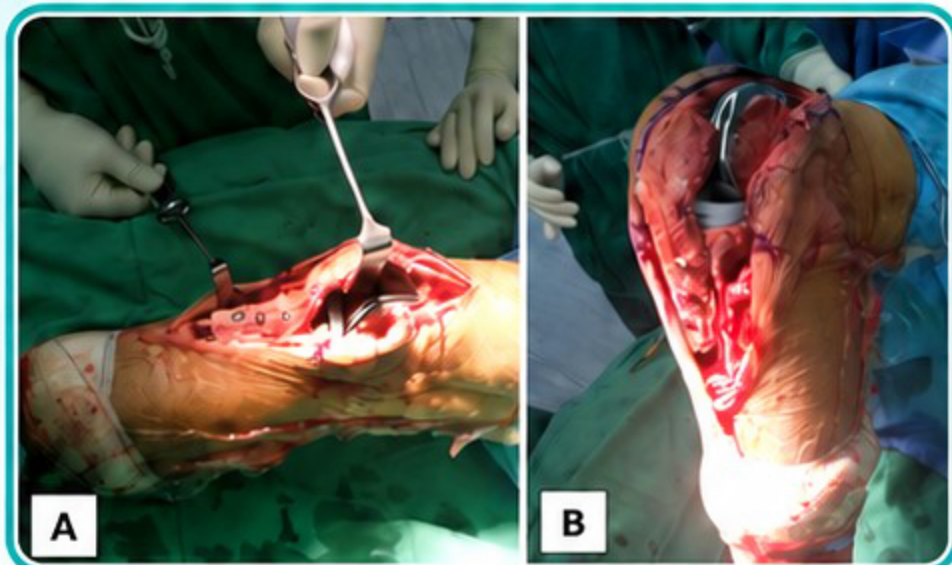
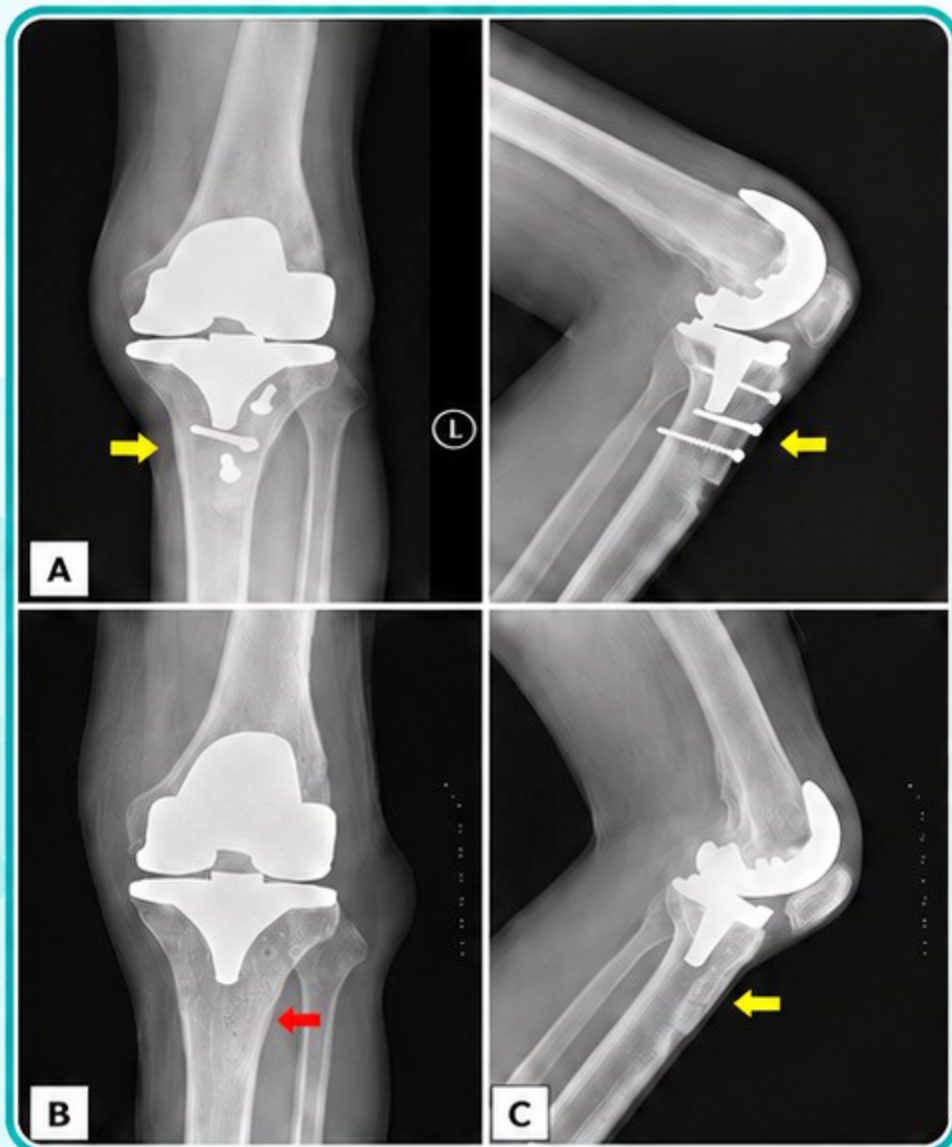




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Volume 25, Issue 4, October 2026

<https://doi.org/10.31436/imjm.v25i04>

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Presbycusis: A Lazy Diagnosis

Presbycusis, or age-related hearing loss, is conventionally defined as a gradual, bilateral sensorineural hearing loss (SNHL) associated with advancing age, initially affecting higher frequencies and subsequently causing difficulty understanding speech, particularly in noisy environments. The pathophysiology of ageing is complex and multifactorial: oxidative stress contributes to progressive loss of cochlear hair cells, atrophy of the stria vascularis, and degeneration of auditory nerve fibres and synapses, as well as central auditory pathway and processing deficits.¹ There is no disputing that the auditory system changes with age, just like any other part of the body. What this article aims to highlight is whether clinicians have the right to make this diagnosis when faced with older patients with SNHL without first taking a thorough history, particularly the often-neglected social history, which should include a detailed occupational history. I would argue that when the diagnosis is made without sufficient enquiry, it becomes something of a lazy diagnosis: age per se is an association, not an aetiology. In my view, presbycusis should scarcely enter the diagnostic vocabulary when considering differentials in patients younger than 60 years. SNHL before then demands an aetiological search rather than the convenient refuge of ageing.

Worsening hearing is more prevalent with advancing age, but this does not mean that hearing loss is inevitable, nor that age alone satisfactorily explains it. Auditory function varies substantially between people of similar chronological age. Some retain good hearing well into advanced age, while others develop significant SNHL much earlier. Concern regarding misuse of the term presbycusis is not new. More than half a century ago, Lowell and Paparella urged clinicians to make every effort to establish the correct diagnosis before attributing SNHL solely to ageing, noting that some patients diagnosed with presbycusis probably had familial or genetic hearing loss.² When faced with a 60-

year-old patient with gradual bilateral SNHL, we should ask not how old the patient's ears are, but what has happened to them over the years. The cochlea of a 60-year-old is not merely a cochlea that has existed for 60 years. It is a cochlea that has experienced 60 years of life. For many Malaysian workers, a substantial part of that life may have been spent in noisy environments.

Noise-induced hearing loss (NIHL) is a well-established consequence of exposure to hazardously loud sound. Workers exposed to chronic loud noise are at risk of permanent SNHL; and because that risk is predictably measurable, this occupational disease is preventable. Under Malaysia's Occupational Safety and Health (Noise Exposure) Regulations 2019, a daily noise exposure level exceeding 82 dB(A) constitutes excessive noise and triggers statutory requirements for assessment and management of occupational noise exposure. A 40-year-old factory worker with bilateral high-frequency SNHL and years of hazardously loud occupational exposure may readily be diagnosed with occupational NIHL following appropriate assessment. The same person with further deterioration in hearing thresholds 20 years later may acquire a new and remarkably convenient diagnosis: presbycusis. This is where indiscriminate use of the term becomes particularly troubling.

Ageing and occupational NIHL are not mutually exclusive processes. Age-related auditory changes superimposed on established noise damage neither render the earlier exposure resolved, nor erase its contribution to the eventual hearing deficit. Turning 60 does not make the preceding 20 years of occupational exposure disappear. Separating the effects of ageing and noise in an individual is undoubtedly difficult. Their effects may be additive, interactive and consequently audiometrically inseparable.³ The typical 4,000 Hz notch associated with NIHL does not obligingly remain

preserved. Continued exposure, progression at neighbouring frequencies and superimposed ageing may flatten or obscure the dip, even alter the audiometric pattern altogether.

By the time a patient presents later in life with a smooth, downward-sloping bilateral SNHL, the audiogram may no longer reveal the history of cochlear injury: it tells us the current pattern and degree of hearing loss, but not its cause. A bilateral sloping high-frequency SNHL may be compatible with presbycusis. It may also be compatible with cumulative occupational noise exposure, ototoxic injury, genetic susceptibility, or combinations of these. Distinguishing NIHL from age-related hearing loss at an individual level is inherently difficult, but that uncertainty should not make exposure history less important. It should make it more important. For older patients, the clinician should establish not merely the present job but a lifetime history of noise exposure, use of personal hearing protection, previous audiograms, documented threshold shifts, co-exposure to ototoxic chemicals, firearm training, and the relation between exposure and hearing deterioration. Age must not become a substitute for taking that exhaustive and yes, tedious history. Nor should the possibility of exposures outside work become an easy means of discounting occupational causation. Hazardous noise, admittedly, no longer belongs only to the workplace. The traditional image of NIHL requires updating, as the acoustic environment of everyday life has changed dramatically. Personal listening devices, earbuds, headphones and gaming devices now accompany almost every waking activity. Many fall asleep listening to music, podcasts, white noise or autonomous sensory meridian response (ASMR) sounds through these devices. Consequently, more than one billion young people may be at risk from unsafe recreational listening.⁴ This should broaden our clinical history, not dilute recognition of occupational NIHL. It tells us that NIHL can occur outside employment; it does not make documented occupational exposure irrelevant. Duration, intensity, intermittency, impulse characteristics, hearing protection, cumulative dose and concurrent exposures

all matter. Recognition of non-occupational exposure should help us understand the totality of cochlear insult. We should be cautious not to shift responsibility for preventable workplace exposure from employer to employee.

This brings us back to presbycusis and the possibility that SNHL reflects noise exposure instead. The term *sociocusis* has been used to describe hearing deterioration associated with the noise of everyday industrialised living rather than biological ageing alone. More recently, Fink challenged the conventional concept more directly. In a 2025 commentary, he argued that SNHL frequently labelled presbycusis or age-related hearing loss may substantially represent cumulative sociocusis and NIHL.⁵ This underscores the uncomfortable but pertinent question: how much SNHL have we attributed to ageing simply because ageing is easier to document than a lifetime exposure history? A diagnosis of exclusion should require some excluding. Presbycusis should never be the first explanation merely because the date of birth seems to fit. Before making the diagnosis, we should consider occupational and non-occupational noise exposure; ototoxic medications and chemical exposure; diabetes and cardiovascular risk; smoking; previous infections and otological disease; head injury; family history; and the rate, symmetry and pattern of progression. Significant asymmetry, unilateral tinnitus, sudden or rapidly progressive loss, fluctuation, vestibular symptoms, neurological findings or disproportionately poor speech discrimination should prompt investigation for alternative pathology. Contemporary clinical guidance similarly recommends further evaluation for asymmetric loss, conductive or mixed loss, or poor word recognition rather than simply treating these findings as manifestations of ageing.

One might argue that none of these matters as the management remains the same. The loss is permanent and irreversible, and the patient will require hearing rehabilitation, hearing aids being foremost regardless of the underlying cause. But calling hearing loss presbycusis suggests inevitability and risks

transforming a potentially preventable disorder into an unavoidable consequence of ageing. It discourages investigation, obscures occupational contribution, weakens prevention and inadvertently normalises disability. There is also something faintly ageist about it. We do not usually explain an older person's dyspnoea simply by saying that lungs age; we investigate cardiovascular and respiratory disease. We do not automatically attribute neurological deterioration to ageing without considering causes. Yet bilateral SNHL in older adults can acquire the presbycusis label with remarkably little resistance. Common is not synonymous with normal, and normal is certainly not synonymous with inevitable. We may never be able to apportion a patient's SNHL precisely between occupational noise, ageing, genetics and other causes. Human biology does not divide itself so obligingly and this uncertainty should not be the justification for giving age all the credit.

So the next time a 60-year-old presents with bilateral SNHL, we should resist the temptation to diagnose the audiogram before diagnosing the patient. Age is crucial, yes, but ask more carefully about the years spent working in hazardous noise. Ask too about ototoxic chemical exposures, medications, illnesses and family history. Only after considering what a lifetime has done to the ears should we decide how much of that damage can be attributed to ageing itself. Presbycusis may well be the correct diagnosis. It should never be the lazy one.

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Architecting Healthy Work in the Era of Occupational Health 5.0

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INTRODUCTION

Occupational Health 1.0 to Occupational Health 5.0

For over a century, the mandate of Occupational Health (OH) physicians has focused on protecting workers from injury and disease as we navigate distinct evolutionary eras.¹ OH 1.0 began in the wake of the Industrial Revolution, with basic safety guarding against the hazards of machines. OH 2.0, then introduced hygiene and toxicology, focusing on aetiologies of occupational diseases such as asbestos and lead. OH 3.0 moved into ergonomics and early psychosocial health, recognising the mind-body connection. OH 4.0 was the digitalisation era, where we adopted computers to track records and monitor risks more efficiently.²

At the cusp of the era of OH 5.0, the world is experiencing a convergence of three unstoppable global megatrends affecting every aspect of workers' lives:

- The explosion of generative artificial intelligence (AI) with cognitive automation at a scale that redefines the essence of human value and effort.³
- Profound demographic shifts with an ageing global workforce that reflects the demand for sustainable employment in which workers must remain productive and neurologically healthy for far longer than previous generations of workers.
- The total digitisation of the environment: the Internet of Things (IoT) means that every tool and every interface can generate actionable data.²

These forces have blurred the traditional boundary between home and work. While traditional hazards persist, the modern "injury" is often invisible, occurring at the level of the synapse and the endocrine system. It is the cognitive overload of the "always-on" culture, the

psychological erosion caused by algorithmic management⁴ and the musculoskeletal strain of sedentary and hybrid work.⁵ However, much of the current legislation and clinical protocols continue to be deeply rooted in the industrial era, building physical and regulatory barriers between the vulnerable human body and the industrial machine. The focus has primarily been on heavy machinery, chemical toxins, physical trauma, and mitigating traditional hazards and reacting to workplace injuries.

At the cusp of OH 5.0, the traditional defensive, reactive posture in the protection of the health and wellbeing of workers is no longer sufficient.

Occupational Health 5.0 and its Impact on the Role of OH Physicians

OH 5.0 is a socio-technical framework that acknowledges that the health of workers is not just a biological state, but the result of complex interactions between the individual, the technology, and their organisational ecosystem.⁶ Five converging simultaneous transformations underpin the emergence of OH 5.0.

First, employers are moving from tools to digital collaborators via AI.⁷ The broadening of digital access at the workplace means that AI is increasingly integrated into business operations, influencing productivity, decision-making, scheduling, monitoring, and worker evaluation. AI and machine learning systems offer substantial potential for improving risk assessment, identifying hidden risks, forecasting future health trends, and supporting preventive interventions at the workplace.⁸ More importantly, AI allows for the automation of routine tasks and administrative burden

of OH management, freeing OH physicians to focus on complex, high-value human interventions. It is important to highlight that it is not about AI replacing OH professionals; it is about tapping on AI to equip OH physicians to act decisively before harm occurs.

Second, there is an increase in the utility of genomics and digital biomarkers in addition to the traditional processes employed for risk assessment for workers and employers.⁹ Advances in genomics, predictive analytics, wearable technology, and digital biomarkers are enabling increasingly personalised approaches to workplace assessments and interventions. Objective, quantifiable physiological data allow the shift from subjective self-reporting, which is often influenced by recall bias, to objective, continuous monitoring. Thereafter, the clinical evidence has always been clear: when workers have access to their own biomarkers, they may support better health-related choices.¹⁰ When aggregated anonymously, this data allows employers to identify "hotspots" of occupational hazards before they lead to detrimental health outcomes.

Third, the nature of work after the COVID-19 pandemic has shifted workers from fixed physical locations to fluid, hybrid, and gig-based models.⁴ Hybrid work, remote work, platform employment, and gig-economy arrangements have profoundly altered traditional employer-employee relationships and challenged conventional occupational health frameworks.

Fourth, climate change is increasingly recognised as a major occupational health hazard on the health and productivity of workers, especially those working outdoors who are often exposed for longer periods and at greater intensities. Hazards include extreme weather events, excessive heat, ultraviolet radiation, air pollution and vector-borne communicable diseases.¹¹

Lastly, the OH profession itself is transforming with OH physicians moving from the back-office clinic to the heart of the boardroom. Businesses globally have

increasingly incorporated Environmental, Social, and Governance (ESG) considerations into strategic decision-making, and integrated social and environmental concerns into their operations.⁶ Occupational safety and health outcomes are now an integral component of ESG that allow businesses to demonstrate accountability, meet compliance requirements, and showcase stronger corporate governance,¹² which has positioned OH physicians as strategic contributors to businesses.

The above five transformations are not independent; they are interconnected. Therefore, the practice of OH in tackling the challenges of OH 5.0 cannot remain merely as "inspectors" or "gatekeepers". The methodology must shift to a new paradigm of systems thinking that allows OH physicians to become the "Architects of Healthy Work". This allows the bridging of a legacy gap between the needs of the modern worker and the episodic, reactive medical models inherited from the past. In rethinking the paradigm, OH physicians need to move beyond just protection toward intentional creation. This is the transition from "safety first" to "health by design". It is about creating a symbiotic relationship where the business flourishes precisely because its workforce is flourishing, supported by a digital ecosystem that anticipates their needs before they manifest as pathology. It is a system where the health of the workforce is considered a primary key performance indicator of business success.

What Will Occupational Health 5.0 Look Like?

Taken together, these five transformations redefine what a healthy workplace will look like in OH 5.0. Three organising pillars capture this redefinition in OH 5.0: Human-Centricity, Sustainability, and Resilience.¹³ They highlight the move beyond the mere absence of disease in a worker to the active promotion of vitality, shifting the focus from preventing harm to actively cultivating the capacity for high performance and well-being over a worker's fifty-year career.

AI and modern wearables are the engine of OH 5.0. In this framework, the field of OH harnesses IoT and machine learning, real-time physiological data, and behavioural science to ensure that work is intrinsically restorative to the workers.¹⁴ The worker is not the only entity being monitored; the workplace is being continuously surveyed too as the workplace itself becomes a diagnostic and therapeutic tool.¹⁴ Through IoT, ambient intelligence with sensor monitoring can be deployed to track environmental and/or workplace indicators (e.g. air quality, noise levels, and even the ergonomic fit of a workstation) in real-time and implement timely interventions. For example, if carbon dioxide levels rise within the building, the sensors automatically increase ventilation of the workplace. If a worker has been sedentary for too long, their desk subtly adjusts to encourage movement.

This allows work itself (i.e. the tasks, the tempo, and the environment) to be tailored to the biological capacity of the individual worker. The workplace acts as an active participant in workers' longevity in the workforce: monitoring, supporting, and adapting the workload to the specific neurophysiological requirements of the worker. This creates a closed-loop system where work design is constantly refined based on the actual, real-time health status of the workers. The integration of the physical and digital environment ensures that the workplace is no longer a source of hazard, but rather a source of restorative health that enhances the worker's daily performance and increases overall labour productivity.¹⁵ This moves from episodic clinical interventions to a continuous, invisible, and life-enhancing support system that protects the worker's long-term vitality, with every data point contributing to a safer, healthier, and more resilient workforce

The combined use of worker data and workplace data allows for digital twinning in OH 5.0: a virtual replica of a worker or a workplace.¹⁶ Unlike a computer simulation, a digital twin will stay connected to the physical worker or workplace to collect live data and update itself in real time to match the real-world scenarios. Employers can

run simulations in the digital twin to predict future health outcomes and allow failures in the virtual world rather than the real one. Clinical interventions such as a new ergonomic tool or a new shift pattern in a simulation can be tested before real-world implementations. This is the ultimate tool for the "Architect of Healthy Work", allowing for a zero-harm design by mitigating risks before they occur in physical reality.

The healthy work ecosystem in OH 5.0 will therefore be a resilient system as it is constantly learning and adapting. It does not wait for a crisis to occur; it evolves continuously to prevent it. This is what is meant by "Architecting Healthy Work" creating a holistic, self-sustaining environment where workforce health is not just a goal, but the core element of the system.

