impacting recovery.[40]

Study Limitations and Future Recommendations

Several limitations of this study must be acknowledged. The relatively small sample size may impact statistical power and introduce biases in data collection and patient selection. Additionally, the mean follow-up period of only two years restricts our ability to assess long-term degenerative changes in the subtalar joint. While the gender distribution reflects the demographic characteristics of patients presenting with calcaneal fractures in our clinical setting, it may raise concerns regarding potential bias. Although a more balanced gender distribution could enhance the generalizability of our findings, we believe our sample adequately represents the population we serve (4). Furthermore, our focus on Bohler's angle, while a well-established measure, limits the comprehensiveness of our analysis, as the exclusion of Gissen's angle restricts insights into subtalar joint integrity. We also could not assess post-fixation varus/valgus alignment due to the lack of weight-bearing radiographs, which were not part of our study protocol.

Future research should focus on larger cohorts and longer follow-up periods to better understand the long-term implications of treatment strategies for calcaneal fractures. Incorporating both Bohler's and Gissen's angles, as well as varus/valgus assessments, would provide a more comprehensive evaluation of alignment post-fixation. Additionally, exploring psychosocial factors, rehabilitation, and comorbidities, along with comparing complication rates with other studies, could enhance our understanding of recovery outcomes. These considerations may lead toward prospective or randomized controlled studies and the adoption of advanced imaging modalities, contributing to improved treatment strategies for calcaneal fractures.

CONCLUSION

Plate osteosynthesis for closed, displaced intraarticular calcaneum fractures results in favourable functional and radiological outcomes, with a significant restoration of anatomical alignment as evidenced by the restoration of Böhler's angle in the majority of patients. While a moderate quality of life was reported post-surgery, the weak correlation between anatomical alignment restoration and functional recovery suggests that additional factors, including psychosocial aspects and rehabilitation protocols, play a critical role in patient outcomes. These findings emphasise the importance of careful surgical technique and comprehensive post-operative care to minimise complications and optimise recovery.

INSTITUTIONAL REVIEW BOARD (ETHICS COMMITTEE)

This study employs a retrospective descriptive design to evaluate the functional and radiological outcomes of patients with closed displaced intraarticular calcaneum fractures treated with plate fixation at a single tertiary referral centre from January 2015 to December 2020. The institutional ethical committee approved the study (Ref. No.: IIUM/215/14/11/3/IREC435).

ACKNOWLEDGEMENT

The authors wish to extend their sincere appreciation to the Medical and Healthcare Research Cluster, Office of the Deputy Vice-Chancellor of Research and Innovation, and the Orthopaedic, Musculoskeletal, Traumatology & Rehabilitation (OMTaR) Research Group of Universiti Sultan Zainal Abidin, for their invaluable support and assistance, which significantly contributed to the successful completion and publication of this research.

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CASE REPORT

Acute Suppurative Thyroiditis with Progression to Thyroid and Retropharyngeal Abscesses: A Case Report

Zainal Abidin Az[a], Mohammad Nasir Z[b], Hoong FV[b]

[a]Department of Otorhinolaryngology - Head & Neck Surgery, Hospital Sultan Abdul Aziz Shah, Universiti Putra Malaysia, Selangor, Malaysia
[b]Department of Otorhinolaryngology - Head & Neck Surgery, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Selangor, Malaysia

Keywords
abscess, acute, suppurative, thyroid, thyroiditis

Corresponding Author
Dr Zuraini Mohammad Nasir
Department of Otorhinolaryngology - Head & Neck Surgery, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Selangor, Malaysia
E-mail: zurainainasir@upm.edu.my

Received: 4th November 2024; Accepted: 8th April 2025

Doi: https://doi.org/10.31436/imjm.v25i02/2758

ABSTRACT

Acute Suppurative Thyroiditis (AST) is an exceedingly rare cause of thyroid gland infection. Due to its rarity and non-specific presenting symptoms, diagnosis and treatment of AST may be delayed. We report a case of an elderly male who presented with five days history of intermittent fever, sore throat, dysphagia and vomiting. Painless thyroid swelling was only noted during admission. Ultrasound scan (USS) of the neck showed a well-defined lesion occupying the left thyroid lobe and computed tomography (CT) of the neck showed a rim enhancing collection occupying the left thyroid lobe, extending to retropharyngeal and retrotracheal spaces. Pigtail drainage was performed with no clinical improvement, necessitating incision and drainage, where necrotic tissue mixed with pus was drained. Intraoperative tissue culture isolated *Enterococcus faecium*, and antibiotic therapy was changed following tissue culture sensitivities (IV Augmentin, 1.2 gram, TDS). This case highlights the importance of early diagnosis of AST particularly in elderly patients with multiple comorbidities, where symptoms may be atypical. Ultrasound and CT scans are important diagnostic modalities in AST and microbiological assessment is crucial in selecting appropriate antibiotics. The choice of type of drainage should be individualized based on disease extension and comorbidities. A multidisciplinary approach is crucial to ensure best treatment outcome.

INTRODUCTION

Acute suppurative thyroiditis (AST) is an exceedingly rare condition of the thyroid gland where there is progression of thyroid gland infection into abscess formation.[1] It is a potentially life-threatening condition due to the complications that may ensue, with a reported mortality rate of about 7%.[2] Herein, we report a case of AST with thyroid and retropharyngeal abscesses followed by discussion on clinical presentation, diagnostic modalities and treatment.

CASE REPORT

A 65 year old gentleman with underlying hypertension, diabetes and chronic kidney disease, presented with five days history of intermittent fever, neck swelling, sore throat, dysphagia and vomiting. He denied shortness of breath, chest pain, abdominal pain, diarrhea, neck pain and foreign body ingestion. Clinically, he appeared unwell and lethargic. His vital signs were stable with good oxygenation. He was noted to have left anterior neck swelling measuring 6x4 cm, firm, non-tender, not warm and fixed (figure 1). The swelling moved upon swallowing, the trachea was deviated to the right and there was no associated cervical lymphadenopathy. Intraoral examination was normal with no trismus. Flexible scope showed slight bulging of posterior pharyngeal wall, oedematous arytenoids and pooling of saliva. Other laryngeal structures were normal including vocal cord mobility.

Blood investigations showed raised white cell count (35.7 10^3/uL), low hemoglobin (7.2g/dL), raised creatinine (435 umol/L) and urea (36.5 mmol/L). C-reactive protein was

raised (265 mg/L) and random blood glucose was elevated (13 mmol/L). Venous blood gas showed uncompensated metabolic acidosis. Thyroid function test was normal.

Ultrasound scan (USS) of the neck was performed and showed a well-defined lesion occupying the left thyroid lobe measuring approximately 2.2cm x 3.6cm x 3.7cm (AP x W x CC) (figure 2). Contrast enhanced computed tomography (CECT) of the neck was done and showed a rim enhancing collection occupying the left thyroid lobe measuring approximately 3.0cm x 3.6cm x 5.8cm (AP x W x CC), extending to retropharyngeal and retrotracheal spaces, which may represent acute purulent thyroiditis complicated with retropharyngeal and retrotracheal abscesses (figure 3). Empiric broad-spectrum antibiotics (IV Ceftriaxone, 1 gram, BD) was started. Ideally, in the presence of abscess, open drainage would be the first-line therapy. However, due to the patient's high surgical risk, pigtail insertion into his left thyroid gland was done on day three of admission, where 5 mLs of pus was drained.

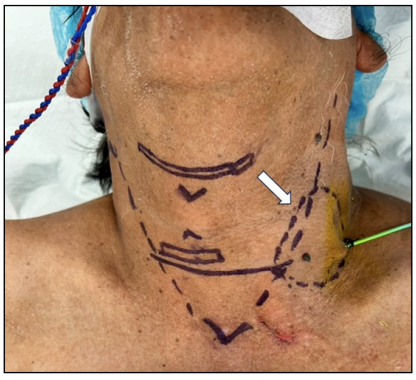

Figure 1: Clinical image of left thyroid swelling (arrow) with deviation of trachea to the right prior to surgery

In view of no clinical improvement and no further drain output from pigtail, incision and drainage of left thyroid collection was performed on day nine of admission. Intra-operatively, necrotic tissue mixed with 10 mLs of pus was drained from left thyroid lobe. The abscess cavity extended into retrotracheal and retropharyngeal spaces. Intraoperative tissue culture isolated *Enterococcus faecium*, sensitive to Amoxicillin/ Clavulanate, Imipenem and Metronidazole. Histopathological examination (HPE) of thyroid tissue and abscess wall was reported as consistent with acute suppurative thyroiditis. Antibiotic therapy was changed following tissue culture sensitivities (IV Augmentin, 1.2 gram, TDS). His condition and infective parameters improved markedly and he was discharged well four days after surgery. He refused further investigations upon follow up at clinic.

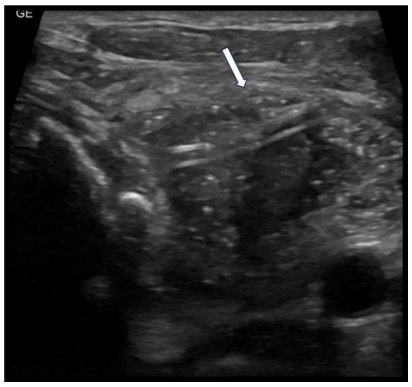

Figure 2: USS neck showed a well-defined lesion occupying the left thyroid lobe (arrow).

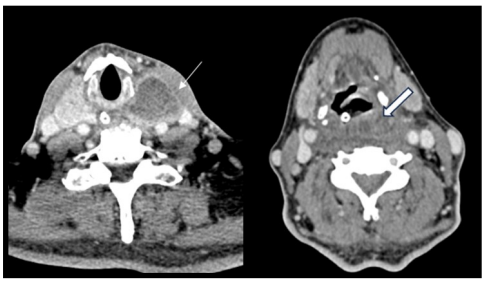

Figure 3: CECT neck showed a rim enhancing collection occupying the left thyroid lobe (thin arrow) extending to retropharyngeal and retrotracheal spaces (thick arrow).

DISCUSSION

Acute suppurative thyroiditis (AST) is a very rare cause of thyroid gland infection, which comprises of less than 1% of all thyroid gland diseases.[1] Thyroid gland is relatively protected from infection due to its encapsulation, high iodine content, rich blood supply and good lymphatic drainage.[1] The likely aetiologies of AST are pre-existing anatomical abnormality such as pyriform sinus fistula, immunosuppression state and hematogenous or lymphatic spread.[2] Iatrogenic cause has also been implicated as AST was reported to occur after fine needle aspiration (FNA) (1). Additionally, Lafontaine et al. reported that 28% of cases are idiopathic.[2] Predisposing factors include Hashimoto's disease, large goiters and thyroid cancer.[1] In our case, the likely cause of AST is immunosuppression state due to chronic kidney disease coupled with uncontrolled Diabetic Mellitus.

AST can affect both children and adults. In children, the underlying cause is often due to third or fourth branchial

arch anomalies or a piriform sinus fistula.[1] Among adults who are affected, majority of them are around 40 years old with female predominance.[2] Left thyroid gland has been reported to be mostly affected.[2] The most common causative pathogen has been found to be gram-positive bacteria.[3] Rarely AST is caused by fungal, tuberculosis or parasitic infections.[2]

Presenting symptoms of AST include fever, neck pain and sore throat.[1] Odynophagia and dysphagia may follow. However, these symptoms are non-specific and patients are often misdiagnosed as common cold or pharyngitis at initial presentation, leading to delayed diagnosis and treatment.[2] Differential diagnoses of AST include subacute or chronic thyroiditis, thyroid cyst rupture, thyroid gland haemorrhage, thyroid nodule infarction and rapidly growing thyroid cancers.[1] It may be difficult to distinguish AST from subacute or chronic thyroiditis as the presenting symptoms are similar.[1] FNA should be done to confirm the diagnosis of abscess, identify causative pathogen and its sensitivities and rule out subacute thyroiditis or malignancy.[4]

Laboratory findings may show elevated White Cell Count, C-reactive protein, erythrocyte sedimentation rate (ESR) and rarely, transient thyrotoxicosis.[5] Thyrotoxicosis may occur due to the release of pre-formed thyroid hormone from the infected gland.[5] Increased thyroglobulin level is helpful in identifying the thyroid gland as the source of inflammation or infection.[1] However, none of these investigations are diagnostic.

Imaging studies are important to establish the diagnosis and to differentiate AST and subacute thyroiditis. Ultrasound scan (USS) of the neck is the best imaging modality for detecting early changes of AST. The changes observed may include perithyroidal hypoechoic space, hypoechoic area in the thyroid gland and effacement of tissue around the thyroid gland.[2] When abscess has formed due to AST, CECT neck is recommended, where it can assess the size and extension of the abscess with better anatomical delineation and identify the presence of anatomical abnormalities such as pyriform sinus fistula.[2]

Prompt treatment is vital as the infection may cause destruction of the thyroid and the parathyroid glands, vocal cord palsy, airway obstruction, spread to mediastinum and other deep neck spaces and fistula to the trachea or oesophagus.[5] Empirical antibiotic therapy should be started immediately, and antibiotics of choice should target Gram-positive and anaerobic bacteria. If there is no clinical improvement, drainage is advocated.[5] However, in unstable patients with airway compromise, urgent drainage must be done. Several options are available to drain abscess: needle aspiration, incision and drainage and thyroidectomy.[2] There is significant variation regarding the choice of drainage to be used. If the abscess is small, needle aspiration or percutaneous catheter drainage may suffice.[2] However, some studies suggest early surgical drainage is advocated to prevent disease progression.[1] In cases with large abscess formation or deep neck space involvement, open surgical drainage is required. Thyroidectomy may be necessary in patients with recurrent AST or underlying thyroid pathology such as Hashimoto's thyroiditis. As identification of anatomic structures in infective state is often difficult, open surgical approach should be performed with caution.[1]