Key Operating Principles of OH Professionals in Occupational Health 5.0

However, realising the vision of workplaces built on Human-Centricity, Sustainability, and Resilience in OH 5.0 will require a new clinical methodology for OH physicians. In the OH 5.0 era, OH professionals as the "Architects of Healthy Work", are involved at the earliest design stages of the organisation. The clinical expertise of OH professionals will remain the foundation, but it is now augmented by data science and organisational psychology, ensuring that human health is built into every process.

A new set of operating principles will be required to translate the pillars of OH 5.0 into the day-to-day practice of the OH physicians.

- *Predictive.* OH 5.0 emphasises prediction rather than reaction. AI and Machine learning can be used to identify physiological and psychosocial risks before they manifest as illness. It shifts the OH professionals' role from reactive to anticipatory, as predictive occupational health enables targeted interventions and improved risk management.¹⁷
- *Personalised.* OH 5.0 moves away from one-size-fits-all guidelines toward interventions tailored to the

unique biology and life stage of a worker, making occupational health strategies more effective and fundamentally more human. Traditional occupational standards frequently rely upon population averages, and exposure limits were based on the average male worker. But clinically, no one is truly "average", as each worker possesses different genetic predispositions, ages, and physiological histories. Health risks and resilience vary considerably across workers. Precision occupational health seeks to tailor workplace interventions according to individual physiological, psychological, and occupational characteristics.⁹

- *Preventive.* OH 5.0 requires a focus on "upstream" systemic causes of ill-health rather than "downstream" symptoms. Work systems should be designed proactively to eliminate hazards and optimise worker well-being.¹⁸ This approach aligns with the hierarchy of controls and systems-based prevention models while extending these principles into emerging digital and psychosocial domains.
- *Participatory.* Research consistently demonstrates that employee participation enhances programme effectiveness, trust, engagement, and sustainability.^{19,20} Workers must remain active partners in workplace health programmes, so that they are the owners of their health data and active co-designers of their work environment.
- *Planetary.* In OH 5.0, worker health is inseparable from the health of the environment in which they work. Climate resilience, sustainability, and planetary health therefore become integral components of OH practice.¹¹ However, it is critical to also ensure that the transition to a "Net Zero" economy is a "Just Transition", one that does not sacrifice the health of the worker for the sake of environmental targets.²¹

These five principles provide the ethical and operational compass for the modern OH professional in the era of OH 5.0. They shift the clinical focus from the historical question of "what happened?" to the future-oriented

question of "what is likely to happen, and how can we optimise the environment for this specific worker?"

Challenges in Occupational Health 5.0

OH 5.0 is fundamentally about the design for human-AI collaboration, using AI to assume the "Dull, Dirty, and Dangerous" tasks, while OH physicians focus on empathy, ethics, and expert judgment. This collaboration requires sophisticated human factors engineering and understanding of how the workers and AI make sense of the cognitive states of each other that underpins the collaboration.²² If an AI is too efficient, it can out-pace the human worker, leading to physical and mental exhaustion. If it is too much of a black box, the worker loses trust. Fundamentally, AI will need to act as a supportive, transparent colleague at the workplace rather than a relentless, opaque supervisor, where the human and the machine together are healthier, safer, and more productive than either could ever be alone.

However, this symbiosis is only possible if there is a solid ethical foundation established. Central to the digital age is the ability to address the potential for surveillance, bias, and the total erosion of privacy,²³ or if not, the entire OH 5.0 framework will fail. There needs to be data sovereignty where the worker also owns their data, algorithmic transparency ensuring no hidden evaluation that can determine a worker's future, and non-discrimination by the AI based on age, gender, or ethnicity.²⁴ This ensures that the AI systems are transparent and explainable, so workers feel in control of their technology, not controlled by it.

Additionally, there has been a rise in mental health-related issues with integrating AI in occupational safety and health,²³ especially with the profound anxiety and loss of control felt by the workers caused by algorithmic management. It is crucial to ensure a psychologically safe digital workplace, establishing digital boundaries to prevent the constant work creep that leads to burnout. The goal is to create a digital environment that supports deep cognitive focus rather than fragmenting it.

CONCLUSION

In this emerging era, the central role of OH physicians will no longer simply be protecting workers from harm. Instead, we must become architects of healthy work systems that design work environments where workers can thrive. OH physicians will increasingly require expertise to inform workplace design, organisational strategy, AI implementation, climate adaptation, workforce planning, and resilience-building initiatives.

CONFLICT OF INTEREST

All authors have no conflicts of interest to declare.

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Exploring the Increased Risk of Vector-Borne Diseases Driven by Climate Change and Proposing Strategic Solutions to Mitigate the Impact. A Narrative Review

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ABSTRACT

Since the middle of the 20th century, human activity has caused Earth's climate to change. The Intergovernmental Panel on Climate Change projects that global temperatures will continue rising in the coming decades, leading to significant environmental and health impacts. This traditional narrative review synthesises evidence from previously published literature to determine the epidemiology of vector-borne diseases caused by climate change, their environmental factors, and solutions to address the issues. The vector-borne diseases, such as West Nile virus, malaria, dengue, Chikungunya, and Zika virus, are related to changing climatic conditions that create favorable environments for the transmission of the disease. The climatic factors include rising temperatures, drought, hurricanes, floods, changes in rainfall patterns, higher relative humidity, and shifts in wind patterns. The findings indicate that climate change not only expands the geographical distribution of vectors such as mosquitoes, ticks, and rodents, but also enhances their breeding and survival rates, leading to increased transmission risks. To mitigate these impacts, this review proposes several strategic solutions, including improved surveillance, adaptation measures, disease risk assessments, mitigation, and public health education.

Keywords

Climate change; global warming; vector-borne disease

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

Doi:
<https://doi.org/10.31436/10.31436/imjm.v25i04/3121>

INTRODUCTION

Climate change is defined by the National Aeronautics and Space Administration (NASA) as a long-term alteration in the weather patterns that characterise the local, regional, and global climates of Earth.¹ Since the middle of the 20th century, the Earth's climate has changed dramatically because of human activity, particularly from the burning of fossil fuels. The Earth's average surface temperature has increased due to this process, which has raised the atmospheric concentrations of heat-trapping greenhouse gases.²

Based on the data from the Intergovernmental Panel on Climate Change (IPCC), the average global temperature over land and ocean surfaces rose by 0.85°C between 1880 and 2012. According to their prediction, the temperature will rise by an additional 1.5°C by the end of the 21st century compared to 1850.³ Surface air temperatures in Southeast Asia are expected to increase by 2°C by 2060 and possibly by 5°C by 2098.⁴ Figure 1 illustrates the effects of greenhouse gas emissions, showing how they contribute to global warming and changes in natural cover, which in turn influence ocean

climate, storms, precipitation, sea levels, droughts, and related phenomena such as floods, fires, and heatwaves, which adapted from.⁵

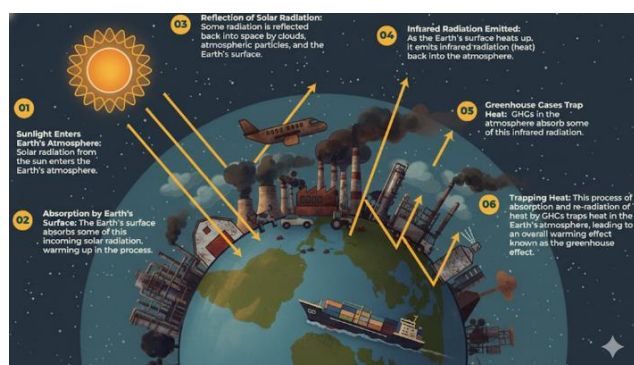


Figure 1: The continuing release of greenhouse gases (GHGs) affects the Earth's system's climatic risks

According to the World Health Organisation (WHO), 24% of all global deaths are attributable to poor environmental conditions annually, mostly owing to climate change.⁶ The ecosystems where diseases, vectors, and hosts interact will be impacted both directly and indirectly by the predicted rise in annual temperatures, altered rainfall patterns, increasing sea levels, and the frequency of extreme weather events.⁷ Infectious microorganisms become more resilient when the environment shifts, thus increasing the frequency and severity of diseases.⁸ Existing studies remain fragmented and often focus on isolated pathogens, targeted regions, or single climatic variables.⁹ Limited integration of climatic drivers, vector ecology, epidemiological trends, and public health strategies, along with inconsistencies in how climate affects disease transmission.¹⁰ An in-depth, comprehensive synthesis that summarises the available data, explains these relationships, and converts scientific findings into practical plans for disease prevention and mitigation is needed. Thus, the purpose of this review is to determine the epidemiology of vector-borne diseases caused by climate change, associated environmental factors, and solutions to address the issues.

MATERIALS AND METHODS

This article is a traditional narrative review to provide an integrative overview of the association between climate change and vector-borne diseases. An extensive literature search was carried out to identify appropriate peer-reviewed articles. It was conducted using the main scientific databases, including PubMed, Scopus, Web of Science, and Google Scholar. Keywords included 'climate change', 'global warming', and 'vector-borne disease'. With a focus on studies addressing epidemiological trends, climatic factors, vector ecology, and mitigation strategies related to climate-sensitive vector-borne diseases, published articles were chosen based on their applicability to this review's objectives. To provide a comprehensive understanding of existing concepts and emerging public health concerns, the chosen studies were critically interpreted and discussed.

VECTOR-BORNE DISEASES CAUSED BY CLIMATE CHANGE

In the previous three decades, the newest disease outbreaks have been either transmitted by vectors or began in animals and then transmitted to people. Vector-borne infections account for more than 17% of all infectious diseases, causing over 700,000 fatalities annually.¹¹ Climate change has a significant impact on arthropod vectors. Pathogens transmitted by mosquitoes and ticks cause vector-borne infections. Due to their distinct biological traits, these two types of vectors will react differently to climate change. Both mosquitoes and ticks are arthropods and ectothermic creatures, which means their surroundings have an impact on the surrounding temperature.¹² Figure 2 illustrates how various weather events can affect vector activity, increase the risk of disease transmission, and impact vector populations. These changes, in turn, affect the spread of vector-borne diseases.

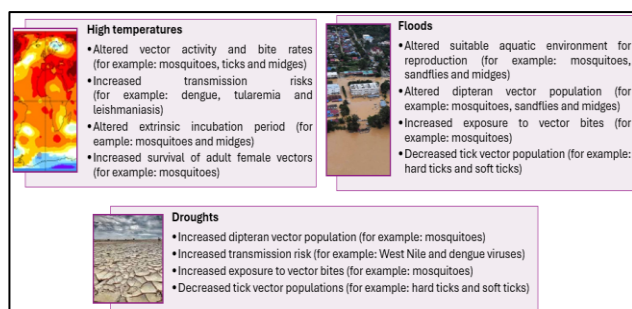


Figure 2: The influence of severe weather events on vectors and vector-borne diseases

One of the most important environmental factors influencing the spread of vector-borne diseases is temperature. Rising temperatures prolong transmission seasons and broaden geographic spread by accelerating mosquito growth, reducing pathogen incubation periods, increasing bite frequency, and improving vector survival.¹³ The increased risk of diseases transmitted by mosquitoes seen under climate change settings is mostly due to these temperature-driven biological interactions.¹⁴

The transmission of vector-borne diseases can be facilitated by international travel, as it brings new vectors to areas with more favorable environmental conditions and can also introduce new pathogens to both native and invasive vector populations.¹⁵ The rate at which pathogens develop and reproduce in mosquitoes is significantly influenced by temperature.¹⁶ People who spend more time outside cleaning up after a hurricane or flood are more vulnerable to mosquito bites. While numerous observational and modelling studies support this association, the magnitude of temperature-related effects varies across regions and vector species, indicating that local ecological conditions play an important modifying role.¹⁷

Vectors have been introduced via trade routes throughout history, with ships playing an essential role in the spread of mosquitoes. These insects were able to adapt in regions with favourable climatic circumstances through their spread.¹⁸ The mosquitoes that act as vectors for spreading mosquito-borne diseases are *Aedes*, *Anopheles*, and *Culex*. These mosquitoes

become carriers of disease-causing germs when they feed on the blood of diseased hosts and then transmit these pathogens to a new host during their next blood meal.¹¹ Several blood-sucking insect species, including the Asian Tiger Mosquito (*Aedes albopictus*), the Stable Fly (*Stomoxys calcitrans*), the Yellow Fever Mosquito (*A. aegypti*), and the Deer Fly (*Chrysops spp.*), contribute to the spread of these diseases.¹⁹

Overwintering can enhance the spread of several species as their development rate rises, notably in Arctic conditions.²⁰ Climate change leads to greater temperatures along altitudinal gradients. Hence, locations with temperate climates and greater altitudes (i.e., upslope) may become more conducive to the spread of diseases by vectors. Since mosquitoes are aquatic insects, the availability of water is essential to their life cycle and larval stage.¹¹ Their biological traits and feeding behaviour are impacted by humidity, which improves vector population dynamics when air humidity levels are high.²¹ During conditions of high humidity, such as during storms, heavy rains, and floods, stagnant water accumulates and provides perfect breeding grounds for mosquitoes.⁴

Mosquito-borne diseases may spread to new areas because of climate change; however, this transmission is also influenced by non-climatic factors such as rapid urbanization, increased population density, global travel, land use change, and socioeconomic inequalities that affect housing quality, sanitation, and access to vector control.²² This occurs when formerly uninhabitable places turn into conducive breeding grounds for mosquitoes that spread the disease.²³ The West Nile virus has expanded to new areas caused by climate change, just like other mosquito-borne illnesses. In 1999, the West Nile virus was initially identified in the United States in New York City, but it has been circulating in Africa since the 1930s.²⁴ In 2010, it led to a major outbreak in Europe that affected nations like Greece, Romania, Hungary, Spain, Russia, Turkey, Italy, France, Portugal, and Serbia. Since then, annual West Nile virus outbreaks have occurred in Eastern and Southern

Europe, suggesting that the virus is still being spread by the expanding mosquito populations.²⁵

In the northern Gulf of Mexico, early-season hurricanes can raise the total yearly number of West Nile Virus by 7.8% and contribute to 94.3% of human neuroinvasive incidence across all locations, enhanced by hurricane damage. *Culex* mosquitoes carry the West Nile virus. Although more than 60% show no symptoms, the infections can pose considerable hazards, particularly for the elderly.²⁶ This mosquito-borne virus can lead to deadly encephalitis in humans, mammals, and birds. Due to increased rainfall and a prolonged mosquito activity season brought on by rising temperatures, the disease's incidence has increased.²¹ The 2010 West Nile virus outbreak was mostly caused by abnormal temperature increases above the monthly average. As temperatures rise, the extrinsic incubation period of the West Nile virus in *Culex* mosquitoes drastically decreases.²⁷

Over the previous 10 years, cases of locally transmitted malaria, dengue, and Chikungunya have been detected in continental Europe.²⁶ The life cycle of dipteran vectors, such as mosquitoes, is relatively short, taking only a few days to complete each stage of development from egg to adult, which can range from a week to several months. These vectors are particularly susceptible to climate fluctuations. Therefore, temperature variations, mostly brought on by global warming, may have an impact on the dynamics of disease transmission, changing the epidemiology of endemic mosquito-borne diseases.²⁸ Global climate suitability for the transmission of dengue has grown by 15.0% for *A. albopictus* and 8.9% for *A. aegypti*, both of which are responsible for spreading the disease.²⁹ The Chikungunya, dengue, and Zika vector *albopictus* has spread throughout the world, including the Mediterranean area and Florida.¹²

The El Niño Southern Oscillation has an impact on the temperature of the sea surface, rainfall, and wind patterns across the Pacific Ocean, which are important factors influencing dengue incidence.³⁰ After Hurricane Mitch in 1998, Central American countries experienced

about 40,000 cases of dengue due to disrupted vector control measures.³¹ A study in Southern Europe emphasizes the potential for future climate conditions to create more susceptible environments for dengue transmission.²⁷ Starting from 2050, climate change is expected to lead to higher temperatures and increased rainfall, which could make certain regions more suitable for the spread of dengue. These regions include southern and western Africa, the southeastern United States of America, northern Argentina, central Mexico, and inland areas of Australia. Meanwhile, coastal towns in eastern China and Japan are anticipated to become more conducive environments to the transmission of dengue by 2050.³²

The Zika virus is mostly transmitted by the bites of infected *Aedes* mosquitoes. It can have serious neurological effects, such as microcephaly in fetuses and, less frequently, Guillain-Barré syndrome, a paralytic autoimmune disease.³³ After a traveller brought the virus to north-eastern Brazil in 2014, the first human case was found in May 2015, sparking an outbreak the same year.³⁴ After that, it expanded to most of the Caribbean and South and Central American nations.²⁷ The Zika virus started to spread widely over the world in the next few years, causing severe outbreaks in South America and circulating in several African and Southeast Asian nations.³⁵ The drought may have caused people to frequently store drinking water in open containers at home, which may have contributed to the outbreak by providing ideal breeding and exposure conditions for disease-carrying vectors.²⁶

Interestingly, vector-borne diseases are regularly affected by extreme weather events. While drought conditions may potentially pose disease risk by encouraging household water storage practices that facilitate mosquito reproduction, flooding events frequently enhance vector populations by creating temporary breeding sites.²⁷ These conflicting mechanisms show that, depending on local infrastructure, water management techniques, and

human behaviour, both excess and scarcity of water may increase the risk of transmission.³⁶

The most prevalent tick-borne disease in temperate Europe is Lyme disease, which is spread by Ixodes ticks carrying bacteria from the *Borrelia* genus.³⁷ The primary vectors of this disease are the Blacklegged Tick (i.e., *Ixodes scapularis*) and Western Blacklegged Tick (*Ixodes pacificus*). The virus that causes numerous cases of tick-borne encephalitis every year in European nations is also spread by these ticks.³⁸ Both Lyme borreliosis and tick-borne encephalitis, which are thought to be the most serious tick-borne diseases in Europe, are mostly spread by *Ixodes Ricinus*.¹² In contrast, *Ixodes scapularis* is the main vector in North America. Figure 3 was adapted from Semenza et al.²⁶ It displays the life cycle of ticks, their interaction with hosts and humans, and how environmental factors such as temperature and humidity could influence tick activity and transmission pathways.

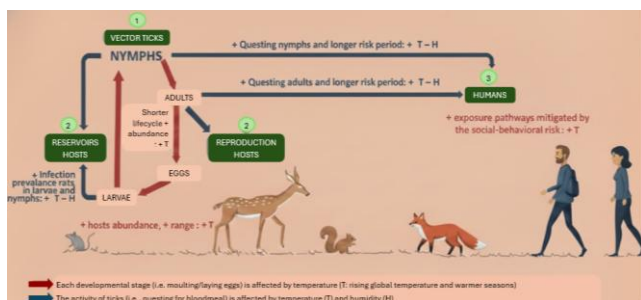


Figure 3: Climatic and meteorological elements that encourage tick life cycles and increase human risk.

Increased tick survival over the winter and an increase in tick populations can result from warmer winter temperatures. In nations like Sweden, Slovakia, and Hungary, moderate winters and warm, humid summers have been linked to a high prevalence of tick-borne diseases.¹² It is noteworthy that the impact of the climate on daily activities may also have an impact on the occurrence of these diseases.¹⁶ People may start outdoor activities early in the spring and continue them into the autumn due to temperature change, coinciding with tick activity. Longer exposure to tick habitats increases the potential of encountering ticks because they are active

from the springtime melting of snow until the autumn return of snow cover.³⁹

A zoonotic disease that is spreading throughout Europe, Russia, and several regions of Asia is tick-borne encephalitis. The yearly incidence rates of tick-borne encephalitis per 100,000 individuals were 2 to 5.4 times higher between 2005 and 2015 than the equivalent national rates.⁴⁰ The European Union recorded 2,057 tick-borne encephalitis cases in 2014. The number of cases reported in endemic areas in Europe has increased by about 400% in the last 30 years; however, this increase can also be linked to better monitoring and diagnosis.¹⁶ According to a study that looked at epidemiological changes in tick-borne encephalitis incidence in the Russian Federation over two decades, Siberia and the Far East are experiencing the biggest changes from 1997 to 2006 and from 2007 to 2016.²⁶

The most prevalent tick-borne disease in the world is Lyme disease. With an estimated 65,000 cases per year, it is often referred to as Lyme borreliosis or tick-borne borreliosis and is the most prevalent common vector-borne disease in the European Union.¹⁶ Erythema migrans rash and non-specific symptoms like headache, fever, exhaustion, and joint and muscle aches are common manifestations. If left untreated, it might escalate to a multisystem disease. Though it is rarely fatal, recent reports have linked deaths to Lyme carditis.³⁹ With a 20% rise in incidence under a 2°C scenario, it is anticipated that the Lyme disease season will spread throughout the United States of America in the upcoming decades. The yearly Lyme disease season is expected to start earlier and last longer because of this increase.¹⁶

Vector-borne disease risk is often shaped by the interaction of socioeconomic and climatic factors. The adverse effects of climate change on health can be worsened by informal settlements, poor drainage systems, inadequate waste management, and limited access to healthcare.⁴¹ Rainfall variability and humidity influence vector breeding through water availability and habitat suitability; however, their effects vary depending

on local infrastructure and human water-use practices.⁴² The significance of social vulnerability in the spread of climate-sensitive diseases is further demonstrated by the fact that equivalent climatic exposures may result in substantially varying disease outcomes among communities.⁴³ Figure 4 provides an overview of five vector-borne diseases, such as West Nile virus, malaria, dengue, Chikungunya, and Zika virus, and how they are impacted by climate change.