Outcomes of AST may vary according to the intervention, the extent of infection, and the patient's comorbidities. A systematic review by Lafontaine et al. has found that patients who had early surgical drainage recovered earlier with lower recurrence rates compared to patients who received antibiotics alone or percutaneous drainage.[2] However, conservative management with percutaneous drainage and prolonged intravenous antibiotics has been reported as a successful alternative in patients with high surgical risk.[1] After resolution of thyroid abscess, it is important to investigate the patients for anatomical abnormality such as fistula by performing barium swallow, CECT neck or microlaryngoscopy.[2]

CONCLUSION

Early diagnosis of acute suppurative thyroiditis (AST) is crucial to prevent life-threatening complications. This case highlights the diagnostic challenges of AST and the

importance of individualized treatment based on the comorbidities of the patients. Atypical presentations of AST may delay diagnosis and treatment; hence, the condition must be considered in patients presenting with anterior neck swelling with signs of infection. FNA, USS or CECT are important diagnostic modalities. Additionally, multidisciplinary care involving endocrinologists, radiologists and infectious disease specialists, is essential to improve management of patients and outcome. Early antimicrobial therapy and surgical drainage are the mainstay treatment for AST. Increased awareness of AST and its potential complications can lead to earlier intervention and improved patient outcomes.

CONFLICT OF INTEREST

No conflict of interest.

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CASE REPORT

Catamenial Pneumothorax: Breathing Through The Menstrual Cycle

Letchumanan S[a], Abdul Rahman R[a], Idris NS[a]*

[a]Department of Family Medicine, School of Medical Sciences, Universiti Sains Malaysia Health Campus, Kelantan, Malaysia

Keywords
Catamenial, endometriosis, menstrual cycle, pneumothorax, rare diseases

Corresponding Author
Assoc. Prof. Dr. Razlina Abdul Rahman
Department of Family Medicine,
School of Medical Sciences
Universiti Sains Malaysia Health
Campus, Kelantan, Malaysia
E-mail: razlina@usm.my

Received: 19th February 2025; Accepted: 25th May 2025

Doi: https://doi.org/10.31436/imjm.v25i02/2869

ABSTRACT

Catamenial pneumothorax (CP) is a unique disease related to thoracic endometriosis. It is often diagnosed in females of reproductive age presenting with recurrent spontaneous pneumothorax aligned with their menstrual cycle. We present a case of a woman presenting with recurrent episodes of dyspnoea coinciding with her menstrual cycle. Radiographic imaging confirmed a recurrent pneumothorax, and thoracoscopy with a pleural biopsy revealed diaphragmatic fenestrations and thoracic endometriosis. Multiple approaches, including medical pleurodesis, surgical pleurodesis, and hormonal therapy were used in her treatment. She recovered well after started on continuous oral Dienogest, and she has been asymptomatic for three years. This case illustrates the importance of recognizing the cyclical pattern of symptoms and a thorough diagnostic workup to confirm CP. This ensures timely management, which includes hormonal therapy and surgical intervention.

INTRODUCTION

Catamenial pneumothorax (CP) is a rare condition of recurrent spontaneous pneumothorax that predominantly affects women of childbearing age, occurring 48 to 72 hours before or after menstruation. About 3-6% of women presenting with spontaneous pneumothorax are believed to have an underlying catamenial cause, and 50-84% of them have concomitant pelvic endometriosis.[1] The incidence of CP may be underreported due to frequent misdiagnosis as spontaneous pneumothorax, mainly due to failure to associate the incidents with patients' menstrual cycle and not performing routine intraoperative diaphragm inspection.[2] A correct diagnosis of CP is vital for the patient, as hormonal therapy plays a role along with surgical management in preventing the recurrence.[3] In this report, we describe a case of CP, the diagnostic approach, multi-disciplinary team management involved, and the importance of a detailed history in a woman of reproductive age presenting with recurrent pneumothorax, for early detection of CP and to prevent its recurrence.

CASE PRESENTATION

A 41-year-old female initially presented to the Emergency Department (ED) during the early COVID-19 pandemic era with a complaint of shortness of breath and a non-productive cough for two days. She had no prior medical illness, and this was her first presentation for the complaint. There was no associated chest pain, palpitations, sore throat, fever or headache. Examination at the time showed that she was afebrile, but tachypneic and tachycardic with a respiratory rate of 34 breaths per minute and a pulse rate of 118 beats per minute. Her oxygen saturation was 94% under room air. Chest auscultations revealed reduced breath sounds on the right side, but no abnormal lung sounds were noted. She was started on a venturi mask with a fraction of inspired oxygen ($Fi0_2$) of 40%, and her oxygen saturation increased to 97%.

Chest radiograph revealed a right pneumothorax (Figure 1A); thus, a chest tube was inserted. Computed tomography (CT) of the thorax showed a small right

interlobar pneumothorax. Her COVID-19 swab test was negative. Due to her symptoms and in view of the current COVID-19 pandemic at the time, coupled with a negative COVID-19 swab test, she was treated as possible atypical pneumonia and started on oral Azithromycin and Oseltamivir. Her chest tube was removed after three days, and she was discharged home well after five days of admission. A follow-up respiratory clinic appointment was given in three months.

However, she returned to the ED with similar symptoms six weeks later. Chest radiograph at the time showed a right pneumothorax. A pigtail catheter was inserted since it has fewer complications and associated with shorter hospital stay (Figure 1C). The chest radiograph taken post -procedure shows an expanded lung field with a small residual ring pneumothorax in the apical region (Figure 1D). Therefore, medical pleurodesis with bleomycin was performed via the pigtail catheter on the fourth day of admission. A repeated CT scan of the thorax showed no new lesions. During this admission, further history revealed that both episodes of pneumothorax occurred within 72 hours of the onset of her menstrual cycle. Her menstrual cycle was usually regular every 28-30 days with the heaviest day occurring on day three of menses. She never has blood clots during her cycles and there was no associated dysmenorrhea or menorrhagia. She also denied any history of dyspareunia or pelvic pain during or around her menstrual cycle. Based on her history and presentation, a possibility of catamenial pneumothorax was very likely and she was referred to the gynaecology team for further management. However, since her pneumothorax had been stabilized and due to lack of personnel during the COVID-19 pandemic, she was only given an outpatient gynaecology clinic appointment.

Unfortunately, she experienced similar symptoms a week later and was readmitted. Since the previous medical pleurodesis had failed, she was then referred to the cardiothoracic team for further management. A thoracoscopy was performed, and it revealed multiple perforations at the centre of the diaphragm. Biopsies were taken from several affected sites on the diaphragm before surgical pleurodesis was carried out. Her symptoms improved after the procedure, and she recuperate well. However, on day five after the procedure, she experienced another episode of pneumothorax once the chest tube was removed. Thus, a mini thoracotomy was carried out to perform mechanical pleurodesis and plication of the central tendon of the diaphragm. She was started on continuous oral Dienogest 2mg and was well at discharge a few days later. The biopsy result of her diaphragm tissue showed endometrial stromal cells, suggesting endometriosis thus confirming the diagnosis of CP. She was advised to continue oral progestin until menopause. She claimed to have irregular menstrual cycle with occasional per vaginal spotting since started on continuous progestin. Otherwise, she is well and still under gynaecology clinic follow up and has not experienced any symptoms of pneumothorax or endometriosis since her last admission three years ago.

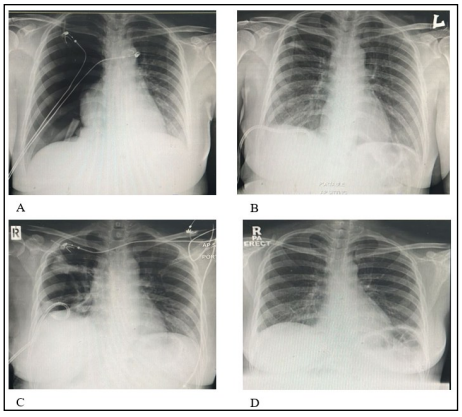

Figure 1: Image in 1A shows right pneumothorax (yellow arrow) and image 1B shows expanded lung field after chest tube drainage. Image 1C shows recurrent right pneumothorax (yellow arrow) after six weeks, while image 1D shows fully expanded lung post pig-tail catheter insertion.

DISCUSSION

CP is a rare cause of spontaneous pneumothorax which occurs in relation to the perimenstrual period. It accounts for 7.3% to 36.7% of all incidences of pneumothorax among women of reproductive age rendering it a clinically significant condition.[4] CP should be suspected in women in the reproductive age group who presented with recurrent spontaneous pneumothorax occurring within 72 hours before or after the onset of menstruation especially if they are known to have endometriosis.[5] CP is one of the entities in thoracic endometriosis syndrome (TES) which refers to the presence of endometrial tissue within the lung parenchyma or on the diaphragm and pleural surfaces causing catamenial haemothorax, haemoptysis, and pulmonary nodules.[6] Among these, CP

is the most frequent presentation and 60% of the cases are associated with pelvic endometriosis.[7] However, in our case, the patient had no known history of endometriosis and never had any prior symptoms nor sonographic evidence of pelvic endometriosis making the possibility of catamenial pneumothorax more remote initially.

The diagnosis of CP requires a comprehensive approach, starting with a detailed patient history to identify the cyclical nature of symptoms. Women with CP typically present with acute pleuritic chest pain and dyspnoea, symptoms that recur in association with their menstrual periods.[1, 6] The temporal relationship between symptom onset and menstruation is a key diagnostic clue that should prompt further investigation. Despite its distinctive cyclical pattern, CP often remains underdiagnosed due to a lack of awareness among healthcare providers and the rarity of the condition. As in this case, the first presentation was treated as spontaneous pneumothorax secondary to atypical Covid-19 related pneumonia as the association with her menstrual cycle was not made. She was also unfortunate since her first presentation occurred during Covid pandemic where the infection may be presented in many guises, hence, the suspicion of Covid related diagnosis. The establishment of temporal relationship between menstrual period and the occurrence of pneumothorax is the only clue for CP since there are no specific signs to distinguish it from other causes of pneumothorax.[8]

Radiographic imaging plays a limited role in the diagnosis and management of CP. The chest X-ray can confirm the presence of pneumothorax and evaluate the extent of lung collapse, but it may not identify small diaphragmatic defects or endometrial implantations.[4] On the other hand, CT scans and Magnetic Resonance Imaging (MRI) could show small diaphragmatic defects, called "air-filled bubbles", thus providing a better value in the diagnosis of CP.[8] A CT scan is usually performed first, as it is readily available. However, MRIs are more sensitive in detecting soft tissue lesions, especially diaphragmatic endometriosis.[4, 8] Both imaging modalities have a higher sensitivity rate if performed during menstruation.[8] Nevertheless, the imaging can only aid to confirm the diagnosis if the initial suspicion has been established. In this case, the role of imaging did not help much in establishing the diagnosis since the CT thorax only showed a right interlobar pneumothorax and not able to identify the diaphragmatic defect.

Once diagnosis has been established, the goal of the management of CP includes treating the acute illness and preventing the recurrence of the condition. Acute management of CP is similar to treating spontaneous pneumothorax. Long-term treatment options include a combination of medical, hormonal, and surgical therapy.[3] Pleurodesis of the lung is an option to prevent recurrence and can be achieved by both chemical and surgical methods.[1] Chemical pleurodesis is usually achieved by inserting a sclerosant through the chest tube aiming to prevent recurrent pneumothorax by causing chronic inflammation and scarring of the pleural surface.[1, 4]However, this method alone without concurrent surgical interventions results in a higher failure rate as illustrated by our patient who returned with a third episode of pneumothorax in just a week after a failed medical pleurodesis.

Video-assisted thoracic surgery (VATS) is the gold standard diagnostic tool for CP and may also function as a treatment modality.[8] It is a minimally invasive surgery that can be used to perform surgical pleurodesis, diaphragm repair, and bleb resections.[4] It has the advantage of smaller incisions, less post-operative pain, and fewer complications compared to thoracotomy which is the other surgical method widely used in the management of CP. Thoracotomy allows a wider surgical space and is useful in repairing diaphragmatic perforations and fenestrations in CP as demonstrated in our case after failed medical pleurodesis.[4] The repair is done by placing mesh over the diaphragm which promotes tissue in-growth thus providing scar tissue over the diaphragm.[4] Our patient underwent a mini-thoracotomy procedure during which her diaphragmatic fenestrations were repaired by mesh placement and enhanced with talc pleurodesis.

Hormonal therapy plays a crucial role in the treatment of CP. It reduces the risk of recurrence by suppressing

menstruation and the associated thoracic endometrial activity.[3] The maintenance of an amenorrhoeic state is vital in preventing the recurrence of CP. One study reported that resumption of menstruation leads to the recurrence of pneumothorax.[9] There are various classes of medications available for this purpose, including combined oral contraceptive pills, gonadotrophin-releasing hormone analogues (GnRHa), progestins, and aromatase inhibitors.[9]

Usually, GnRHa is used as first-line therapy as they are highly effective in suppressing the hypothalamic-pituitary-ovarian axis and the growth of endometrial cells. However, prolonged use of GnRHa may cause menopausal-like symptoms and loss of trabecular bone density. Thus, their use is limited to six to twelve months.[10] In view that our patient will be needing a long-term use of hormonal treatment, the GnRHa was not the best choice for her post operative treatment. On the other hand, progestins are found to be of similar efficacy as GnRHa but with a lower incidence of hypoestrogenic side effects.[9] Hence, continuous progestin was the hormone of choice in our patient who required effective long term treatment. Other issues which deserve consideration in choosing the type of hormonal treatment is the patient's fertility wishes. In our case, the patient has completed her family. Thus, being on continuous progestin is not an issue for her. However, in cases where patient wishes to conceive, the treatment might have to be changed to intermittent hormonal therapy to allow windows for fertility attempts.