Type of vector-borne diseases	Geographic distribution of the disease incidence	Climate change factors that impact the diseases	Examples of animals that enhance the diseases
 West Nile	- In less than 10 years after arriving in New York City in 1999, it spread across all North America, including Mexico and Canada, and entered South America. - It has been detected in all conterminous United States of America, Colombia, and Puerto Rico.	- Higher temperatures - Early spring temperature - Drought in summer - Warm winter - Hurricane and flood	- Primary vectors: Mosquitoes (mainly <i>Culex</i> species) - Primary reservoirs: Birds (especially crows and jays) - Other potential hosts: Horses, humans
 Malaria	- Endemic in 91 countries and territories across the world, mostly in Africa, parts of Asia, and Latin America.	- Increasing temperature - Changes in rainfall patterns - Relative humidity	- Primary vectors: Anopheles mosquitoes - Primary reservoirs: Humans - Other potential hosts: Some primates (for certain <i>Plasmodium</i> species)
 Dengue	- Endemic in more than 100 countries, with the Americas, Southeast Asia, and Western Pacific regions being the most seriously affected.	- Rising temperature - Increased rainfall - Higher relative humidity - El Niño Southern Oscillation effects	- Primary vectors: Aedes mosquitoes (mainly <i>A. aegypti</i> and <i>A. albopictus</i>) - Primary reservoirs: Humans
 Chikungunya	- The outbreaks have been reported in Africa, Asia, the Americas, and Europe. - Major outbreaks have occurred in countries such as India, Indonesia, Myanmar, Maldives, Malaysia, Thailand, France, Italy, Gabon, Republic of Congo, the Central African Republic, Democratic Republic of Congo, Sudan, South Sudan, Kenya, Tanzania, Uganda, Malawi, and Mozambique.	- Temperature rise - Heavy precipitation - Wind pattern	- Primary vectors: Aedes mosquitoes (mainly <i>A. aegypti</i> and <i>A. albopictus</i>) - Primary reservoirs: Humans - Other potential hosts: Monkeys, rodents, birds (in sylvatic cycles)
 Zika	- Major outbreaks have occurred in Brazil, Colombia, El Salvador, French Guiana, Guatemala, Haiti, Honduras, Martinique, Mexico, Panama, Puerto Rico, Suriname, and Venezuela. United States of America.	- High temperature - Severe drought condition	- Primary vectors: Aedes mosquitoes (mainly <i>A. aegypti</i>) - Primary reservoirs: Humans and non-human primates - Other potential hosts: Some rodents and other mammals (in experimental settings)

Figure 4: Climate change impacts on the geographic distribution, transmission mechanisms, and vector ecology of five major vector-borne diseases

Much research relies on ecological or modelling methodologies, which may limit causal inference, despite increasing evidence connecting vector-borne diseases with climate change. Variability in findings can be attributed to differences in study design, data quality, surveillance effectiveness, and regional reporting systems.⁴⁴ These limitations emphasize the need for further multidisciplinary, longitudinal, and standardized research to more accurately measure the links between climate change and vector-borne diseases.

SOLUTIONS TO ADDRESS THE EFFECTS OF CLIMATE CHANGE ON VECTOR-BORNE DISEASE

To detect and control vector-borne disease epidemics, surveillance is crucial. It entails collecting and evaluating information regarding vector-borne diseases. By offering insights into frequency, trends, affected demographics, and geographic distribution, this approach helps in the management and control of the diseases. In addition, it is crucial to adopt a One Health approach that considers the epidemiology of animal infections.⁴⁵ The identification of emerging pathogens, a greater emphasis on vectors, enhanced control for pathogens, and the integration of extensive meteorological data into human and animal epidemiological studies will necessitate an increase in funding, as well as the hiring and training of qualified staff.⁴⁶ Clinicians should receive training from medical schools, residency programs, fellowships, and continuing medical education to anticipate and handle these changing issues.⁴⁷ Furthermore, ENSO forecasts can be included in vector-borne disease prediction models, anticipating El Niño episodes up to two years in advance. It entails creating and adopting practical plans, regulations, and measures to raise public awareness, lower those risks, and enhance readiness, response, and recovery procedures from the effects of climate change.⁴⁸

Moreover, the primary focus of risk assessment should be on potential hazards such as contaminated water sources, inadequate sanitation and cooking facilities, hazardous shelter conditions, population displacement leading to overcrowding, increased exposure to disease vectors, and limited access to healthcare services.⁴⁹ Vaccination can provide direct population-level protection against selected vector-borne infections, thereby reducing disease severity, transmission potential, and outbreak magnitude. However, vaccine availability remains limited for many climate-sensitive diseases, highlighting the continued importance of integrated vector control measures. These include environmental management to reduce breeding sites, use of insecticide-treated materials, biological control approaches, and

community-based interventions.⁵⁰ Optimising scarce resources to counter the global threat of vector-borne diseases requires a deeper comprehension of future vaccination demand, as well as the impact of animal migration and commerce.

CONCLUSION

Understanding the impact of climatic factors on vector-borne disease transmission is essential for developing effective strategies to mitigate risks. Diseases such as West Nile virus, Malaria, Dengue, Chikungunya, and Zika virus are closely linked to rising temperatures, drought, hurricanes, floods, changes in rainfall patterns, increasing temperature, higher relative humidity, and shifts in wind patterns, which affect the survival and development of disease-carrying vectors. To address these challenges, comprehensive surveillance, systematic data analysis, and adaptation strategies are necessary. Evidence from epidemiological and modelling studies demonstrates that integrated vector control strategies, climate-informed surveillance systems, and early warning systems can improve outbreak prediction and reduce transmission risk for vector-borne diseases. Campaigns for community health education are essential for increasing awareness and enabling communities to lower the risks related to vector-borne diseases and climate change. Future research should prioritise longitudinal, region-specific studies that integrate climatic variables, vector ecology, and socioeconomic factors to better quantify causal relationships between climate change and disease transmission. Methodological approaches combining epidemiological surveillance, climate modelling, and One Health frameworks are needed to evaluate the effectiveness of mitigation strategies and support evidence-based public health policy in vulnerable settings.

DECLARATION

Ethics approval and consent to participate are not applicable. This study is a narrative review based exclusively on previously published literature and did not involve human participants or animal subjects.

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Research Gaps in the Relationship Between Serum Brain-derived Neurotrophic Factor (BDNF) and Trunk Control After Stroke: A Scoping Review of the Last Decade (2014–2024)

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ABSTRACT

Brain-derived neurotrophic factor (BDNF) plays a crucial role in neuroprotection and neuroplasticity, positioning it as a key target for enhancing rehabilitation outcomes in stroke survivors. This scoping review aimed to explore the relevance of serum BDNF levels in improving trunk control and balance performance among this population. Using the PICO framework, the review focused on stroke patients (Population), undergoing rehabilitation (Intervention), compared to healthy individuals (Comparison), with outcomes including trunk control, balance, and serum BDNF levels (Outcome). A systematic search was conducted across five major databases: MEDLINE, PsycINFO, Embase, CINAHL Plus, and Cochrane Central, targeting full-text English studies published between 2014 and 2024. Studies meeting the inclusion criteria were analysed to identify patterns and research gaps. Five studies met the inclusion criteria. The findings suggest that serum BDNF levels increase following rehabilitation interventions and correlate with the duration of mobilisation. However, none of the included studies directly assessed trunk control, highlighting significant research gaps in understanding the direct impact of BDNF on trunk recovery after stroke. Further research is needed to elucidate how BDNF may facilitate trunk recovery, enhance early ambulation, and improve functional outcomes in individuals with stroke. This review highlights the absence of direct evidence linking serum BDNF to trunk-specific recovery and emphasises the need for targeted research in this area. Most research focuses on gait and balance, which serve as surrogate measures for trunk control, and emphasises spasticity in the extremities. Addressing these gaps through targeted research could optimize rehabilitation strategies and improve outcomes for stroke survivors.

Keywords

cerebrovascular accident, neurorehabilitation, neurotrophins, synaptic plasticity, stroke survivors

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Received: 2nd February 2025; Accepted: 5th
August 2026

Doi:
<https://doi.org/10.31436/10.31436/imjm.v25i04/2850>

INTRODUCTION

Brain plasticity is a key area in neurorehabilitation, particularly in stroke recovery.¹⁻³ Research has highlighted the significance of neurotrophins in stroke

recovery, identifying them as valuable prognostic biomarkers. Among these, brain-derived neurotrophic factor (BDNF) stands out for its essential role in supporting neural plasticity and its frequent use as a

prognostic indicator in post-stroke rehabilitation. BDNF is widely distributed throughout the healthy human brain, where it induces anti-apoptotic mechanisms and reduces lesion size, promoting neuronal survival.⁴ Additionally, BDNF supports neuronal differentiation and maturation,^{4,6} essential for maintaining neural health and function.

Following brain injury, BDNF is pivotal in promoting neuronal growth and healing. It facilitates the formation of new neuronal connections, strengthens protective mechanisms in nerve cells, and enhances overall neuronal health and vitality.⁷ Rising BDNF levels in the cortex have been linked to the brain's ability to reorganize itself, creating new connections through synaptogenesis, strengthening dendritic structures, and ramification. These adaptations are essential for motor learning and recovery after a stroke.^{6,8,9} Moreover, BDNF has been shown to reduce the degree of cerebral infarction and aid the natural salvage of damaged nerve cells.¹⁰

Stroke patients typically present with multiple motor impairments, including deficits in the trunk, upper, and lower limbs, which significantly hinder their ability to perform activities of daily living. Poor trunk control is a major concern, as it affects patients' ability to shift weight appropriately due to trunk muscle weakness and reduced proprioception on the paretic side.¹¹⁻¹⁴ This impairment in trunk control can lead to balance disorders, gait abnormalities, limited stability in both sitting and standing positions, and dysfunctions in speech and respiratory functions.^{15,16} Effective trunk control is therefore crucial for overall functional recovery, particularly in the early phase of stroke rehabilitation.^{14,17}

Despite the recognised role of BDNF in stroke recovery, most literature has concentrated on upper limb motor function, with comparatively few studies addressing lower limb or trunk control. The impact of stroke on BDNF production and its relevance to trunk-specific

recovery and balance remain underexplored, and to our knowledge, no published study to date has directly

evaluated trunk-specific outcomes in relation to serum BDNF following rehabilitation. Existing studies have primarily assessed balance and overall functional performance, which may only indirectly reflect trunk stability, leaving their relationship with serum BDNF uncertain. This scoping review maps the available literature from the past decade (2014–2024) to define the extent and nature of current evidence, identifies significant research gaps in the literature, and highlights research priorities to inform more targeted, evidence-based rehabilitation strategies.

MATERIALS AND METHODS

Protocol and registration

The review protocol was developed based on the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) guidelines.¹⁸⁻²⁰ The protocol was not registered but adhered to the principles of transparency and reproducibility in the scoping review methodology.

Eligibility criteria

Studies were selected based on predefined eligibility criteria using a PICO (Population, Intervention, Comparison, and Outcome) model framework. The population of interest included human participants diagnosed with stroke in acute, sub-acute, or chronic phases. Interventions considered were rehabilitation programs focusing on task-specific training and neuroplasticity-based therapies. Comparisons included studies contrasting stroke patients with healthy individuals or those receiving alternative or standard care. The outcomes of interest were trunk control, balance, and serum BDNF levels. Eligible study designs included randomized controlled trials, cohort studies, cross-sectional studies, and case-control studies. Only articles published in English were included. Studies were excluded if they were investigating induced stroke in animals, focused on infantile or paediatric stroke, or

other neurodegenerative diseases, or were non-original articles such as reviews or conference abstracts.

Information sources

The literature search used five major electronic databases: MEDLINE, PsycINFO, Embase, CINAHL Plus, and Cochrane Central. Additional references were identified through manual searches of reference lists from included studies.

Search strategies

The search strategy was developed collaboratively with the study authors to ensure relevance and comprehensiveness. Keywords and Medical Subject Headings (MeSH) terms were tailored to each database and combined using Boolean operators (AND, OR). The search terms included: "stroke," "trunk control," "balance," "neurotrophins," "brain-derived neurotrophic factor (BDNF)," and "rehabilitation." The complete search strategy is detailed in Table I. The search was limited to studies published between 2014 and 2024 based on three key scientific developments that established modern standards in stroke rehabilitation research: (1) standardization of BDNF measurement protocols,²¹⁻²³ (2) widespread PRISMA guideline adoption,^{20,24,25} and (3) validation of trunk-specific assessment tools.²⁶⁻²⁹ It captures the period when neurorehabilitation research achieved sufficient methodological consistency for reliable evidence synthesis, while excluding earlier studies that used heterogeneous assays or lacked consensus on outcome measures. The selected timeframe ensures our review reflects current clinical practices and technological advances without compromising comprehensiveness, particularly for studies examining BDNF's role in post-stroke recovery.

Selection of sources of evidence

Three reviewers (AMU, AAA, and MAS) independently screened the titles and abstracts retrieved from the searches. Full-text articles were assessed for eligibility, and disagreements were resolved through discussion

with a fourth reviewer (NBR). The selection process was systematically documented using a PRISMA-ScR flow diagram.

Data extraction and synthesis of results

Data from the included studies were extracted using a predefined charting form in Microsoft Excel. The form

Table I: Search strategy for BDNF, trunk control, and balance in stroke care

Query	Search
Medline via Ovid	1: stroke/ 2: stroke.ab,kw,ti. 3: Sub-acute stroke.ab,kw,ti. 4: acute stroke.ab,kw,ti. 5: chronic stroke.ab,kw,ti. 6: cerebrovascular accident.ab,kw,ti. 7: cerebrovascular diseases/ 8: cerebrovascular diseases.ab,kw,ti. 9: cerebrovascular attack.ab,kw,ti. 10: 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 11: Trunk control.ab,kw,ti. 12: balance.ab,kw,ti. 13: 11 OR 12 14: Brain derived neurotrophic factor/ 15: Brain derived neurotrophic factor.ab,kw,ti. 16: BDNF.ab,kw,ti. 17: Neurotrophin.ab,kw,ti. 18: peripheral BDNF.ab,kw,ti. 19: 14 OR 15 OR 16 OR 17 OR 18 20: 10 AND 13 AND 20
PsycINFO via Ovid	1: stroke.ab,ti. 2: sub-acute stroke.ab,ti. 3: acute stroke.ab,ti. 4: chronic stroke.ab,ti. 5: cerebrovascular diseases.ab,ti. 6: cerebrovascular accident/ 7: cerebrovascular accident.ab,ti. 8: cerebrovascular attack.ab,ti. 9: 1 OR 2 OR 3OR 4 OR 5 OR 6 OR 7 OR 8 10: Trunk control.ab,ti. 11: balance.ab,ti. 12: 10 OR 11 13: Brain derived neurotrophic factor / 14: Brain derived neurotrophic factor.ab,ti. 15: BDNF.ab,ti. 16: Neurotrophin.ab,ti. 17: peripheral BDNF.ab,ti. 19: 13 OR 14 OR 15 OR 16 OR 17 OR 18 20: 9 AND 12 AND 19
Embase via Ovid	1: stroke.ab,kw,ti. 2: sub-acute stroke.ab,kw,ti. 3: acute stroke.ab,kw,ti. 4: chronic stroke.ab,kw,ti. 5: cerebrovascular diseases/ 6: cerebrovascular diseases.ab,kw,ti. 7: cerebrovascular accident/ 8: cerebrovascular accident.ab,kw,ti. 9: cerebrovascular attack.ab,kw,ti. 10: 1 OR 2 OR 3OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 11: Trunk control.ab,kw,ti. 12: balance.ab,kw,ti. 13: 11 OR 12 14: Brain derived neurotrophic factor / 15: Brain derived neurotrophic factor.ab,kw,ti. 16: BDNF.ab,kw,ti. 17: Neurotrophin/ 18: Neurotrophin.ab,kw,ti. 19: peripheral BDNF. ab,kw,ti. 20: 14 OR 15 OR 16 OR 17 OR 18 OR 19 21: 10 AND 13 AND 20
CINAHL Plus	S1: (MH "stroke") S2: TI "stroke" OR AB "stroke" S3: TI "sub-acute stroke" OR AB "sub-acute stroke" S4: TI "acute stroke" OR AB "acute stroke" S5: TI "chronic stroke" OR AB "chronic stroke"

S6: TI "cerebrovascular disease" OR AB "cerebrovascular disease"
 S7: TI "cerebrovascular accident" OR AB "cerebrovascular accident"
 S8: TI "cerebrovascular attack" OR AB "cerebrovascular attack"
 S9: S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8
 S10: (MH "balance")
 S11: TI "balance" OR AB "balance"
 S12: TI "trunk control" OR AB "trunk control"
 S13: S10 OR S11 OR S12
 S14: (MH "Brain derived neurotrophic factor")
 S15: TI "Brain derived neurotrophic factor" OR AB "Brain derived neurotrophic factor"
 S16: TI "BDNF" OR AB "BDNF"
 S17: TI "Neurotrophin" OR AB "Neurotrophin"
 S18: TI "peripheral BDNF" OR AB "peripheral BDNF"
 S20: S14 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19
 S21: S9 AND S13 AND S20
 1: stroke.sh.
 2: stroke.ab,kw,ti.
 3: sub-acute stroke.ab,kw,ti.
 4: acute stroke.ab,kw,ti.
 5: chronic stroke.ab,kw,ti.
 6: cerebrovascular accident.ab,kw,ti.
 7: cerebrovascular disease.ab,kw,ti.
 8: cerebrovascular attack.ab,kw,ti.
 9: 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8
 10: Trunk control.ab,kw,ti.
 11: balance.ab,kw,ti.
 12: 10 OR 11
 13: Brain derived neurotrophic factor.sh.
 14: Brain derived neurotrophic factor.ab,kw,ti.
 15: BDNF.ab,kw,ti.
 16: Neurotrophin.ab,kw,ti.
 17: peripheral BDNF.ab,kw,ti.
 19: 13 OR 14 OR 15 OR 16 OR 17 OR 18
 20: 9 AND 12 AND 19

Cochrane Central

captured the author(s) and year of publication, sample characteristics, inclusion and exclusion criteria, intervention specifics (type, duration, and intensity), outcome measures, results, and conclusions. The three independent reviewers piloted the charting process on a subset of studies to ensure consistency.

The results of the included studies were synthesized narratively, focusing on the interventions and their outcomes. Data were organized thematically and presented in an evidence table to enhance clarity and accessibility.

RESULTS

Study selection

The flow of studies through the selection process is illustrated in Figure 1. A total of 163 articles were identified through database searches and manual reference checks. After removing 39 duplicates, 124 articles were screened for relevance based on titles and abstracts. Most of the studies screened, primarily

conducted by physiotherapists, were considered unrelated to the particular emphasis of this review concerning the function of serum BDNF in enhancing trunk control in stroke patients following rehabilitation. Subsequently, eight full-text articles were assessed for eligibility, with three excluded due to not meeting the inclusion criteria. After a thorough evaluation, only five studies were included in the review, as detailed in Table I.