The duration for hormonal treatment varies depending on the severity of endometriosis. Study found that 4mg of progestin daily was successful in maintaining amenorrhoea and preventing recurrent CP at a six-month follow-up.[9] Most studies suggest a duration of six to twelve months, but patients with recurrence of CP like our patients may require a longer duration. Patients with CP especially those requiring long-term hormonal treatment will need to undergo surveillance at least biannually for clinical symptoms of recurrence and to monitor for side effects of the medication.

CONCLUSION

CP is a complex and rare condition that demands a comprehensive and multidisciplinary approach for effective diagnosis and management. This case report highlights the significance of recognizing CP in women of reproductive age who present with recurrent pneumothorax associated with their menstrual cycle.

FUNDING

The writing of this case report did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors

CONFLICT OF INTEREST

The authors have no potential conflict of interest relevant to this case report to declare.

INSTITUTIONAL REVIEW BOARD (ETHIC COMMITTEE)

The authors certify that all required patient consent forms have been received.

ACKNOWLEDGMENT

We thank the Director General of the Ministry of Health and the patient for their consents for writing of this case.

AUTHOR'S CONTRIBUTION

SL wrote the original draft and obtained the images. NSI conceptualized the case report, its aims and reviewed the initial draft. RAR revised it critically for intellectual content and edited the case for final submission. All the authors critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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CASE REPORT

A Rare Case of Extramammary Paget's Disease Mimicking Chronic Dermatitis

Amran NA[ab], Md Monoto EM[a], Rosli N[c], Kah Teik C[d]

[a]Department of Family Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur
[b]Ministry of Health, Malaysia
[c]Department of Pathology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur
[d]Department of Obstetrics and Gynaecology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur

Keywords
Paget's disease, extramammary, dermatitis, skin neoplasms, rare diseases

Corresponding Author
Assoc. Prof. Dr. Ezura Madiana Md Monoto
Department of Family Medicine,
Faculty of Medicine, Universiti
Kebangsaan Malaysia, Kuala Lumpur.
E-mail: drezura@ukm.edu.my

Received: 24th October 2024; Accepted: 8th April 2025

Doi: https://doi.org/10.31436/imjm.v25i02/2750

ABSTRACT

Extramammary Paget`s disease (EMPD) is a rare malignant dermatological condition that usually occurs in regions with high concentrations of apocrine sweat glands. The vulva is the most commonly affected region, but it can also involve the skin of the penis, perianal area, scrotum, and perineum. This is a case of a 77-year-old postmenopausal lady who presented with a non-resolving and persistent itchy skin lesion on her genital area that had been spreading over three years and had not responded to topical and systemic steroids or antifungals. This case highlights the diagnosis challenges due to its almost similar features to genital dermatitis and fungal infection. Early recognition of this disease at the primary care level is important due to the high incidence of associated invasive disease with this rare condition.

INTRODUCTION

Extramammary Paget's disease (EMPD) is a rare form of intraepithelial adenocarcinoma.[1] It often affects the vulva in women and the perianal region in men, though it can also affect other cutaneous sites of the body that are rich in apocrine glands.[1] Only a few hundred cases of EMPD have been documented globally in the literature, making it a very rare condition.[2] Primarily, the disease manifests in the epidermis or cutaneous adnexa in its original form. Secondary EMPD, which is less common, is when EMPD is linked to an underlying cancer, usually affecting the urinary tract or lower gastrointestinal system.[3] The diagnosis of EMPD should be considered in all patients with chronic pruritic skin lesions in regions of the body with high concentrations of apocrine sweat glands, especially if the conditions do not respond to the usual antifungal and anti-inflammatory treatment. This is so that an early referral for skin biopsy can be made and the diagnosis is not further delayed. In the present case, the clinical manifestations, biopsy findings, and the management strategies of this rare dermatologic condition are discussed in detail. The importance of early diagnosis is essential to optimize the treatment outcomes.

CASE PRESENTATION

A 77-year-old postmenopausal woman with underlying hypertension and dyslipidaemia experienced pruritus over her vulva region for over three years. She first noticed a small red patch in the bilateral vulval region, which eventually spread over time. The lesion was itchy and became easily inflamed. Constitutional symptoms or any symptoms suggestive of underlying visceral malignancy were also absent. The lesion was initially managed as tinea cruris by several general practitioners. She had been treated with four courses of oral antifungal, topical antifungal, topical steroids, and oral antihistamine for over three years, however, with no improvement.

Local examination revealed a well-demarcated erythematous plaque over her bilateral labia majora, extending to her bilateral inguinal region. (Figure 1). No similar lesions were seen in the nipple area or other parts of the body. Inguinal lymph and axillary nodes were not palpable bilaterally. Per speculum examination was normal. Other systemic examinations were unremarkable.

Baseline investigations, including full blood count, fasting blood glucose, liver function test, and renal function test, were normal. Urine analysis showed microscopic haematuria. High vaginal swab test revealed normal genital flora. Liquid-based cytology for the Human Papilloma Virus (HPV) DNA PCR test was negative for both high-risk and low-risk groups of HPV DNA viruses. Her pap smear was normal, with no evidence of malignancy or infection.

A skin biopsy of the labia majora was done, and the histopathology findings confirmed the diagnosis of EMPD (Figure 2). Paget`s cells were observed within the epidermis, where the tumour cells exhibit vesicular, round to oval nuclei, prominent nucleoli, and mitotic activity. The underlying dermis showed mild infiltration by chronic mononuclear inflammatory cells, with focal pigmentary incontinence seen. The tumour cells were positive for CK7, CEA, and PAS with diastase and mucicarmine, and negative for CK20. She was subsequently referred to the gynae-oncology team for further occult malignancy screening and further management.

DISCUSSION

Extramammary Paget's disease (EMPD) is a rare form of intraepithelial adenocarcinoma which affects anatomic regions with a high concentration of apocrine sweat glands.[3] Up to 65% of EMPD cases involve the vulva, although other frequently affected areas include the perianal area (20%) and male genitalia (14%), such as the scrotum or penis.[4] It most commonly affects individuals between the ages of 50 and 80, with a peak occurrence at 65 years old.[2] The higher occurrence in this age group is likely due to age-related factors, such as cumulative genetic mutations, hormonal changes, and prolonged exposure to potential carcinogens, all of which increase the risk of developing these malignancies in older adults.[4] To the best of our knowledge, the prevalence of EMPD in Malaysia has not been formally documented, likely due to its rarity, although several individual cases have been reported. The most recent data on EMPD comes from mainland China, where its prevalence was approximately 0.04 per 100,000 people in 2016, with a higher incidence in males.[5] However,our case highlights that females can also be affected.

Figure 1: Well-demarcated erythematous plaque is seen over the vulvar region, extending into the bilateral inguinal region, with the left side being more prominent.

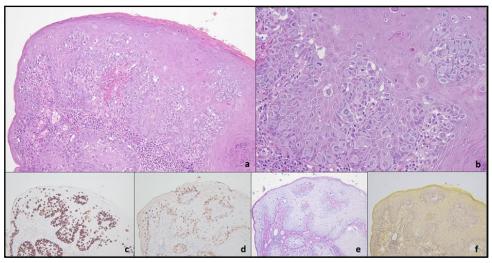

Figure 2: a) Section from the labia majora skin tissue exhibit epidermal infiltration by clusters and singly dispersed tumour cells (H&E, 100x), b) The tumour cells are polygonal epithelial cells with pale-staining, finely granular to vacuolated cytoplasm (Paget's cells), exhibiting vesicular, round to oval nuclei, prominent nucleoli and mitotic activity (H&E, 200x). The tumour cells demonstrate positive staining towards c) CK7, d) CEA, e) PAS with diastase and f) mucicarmine.

The disease most frequently manifests as a primary form that starts in the cutaneous adnexa or epidermis. Although invasive disease may be associated with a worse prognosis, primary EMPD is not life-threatening when it is restricted to the epidermis.[3] As seen in our patient's histopathology report, the Paget's cells are confined to the epidermal region, thus confirming the diagnosis of

primary EMPD. Meanwhile, the secondary form of EMPD is caused by the epidermal invasion of malignant adenocarcinoma cells and is linked to an underlying remote adenocarcinoma.[4] The occurrence of concurrent adnexal and other visceral cancers is highly correlated with EMPD.[7] Between 11 to 20% of cases of vulvar EMPD are linked to a distant carcinoma of the breast, cervix, vagina, bladder, colon, rectum, ovary, liver, gallbladder, or skin (melanomas, basal cell carcinomas), whereas 4 to 17% of cases of vulvar EMPD are linked to an underlying adnexal carcinoma, arising from apocrine sweat glands or Bartholin's glands.[4]

In addition to melanoma, lichen sclerosis, psoriasis, mycosis fungoides, and fungal infections, contact dermatitis is among the differential diagnoses for EMPD.[6] A strong clinical suspicion of EMPD should be considered when a skin lesion in the vulvar, perianal, genital, or axillary regions fails to respond to conventional topical treatments.[3] This is consistent with our patient–who developed a chronic, itchy skin lesion on her genital area for three years and did not show any improvement with topical, systemic steroids and antifungals. Misdiagnosis resulting from non-specific clinical symptoms frequently delays diagnosis and proper treatment.[7] In the case of our patient, it took three years to establish the correct diagnosis. Individuals diagnosed with EMPD usually exhibit distinct, long-lasting, and non-healing erythematous or eczematous plaques, which may be accompanied by crusting, scaling, papillomatous lesions, lichenification, ulceration, or bleeding features.[6]

Diagnosis of EMPD is done histopathologically. The diagnosis is typically obtained following a histological examination conducted in the presence of a chronic dermatosis that is not responding to local therapies (such as corticosteroids and antifungals) and is frequently made after the disease has progressed by an average of two years.[5] The presence of Paget cells is a key diagnostic feature. Paget cells are characterized by polygonal epithelial cells with pale-staining, vacuolated cytoplasm, vesicular nuclei, prominent nucleoli, and mitotic activity, infiltrating the epidermis. These cells are absent in both dermatitis and fungal infections on histopathological examination (HPE).

Furthermore, the tumour cells obtained from our patient were positive for CK7, CEA, PAS with diastase, and mucicarmine, which are characteristic of EMPD. Special stains play a crucial role in supporting the diagnosis. The CK7 and CEA immunostains specifically highlight Paget cells, while PAS with diastase confirms the presence of cytoplasmic mucin within these cells, further distinguishing EMPD from other dermatological conditions. In contrast, fungal infections typically exhibit fungal hyphae or spores on histopathological examination, whereas dermatitis presents with non-specific inflammatory changes without Paget cells or positive immunohistochemical markers. The main challenge lies in distinguishing these conditions clinically.

For every patient with biopsy-proven EMPD, a comprehensive work-up for occult malignancy should be conducted.[7] The recommended approach is to start with a review of systems of the patient, particularly with emphasis on genitourinary and gastrointestinal symptoms, and should be followed by a physical examination that includes breast examination and a screening for lymphadenopathy and multifocal diseases.[8] Further investigations for all patients should include urine cytology, cystoscopy, chest X-rays, imaging of the abdomen and pelvis, colonoscopy, and other tests such as serum prostate-specific antigen for male patients, as well as Pap smear and mammography for female patients.[6]

Surgical excision continues to be the cornerstone of care for EMPD. Mohs Micrographic Surgery (MMS), which offers accurate margin control and lower recurrence rates, is regarded as the preferred method.[2] MMS has shown significant promise, particularly in its capability to precisely excise and manage the margins of both deep and peripheral resections within a single plane. This technique improves accurate orientation, mapping, and targeted re-excision of microscopic tumour extensions, leading to better surgical outcomes.[7] Relapses are common due to the subclinical nature of the disease, even after surgical excision with wide margins and micrographic surgery.[9]

Alternative treatment modalities, including topical chemotherapy, photodynamic therapy, and radiation therapy, may be advantageous for patients who are reluctant to pursue surgical options or who do not qualify for surgical intervention.[1] In addition, nonsurgical treatment may be appropriate in situations when surgery is not feasible or as an adjuvant or salvage therapy to surgery.[10] Since relapses are common with all known therapy methods, prolonged periods of close observation is required for every patient.[9] Surgical excision with negative margins remains the most effective method to reduce the risk of local recurrence and enhance long-term recovery in non-invasive diseases.[10] In our case, after a thorough evaluation, no occult malignancy was detected. Given the patient's advanced age, a nonsurgical approach was chosen, with topical chemotherapy using imiquimod cream as the preferred treatment.

As EMPD is frequently associated with underlying malignancies, it is crucial for primary care providers to recognize this condition early. Timely identification allows for appropriate referrals and interventions, potentially enhancing patient outcomes through the prompt management of any related by malignancies.

CONCLUSION

EMPD should be considered in older patients with chronic, non-resolving skin lesions in apocrine-rich areas, particularly when standard treatments fail. While this is not the first case of EMPD in Malaysia, previously published cases demonstrate variability in the anatomical sites affected and the extent of skin involvement. Notably, a common feature across these cases is a prolonged delay in diagnosis, often spanning several years which highlights the ongoing challenge if limited awareness of this rare dermatological condition among primary healthcare providers. It is imperative that primary care physicians possess a comprehensive understanding of the clinical manifestations of EMPD and conduct thorough physical and systemic examinations to identify potential underlying malignancies. Early detection is essential for facilitating timely referrals and optimizing patient outcomes.

CONSENT

Written informed consent was obtained from the patient for the publication of this case report and the accompanying clinical images.