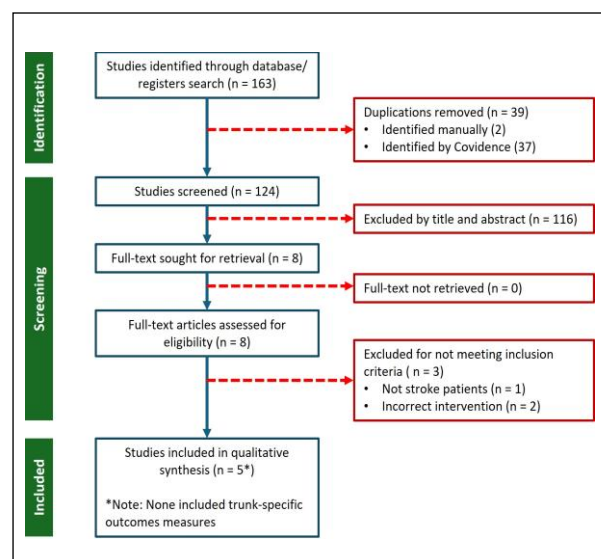


Figure 1: PRISMA-ScR flow chart of the study

Table II: Evidence table of included studies

First author	Sample	Inclusion criteria	Interventions	Outcomes	Results*	Conclusion
Rahayu et al. ³⁰	40 patients recruited based on specific inclusion criteria, randomly divided into two groups: (1) treatment group (n=20) receiving early mobilisation (EM) at 24 hours and (2) control group (n=20) receiving EM at 48 hours post-ischemic stroke diagnosis via CT scan.	1. Ischemic stroke diagnosis with motor control reduction. 2. Sensory and proprioceptive deficits with a muscle strength score of at least 2+. 3. First-stage stroke confirmed unilateral hemiparesis without neurological deterioration. 4. No aphasia or severe cognitive impairment (MMSE >19)	Mobilization lasted 30-60 minutes, focusing on exercise progression from cognitive to associative stages; the control group did not have graded exercises.	No specific trunk control outcome measured via the Berg Balance Scale. Functional ability via the Barthel Index on days 5 and 7.	Significant differences were noted on day 7 for both balance (p=0.038) and functional ability (p=0.021); on day 5, only functional ability showed a significant difference (p=0.002), with no significant difference in balance (p=0.147).	Early mobilisation at 24 hours post-ischemic stroke showed better outcomes in balance and functional ability compared to 48 hours.

Cont.						
Rahayu et al. ³¹	69 participants were recruited, with 64 completing the study.	Patients diagnosed with ischemic stroke 24 hours post-attack without neurological deterioration, experiencing decreased motor control, sensory and proprioceptive deficits, muscle strength of at least 2+ by manual testing, no aphasia, and agreed to participate	Neurorestoration intervention involved three stages: cognitive, associative, and automation, with intensity varying by participant performance. Standard protocols, tailored daily to patients' needs, included: Bobath PNF Rood approach Carr & Shepherd model CIMT.	No specific trunk control outcome measured BI evaluated ADL, Berg Balance Scale test BDNF analysis	Both groups showed improvements in all areas, but only balance and functional performance had statistically significant outcomes.	The neurorestoration protocol, combining various physiotherapy interventions, effectively improved balance and functional ability in stroke patients within seven days.
He et al. ³²	200 post-stroke hemiplegic patients were admitted from March 2022 to February 2023, evenly and randomly divided into control (C) and observation (O) groups.	Adherence to diagnostic criteria of the Chinese Guidelines for Diagnosis and Treatment of Acute Ischemic Stroke via CT or MR imaging. First onset. Unilateral limb dysfunction post-onset. No progression in mild or moderate cases within 24 hours, stable vital signs, and no worsening neurological function in severe cases. Normal swallowing function.	MDT writing collaboration group established and provided functional rehabilitation training, psychological counselling, and nutritional support for the observation group, while the control group followed a routine rehabilitation protocol. Functional limb exercises were conducted daily in two groups with 10 repetitions each and a rest period of 1 minute, over a 4-week intervention.	No specific trunk control outcome measured Neurotrophin levels (NGF, BDNF, IGF-1). Nutritional status. Neurological impairment assessed via NIHSS. Quality of life via SS-QOL. The Fugl-Meyer (FM) scale used for motor function assessment (upper and lower limbs). BDNF analysis	No statistically significant differences ($p>0.05$) in NGF, BDNF, IGF-1, haemoglobin (HGB), albumin (ALB), transferrin (TRF), limb motor function, balance, neurological deficits, or quality of life scores between groups; however, post-intervention, NGF, BDNF, IGF-1, HGB, ALB, and TRF levels in the observation group were significantly higher ($p<0.05$). BDNF levels increased significantly during AR rehabilitation; treated patients showed similar patterns in BDNF levels, whereas untreated patients had lower levels at the endpoint.	MDT collaboration significantly enhances neurotrophin levels, mitigates nerve defects, and fosters recovery in limb function, balance, and quality of life for stroke patients with hemiplegia.
Koroleva et al. ³³	50 patients after acute recovery from ischemic stroke: 21 received classical rehabilitation on followed by motor rehabilitation on with motion sensors and augmented reality (AR), 14 only received AR rehabilitation on, and 15 were observed	Ages between 18 and 80 years. Mild-to-moderate upper limb hemiparesis (NIHSS <12 , mRS score <4 , MAS score ≤ 2). Absence of cognitive impairment (MMSE ≥ 22) or behavioural dysfunction.	Classical rehabilitation and motor rehabilitation using motion sensors and augmented reality (AR) rehabilitation	No specific trunk control outcome measured Motor impairment quantified via Fugl-Meyer (FM) scale Functional disability and (ADL) measured with mRS. BDNF analysis	BDNF levels increased significantly during AR rehabilitation; treated patients showed similar patterns in BDNF levels, whereas untreated patients had lower levels at the endpoint.	BDNF changes do not consistently correlate with motor improvement but respond to active treatment.
Astuti et al. ³⁴	87 patients with suspected acute ischemic stroke were recruited on admission; 68 completed the study, categorised into dependent ($n=22$) and independent ($n=46$) groups based on BI scores on day 30 post-stroke.	First-time acute ischemic stroke. Ability to participate until the following month. Cooperative. No history of other CNS damage (tumour, trauma, encephalitis). Parkinson's disease, previous stroke, or previous physical disability.	Routine physiotherapy intervention	No specific trunk control outcome measured BI used for functional assessment BDNF analysis	Mean serum BDNF level in the acute phase was significantly higher in the independent group (27,152.28 vs 23,143.41; $p=0.044$), consistent in chronic phase measurements (27,526.48 vs 22,818.91; $p=0.036$).	Serum BDNF levels in both acute and chronic phases potentially predict functional outcomes in patients with acute ischemic stroke.

*Findings are reported as described by the authors of the individual studies.

ADL: activities of daily living; BDNF: brain-derived neurotrophic factors; BI: Barthel Index; CIMT: Constraint-Induced Movement Therapy; CNS: central nervous system; CT: computed tomography; IGF: insulin-like growth factor; MAS: Modified Ashworth Scale; MDT: multidisciplinary team; MMSE: Mini-Mental State Examination; MR: magnetic resonance; mRS: Modified Rankin Scale; NGF: nerve growth factor; NIHSS: National Institutes of Health Stroke Scale; PNF: proprioceptive neuromuscular facilitation; SS-QOL: Specialized Stroke Quality of Life Scale.

Characteristics of included studies

All five studies focused on stroke rehabilitation and examined the effects of various interventions. The study designs included randomised controlled trials and cohort studies, reflecting a robust methodological approach. Sample sizes varied between 40 and 200 participants, with diverse demographic characteristics. The interventions differed across studies, with strategies such as early mobilisation, neurorestorative protocols, and augmented reality-based rehabilitation being implemented. Commonly reported outcome measures included serum BDNF levels, balance metrics (e.g., Berg Balance Scale), and functional assessments (e.g., Barthel Index), underscoring a consistent focus on evaluating functional recovery and biomarker relevance in stroke rehabilitation.

Population sample and inclusion criteria

The population in this review consisted of adult ischemic stroke patients who had experienced their first stroke, characterised by an acute onset affecting one hemisphere. Eligibility criteria across the studies required participants to have mild complications, a muscle strength score of at least 2+, and the ability to ambulate without severe cognitive impairment.³⁰⁻³² Most studies included had sample sizes greater than 30 participants, which is often considered a minimum

threshold for achieving adequate statistical power in clinical research. However, the actual power of each study depends on factors such as effect size and data variability, highlighting the importance of context in interpreting results. One study reported the largest cohort, with 200 participants randomised into experimental and control groups.³² Despite the relatively rigorous inclusion criteria, a notable limitation was the lack of direct assessments targeting trunk impairments after stroke, which highlights a significant research gap. These limitations, coupled with small sample sizes in certain studies,^{30,33} emphasise the need for further exploration in this domain.

Rehabilitation interventions and trunk stabilisation

The reviewed studies collectively highlighted the significance of rehabilitation interventions in enhancing functional recovery in stroke patients, although none explicitly focused on trunk muscle control. Mobilisation exercises, implemented in both early and late phases, emerged as a crucial component of stroke rehabilitation. Most interventions were administered for a duration of 30 minutes to one hour per day, three to five days a week, over four weeks. One study emphasised the role of early mobilisation in improving overall balance, indirectly benefiting trunk stabilisation.³⁰ These findings align with another study that demonstrated the efficacy of neurorestorative interventions in enhancing balance and functional impairments.³¹

Another study further highlighted the positive effects of augmented reality-based rehabilitation on motor impairments and neurotrophic factor levels, pointing to its potential for promoting trunk-related recovery.³³ Despite these promising results, most studies did not specifically address trunk muscle stabilisation or establish a direct correlation between serum BDNF levels and balance performance. This gap highlights the need for future research to elucidate the mechanisms through which rehabilitation interventions influence trunk-specific recovery outcomes. These findings collectively emphasise the importance of tailored

rehabilitation strategies to optimise functional outcomes in stroke survivors.

Balance and trunk stability outcomes

The included studies consistently demonstrated improvements in balance, overall functional ability, and quality of life following rehabilitation interventions,^{31,33,34} even though trunk muscle control was not explicitly assessed. Some studies highlighted the effectiveness of early mobilisation and neurorestorative protocols in improving balance metrics within seven days, emphasising their potential indirect benefits for trunk stabilisation.^{30,31} Similarly, augmented reality-based rehabilitation was associated with enhanced balance and motor function compared to standard rehabilitation approaches.³³ These findings illustrate the role of innovative rehabilitation strategies in achieving better balance outcomes in stroke survivors. However, while the studies collectively underscore the significance of balance function following a stroke, the absence of direct assessments of trunk control creates a gap in our understanding of how serum BDNF levels and trunk control rehabilitation influence trunk-related recovery.

While these studies collectively demonstrated the importance of balance improvements, they lacked direct assessments of trunk muscle stabilisation, leaving a gap in understanding the specific mechanisms linking rehabilitation to trunk-related recovery. This highlights the need for future research targeting trunk-specific interventions and their effects on balance and functional outcomes.

Serum BDNF levels

Rehabilitation interventions were consistently associated with increased serum BDNF levels across the included studies. One study observed significant elevations in serum BDNF and other neurotrophic factors following multidisciplinary team-based interventions.³² Similarly, another study found a positive relationship between early mobilisation and serum BDNF levels in acute ischemic stroke patients.³⁰ Higher serum BDNF levels

in both acute and chronic phases were also correlated with better functional independence, further supporting the role of neurotrophic factors in post-stroke recovery.³⁴

However, one study noted variability in the relationship between serum BDNF levels and motor improvements, suggesting that additional factors may influence these outcomes.³³ Despite these variations, the findings highlight the potential of serum BDNF as a biomarker for recovery, particularly in enhancing balance and motor function. However, the impact of BDNF on trunk control following a stroke remains uncertain, as none of the studies included in the review directly assessed trunk control.

DISCUSSION

This scoping review reveals a critical gap in the literature: despite extensive research on BDNF's role in stroke recovery, no studies have directly investigated its relationship with trunk-specific rehabilitation outcomes. While included studies examined balance and functional measures, often used as proxies for trunk control, none employed validated trunk assessment tools, highlighting a significant research need.

The restorative processes of neural repair after stroke or brain injury, such as neurogenesis, gliogenesis, and axonal sprouting, are critical for balance and functional recovery. Neurotrophic factors such as BDNF, nerve growth factor (NGF), neurotrophin-3 (NT-3), and neurotrophin-4/5 (NT-4/5) are a group of secreted proteins that play pivotal roles in the development, growth, survival, and differentiation of the nervous system.³⁵ As the most abundant neurotrophin in the nervous system,³⁶ BDNF has been identified as a key marker in these processes.^{2,8,14} It facilitates the generation of epigenetic mechanisms by signalling through excitatory neurotransmitters like glutamate and its inhibitory counterpart, gamma-aminobutyric acid (GABA). These epigenetic changes alter BDNF activity, promoting positive stroke outcomes.⁸ Studies

have identified that BDNF release is activity-dependent. Research has shown significantly lower BDNF concentrations in acute stroke patients, attributing this reduction to altered neuronal excitability and downstream signalling in excitatory neurotransmitters.^{8,37}

Several neuroplasticity techniques were conducted to stimulate the release of BDNF post-neurological deficit, including stroke. Repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) are non-invasive techniques that are widely used to enhance BDNF release.³⁸ tDCS is a widely used technique compared to rTMS as it has lower cost, portability, and ease of use. tDCS protocols typically target lesional (anodal) and contralesional (cathodal) motor cortex to promote perilesional recovery while reducing transcallosal inhibition.³⁸ Epidural cortical stimulation (ECS) is another invasive technique with a potential effect on cortical excitability and BDNF release.³⁸ Additionally, various neuroplasticity physical interventions, including aerobic training, task-specific exercises, and proprioceptive neuromuscular facilitation, have been proven to effectively elevate BDNF levels after stroke.³⁹

BDNF levels have been found to correlate with infarct volume. Larger infarct volumes have been associated with lower acute-phase BDNF levels.^{5,40-43} This relationship suggests BDNF's potential as a biomarker for stroke severity.⁴⁴ Spontaneous motor recovery often occurs after ischemic events, with significant progress seen in the first 30 days, continuing over the next 30 to 90 days.³³ BDNF plays a crucial role in this early motor recovery by resolving acute metabolic depression, enabling other muscle groups to execute motor tasks, and facilitating local and distant rewiring of the central nervous system.⁴³⁻⁴⁵ Additionally, BDNF helps adapt the activity of intracortical and corticofugal excitatory pathways necessary for motor task execution, regulating long-term potentiation (LTP) at glutamatergic synapses.^{46,47}

Our review highlights the established role of BDNF in neurorehabilitation, while also revealing a critical gap: the scarcity of studies examining its direct impact on trunk control following stroke. Although the reviewed studies consistently demonstrated improvements in balance and functional independence following targeted rehabilitation interventions, the role of BDNF in trunk control recovery remains largely speculative. Improvements in balance and gait parameters, often used as surrogate measures for trunk stability, may suggest the importance of neuroplasticity interventions and BDNF-driven neuroplasticity;^{31,33} however, this connection remains unproven and requires direct validation. Additionally, the variability in neurotrophic responses indicates that factors such as intervention type, timing, and intensity could influence outcomes.³³ Another limitation of the reviewed studies is their focus on relatively stable and functionally capable patients, which restricts findings to those with moderate stroke impairments.

This gap in the literature highlights a critical area for future research, emphasising the need for targeted investigations exploring the direct relationship between serum BDNF and direct trunk control recovery outcomes. While BDNF is widely recognised for its role in neuroplasticity and motor recovery, its potential to facilitate early ambulation and enhance trunk recovery in stroke patients warrants further exploration.³ Integrating serum BDNF as a biomarker could aid in developing personalised rehabilitation strategies for stroke survivors. Additionally, other neurotrophic biomarkers, such as nerve growth factor (NGF) and insulin-like growth factor-1 (IGF-1), have shown associations with post-stroke recovery and may complement BDNF in a multimodal biomarker approach.³² Future studies could incorporate these biomarkers alongside trunk-specific assessments to better characterise neuroplastic potential.

LIMITATIONS

This review has several limitations that should be considered. First, the scarcity of studies directly investigating BDNF's role in post-stroke trunk control

restricts the generalisability of our findings. The available evidence is further limited by geographic underrepresentation, highlighting the need for more diverse, globally inclusive research. Second, our search strategy, which focused on major electronic national library databases, may have missed relevant studies in grey literature or less accessible sources, potentially omitting valuable insights. Additionally, this review specifically examined trunk control and excluded studies on BDNF's effects in upper or lower limb rehabilitation, which may have provided indirect evidence relevant to trunk recovery. Finally, newly published studies after our search cutoff were not included, possibly overlooking recent advancements in this field.

Implications for future work

Future research should prioritise direct investigations into the relationship between serum BDNF levels and trunk-specific recovery following stroke. Studies should integrate direct trunk control assessments such as the Trunk Impairment Scale, while simultaneously measuring BDNF concentrations to establish potential correlations. Standardised protocols are needed to examine how neurotrophic factors, including BDNF, NGF, and IGF-1, collectively influence trunk control mechanisms during rehabilitation. Future trials should also expand participant selection to include individuals with severe stroke impairments and complex comorbidities, as current evidence remains limited to moderately affected populations. Additionally, multicentre collaborations across diverse geographic regions would enhance the generalisability of findings and address current disparities in representation. Such studies should also explore the optimal timing, duration, and intensity of BDNF-modulating interventions, including both neuromodulation techniques and physical therapies, to maximize functional recovery. By addressing these gaps, researchers can better elucidate BDNF's potential as both a biomarker and therapeutic target, thus informing more personalised and effective rehabilitation strategies for stroke survivors with trunk control deficits.

CONCLUSION

The reviewed studies collectively highlight the relevance of serum BDNF in improving balance and functional outcomes after stroke. However, the lack of direct trunk control measures represents a significant gap. This review reveals the lack of available studies investigating the influence of serum BDNF levels on trunk control after stroke. Clinicians and researchers should prioritise exploring these areas to develop more effective interventions and enhance the quality of life for individuals recovering from stroke.

ACKNOWLEDGEMENT

The authors would like to thank 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.

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Exploring the Role of The Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) Diet on Psychological Disorders in Adults: A Scoping Review

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ABSTRACT

Psychological disorders are a major global health concern, affecting millions of adults worldwide. The Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet has emerged as a potential dietary approach for reducing the risk of psychological disorders. This scoping review aimed to map and synthesize the existing evidence on the association between MIND diet adherence and psychological disorders among adults. This review followed the Arksey and O'Malley (2005)'s framework and the PRISMA-ScR 2020 guidelines. Four databases (Scopus, Web of Science, PubMed, and the Cochrane Library) were searched. Of 236 records identified, 17 studies met the inclusion criteria (eight cross-sectional, five cohort, one case-control, and three randomized controlled trials (RCTs)). Most studies were conducted in Asia, particularly Iran, China and Pakistan. Three cross-sectional studies reported higher MIND diet adherence was associated with lower depression and anxiety, while one study demonstrated significant reductions in depression, anxiety and stress. However, other studies found no significant association with stress. Cohort study findings were inconsistent, with most reporting weak or non-significant associations, although two studies observed reduced depressive symptoms with higher MIND diet adherence. Two RCTs found no significant effects on psychological outcomes, whereas one reported significant improvements in depression and anxiety. The case-control study demonstrated an inverse association between MIND diet adherence and anxiety disorders. Although current evidence suggests that MIND diet adherence may improve psychological health, findings remain inconsistent across study designs. Further high-quality longitudinal studies and well-designed RCTs are needed to establish its effectiveness in preventing and managing psychological disorders in adults.

Keywords

MIND diet, psychological disorder, mental health, depression, anxiety

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Received: 24th December 2025; Accepted:
7th August 2026

Doi:
<https://doi.org/10.31436/10.31436/imjm.v25i04/2959>

INTRODUCTION

Psychological disorders are mental conditions that affect cognition, emotion, behaviour, and brain function, leading impairing daily functioning.¹ Common psychological disorders include depression, anxiety

disorders, and attention-deficit/hyperactivity disorder (ADHD). Although neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease may co-exist or influence psychological symptoms, they are distinct

disorders with different underlying pathologies.² It is estimated that more than 300 million people worldwide, representing approximately 4.4% of the global population, experience major depressive disorders, while a similar number are affected by anxiety disorders, which frequently co-occur with depression.³ Furthermore, the Global Burden of Disease (GBD) Study found that approximately 970 million people, or one in eight individuals worldwide, were living with a psychological disorder in 2019.⁴ In Malaysia, the National Health and Morbidity Survey (NHMS) 2023 reported that the prevalence of depression has doubled since 2019, affecting approximately one million people (4.6% of individuals aged 15 and above). Alarming, nearly half of those affected reported experiencing thoughts of self-harm or suicide, particularly among individuals aged 16-29 years.⁵

Dietary habits and healthy lifestyle practices play important roles in promoting overall health and preventing psychological disorders.⁶ However, identifying the most effective dietary pattern for maintaining brain health remains an active area of research. Evidence suggests that dietary components such as nuts, berries, fish, and the Mediterranean dietary pattern possess neuroprotective properties compared with the Western dietary pattern.⁷ The Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet combines key components of the Mediterranean diet and the Dietary Approaches to Stop Hypertension (DASH) diet.⁸ The MIND has been proposed as a modifiable lifestyle strategy to promote brain health and cognitive function. The MIND diet is rich in nutrients with anti-inflammatory and antioxidant properties, including lutein, zeaxanthin, vitamin E, and folate, which are believed to contribute to neuroprotection and cognitive health.⁹

In recent years, growing evidence has demonstrated that both the Mediterranean and DASH dietary patterns are associated with improved psychological well-being. The MIND diet emphasizes a high consumption of leafy greens, berries, olive oil, nuts, whole grains, legumes, and

other plant-based foods.¹⁰ Conversely, it limits the consumption of foods derived from animals and foods high in saturated fat, such as red meat, and its byproducts, butter, cakes, including pastries.¹¹ Although previous studies have highlighted the beneficial effects of the MIND diet on cognitive health,^{8,12,13} its potential role in preventing or managing psychological disorders, including depression and anxiety, remains less well established, particularly across diverse populations. Therefore, this scoping review aims to synthesize existing evidence on the association between adherence to the MIND diet and psychological disorders among adults and to evaluate its potential as a dietary strategy for promoting mental health.

METHODOLOGY

This scoping review has been performed relying on the framework outlined by Arksey and O'Malley (2005) and in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.^{14,15} A PRISMA diagram detailing the review process is included. The review process followed five stages, as described below. The review protocol was submitted for registration on the Open Science Framework on 16 July 2024 (Registration number: osf.io/zp3da).

Identifying Research Questions

This review aims to map the existing literature on the MIND diet's association with psychological outcomes in adults, using a scoping review framework to identify knowledge gaps and guide future research. The research question was formulated to guide the review and identify relevant research. As a result, the main question of the review is – what is the association between adherence to the MIND diet and psychological disorders among adults? was the basis for this scoping review.

Identifying Relevant Studies

Search Strategy

This scoping review queried four databases: Scopus, Web of Science (WoS), PubMed, and Cochrane Library

for studies published between 2015 and 2025 to systematically identify relevant publications. The PICO (Population, Intervention, Comparator, and Outcome) guided the selection criteria, focusing on adults with psychological disorders as the target population, MIND diet as the intervention, and psychological disorders as the outcome which are detailed in Appendix 1. Reviewers meticulously analysed Medical Subject Headings (MeSH) for important terms associated with the MIND diet, psychological disorders, and adults. Truncation and wildcard parameters, including Boolean connectors “AND/OR” techniques, were applied to ensure that the search focused on the specific key terms. The search string employed in this review is detailed in Appendix 2.

Study Selection

Inclusion Criteria:

- Studies reporting on the MIND diet and psychological disorders
- Peer-reviewed full-text articles published in English between 2015 - 2025
- Studies with adult participants (≥18 years)

Exclusion Criteria:

- Editorials, reviews, abstracts only publications
- Non-human studies
- Non-English publications

Two reviewers independently screened titles and abstracts, followed by full-text assessment. Discrepancies were resolved through discussion or consultation with a third reviewer.

Charting the Data

All the selected data gathered from the journal databases were categorized utilizing EndNote software. A standardized data extraction form was developed and pilot-tested by the review team to ensure consistency and accuracy, and this form was subsequently used to extract all relevant variables from the included studies. The extracted information includes the author(s), publication year, study objectives and purposes, and

participants' characteristics - age, study design, settings, duration of study, study populations, features, outcomes, and findings.

Collating, Summarizing and Reporting Results

Following the Arksey and O'Malley (2005) guideline, the final step involved organizing the relevant findings according to the review questions, with a focus on the relationship that exists between the MIND diet and psychological disorders in adults. Figure 1 presents the flow diagram for this scoping review, which outlines the studies considered for this work.

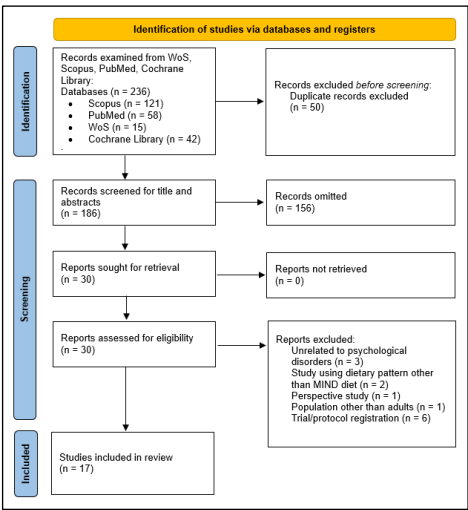


Figure 1: The PRISMA 2020 for association between MIND diet with psychological disorders among adults.

RESULTS

Characteristics of the Selected Studies

Table I displays the characteristics of the selected studies, which were published between 2019 and 2024. Note that the research designs include eight (47.1%) cross-sectional studies, five (29.4%) cohort studies, three (17.6%) randomized clinical trials, and one (5.9%) case-control study. While most studies included both men and women, encompassing adults and older adults, only two studies focused exclusively on women. Besides, most studies were also conducted in Iran and were primarily cross-sectional (8 of 17). The sample sizes varied from 52 to 15,980 participants, with age spanning from 18 to 79 years old.

Author(s) (Year)	Country	Study Design	N	Participants	Age Range (Mean Age)
Ardekani <i>et al.</i> (2023)	Iran	Cross-sectional study	339	Obese adults	20 to 50 years (40.6 years)
Barkhordari <i>et al.</i> (2022)	Iran	Cross-sectional study	7165	Adults	20 to 70 years
Seifollahi <i>et al.</i> (2022)	Iran	Cross-sectional study	282	Obese and overweight women	18 to 56 years (36.5 years)
Rostami <i>et al.</i> (2022)	Iran	Cross-sectional study	400	Health professional males	- (38.7 years)
Haghighatdoost <i>et al.</i> (2020)	Iran	Cross-sectional study	2818	Adults	-
Salari-Moghaddam <i>et al.</i> (2019)	Iran	Cross-sectional study	3176	Adults	18 to 55 years
Kamrani <i>et al.</i> (2024)	Iran	Cross-sectional study	4579	Healthy government employees	30 to 70 years
Kabiri <i>et al.</i> (2024)	Iran	Randomized clinical trial	52	Women with PCOS	18 to 45 years
Lawrie <i>et al.</i> (2023)	United Kingdom	Cross-sectional study	162	Adults diagnosed with Parkinson's Disease	- (62.0 years)
Ma <i>et al.</i> (2023)	United Kingdom	Randomized controlled trial	314	Healthy individuals	18 to 79 years (40.6 years)
Arshad <i>et al.</i> (2024)	United Kingdom	Cohort study	4824	Civil servants	35 to 55 years
Wang <i>et al.</i> (2023)	China	Cohort study	2724	Older adults	>65 years
Yau <i>et al.</i> (2022)	China	Randomized controlled pilot study	72	Older adults with hypertension	> 50 years (66.9 years)
Cherian <i>et al.</i> (2021)	United States	Cohort study	709	Older adults	- (80.4 years)
Cherian <i>et al.</i> (2022)	United States	Cohort study	86	Older adults with history of stroke	- (82.0 years)
Torabynasab <i>et al.</i> (2023)	Pakistan	Case-control study	255	85 patients with anxiety disorders 170 healthy adults	18 to 60 years
Fresan <i>et al.</i> (2019)	Spain	Cohort study	15,980	University graduates	-

Table I: General characteristics for the selected studies ($n=17$)

Construction of the MIND Diet Scores in the Selected Studies

Table II summarize the comparison of food components between the primary version of the MIND diet and those used in the selected studies. Originally, the primary MIND diet consisted of 15 components, having 10 brain-healthy and 5 brain-unhealthy food groups being studied.⁸ In the chosen studies, the primary MIND diet was also utilized with elimination of certain food groups. Wine is eliminated in most of the selected studies, due to insufficient data on wine consumption; and the prohibition of consuming wine in the study population.¹⁶⁻²⁴ Besides, four studies eliminated the component of olive oil consumption due to limited information as well.^{18,20,22,25} The rest of selected studies considered all components in the primary MIND diet.

Table III presents the tools in which the MIND diet scores are estimated in the selected studies. Eight cross-sectional studies (47.1%) used a validated semi-quantitative food frequency questionnaire to estimate the participants' dietary intake, which the authors have indicated that the food frequency questionnaires are reliable and validated to be applied in the study populations.^{16-20,23,26,27}

Type and Its Assessment of Psychological Disorders

This review identified several psychological disorders that were examined in association with the MIND diet, as demonstrated in Table 3. The most commonly studied disorders were depression and anxiety, which were assessed in multiple studies.^{16,17,19-31} Additionally, stress was also evaluated in several studies.^{16,17,19,23,24,26} Other psychological outcomes investigated included sleep disorders, mood disorders, day-time sleepiness, insomnia, psychosomatic complaints, and psychological distress. A variety of validated assessment tools were employed to measure psychological disorders across the studies. The Depression Anxiety Stress Scales (DASS-21) is commonly utilized to evaluate anxiety, depression, and stress.^{16,17,19,23,24,26}

The Association between MIND Diet and Psychological Disorders

Table III provides a summary regarding the results of the selected research. Of the 17 studies incorporated in this review, 15 explored the connection between the MIND diet and psychological outcomes, for example, anxiety, depression, or stress. Notably, among the eight cross-sectional studies, three studies found substantial associations between the MIND diet and depression, two studies reported significant associations with anxiety, and one study found a significant association with stress.^{16-20,23,26,27} In addition, five cohort studies also explored these psychological outcomes.^{22,25,28,29} Among them, only two found a relevant association between the MIND diet and depression. Three RCTs were included however only one recorded a substantial association between the MIND diet with depression

Table II: Comparison of food components in primary MIND diet and selected studies

Selected studies	MIND diet Food Components														
	Whole grains	Green leafy vegetables	Other vegetables	Berries	Olive oil	Fish (not fried)	Beans	Nuts	Poultry (not fried)	Wine	Pastries and sweets	Butter, margarine	Cheese	Red meat and products	Fried/fast foods
Morris <i>et al.</i> (2015)*	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Barkhordari <i>et al.</i> (2022)	✓	✓	✓	✓	✓	✓	✓	✓	✓	X	✓	✓	✓	✓	✓
Torabynasab <i>et al.</i> (2023)	✓	✓	✓	✓	✓	✓	✓	✓	✓	X	✓	✓	✓	✓	✓
Seifollahi <i>et al.</i> (2022)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Fresan <i>et al.</i> (2019)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Ardekani <i>et al.</i> (2023)	✓	✓	✓	✓	✓	✓	✓	✓	✓	X	✓	✓	✓	✓	✓
Rostami <i>et al.</i> (2022)	✓	✓	✓	✓	✓	✓	✓	✓	✓	X	✓	✓	✓	✓	✓
Haghighatdoost <i>et al.</i> (2020)	✓	✓	✓	✓	X	✓	✓	✓	✓	X	✓	✓	✓	✓	✓
Salari-Moghaddam <i>et al.</i> (2019)	✓	✓	✓	✓	X	✓	✓	✓	✓	X	✓	✓	✓	✓	✓
Yau <i>et al.</i> (2022)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Cherian <i>et al.</i> (2022)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Cherian <i>et al.</i> (2021)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Wang <i>et al.</i> (2023)	✓	✓	✓	✓	X	✓	✓	✓	X	X	✓	X	X	X	X
Lawrie <i>et al.</i> (2023)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Ma <i>et al.</i> (2023)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Kabiri <i>et al.</i> (2024)	✓	✓	✓	✓	✓	✓	✓	✓	✓	X	✓	✓	✓	✓	✓
Arshad <i>et al.</i> (2024)	✓	✓	✓	✓	X	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Kamrani <i>et al.</i> (2024)	✓	✓	✓	✓	✓	✓	✓	✓	✓	X	✓	✓	✓	✓	✓

*Primary version of the MIND diet; MIND, Mediterranean-DASH Intervention for Neurodegenerative Delay

and anxiety.²⁴ Meanwhile, one case-control study found a significant association between higher MIND diet adherence and lower anxiety.²¹

Regarding dietary intake, four cross-sectional studies, two cohort studies, and one case-control study reported higher fruit and vegetable intake among participants with the highest MIND diet scores. However, significant associations with psychological outcomes (depression, anxiety, or stress) were only found in four studies.^{16,17,21,25} Among the 17 studies, 13 studies incorporated olive oil in their assessment of the MIND diet score. However, only five studies reported significant associations with psychological outcomes, for instance, anxiety, depression, or stress.^{16,17,21,23,24} Apart from that, four studies reported relatively high intake of legumes such as nuts and beans among participants regarding the top quartiles of MIND diet score and found significant associations with depression, anxiety, or stress.^{16,17,21,25} Regarding the intake of unhealthy foods, seven studies reported lower consumption among participants with higher MIND diet scores.^{16-19,21,25,28} However, only four of

these studies found significant associations with depression, anxiety, or stress.^{16,17,21,25}

DISCUSSION

Key Findings

This scoping review examined how adherence to the MIND diet is associated with psychological disorders in adults. Our comprehensive analysis of the literature revealed mixed findings regarding the association between the MIND diet and psychological disorders. While some studies suggest a positive association, the overall findings indicate variability in results. Notably, observational studies tended to show stronger associations than RCTs, possibly reflecting differences in follow-up duration or confounding factors. The review encompassed a range of psychological disorders including stress, sleep disorders, mood disorders, psychosomatic complaints and psychological distress, with depression and anxiety being the most frequently studied.

Table III: Estimation of the MIND diet scores, type of assessment tools, psychological disorders measures and outcomes of the selected research.

Author/ Year/ Country	Estimation of MIND Diet Score	Psychological Disorders Assessment	Psychological Disorders Measured	Outcome
Barkhordari et al. (2022) Iran	178-item Semi- quantitative FFQ	DASS-21 questionnaire	Depression Anxiety Stress	High MIND diet adherence was linked to lower odds concerning depression (OR=0.62, 95% CI 0.40 – 0.96; P=0.02) and anxiety (OR=0.61, 95% CI 0.41-0.91; P=0.01) but indicated no association with stress (OR=0.57, 95% CI 0.28 – 1.14; P=0.83).
Torabynasab et al. (2023) Pakistan	147-item validated FFQ	Generalized Anxiety Disorder-7 (GAD-7) questionnaire	Anxiety	Higher MIND diet adherence significantly reduced the risk concerning anxiety disorders (OR: 0.03, 95% CI: 0.01, 0.09) (p<0.001). Insignificant associations were found between MIND diet adherence and severity regarding depression (OR = 0.87 95%, CI: 0.7–1.09, P = 0.23), anxiety (OR = 1.02, 95% CI: 0.81–1.27, P = 0.86), stress (OR = 0.99 95%, CI: 0.79–1.23, P = 0.92) or sleep quality (OR = 0.99 95%, CI: 0.77–1.27, P = 0.96).
Seifollahi et al. (2022) Iran	Semi- quantitative FFQ	Pittsburgh Sleep Quality Index (PSQI) DASS	Sleep disorders Depression Anxiety Stress	No association was assessed between MIND diet adherence and depression [HR 0.96 (95% CI 0.89, 1.04)].
Fresan et al. (2019) Spain	136-item validated FFQ	Self-reported depression or/and antidepressant medication use at baseline or within the first 2 years upon entry to the cohort.	Depression	Higher MIND diet adherence was correlated to lower stress in fully adjusted model (OR: 0.913; 95% CI: 0.842-0.990). However, no significant correlations were found for depression and anxiety.
Ardekani et al. (2023) Iran	168-item semi- quantitative FFQ	Self-administered DASS-21 questionnaire	Depression Anxiety Stress	MIND diet adherence was associated with better sleep quality (OR for T3 vs. T1: 0.56 (95% CI: 0.34, 0.92), P- trend =0.023) and reduced daytime sleepiness (P- trend<0.05) and insomnia (OR for T3 vs. T1: 0.54 (95% CI: 0.31, 0.93), P trend =0.031), though insignificant correlations were determined for stress, anxiety, or depression (P>0.05).
Rostami et al. (2022) Iran	168-item semi- quantitative FFQ	PSQI DASS Standard questionnaire	Sleep quality Depression Anxiety Stress Day-time sleepiness and insomnia	A non-significant trend towards fewer depressive symptoms was found with higher MIND diet adherence (T3 vs. T1: β = -0.1559 (SE=0.0840, p=0.06); p trend=0.08).
Cherian et al. (2021) United States	144-item semi- quantitative FFQ	10-item version concerning the Center for Epidemiologic Studies Depression (CESD) scale	Depression	No significant difference was found for anxiety or mood disorders after MIND diet intervention.
Yau et al. (2022) Hong Kong	163-item semi- quantitative Harvard FFQ	Self-reported Chinese questionnaires regarding State and Trait Anxiety Inventory (STAI) The Profile of Mood States Short Form (POMS-SF)	Anxiety Mood disorders	

Cont.

Wang et al. (2023) China	100-item non- quantitative FFQ	100-item non- quantitative FFQ	Depression	Higher MIND diet adherence minimized the risk of depression, especially in older adults exposed to indoor pollution (HR: 1.72, 95% CI: 1.24,2.38).
Haghighatdoost et al. (2020) Iran	106-item self- completed dish-based FFQ	Self- administered Persian validated questionnaire	Psychosomatic complaints	Highest adherence to the MIND diet possessed lower risk of psychological complaints (OR = 0.60, 95% confidence interval (CI): 0.42, 0.86; P trend < 0.0001), and pharyngeal-respiratory (OR = 0.57, 95% CI: 0.41, 0.79; P = 0.002).
Salari- Moghaddam et al. (2019) Iran	106-item semi- quantitative dish-based FFQ	Iranian validated version of Hospital Anxiety and Depression Scale (HADS) General Health Questionnaire (GHQ)	Depression anxiety Psychological distress	Highest adherence to the MIND diet possessed lower odds of depression (OR = 0.68, 95% CI: 0.53-0.89) and psychological distress (OR = 0.68, 95% CI: 0.52–0.89). However, there was no significant correlation with anxiety.
Ma et al. (2023) United Kingdom	Positive and Negative Affect Schedule (PANAS) questionnaire	Positive and Negative Affect Schedule (PANAS) questionnaire	Mood	Highest adherence to the MIND diet possessed lower odds of depression (OR = 0.68, 95% CI: 0.53–0.89) and psychological distress (OR = 0.68, 95% CI: 0.52–0.89). However, there was no significant correlation with anxiety.
Cherian et al. (2022) United States	144-item semi quantitative FFQ	10-item version of the CESD scale	Depression	Insignificant differences were found between tertiles of MIND diet adherence and depressive symptoms in stroke survivors (P = 0.34), even after adjusting for confounding variables.
Lawrie et al. (2023) United Kingdom	130-item semi- quantitative European Prospective Investigation into Cancer FFQ (EPIC FFQ)	Beck Depression Inventory HADS Epworth Sleepiness Scale Unified Parkinson's Disease Rating Scale (UPDRS)	Depression Anxiety Daytime sleepiness Sleep problems	Insignificant correlations were found between the MIND diet and depression, anxiety, sleep problems, or daytime sleepiness.
Kabiri et al. (2024) Iran	3-day food record	Iranian- validated DASS-21 questionnaire	Depression Anxiety Stress	MIND diet resulted in substantial decreases in depression and anxiety scores (P = 0.011 and P = 0.024, respectively), having no substantial changes regarding stress score (P = 0.689) in comparison to the control group.
Arshad et al. (2024) United Kingdom	127-item food frequency questionnaire	CESD scale	Recurrent depressive symptoms	Highest adherence to the MIND diet possessed lower odds of recurrent depressive symptoms (OR = 0.74, 95% CI: 0.58 to 0.93) after adjusting for potential confounders.
Kamrani et al. (2024) Iran	118-item semi- quantitative food frequency questionnaire (FFQ)	DASS-21 questionnaire	Depression Anxiety Stress	Depression, Anxiety Stress, Highest adherence to the MIND diet had substantially lower risks concerning depression (OR: 0.611, 95% CI: 0.447–0.836; P=0.005), anxiety (OR: 0.559, 95% CI: 0.418-0.746; P<0.001), and stress (OR: 0.629, 95% CI: 0.419–0.944; P=0.008).

FFQ, Food Frequency Questionnaire; MIND, Mediterranean-DASH Intervention for Neurodegenerative Delay; OR, Odd Ratio; CI, Confidence Interval; HR, Hazard Ratio.

Associations of MIND diet and Psychological Disorders

This review found both positive and inconclusive associations, varying by study design and psychological outcome. While some studies demonstrate promising connections between higher MIND diet scores and a lower risk or severity of certain psychological disorders, others show mixed or inconclusive results. Table IV summarises the findings on the MIND diet and psychological disorders based on the research's outcomes included.