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CASE REPORT

Central Nervous System Tumour in Pregnancy, a Diagnostic Challenge or Management Quandary

Abd Malik NR[a], Ismail H[a], Ali Yeon AA[a], Mohd Rashid NN[b], Wahab MG[c], Awang MS[d]

[a]Department of Obstetrics and Gynaecology, Kulliyyah of Medicine, International Islamic University Malaysia, Kuantan, Pahang
[b]Department of Obstetrics and Gynaecology, Sultan Ahmad Shah Medical Centre, International Islamic University Malaysia, Kuantan, Pahang
[c]Department of Neurosurgery, Kulliyyah of Medicine, International Islamic University Malaysia, Kuantan, Pahang
[d]Department of Neurosurgery, Sultan Ahmad Shah Medical Centre, International Islamic University Malaysia, Kuantan, Pahang

Keywords
CNS tumour, central nervous system tumour, pregnancy

Corresponding Author
Asst. Prof. Dr. Nur Rashidah Abd Malik
Department of Obstetrics and Gynaecology, Kulliyyah of Medicine, International Islamic University Malaysia,
Kuantan, Pahang
E-mail: rashidahmalik@iium.edu.my

Received: 2nd August 2024; Accepted: 6th January 2026

Doi: https://doi.org/10.31436/imjm.v25i02/2685

ABSTRACT

Central nervous system (CNS) tumour, being rare in pregnancy, posed different challenges. We report three challenging cases managed at our centre. The first case was a diagnostic puzzle, bringing a myriad of differentials since the eighth week of gestation. Diagnosis made after magnetic resonance imaging (MRI) post-delivery at 35 weeks of gestation led to cervical spine meningioma excision surgery and subsequent progressive, remarkable neurologic recovery. Two additional cases were not a diagnostic mystery, yet they posed management challenges. The second case was diagnosed with a cerebellar tumour complicated with hydrocephalus at a pre-viable gestation. Pregnancy was able to be prolonged up to viability at extreme prematurity at 26 weeks when she needed delivery with subsequent cerebellar haemangioma excision and recovery. However, the third case became pregnant during follow-up after radiation therapy for brain glioma, with persistent symptoms necessitating termination of pregnancy.

INTRODUCTION

CNS tumour has a low prevalence of one in 1000 to 2000 pregnancies[1,2], with a tertiary neurosurgical centre in the United Kingdom reporting only 33 cases in pregnancy over 10 years.[3] We report three cases of pregnancy with CNS tumour, one posed a diagnostic challenge, and the other two cases posed a management predicament.

CASE REPORT

CASE 1

A 40 year old, Gravida 4 Para 3, presented to orthopaedics at 8 weeks' gestation with a one-year history of hand and foot numbness. Cervical myelopathy was diagnosed, and physiotherapy partially alleviated her symptoms. At 20 weeks, the numbness worsened, and she had right limb weakness necessitating ambulation with a wheelchair. Neuromedical assessment showed upper motor neuron lesion with bilateral C5 to T1 hypertonia and hyperreflexia, right-sided reduced muscle power, and hemianaesthesia. Multiple sclerosis was suspected, but unfortunately, MRI was withheld due to an incompatible right knee implant, which she denied for removal.

She was seen by Obstetrics and Gynaecology at 28 weeks' gestation and followed up fortnightly with neuromedical consults on each visit. There was no progressive neurological impairment, and the foetus was growing well. She was on thromboprophylaxis due to her limited mobility. Further deliberation with orthopaedic and radiological teams at 33 weeks of gestation concluded that, due to long-term placement of the implant, MRI is safe without migration risk but with heating effect. She was planned for an MRI at 36 weeks under the same general anaesthesia (GA) for caesarean section (CS).

Unfortunately, she had progressive weakness involving the left limbs at 35 weeks' gestation, necessitating earlier delivery. The multidisciplinary team decided to combine the delivery with intubation and MRI in the same setting,

prioritising maternal safety and avoiding further delay in diagnosis or intervention. Post-caesarean MRI revealed a 1.5cm X 1.7cm X 2.6cm intradural, extramedullary right dorsolateral cervical spine mass from the cervicomedullary junction to the C3 level (figure 1). This caused compression and left posterolateral displacement of the C1 and C2 spinal cord, with C2 and C3 right neural foramina exiting nerve roots obliteration.

Seven days later, she underwent suboccipital craniotomy with C1/C2 and partial C3 laminectomy and tumour excision (figure 1), after which she had progressive neurological improvement with rehabilitation physiotherapy.

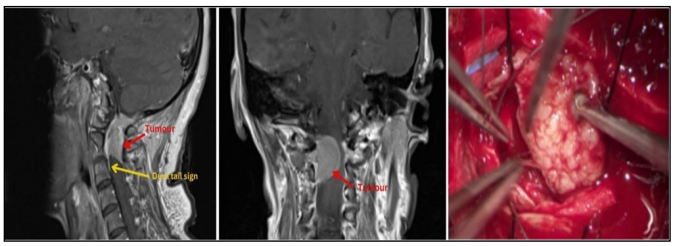

Figure 1: (from left to right): Intradural Extramedullary cervical spine tumour with dura tail sign in sagittal and coronal section MRI and midline durotomy at C1-C3 level with near total tumour removal

Two months later, she needed minimal help with daily activities and ambulating without wheelchair, and was completely independent in daily living activities one year after. Her baby, born at 2.05kg, was also thriving well. Histopathologic examination (HPE) of the tumour showed meningiothelial meningioma (grade 1).

CASE 2

A 36-year-old Gravida 2 Para 1 at 23 weeks of gestation presented with a four-month history of recurrent headache, intermittent vomiting, and new onset of blurred vision. She exhibited positive cerebellar signs with left-sided unbalanced gait. MRI revealed a left cerebellar tumour with hydrocephalus.

An Ommaya catheter insertion enabling daily tapping of cerebrospinal fluid (CSF) drainage relieved her recurring symptoms for 19 days. However, her symptoms worsened despite regular tapping of CSF and administration of intravenous steroids. Intravenous magnesium sulphate was given for fetal neuroprotection, and Caesarean section was performed under GA at 26 weeks, delivering a 1.17kg baby with a good APGAR score and placed under neonatal intensive care support for extreme prematurity. A repeated MRI showed a 3.1cm X 2.5cm X 2cm left cerebellar mass with perilesional oedema and mass effect onto the left midbrain, pons, and medulla oblongata. There was fourth ventricle compression with dilated bilateral lateral and third ventricles with crowding of cerebellar tonsils and tonsillar herniation (figure 2).

She had a left cerebellar suboccipital craniotomy and tumour excision (Figure 2) three days post-delivery.

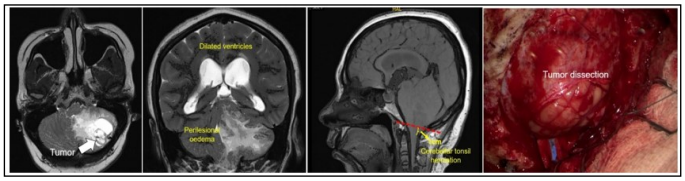

Figure 2: (from left to right): Cerebellar tumour with perilesional oedema in MRI axial section, coronal section, cerebellar tonsil herniation in MRI sagittal section, and left cerebellar suboccipital craniotomy and tumour excision.

She was discharged well three days after surgery. One month later, she remained asymptomatic with no residual tumour on MRI. Her child was discharged at 2.41kg after three months. HPE of the tumour reported as haemangioma.