This review illuminated that the MIND diet may offer unique advantages over other dietary patterns due to its emphasis on neuroprotective components such as berries and green leafy vegetables. The MIND diet distinguishes itself from other dietary patterns through its recommendation for consumption of berries, which have lots of antioxidants, instead of other fruits (suggested in the Mediterranean and DASH diets) and emphasizes the importance of consuming green leafy vegetables, which are packed with vital nutrients. Saghafian et al. (2018) found that vegetable and fruit intake was positively linked to a lower risk concerning depression.³² The high levels of minerals, vitamins, and polyphenols in berries and green leafy vegetables help protect against free radicals.³³ These foods, key components with regard to the MIND diet, are abundant in antioxidants as well as possess anti-inflammatory properties (such as Vitamin E). They also contribute to the inhibition of β -amyloid deposition (via folate, Vitamin E, carotenoids, and flavonoids) and prevent neurotoxic cell death (through flavonoids, Vitamin E), demonstrating their beneficial and direct connection to mental health.³⁴ These effects may be mediated by antioxidant and anti-inflammatory pathways, though causal mechanisms remain speculative and require further investigation.

However, given the high cost and limited availability of berries in Asia markets, the direct adoption of the original MIND diet may not be fully appropriate for Southeast Asian populations. Previous work adapting

the MIND diet for Malaysia (MY-MINDD©) has already addressed this issue by replacing the berries group with locally available, flavonoid-rich fruits such as dried prunes, roselle, raisins, pomegranate, red dragon fruit, and pink guavas.¹⁰ These fruits contain substantial amounts of anthocyanins, flavonoids, and other neuroprotective bioactive compounds comparable to those found in berries.

The findings of this review demonstrate that the MIND diet consistently emphasizes fish consumption, with all included studies incorporating fish as a key component. Reduced fish consumption appears to be linked to an increased incidence of depression.³⁵ Fish is a primary dietary source of omega-3 polyunsaturated fatty acids (PUFAs), which have been discovered to influence inflammatory pathways and neurotransmitter function, which are critical in managing depressive symptoms.^{36,37} Besides, whole grains are an essential element of the MIND diet, consistently included in all selected studies. Whole grains are high in bioactive compounds, comprising fiber, vitamins B and E, antioxidants, magnesium, and phytoestrogens, which have been proven to lower the risk concerning psychological disorders.³⁸ El Mikkawi et al. (2024) revealed that a strong adherence to the Mediterranean diet, which is marked by a high intake of whole grains, was linked to lower anxiety and stress level.³⁹ Whole grain consumption may reduce insulin resistance, which is linked to improved mood and reduced anxiety.⁴⁰

Majority of the selected studies considered olive oil in the MIND diet. According to RCT, numerous observational studies have found a negative relationship between olive oil consumption and the risk of depression.⁴¹ Moreover, olive oil, an essential part of the Mediterranean diet, has been associated with a reduced risk of depression according to a longitudinal analysis and randomized trial.⁴² The monounsaturated fatty acids and bioactive phenolic compounds found in olive oil are probably responsible for its biological effects in combating depression and mood disorders.⁴¹ Legumes are abundant in bioactive compounds having anti-

Table IV: Summary of findings

Selected studies	Study design	Associations of MIND diet and Psychological Disorders								
		Depression	Anxiety	Stress	Sleep disorders	Day-time sleepiness	Insomnia	Mood disorders	Psychosomatic complaints	Psychological distress
Salari-Moghaddam <i>et al.</i> (2019)	Cross-sectional	– ^a	=	NA	NA	NA	NA	NA	NA	– ^a
Haghighatdoost <i>et al.</i> (2020)	Cross-sectional	NA	NA	NA	NA	NA	NA	NA	– ^a	NA
Barkhordari <i>et al.</i> (2022)	Cross-sectional	– ^a	– ^a	=	NA	NA	NA	NA	NA	NA
Scifollahi <i>et al.</i> (2022)	Cross-sectional	=	=	=	=	NA	NA	NA	NA	NA
Rostami <i>et al.</i> (2022)	Cross-sectional	=	=	=	– ^a	– ^a	– ^a	NA	NA	NA
Ardekani <i>et al.</i> (2023)	Cross-sectional	=	=	– ^a	NA	NA	NA	NA	NA	NA
Lawrie <i>et al.</i> (2023)	Cross-sectional	=	=	NA	=	=	NA	NA	NA	NA
Kamrani <i>et al.</i> (2024)	Cross-sectional	– ^a	– ^a	– ^a	NA	NA	NA	NA	NA	NA
Fresan <i>et al.</i> (2019)	Cohort	=	NA	NA	NA	NA	NA	NA	NA	NA
Cherian <i>et al.</i> (2021)	Cohort	=	NA	NA	NA	NA	NA	NA	NA	NA
Cherian <i>et al.</i> (2022)	Cohort	=	NA	NA	NA	NA	NA	NA	NA	NA
Wang <i>et al.</i> (2023)	Cohort	– ^a	NA	NA	NA	NA	NA	NA	NA	NA
Arshad <i>et al.</i> (2024)	Cohort	– ^a	NA	NA	NA	NA	NA	NA	NA	NA
Yau <i>et al.</i> (2022)	RCTs	NA	=	NA	NA	NA	NA	=	NA	NA
Ma <i>et al.</i> (2023)	RCTs	NA	NA	NA	NA	NA	NA	=	NA	NA
Kabiri <i>et al.</i> (2024)	RCTs	– ^a	– ^a	=	NA	NA	NA	NA	NA	NA
Torabynasab <i>et al.</i> (2023)	Case-control	NA	– ^a	NA	NA	NA	NA	NA	NA	NA

^asignificant association with MIND diet; – negative/inverse association with MIND diet; = no difference/association

inflammatory properties, essential for reducing inflammation and oxidative stress. Other than that, they provide valuable protein, minerals, vitamin B, as well as beneficial phytochemicals with biological effects.¹⁰ A study examining the link between the Dietary Phytochemical Index (DPI) and psychological disorders found that a higher intake of phytochemical-rich foods was inversely related to the likelihood of experiencing depression and anxiety symptoms.⁴³

Moreover, the MIND diet comprises limited amounts of unhealthy foods. It includes butter, red meat, fried/fast foods, pastries, and sweets which promote inflammation and oxidative stress, that may be damaging to brain health.⁸ The intake of butter, red meat, and margarine has been discouraged in MIND diet. Many prospective research works have examined a correlation between a diet low in saturated and trans-unsaturated (hydrogenated) fats, which slows the rates of psychological disorders.^{44–46} Frying, as a cooking method, greatly reduces the levels of n-3 and n-6 fatty acids.⁴⁷ Long-term exposure to acrylamide, a common contaminant in fried foods, encourages lipid peroxidation as well as oxidative stress, which

contributes to neuroinflammation in the brain that may lead to psychological disorders.⁴⁸ Excessive consumption of sweets/sugar can also disrupt insulin and glucose metabolism. It increases neuroinflammation and oxidative stress, leading to structural changes in the brain which would impact mental health.¹²

The Potential Role of MIND diet in Sleep Disorders

Among the studies reviewed, only one explored the correlation that exists between the MIND diet and sleep disorders, discovering a significant association. Sleep is a critical component of overall well-being and disruptions in sleep have been linked to a variety of psychological disorders.^{49,50} High intake of MIND diet food components, vegetables, beans, berries and whole grains, was linked to improved sleep quality, with reduced insomnia and daytime sleepiness.¹⁹ The MIND diet, rich in anti-inflammatory components like omega-3 fatty acids found in walnuts and fish, folate in green leafy vegetables, vitamin E in olive oil and nuts, and flavonoids in berries, may provide stronger anti-inflammatory effects than Mediterranean or DASH diets alone.⁵¹ Therefore, the MIND diet could serve a practical function in enhancing sleep quality and possibly

reducing the risk of sleep disorders. This underscores the necessity for further research exploring the correlation that exists between the MIND diet and sleep disorders.

STRENGTHS

This review possesses several notable strengths. First and foremost, this review lies in its comprehensive coverage of research conducted since the MIND diet's establishment in 2015. By focusing on studies from this period, it provides a timely and relevant snapshot of the emerging evidence linking the MIND diet to psychological disorders, ensuring that the analysis reflects the most current insights in this evolving field. Besides, the inclusion of studies that span various psychological disorders like depression, anxiety, stress, and sleep disturbances, offering a comprehensive understanding with regard to the possible impacts concerning the MIND diet. Additionally, the variety of study designs (e.g., cross-sectional studies, RCTs, and cohort studies) enhances the analysis by integrating diverse methodological perspectives and results. While the benefits of the MIND diet for cognitive health were extensively studied, this is among the first reviews that specifically focus on its link to psychological disorders like depression, anxiety, and stress.

LIMITATIONS

Upon reviewing the current literature on the MIND diet and psychological disorders, several studies reported no significant associations. This heterogeneity among the included studies could be due to variations in sample size, participant characteristics, and health status, differences in the FFQ employed to examine food intake and the psychological health assessment questionnaires, and the methods for calculating MIND diet scores. Besides, most studies focus on depression and anxiety, leaving other psychological disorders comparatively understudied. For instance, there is limited research on the MIND diet's effects on bipolar disorder, schizophrenia, or eating disorders.

Furthermore, most studies use cross-sectional designs, which are unable to determine causality or investigate the long-term effects concerning the MIND diet with regard to mental health. Longitudinal studies are scarce, with only a few examining outcomes over time.^{28,29} Apart from that, there is a shortage of RCTs that could provide stronger evidence for the diet's efficacy. There is also limited exploration concerning the potential mechanisms through which the MIND diet could impact mental health, including its effects on inflammation, oxidative stress, or gut microbiota. Therefore, addressing these gaps in future research would significantly enhance our comprehension regarding the MIND diet's role in psychological health.

CONCLUSIONS

This scoping review highlights the potential roles of the MIND diet in reducing the risk of psychological disorders, particularly depression, anxiety, and stress. Although the available evidence suggests promising associations, the underlying mechanisms through which the MIND diet influences psychological health remain unclear. Future research should focus on elucidating these biological and behavioural mechanisms, particularly across diverse populations and cultural. In addition, investigating the role of gut microbiota modulation and the gut–brain axis may provide valuable insights into the relationship between the MIND diet and psychological health. Further, integrating the MIND diet into dietary guidelines could serve as a preventive strategy for mental health, particularly in populations at higher risk for psychological disorders.

FUNDING

This study is funded by Universiti Kebangsaan Malaysia under the Research University Grant (GUP-2024-019).

CONFLICT OF INTEREST

The authors acknowledge no conflict of interest.

ACKNOWLEDGEMENTS

I sincerely thank all the co-authors for their contributions to this review and the research team for their unwavering dedication and support.

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Mapping the Research Landscape of Ambulatory Blood Pressure Monitoring in Pregnancy (2000-2025): A Bibliometric Study

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ABSTRACT

Ambulatory blood pressure monitoring (ABPM) has gained recognition as a valuable tool for diagnosing and managing hypertensive disorders during pregnancy. However, the research landscape and emerging trends in this field have not been comprehensively mapped. This study aimed to conduct a bibliometric analysis to evaluate global research trends, scientific productivity, collaboration patterns, and thematic developments related to ABPM in pregnancy. Publications were retrieved from the Scopus database and analysed using bibliometric mapping and visualisation tools. Bibliometric indicators included publication output, citation patterns, co-authorship networks, and keyword co-occurrence analyses to identify research themes and emerging trends. The analysis revealed 148 original articles and 26 reviews from 2020-2025. Research productivity increased steadily over the past two decades, with the United States, United Kingdom, Spain, and Australia emerging as the most influential contributors. Collaboration networks revealed strong regional clusters, particularly across Europe, with the United States serving as a central hub for international partnerships. Keyword analysis identified five thematic clusters: clinical aspects of ABPM, pregnancy complications and outcomes, cardiovascular and metabolic risk factors, maternal–foetal characteristics, and methodological and interventional studies. Term co-occurrence analysis highlighted interconnected themes spanning maternal outcomes, cardiovascular risk predictors, and clinical management. Research on ABPM in pregnancy has expanded in scope and depth, reflecting its growing clinical importance. Nonetheless, contributions remain concentrated in high-income countries, with limited representation from low- and middle-income regions. Future research should emphasise broader international collaboration, standardisation of ABPM protocols, and investigation into long-term maternal and offspring cardiovascular outcomes.

Keywords

Blood Pressure Monitoring, Ambulatory, Hypertension, Pregnancy-Induced, Pre-Eclampsia, Bibliometrics

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Received: 10th September 2025; Accepted:
5th July 2026

Doi:
<https://doi.org/10.31436/10.31436/imjm.v25i04/3068>

INTRODUCTION

Hypertensive disorders of pregnancy (HDP), including pregnancy-induced hypertension (PIH) and pre-eclampsia (PE), remain a leading cause of maternal and

perinatal morbidity and mortality worldwide.¹ Accurate blood pressure measurement is crucial for early detection and risk stratification in this population.

Conventional clinic-based blood pressure monitoring often underestimates true risk due to phenomena such as white-coat and masked hypertension, potentially leading to misclassification of patients.² Ambulatory blood pressure monitoring (ABPM) has emerged as a valuable tool, offering 24-hour assessment of blood pressure variability and nocturnal patterns that are not captured by office readings.³ Recent systematic reviews and meta-analyses have demonstrated that ABPM provides more reliable prognostic information during pregnancy and the postpartum period, with superior predictive value for adverse outcomes compared to clinic measurements.⁴ Additionally, recent narrative reviews emphasise the potential of ABPM in optimising risk stratification and guiding management of HDP.⁵

Ambulatory blood pressure monitoring (ABPM) has emerged as a critical tool in pregnancy, improving detection of masked and white-coat hypertension beyond office readings.^{6,7} Early studies demonstrated its diagnostic value, and recent work has reinforced its role in clinical practice while revealing regional disparities in use.^{8,9} However, a gap persists between evidence and routine obstetric application.¹⁰ Research has advanced from small cohorts to systematic reviews and meta-analyses, strengthening guideline recommendations, while new wearable and digital technologies enable continuous monitoring for personalised care.^{4,11} Increasingly embedded in risk prediction and precision medicine, ABPM is becoming integral to maternal cardiovascular research and the management of HDP.

Despite increasing clinical evidence supporting the utility of ABPM in pregnancy, the broader scientific landscape in this field has not been systematically mapped. Previous systematic reviews and meta-analyses have primarily synthesised clinical outcomes and diagnostic accuracy, while narrative reviews have highlighted methodological considerations and optimisation strategies.^{2,4,5} However, little is known about the publication trends, influential contributors, collaborative networks, and evolving research themes related to ABPM in pregnancy. Without such insights,

it is difficult to identify research gaps, guide funding priorities, or foster global collaboration. A bibliometric analysis is therefore warranted to complement existing clinical syntheses by providing a macroscopic overview of how the field has evolved, who the key contributors are, and where future research directions may be most impactful. This study aims to provide a bibliometric overview of research on ambulatory blood pressure monitoring (ABPM) in pregnancy between 2000 and 2025. Specifically, it examines trends in publications and citations, identifies leading authors, institutions, and countries, and maps patterns of collaboration within the field. In addition, it highlights the most highly cited papers and influential journals while tracing the evolution of research themes to uncover emerging topics and underexplored areas.

This study will address the following research questions:

1. How has research output on ambulatory blood pressure monitoring (ABPM) in pregnancy evolved between 2000 and 2025 in terms of publication and citation trends?
2. Who are the most influential authors, institutions, and countries contributing to this field?
3. What patterns of collaboration exist among researchers, institutions, and countries?
4. Which journals and publications have had the greatest impact on advancing knowledge of ABPM in pregnancy?
5. How have research themes and keywords developed over time, and what emerging areas can be identified for future investigation?

METHODS

This bibliometric analysis investigated trends of ABPM in pregnancy research. We followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) reporting guidelines.¹² We collected data from the Scopus database, a well-regarded source of peer-reviewed publications on 14th August 2025.¹³ The keyword search strings used were as

follows: (TITLE-ABS-KEY ("ambulatory blood pressure") AND TITLE-ABS-KEY (pregnancy)) AND PUBYEAR >1999 AND PUBYEAR <2026 AND (LIMIT-TO (SUBJAREA , "MEDI") OR LIMIT-TO (SUBJAREA , "BIOC") OR LIMIT-TO (SUBJAREA , "NURS") OR LIMIT-TO (SUBJAREA , "HEAL") OR LIMIT-TO (SUBJAREA , "IMMU")) AND (LIMIT-TO (DOCTYPE , "ar") OR LIMIT-TO (DOCTYPE , "re")) AND (LIMIT-TO (LANGUAGE , "English")). In total, we identified 273 documents from the Scopus database in our initial dataset.

Data Screening

We screened the dataset to ensure relevance and accuracy, as shown in Figure 1. Publications unrelated to medicine and health, such as those in mathematics, computer science, and engineering, were excluded, narrowing the final dataset to 266. We also excluded non-empirical materials such as technical reports, letters and editorials, leaving 242 publications. We then restricted the dataset to English-language publications and further narrowed it to 220. Following a thorough review, 174 articles published between 2000 and 2025 were included in the final analysis. The dataset on these publications was exported from Scopus database in comma-separated values (.csv) format for further analyses.

Data Analysis

We carried out data analyses and generated graphic visualisation of our dataset using several tools designed for bibliometric research, which are Scopus analyser and VOSviewer (<http://www.vosviewer.com>) software.¹⁴ The .csv file was imported into VOSviewer. These tools supported the identification of keyword patterns, keyword co-occurrence, citation trends, thematic clusters, and network visualisation to explore research connections and patterns. The resulting dataset offered a clear basis for understanding the relationships and thematic areas within the literature, shedding light on ABPM in pregnancy research.

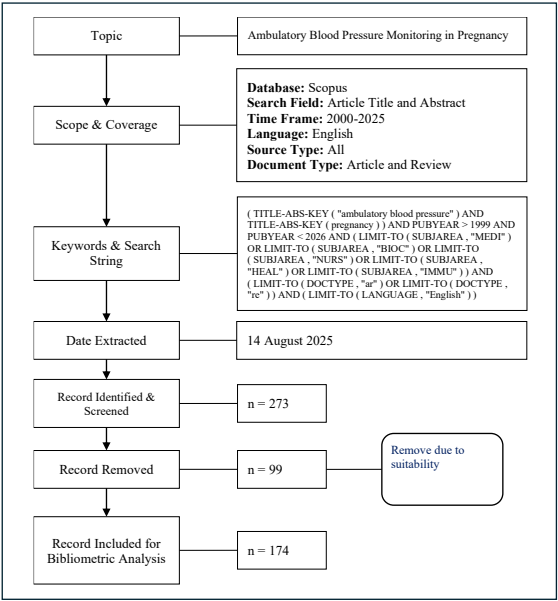


Figure 1: Flow diagram of the search strategy. Source: Zakaria et al. (2021)¹⁵

RESULTS

Publication profiles and trends

We retrieved a total of 148 original articles and 26 reviews. All were journal articles written in English. These articles were published in 101 different journals. Most of the publications covered Medicine (72.1%), Biochemistry, Genetics and Molecular Biology (18.0%), and Nursing (3.4 %) as the topics. The publication trend from 2000 to 2025 shows fluctuating activity with notable peaks in 2001 (12 articles) and 2013 (13 articles), followed by periods of decline. However, from 2018 onwards there has been a sustained increase, with outputs stabilising at a higher level and peaking again in 2018, 2023, and 2024 (Figure 2). This pattern indicates a renewed and growing research interest in recent years.

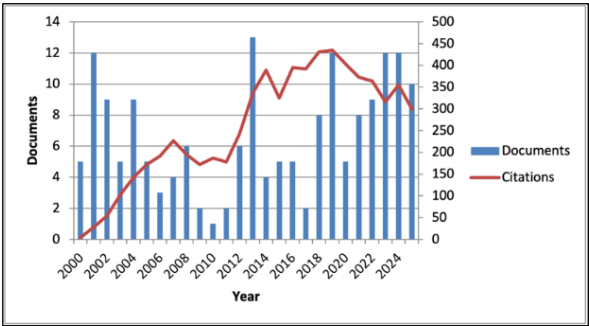


Figure 2: Total Publications and Citations by Year

Citation metrics and highly cited documents

The citation metrics indicate that a total of 155 documents were published on ambulatory blood pressure monitoring in pregnancy between 2000 and 2025, collectively receiving 6,710 citations (Figure 2). This corresponds to an average of approximately 43.3 citations per document. The field has an h-index of 34. Annual citations steadily increased from 2000, peaking between 2013 and 2016 with over 450 citations per year. Although a gradual decline has been observed since, citation levels remain relatively high (300-400 annually).