CASE 3

A 40-year-old lady presented with a generalized tonic-clonic seizure. MRI showed a minimally enhancing tumour in the left frontal region measuring 4cm X 3cm X 2.6cm. She underwent a parietal craniotomy and tumour debulking surgery (Figure 3). A postoperative MRI one month later revealed residual tumour measuring 2.4cm X 2cm X 3cm. HPE reported as diffuse astrocytoma (grade II).

She completed 5 fractions of stereotactic radiotherapy. Her seizure was poorly controlled despite optimum anti-epileptic medication. Three months after the completion of radiotherapy, she was pregnant with twin pregnancy at 9 weeks. An urgent multidisciplinary team discussion was organized. Her conception was calculated to be after completion of her radiotherapy.

In view of poor seizure control on anti-epileptic and risk of contrasted MRI to fetus, which was essential in disease

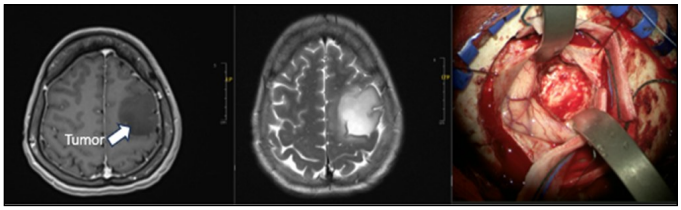

Figure 3: (from left to right): Minimally enhanced left frontal tumour on axial T1-weighted image with gadolinium and hyperintense on T2-weighted image. Intraoperative picture showing tumour debulking.

assessment and management, the managing team has collectively opted for termination of pregnancy (TOP) under general anesthesia. This decision for pregnancy termination was reached following consensus among the treating neurology, neurosurgery, obstetrics, and Shariah teams, in discussion with the patient and her husband.

MRI post-termination of pregnancy showed a residual tumour of 3.9cm X 2.7cm X 2.8cm with post radiation necrosis component and worsening local mass effect (Figure 4). She was commenced on long-acting contraception with progesterone implant and subsequently started on a course of corticosteroid therapy with a single anti-epileptic. With ongoing reassessment and monitoring, she has remained seizure-free for up to eight months following the termination of pregnancy.

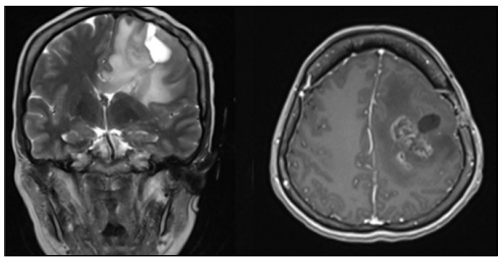

Figure 4: A coronal T2-weighted image showing left frontal cystic encephalomalacia with local mass effect, and residual tumour plus post-radiation necrosis seen on axial T1-weighted image with gadolinium

DISCUSSION

Diagnostic challenges of CNS tumour in pregnancy are contributed by its rarity and mimicry of pregnancy-related symptoms[1,4,5,6], such as vomiting, back pain, and numbness of extremities.[7] Pre-existing tumours may only first manifest symptoms in pregnancy due to rapid growth attributable to pregnancy hemodynamic and hormonal changes[5,6,7,8] and increased growth and angiogenic factors.[1,2]

Pregnancy has been associated with tumour-accelerated growth. Meningioma, as illustrated in Case 1, is among the commonest spinal tumours that is slow growing and may be asymptomatic for years.[6] Reports have shown meningioma expressing progesterone and oestrogen receptors[3,4,6], therefore causing the accelerated growth in pregnancy. Haemangioma has also been shown to only become symptomatic in pregnancy with rapid worsening symptoms in the third trimester, due to oestrogen and progesterone angiogenic growth-promoting effect[9] alongside increased blood volume[1] and elevated venous pressure, especially in the third trimester[5,6] as evident in Case 2.

Henceforth, delayed diagnosis compounded by pregnancy -associated accelerated growth would jeopardise maternal safety and increase morbidity and mortality.[2] Therefore, a high index of suspicion followed by proper investigation is imperative in women with neurologic symptoms in pregnancy.

MRI is best in identifying deep soft tissue structure, is safe in the second and third trimesters, with some reservations in the first trimester.[1] Gadolinium contrast is shown to have no additional risk to pregnant women, but inconclusive in foetal safety, with yet undocumented long -term concerns on kidney and neurodevelopment, but teratogenicity in animal studies has been shown only with high repeated dosing.[1] Nonetheless, when benefit outweighs the risks, the judicial use of MRI in pregnancy is justified.

Despite the unfortunate delay due to an MRI-incompatible implant in Case 1, postpartum diagnosis enabled immediate surgical intervention for the spinal tumour.

In contrast**,** diagnosis was not a challenge in Cases 2 and 3, but the management quandary in diagnosed CNS tumour in ongoing pregnancy is to have timely intervention for optimal maternal and foetal outcome.[4,9] Conservative approaches would reduce premature foetal morbidity and mortality, but in extensive and rapid neurological involvement, immediate intervention is needed.[3,5]

Antepartum surgery has multiple challenges with difficult prone positioning in the third trimester,[8] increased risk of epidural venous bleeding[8] and risk of foetal compromise[2] with difficult monitoring[8] during surgery. Hence, when pregnancy reaches 32 weeks, early delivery followed by surgery is recommended [4,5,7]

In Case 2, the diagnosis was at 23 weeks. The initial management goal was to prolong pregnancy to a viable gestational age while maintaining maternal stability. However, ensuing neurological deterioration despite maximal supportive measures necessitated immediate tumour resection. Despite severe prematurity at 26 weeks, the timely multidisciplinary reassessments and subsequent decision for delivery of the foetus with neonatal support, followed by surgical tumour resection, have brought a favourable outcome for both mother and baby.

Case 3 demonstrates maternal morbidity early on in pregnancy; hence, TOP is appropriate to prevent further maternal deterioration and mortality. Although no reported increase in miscarriages was reported from a recent systematic review[10], the patient has conceived within three months' post-radiotherapy for diffuse astrocytoma, before reassessment of treatment response and operability could be performed.

MRI with gadolinium contrast, essential for differentiating post-radiation necrosis from tumour recurrence, was avoided due to foetal safety concerns. Thus, continuation of pregnancy would have hindered appropriate imaging and treatment planning, delaying critical management. Following multidisciplinary deliberation, termination was recommended to permit full diagnostic evaluation and timely oncologic intervention to optimise maternal outcome.

On the other hand, these three cases underscore the critical importance of contraception during the evaluation and follow-up of reproductive-age women with CNS manifestations.

CONCLUSION

Despite their rarity, CNS tumours may contribute to neurological symptoms during pregnancy. Suspicion is crucial, and an MRI is recommended for an early diagnosis. The management of CNS tumours is determined by maternal neurological symptoms and foetal maturity. Most importantly, early multidisciplinary commitment and cooperation are critical, often demonstrating improved patient outcomes.

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