The most highly cited documents are dominated by guideline and position papers authored by O'Brien et al., including the 2003 European Society of Hypertension (ESH) recommendations, the 2013 ESH position paper, and the 2000 British Hypertension Society recommendations.¹⁶⁻¹⁸ Other influential works on pregnancy-induced hypertension, aspirin chronotherapy in pregnancy, and other studies are listed in Table I.¹⁹⁻²⁵

Publications by Authors, Source, Institutions, and Countries

The most productive authors in this field include Ayala D.E. and Hermida R.C. from the University of Vigo, Spain, each with 13 publications, 449 citations, and an h-index of 10. Brown M.A. from the University of New South Wales, Australia, contributed 9 papers with the highest citation count (488) and the highest citation rate (54.2 per paper; 61 per cited paper), with an h-index of 8. From Argentina, Espeche W.G. and Salazar M.R. of Universidad Nacional de La Plata each published 8 papers, garnering 90 citations (11.3 per paper; 12.9 per cited paper) and an h-index of 5. The most active sources for publications with a minimum of five publications are listed in Table II.

The most productive institution is the University of Vigo (Spain) with 13 publications, 449 citations, and an h-index of 10. In Australia, both St George Hospital and

the University of New South Wales are highly active, each producing 9 papers; the University of New South Wales has the highest citation count (505) and h-index (9), while St George Hospital shows strong impact with 488 citations and a high citation rate per cited paper (61). From Argentina, the Universidad Nacional de La Plata contributed 7 publications with 87 citations and an h-index of 5. Remarkably, although producing only 5 papers, IRCCS Istituto Auxologico Italiano (Italy) achieved exceptional influence with 2,837 citations averaging 567.4 citations per paper and 709.3 per cited paper.

Table I: Top 10 highly cited articles

No.	Authors	Title	Cites	Cites per Year
1	O'Brien et al. (2003) ¹⁶	European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement	1513	58.2
2	O'Brien et al. (2013) ¹⁷	European society of hypertension position paper on ambulatory blood pressure monitoring	1200	46.2
3	O'Brien et al. (2000) ¹⁸	Use and interpretation of ambulatory blood pressure monitoring: Recommendations of the British Hypertension Society	400	15.4
4	Kintiraki et al. (2015) ¹⁹	Pregnancy-Induced hypertension	225	8.7
5	Ayala et al. (2013) ²⁰	Chronotherapy with low-dose aspirin for prevention of complications in pregnancy	164	6.3
6	Higgins & de Swiet (2001) ²¹	Blood-pressure measurement and classification in pregnancy	150	5.8
7	Head et al. (2012) ²²	Ambulatory blood pressure monitoring in Australia: 2011 consensus position statement	119	4.6
8	Lazdam et al. (2012) ²³	Unique blood pressure characteristics in mother and offspring after early onset preeclampsia	109	4.2
9	Brown et al. (2005) ²⁴	The natural history of white coat hypertension during pregnancy	107	4.1
10	Tenhola et al. (2006) ²⁵	Maternal preeclampsia predicts elevated blood pressure in 12-year-old children: Evaluation by ambulatory blood pressure monitoring	100	3.8

Table II: Most active source titles with a minimum of 5 publications

Source Title	TP	TC	Publisher	Cite Score	SJR 2024	SNIP 2020
Journal of Hypertension	17	3193	Wolters Kluwer Health	7.8	1.097	1.634
Pregnancy Hypertension	8	92	Elsevier	5.4	1.102	1.132
Hypertension	7	329	Wolters Kluwer Health	13.1	2.788	2.101
Blood Pressure Monitoring	5	67	Wolters Kluwer Health	2.1	0.330	0.433
Hypertension Research	5	96	Springer Nature	7.0	1.071	1.058
Hypertension in Pregnancy	5	106	Taylor & Francis	2.8	0.522	0.424
Journal of Human Hypertension	5	39	Springer Nature	6.5	0.937	0.943

The United States leads in output with 25 publications and 3,009 citations, with an h-index of 11. Spain follows with 21 publications and 3,212 citations, achieving the highest h-index (13) alongside the United Kingdom, which, despite fewer publications (17), has the strongest citation impact with 3,735 citations. Australia also demonstrates high influence, producing 19 publications with 3,532 citations and the highest h-index (14). Italy contributed 14 papers and 2,964 citations with a moderate h-index of 9, while Argentina, though with 11 publications, recorded only 139 citations and an h-index of 7.

Co-authorship by countries

Analysis of country-level co-authorship revealed strong international collaboration within the field. The United States emerged as the principal collaboration hub, maintaining extensive research partnerships with Spain, the United Kingdom, Australia, and Italy. European countries, including Spain, Italy, the United Kingdom, the Netherlands, Switzerland, and Greece, demonstrated particularly strong regional collaboration, while Australia maintained active links with both Europe and the United States. In contrast, countries such as Argentina, Brazil, Turkey, China, and Canada exhibited comparatively fewer international collaborations. Overall, research in this field is largely driven by collaborative networks spanning North America, Europe, and Australia, with

more limited participation from South America and Asia.

Co-occurrence Analysis

Co-occurrence analysis of author's keywords

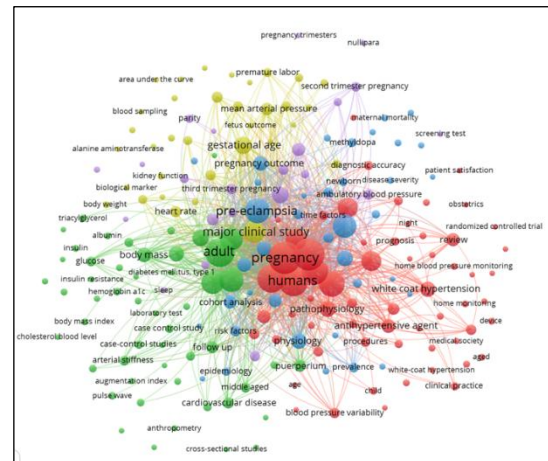


Figure 3: Network visualisation of the author’s keywords

The co-occurrence analysis of author keywords revealed five main thematic clusters (Figure 3). The largest cluster centred on clinical aspects, including humans, pregnancy, antihypertensive agents, pathophysiology, and white coat hypertension. A second cluster focused on pregnancy complications and outcomes, with keywords such as pre-eclampsia, gestational age, pregnancy outcome, and maternal mortality. The third cluster highlighted metabolic and cardiovascular risk factors, including body mass index, glucose, insulin resistance, arterial stiffness, and cardiovascular disease. Another cluster was linked to maternal and foetal characteristics and measurements, such as mean arterial pressure, parity, trimesters of pregnancy, and foetal outcome. The final cluster reflected methodological and interventional studies, with terms like methyl dopa, randomised controlled trial, and screening test.

Co-occurrence analysis of terms based on title and abstract

The network visualisation of term co-occurrence based on title and abstract fields reveals three major thematic clusters (Figure 4). The green cluster is centred on pregnancy-related terms such as delivery, gestational age,

trimester, and normotensive women, reflecting research on maternal outcomes and comparisons between hypertensive and normotensive groups. The blue cluster includes terms like age, body mass index, cardiovascular disease, and arterial stiffness, highlighting demographic and clinical predictors associated with blood pressure variation and cardiovascular risk. Meanwhile, the red cluster comprises terms such as diagnosis, blood pressure measurement, treatment, management, and white coat hypertension, representing studies on the clinical use, diagnosis, and management of hypertension with ambulatory blood pressure monitoring. The strong interconnections across clusters indicate that research in this field integrates maternal health, risk predictors, and clinical management into a closely related body of evidence.

these regions.^{19,21} The dense European collaboration clusters further demonstrate the role of regional networks in accelerating methodological refinement and clinical application of ABPM. Conversely, more limited engagement from South America and Asia suggests barriers such as resource constraints or competing research priorities. Nonetheless, the contributions from Argentina and Brazil indicate growing participation, which may enhance the diversity of study populations and clinical perspectives.^{29,30}

The co-authorship network shows how ABPM research in pregnancy is being shaped through collaborative models. The United States emerges as the central connector, linking researchers across continents, while European countries form a tight-knit cluster of mutual collaboration. Australia holds a bridging position, maintaining strong ties with both Europe and North America. Such patterns reflect a maturing research ecosystem where international partnerships are essential for conducting large-scale studies and validating findings across diverse populations.^{20,27}

Importantly, these collaborative and citation trends align with the trajectory of recent research. Contemporary studies have extended the utility of ABPM beyond diagnosis to risk stratification and long-term follow-up. For example, ABPM has been used to refine the detection of blood pressure phenotypes, optimise monitoring protocols during pregnancy, and characterise postpartum trajectories following HDP.^{5,26,27} These directions illustrate how international collaboration is not only increasing productivity but also fostering innovation in the use of ABPM, which has the potential to change clinical management strategies for women with HDP.

Interpretation of Thematic Trends

The thematic clusters identified through both keyword co-occurrence and title/abstract analysis provide a comprehensive picture of the evolving research landscape on ABPM in pregnancy. The strong presence of pregnancy-related terms such as delivery, gestational

age, trimesters, and normotensive women shows that the central focus is on maternal outcomes and comparisons across hypertensive and normotensive groups. This reflects how ABPM has become an indispensable tool for distinguishing physiological adaptations of pregnancy from pathological conditions, thereby supporting timely diagnosis and management strategies.²⁵⁻³¹ The second thematic focus on demographic and cardiometabolic predictors including age, body mass index, insulin resistance, and arterial stiffness demonstrates a shift toward understanding the broader determinants of HDP. These patterns reinforce pregnancy as a unique “window” into a woman’s future cardiovascular health. For instance, the association of non-dipping blood pressure patterns with higher risk of pre-eclampsia and subsequent hypertension suggests that ABPM offers valuable prognostic insights that extend beyond the perinatal period.^{32,33} Meanwhile, the third cluster centred on diagnosis, blood pressure measurement, treatment, and management highlights the clinical utility of ABPM. This focus indicates that research is not only descriptive but also oriented toward improving practice. The inclusion of terms such as white coat hypertension and screening test reflects the recognition that traditional office-based measurements may be inadequate, and that ABPM provides superior risk stratification for both maternal and foetal outcomes. Such insights align with recent protocols like PREECARDIA, which position pre-eclampsia as a predictor of early-onset cardiovascular disease, thereby broadening the scope of ABPM research from pregnancy-specific care to long-term health surveillance.¹¹ The interconnections across clusters suggest that the field is increasingly interdisciplinary. Maternal health, demographic risk factors, and clinical management are no longer studied in isolation but rather as part of an integrated framework of evidence. This convergence reflects broader global trends in maternal health research, where pregnancy is conceptualised as both a clinical event and a sentinel marker for chronic disease prevention.

The patterns revealed by co-occurrence networks show that ABPM research in pregnancy is at a transitional stage. It is moving from descriptive and clinical applications toward predictive and preventative frameworks, yet still faces gaps in interventional evidence and global applicability.^{34,35} Bridging these gaps through more diverse population studies, technology-driven monitoring, and long-term follow-up will be critical in ensuring that the field delivers on its promise of reducing maternal and cardiovascular risk across the life course.

Future Research Directions

Future research on ABPM in pregnancy should prioritise expanding global participation, as current evidence is largely driven by North America, Europe, and Australia, leaving Asia, South America, and Africa underrepresented despite their high burden of hypertensive disorders.^{11,32} Strengthening international collaborations with regions most affected by HDP would not only enhance external validity but also promote equity in maternal health research.¹¹ Beyond refining diagnostic applications, studies should explore innovative therapeutic approaches and digital health solutions informed by ABPM data, as well as adopt longitudinal designs to clarify how hypertensive changes in pregnancy evolve into long-term cardiovascular risk.⁵ Investigating the effect of maternal comorbidities such as pregnancy-onset obstructive sleep apnoea and extending ABPM beyond the postpartum period for the detection of masked hypertension are also critical directions, particularly given evidence linking non-dipping blood pressure patterns in pregnancy to future hypertension and adverse maternofetal outcomes.^{31,32,36,37}

This study has several limitations that should be acknowledged. This bibliometric analysis was dependent on the coverage and indexing practices of Scopus, which may have excluded relevant publications not indexed or those published in non-English journals. Citation counts are also influenced by the time since publication, potentially underestimating the impact of

more recent studies. Furthermore, co-authorship and co-occurrence analyses capture structural patterns of collaboration and thematic focus but may not fully reflect the quality or clinical impact of the research.

CONCLUSION

This bibliometric analysis highlights the evolving research landscape of ABPM in pregnancy, revealing growing productivity, significant international collaboration, and diverse thematic directions. Citation and productivity metrics indicate that a small number of highly influential studies have shaped the field, while recent increases in output suggest a sustained interest in ABPM as both a diagnostic and prognostic tool for HDP. Collaboration networks reflect the leading role of high-income countries such as the United States, the United Kingdom, Spain, and Australia, with more limited but emerging contributions from South America and Asia. Thematic mapping demonstrates three interconnected research foci: maternal outcomes, cardiovascular risk predictors, and clinical diagnosis and management, reflecting a holistic integration of epidemiology, clinical care, and maternal health outcomes. Together, these findings emphasise that research on ABPM in pregnancy is both multidisciplinary and collaborative, with a strong translational potential for improving risk stratification, diagnosis, and long-term cardiovascular health in women. ABPM research in pregnancy is gaining momentum, bridging clinical care and maternal cardiovascular health, with clear opportunities for broader global engagement and innovation.

FUNDING STATEMENT

This bibliometric analysis is one of the outputs for a study funded by SRG25-124-0124 SASMEC Research Grant.

CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest regarding the publication of this paper.

ACKNOWLEDGEMENT

The authors would like to thank the Departments of Basic Medical Sciences, Obstetrics and Gynaecology, and Internal Medicine, Kulliyah of Medicine, International Islamic University Malaysia, for their support throughout this study. The authors also gratefully acknowledge the research funding provided by Sultan Ahmad Shah Medical Centre @ IIUM (SASMEC@IIUM) and the support of the Department of Education and Research, Sultan Ahmad Shah Medical Centre, in facilitating this research.

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Corpus Callosum Morphometric Analysis in Paediatric Epilepsy: A Retrospective MRI Study

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ABSTRACT

INTRODUCTION: The corpus callosum (CC) plays a central role in interhemispheric communication and seizure propagation. Structural alteration of the CC in paediatric epilepsy has been inconsistently reported, highlighting the need for further comparative morphometric analysis during this critical neurodevelopmental period. This study aimed to evaluate differences in CC morphometry between epileptic and non-epileptic children aged 6-17 years.

MATERIALS AND METHODS: This retrospective case-control study analysed brain magnetic resonance imaging (MRI) scans acquired between July 2023 and October 2024 at a single tertiary hospital, including 50 epileptic and 42 non-epileptic children. CC morphometry, including anterior-posterior diameter, total length, and thickness of genu, body, isthmus, and splenium, was measured on mid-sagittal T2-weighted images. Statistical analyses were performed using the independent t-tests and Mann-Whitney tests as appropriate. **RESULT:** No significant overall differences were found in CC morphometry between epileptic and non-epileptic groups. However, subgroup analysis revealed significantly reduced body thickness in epileptic children aged 12-14 years and shorter total CC length among epileptic females. In contrast, epileptic children without extra-callosal abnormalities showed greater genu thickness compared to non-epileptic controls. These findings were associated with a moderate-to-large effect size (Hedges' $g > 0.6$), suggesting subtle deviations in callosal maturation patterns. **CONCLUSION:** Epilepsy may be associated with region-specific and sex-related variation in CC morphometry during critical stages of brain maturation. Although these differences are subtle and not evident on conventional MRI, quantitative CC morphometry may serve as a complementary, hypothesis-generating approach to investigating neurodevelopmental alterations in paediatric epilepsy.

Keywords

epilepsy, corpus callosum, morphometry, magnetic resonance imaging, paediatric

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Received: 18th October 2025; Accepted: 22nd
May 2026

Doi:
<https://doi.org/10.31436/10.31436/imjm.v25i04/3104>

INTRODUCTION

Epilepsy is the most common chronic neurologic condition that, if left untreated, causes lifelong disability, premature death, carries social stigma, and a significant economic burden on a country. In a developing country, paediatric epilepsy incidence ranges between 33 and 82 cases per 10,000 children. However, this number is often higher due to irregular reporting, diagnostic difficulties,

lack of management standardisation, and limited availability of paediatric neurologists, which worsens the accuracy of diagnosis and reporting of these cases¹. Paediatric epilepsy also often associated with structural abnormalities of the brain, including morphometric changes in the corpus callosum.^{2,3}

The corpus callosum (CC) connects two cerebral hemispheres and facilitates interhemispheric communication. It contributes to seizure generalisation by transmitting unilateral seizure activity to the contralateral hemisphere.^{4,5} CC abnormalities are frequently observed alongside neuronal migration disorders, such as lissencephaly, pachygyria, and hemimegalencephaly during brain development, which disrupt brain structure and increase seizure risk.^{6,7} Vice versa, recurrent seizures in epilepsy can have a profound effect on brain development and function. Understanding the morphometry differences as structural projections between epileptic and non-epileptic children is essential for explaining the neurodevelopmental impact of epilepsy.

Studies examining the relationship between CC structure and epilepsy have a long history. However, studies in pediatric epilepsy were limited, and findings have been inconsistent. In one study, thickened CC was observed in 9 of 37 children aged 7-14 years, with genu, isthmus, and splenium thicknesses exceeding those of the adult CC segment.⁷ Another study reported that an epileptic was found in 14 of 39 subjects with CC dysgenesis, ranging from hypoplasia to agenesis of the CC spectrum.⁸ This inconsistency highlights the need for further investigation into specific methods. By focusing on comparative analysis of CC morphometry between epileptic and non-epileptic paediatric groups, this study aims to understand whether epilepsy affects brain structure during critical developmental periods. Our primary hypothesis is that there is a significant difference in CC morphometry between the two groups, especially with specific age and sex-related factors.

MATERIALS AND METHODS

Study Population

We retrospectively and consecutively included 256 head MRI examinations of children aged 6-17 years who underwent head MRI scans at our center from July 2023 to October 2024. We then stratified them into epileptic and non-epileptic groups based on their clinical

referral information. The study initially excluded one epileptic patient with complete CC agenesis and 163 non-epileptic patients due to their brain parenchymal abnormalities, resulting in 50 epileptic subjects and 42 non-epileptic subjects. The clinical profiles were reviewed from the medical record, including seizure onset and clinical companion. This study was approved by the local Ethics Committee in Human Research (1981/LOE/301.4.2/V/2025) before starting the study.

Data Image and Protocol

We used MRI image data obtained from both 3T (Magnetom SKYRA, Siemens AG Healthcare Sector, Erlangen, Germany) and 1.5T (Optima MR360, GE Healthcare, Wisconsin, USA) scanners. Morphometric measurements were performed on T2-weighted mid-sagittal images with a slice thickness of 4-5mm and an interslice gap of 0.4-0.5mm.

Although MRI examinations were acquired using both 1.5T and 3T scanners, slice thickness and interslice gaps were comparable across systems. Morphometric measurements were restricted to clearly defined mid-sagittal images using standardised selection criteria to minimise acquisition-related variability.

The mid-sagittal slice was manually selected based on clear visualisation of the cerebral aqueduct, third ventricle, and full rostro-caudal extent of the corpus callosum. All measurements were performed using Horos DICOM Viewer (version 3.3.6, Horos Project) with standardised zoom and window settings applied consistently across all cases to ensure consistency.

Morphometric parameters included antero-posterior diameter (APD), length of the CC (LCC), genu thickness (GT), body thickness (BT), isthmus thickness (IT), and splenium thickness (ST) as illustrated in Figure 1.

All measurements were performed once by a single observer who was blinded to the clinical diagnosis and group allocation at the time of measurement, following

a predefined standardised measurement protocol under the supervision of the three board-certified radiologists. Repeat measurements for inter- or intra-observer reliability analysis were not performed due to the retrospective nature of the study and the absence of duplicated standardised imaging datasets. In the epileptic group, findings of brain abnormalities outside the CC were also recorded.

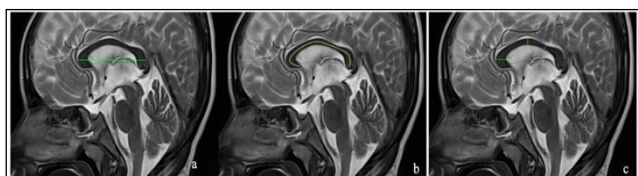


Figure 1: Morphometry measurement method in T2 FSE sequence in midline sagittal sections (a) antero-posterior diameter; (b) length of the CC (LCC); (c) segmental thickness: genu thickness (GT) in green, body thickness (BT) in yellow, isthmus thickness (IT) in orange, and splenium thickness (ST) in blue

Statistical Analysis

Demographic data were tested for homogeneity using the Chi-Square and Mann-Whitney tests. Analytical data were first tested for normality using the Shapiro-Wilk test. If the data were normal, the analysis proceeded with an independent T-test. For non-normal data, the Mann-Whitney test was applied. The analysis compared the epileptic and non-epileptic groups. We also performed a comparative analysis between the two groups based on age and sex. Furthermore, we compared the CC morphometry between the epileptic group without abnormalities outside the CC and the non-epileptic group. All the tests were performed using the 26th version of IBM SPSS statistical analysis with a significance value of $p < 0.05$.

RESULT

Demographic Result

Out of 92 patients, 49 (53.3%) were boys, and 43 (46.7%) were girls, with 38 subjects (41.3%) aged 6-8 years, 26 subjects (28.3%) aged 9-11 years, 18 subjects (19.6%) aged 12-14 years, and 10 subjects (10.8%) aged 15-17 years. Table I shows the summary of clinical and imaging findings characteristic of the epileptic group, while Figure 2 shows some recorded extra-callosal abnormalities.

Table I: Clinical and imaging findings characteristic of the epileptic group

Characteristic	n (%)
Seizure onset	Infant (0-2 years)
	16 (32)
	Early Childhood (3-5 years)
	10 (20)
	Middle Childhood (6-12 years)
Clinical companion	19 (38)
	Adolescent (> 12 years)
	1 (2)
	No data
	4 (8)
Imaging findings of abnormalities outside the CC	Brain infection history
	2 (4)
	Developmental disability
	8 (16)
	Intellectual disability
No extra-callosal abnormality	5 (10)
	No clinical companion
	35 (70)
	Cortical disorders
	10 (20)
Hamartoma	1 (2)
	Hippocampal disorders
	9 (18)
	Ventricular disorders
	1 (2)
Brain infarction	1 (2)
	Brain infection
	2 (4)
	Mixed disorders
	4 (8)
No extra-callosal abnormality	22 (44)

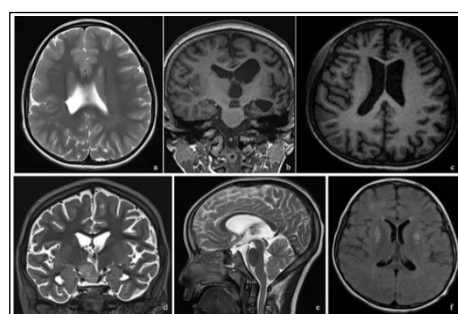


Figure 2: Some recorded extra-callosal abnormalities (a) *pachygyria* of the right frontoparietal lobe; (b) mixed of the left hemi atrophy, *hydrocephalus*, and hippocampal atrophy; (c) *polymicrogyria* of the right frontotemporoparietal lobe; (d) hamartoma; (e) *hydrocephalus*; (f) infarction of the bilateral basal ganglia and the right frontal subcortical

Statistical Result

No significant differences in corpus callosum morphometry were observed between epileptic and non-epileptic groups across all measurement parameters, as all P values exceeded 0.05 (data not shown). However, in the comparative analysis between the two groups based on age (Table II), there is a significant difference in BT parameter in the 12-14 years' age category ($p = 0.03$, Cohen's $d = 1.12$, Hedges' $g = 1.07$), in which the non-epileptic group has a thicker CC body when compared with the epileptic group with a large effect size. Meanwhile, in the comparative analysis based on sex (Table III), there is no significant difference in all parameters in the male category but there is a significant difference in LCC parameter in the female category ($p = 0.013$, Cohen's $d = 0.73$, Hedges' $g = 0.72$), in which the female epileptic group has lower

LCC compared with the non-epileptic group with a moderate-to-large effect. We also analysed the CC morphometry between the epileptic group without extra-callosal abnormalities and the non-epileptic group (Table IV). There is a significant difference in the GT parameter ($p=0.012$, Cohen's $d=0.63$, Hedges' $g=0.62$), with the epileptic group having greater GT compared with the non-epileptic group. It has a moderate effect size.

Table II: CC morphometry comparison between the epileptic and non-epileptic groups based on age

Age	Parameters	Mean (SD) (mm)		P value	Cohen's d	Hedges' g
6-8 years	APD	62.43 (3.59)	62.16 (6.08)	0.872		
	LCC	81.33 (4.54)	78.90 (8.50)	0.275		
	GT	9.17 (1.34)	9.39 (2.07)	0.704		
	BT	5.05 (0.75)	5.03 (1.19)	0.957		
	IT	2.88 (0.61)	2.77 (0.70)	0.368		
	ST	8.16 (1.00)	8.06 (2.01)	0.839		
9-11 years	APD	63.27 (2.79)	63.32 (5.51)	0.53		
	LCC	82.42 (5.51)	80.57 (7.52)	0.50		
	GT	9.41 (1.46)	9.37 (2.39)	0.97		
	BT	5.39 (1.25)	5.09 (1.82)	0.76		
	IT	3.30 (1.13)	3.26 (0.98)	0.92		
	ST	9.11 (1.48)	8.92 (2.01)	0.79		
12-14 years	APD	68.89 (2.93)	67.13 (2.66)	0.20		
	LCC	87.31 (5.33)	83.27 (10.53)	0.34		
	GT	9.57 (0.91)	10.15 (2.68)	0.54		
	BT	5.29 (1.00)	3.90 (1.39)	0.03	1.12	1.07
	IT	2.81 (0.98)	2.76 (0.62)	0.89		
	ST	9.94 (1.20)	8.90 (2.19)	0.25		
15-17 years	APD	67.26 (4.48)	67.44 (4.65)	0.95		
	LCC	85.69 (5.18)	82.16 (7.79)	0.42		
	GT	10.79 (2.15)	10.84 (1.64)	0.97		
	BT	5.02 (1.24)	5.32 (1.42)	0.73		
	IT	3.87 (1.35)	3.98 (1.30)	0.90		
	ST	10.30 (1.88)	9.90 (2.06)	0.76		

Table III: CC morphometry comparison between the epileptic and non-epileptic groups based on sex

Parameters	Mean (SD) (mm)		<i>P</i> value	Cohen's d	Hedges' g
	Non epileptic	Epileptic			
MALE					
APD	63.81 (4.91)	65.53 (4.46)	0.207		
LCC	82.88 (5.93)	82.98 (7.26)	0.958		
GT	9.57 (1.64)	9.97 (2.28)	0.483		
BT	5.48 (0.90)	4.98 (1.46)	0.162		
IT	3.26 (1.12)	3.29 (1.01)	0.912		
ST	8.92 (1.84)	8.91 (2.10)	0.980		
FEMALE					
APD	65.31 (2.94)	63.13 (6.28)	0.424		
LCC	83.8 (4.71)	78.22 (9.12)	0.013	0.73	0.72
GT	9.42 (1.20)	9.39 (2.23)	0.967		
BT	4.73 (0.94)	4.73 (1.56)	0.873		
IT	2.88 (0.66)	2.70 (0.77)	0.419		
ST	9.11 (0.89)	8.43 (2.05)	0.147		

Table IV: CC morphometry comparison between the epileptic with no abnormalities outside the CC and non-epileptic groups

Parameters	Mean (SD) (mm)		P value	Cohen's d	Hedges' g
	Non Epileptic	Epileptic			
APD	64.46 (4.20)	64.60 (4.81)	0.904		
LCC	83.27 (5.40)	81.46 (7.08)	0.257		
GT	9.50 (1.45)	10.45 (1.54)	0.012	0.63	0.62
BT	5.16 (0.98)	5.56 (1.12)	0.144		
IT	3.10 (0.96)	3.30 (0.80)	0.289		
ST	9.00 (1.49)	9.59 (1.61)	0.148		

DISCUSSIONS

CC plays a pivotal role in the pathophysiology of epilepsy, serving as the main commissural pathway that connects the two cerebral hemispheres and facilitates interhemispheric communication. Structural abnormalities such as CC agenesis or dysgenesis can disrupt these interhemispheric connections and contribute to seizure generation and propagation. Although the CC consists primarily of white matter and lacks active neuronal bodies, it can facilitate the bilateral spread of seizure activity by transmitting excitatory impulses from one hemisphere to the other.^{4,5}

In the present study, no significant differences were observed in overall CC morphometric parameters between epileptic and non-epileptic groups (data not shown). This finding aligns with previous reports that found no major volumetric or linear differences in CC structure among children with epilepsy.^{9,10} However, morphometric measurements reflect only macroscopic geometry and may not directly correspond to microstructural integrity. Studies using diffusion tensor imaging (DTI) have demonstrated that even in the absence of morphometric differences, epileptic children may show altered white matter organisation, including reduced fractional anisotropy (FA) and increased mean diffusivity (MD) in callosal fibres.¹⁰⁻¹² These results suggest that CC morphology alone represents only one aspect of callosal anatomy. Future analyses integrating morphometric and diffusion metrics could provide a more comprehensive understanding of white matter abnormalities in epilepsy.

Recent work has also proposed alternative morphometric approaches, such as surface-based and voxel-based morphometry, which offer greater sensitivity in detecting subtle shape variations.¹³ Incorporating these advanced methods in future pediatric epilepsy research may refine morphometric characterisation and improve reproducibility across imaging centers.

The epileptic cohort in this study was biologically heterogeneous, encompassing a wide range of etiologies including structural abnormalities, developmental disorders and acquired brain lesions. Such heterogeneity may have diluted global morphometric differences when epilepsy is analysed as a single entity and underscores the importance of stratified analyses in pediatric epilepsy research.

When analysed by age, a significant difference was observed in body thickness (BT) among subjects aged 12-14 years, with thinner BT in the epileptic group. This developmental period is critical for callosal maturation, as substantial myelination and remodeling occur throughout adolescence. Previous studies have shown significant increases in callosal area and callosal-to-supratentorial ratios between early childhood and mid-adolescence.^{12,14} Dysregulated maturation during this sensitive window may therefore explain the observed BT thinning in epileptic adolescents. Interictal discharges and neuroinflammation have been implicated as potential mechanisms interfering with normal callosal development.¹⁵⁻¹⁷ The effect size of this difference was large, suggesting a substantial deviation in callosal body thickness associated with epilepsy in this age group. Nevertheless, given the modest sample sizes and retrospective design, these results should be interpreted cautiously and require confirmation in larger, prospective cohorts.

Sex-based comparison (Table III) revealed a significantly shorter total CC length (LCC) in females with epilepsy compared to non-epileptic females with moderate effect size. This observation is consistent with previous

findings showing a steeper developmental slope and earlier callosal maturation in females.^{14,18} Because females experience accelerated CC development, any neurodevelopmental disturbance may become more pronounced earlier in adolescence. While our sample size limits generalisation, this pattern warrants further longitudinal evaluation.

Linear CC measurements without normalisation to intracranial volume or total brain size may partially reflect individual differences in head size or developmental stage. Therefore, the observed age- and sex-related differences should be interpreted as relative morphometric trends rather than absolute anatomical differences.

Analysis restricted to epileptic children without extra-callosal abnormalities (Table IV) showed thicker genu (GT) compared to the non-epileptic peers. This result is consistent with the findings of Schupper et al, who reported increased CC thickness in a subset of children with epilepsy.⁷ Given that callosal development follows a rostro-caudal pattern, where posterior regions mature earlier,^{14,19} a thicker genu may reflect asynchronous anterior callosal development rather than a definitive compensatory growth pattern. The effect size of this difference was moderate, suggesting that the observed alteration reflects a meaningful deviation in callosal growth trajectory among epileptic children. This moderate magnitude reinforces the notion that epilepsy may subtly influence regional neurodevelopment rather than producing gross structural abnormalities, potentially representing adaptive remodeling in response to disrupted interhemispheric signaling.

Overall, the observed differences suggest that epilepsy may be associated with deviations in normal callosal maturation patterns. However, these findings should be interpreted with caution, given the retrospective and correlative nature of the study. The results do not imply causality but highlight subtle morphometric trends that

may reflect altered neurodevelopmental timing in paediatric epilepsy.

Several limitations should be acknowledged. First, its retrospective design inherently limits control over data completeness and uniformity. MRI and clinical data were derived from pre-existing hospital records, restricting the ability to account for important confounders such as epilepsy subtype (generalised versus focal), seizure frequency, illness duration, and anti-epileptic drug exposure. These factors are known to influence both global brain morphology and corpus callosum development, and their absence may have introduced bias.

Second, inter- and intra-observer reliability analyses were not performed, which may limit measurement reproducibility. However, to minimise variability, all measurements were performed using predefined anatomical landmarks, fixed zoom and window settings, and supervised by experienced radiologists. Future prospective studies should incorporate repeated measurement and reliability testing. Nevertheless, the use of different scanner field strengths and slice parameters may still have influenced linear measurement precision and represent a limitation of this study.

Third, corpus callosum dimensions were not normalised to intracranial or total brain volume. Although the age range was restricted to 6-17 years to minimise developmental variation, linear measurements may still be influenced by head size, sex-related brain differences, or maturational stage. This limitation should be considered when interpreting the observed sex- and age-related morphometric differences.

Finally, the relatively small sample size limits the statistical power to detect subtle morphometric differences. A larger, prospectively collected and multicenter data set would allow for more robust subgroup analysis, particularly regarding epilepsy types, duration, and sex-specific maturation patterns.

Future research should incorporate longitudinal follow-up to track callosal development over time and combine conventional morphometry with diffusion tensor imaging (DTI) or advanced surface-based approaches. Integration of these methods may yield a more comprehensive understanding of structural and microstructural alterations associated with pediatric epilepsy and improve the interpretability of neurodevelopmental trajectories

CONCLUSION

While epilepsy does not produce a uniform reduction in CC morphology across all paediatric age groups, specific morphometry differences may emerge during critical periods of brain maturation and appear to be influenced by sex, even in the absence of overt parenchymal abnormalities on conventional MRI. Recognising these subtle findings contributes to a better understanding of the neurodevelopmental impact of pediatric epilepsy and supports the role of quantitative neuroimaging as a hypothesis-generating, complementary approach in research settings.

ACKNOWLEDGEMENTS

The authors would like to express sincere gratitude to the Head of department and the Study Program Coordinator for granting permission to conduct this research and our colleagues for their invaluable support.

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Detection of High-Risk Pathogenic Alleles for Young-Onset Myocardial Infarction in a Malaysian Cohort: A Pilot Study

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ABSTRACT

INTRODUCTION: Identifying pathogenic genetic variants associated with young-onset myocardial infarction (YOMI) may facilitate early risk stratification and enable timely preventive intervention. This pilot study aimed to compare the genetic profiles of patients with YOMI with healthy controls to identify high-risk genetic variants and evaluate the utility of polygenic risk scores (PRS) in differentiating genetic susceptibility between the two groups.

MATERIALS AND METHODS: Genomic DNA was extracted from patients with YOMI (n=30; mean age = 37.47 ± 3.29 years) and healthy controls (n=12; mean age = 34.67 ± 2.71 years). Samples were genotyped using the Asian Screening Array (Infinium®, Illumina). Genetic variants associated with cardiovascular risk were identified through annotation against the Genome-Wide Association Studies (GWAS) database. Polygenic risk scores were calculated and compared between the two groups. **RESULTS:** Thirty-seven single nucleotide polymorphisms (SNPs) with odds ratios greater than 2 were identified, including variants associated with coronary heart disease, venous thromboembolism, and atrial fibrillation. The rs13082914 variant in *KCNAB1* showed a strong association with young-onset myocardial infarction (OR=8.63; P<0.05). Polygenic risk score analysis revealed higher risk loads in YOMI patients for Brugada syndrome, myocardial infarction in CAD, peripheral artery disease, and non-BMP2 pulmonary arterial hypertension.

CONCLUSION: This pilot study demonstrated the potential value of genetic screening to identify individuals at risk of developing YOMI. However, larger prospective studies are required to validate these findings and to determine their clinical utility in risk prediction and preventive cardiovascular care.

Keywords

pathogenic alleles, young, myocardial infarction

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Received: 6th September 2025; Accepted: 5th July 2026

Doi:

<https://doi.org/10.31436/10.31436/imjm.v25i04/3104>

INTRODUCTION

Cardiovascular disease remains the leading cause of death worldwide, with mortality increasing from 12.1 million in 1990 to 18.6 million in 2019.¹ The World Health Organization (WHO) estimated that 17.6 million

people died from cardiovascular disease in 2016, with most of these deaths (80%) occurring in low- and middle-income countries.² In Malaysia, the average age of patients with cardiovascular disease is 58.5 years, which is younger than in neighbouring countries such

as Singapore (68.3 to 69.2 years) and Thailand (63.5 years).³ Risk factors for cardiovascular diseases include high blood pressure, sex, age, smoking, diabetes, lack of exercise, obesity, high blood cholesterol, poor diet, and excessive alcohol consumption.⁴ It is estimated that more than 30% of elderly Malaysians are obese and also have hypertension and diabetes.⁵ Most cardiovascular diseases are preventable. Preventive measures to reduce cardiovascular risk include adopting a healthy lifestyle, such as maintaining a balanced diet, engaging in regular physical activity, and undergoing routine cardiovascular health assessments.⁶

With the advent of precision medicine, where medical treatment is personalised to the individual rather than the entire population, screening for high-risk alleles that contribute to cardiovascular diseases becomes essential. Genome-wide association studies (GWAS) have provided significant insights into the link between high-risk alleles and cardiovascular conditions, including incident myocardial infarction, coronary artery disease, atrial fibrillation, and reduced left ventricular function.^{7,8} Mapping single-nucleotide polymorphisms (SNPs) with the genotype-phenotype database of GWAS helps in identifying risk alleles associated with disease development and ultimately aids in developing prevention strategies for high-risk individuals.⁹ Developed countries have adopted GWAS, mainly among those of European ancestry, to identify SNPs linked to cardiovascular diseases.¹⁰ However, populations from developing countries remain underrepresented in GWAS, and significant disease associations observed in populations from developed nations might not apply to those in developing countries.

Given the significant economic and health impact of cardiovascular diseases, screening for high-risk alleles associated with these conditions is crucial for prevention. Furthermore, many individuals in Malaysia face a risk of developing cardiovascular diseases due to the widespread presence of risk factors within the country. Although these diseases predominantly

affect the elderly, there is a rising trend of young-onset myocardial infarction (YOMI) in Malaysia. Since the underlying mechanisms of YOMI remain unclear, we investigate the potential genetic predisposition of local patients with YOMI to identify predictive markers, aiming to facilitate the implementation of preventive medicine.

MATERIALS AND METHODS

Study population and sample collection

The study population included patients aged ≤ 40 years admitted to UiTM Medical Center (UMC) with myocardial infarction. Since there is no universal definition for young-onset myocardial infarction, we selected patients under 40 years old, as this age group represents an early presentation of the condition, consistent with previous studies.¹¹ Data on risk factors such as age, smoking status, diabetes mellitus, hypertension, and family history of myocardial infarction were collected from the patients. Whole blood samples were drawn from the patients and placed into EDTA tubes for SNP genotyping analysis. The genotype of the YOMI group was compared with that of the established healthy genome sequence database of Malaysians of the same age without cardiovascular diseases.

Sample processing (DNA extraction) and SNP analysis

DNA was extracted from blood samples using QIAamp® DNA Blood Mini Kits following the manufacturer's protocol (Qiagen Biotech Malaysia, Kuala Lumpur, Malaysia). For SNP genotyping analysis, DNA was prepared according to the Infinium Asia Screening Array protocol (Illumina, San Diego, CA, USA).

SNP calling, annotation, and the GWAS database

SNP or variant calling was performed using the GenomeStudio 2.0 software (Infinium Genotyping Data Analysis), and the identified SNPs or variants were annotated with traits related to cardiovascular diseases in the GWAS database. We obtained information,

including rsIDs, traits, risk alleles, and odds ratios (or Beta values) from the GWAS database. The polygenic risk score for individual patients was calculated using a previously published formula.¹²

Annotation of genetic variants associated with MI

We searched for genetic variants linked to myocardial infarction (MI) using the GWAS database. All cardiovascular-related variants from the GWAS database, that is, 31 traits and 878 SNPs, were successfully retrieved. After removing duplicates and unrelated traits, 391 SNPs and 31 traits remained. We further excluded non-related SNPs and traits in subsequent analyses. Ultimately, 19 cardiovascular-related traits and 316 SNPs were selected for further analysis to assess the significance of the risk alleles for myocardial infarction. The odds ratio/beta values, as well as the polygenic risk scores, were calculated for the pathogenic alleles.

Statistical analysis

The association between genotypes and the risk of myocardial infarction was analysed using Fisher's exact test. The odds ratio was calculated with a 95% confidence interval. A p-value of 0.05 was regarded as significant. All analyses were conducted using the Statistical Package for the Social Sciences (IBM SPSS) version 22.

Bioinformatics analysis

PredictSNP1 and PredictSNP2 were used to predict the pathogenicity of SNPs sourced from the GWAS database.^{13,14} PredictSNP1 evaluates the pathogenicity of protein mutations using eight established bioinformatics tools available for this purpose: 1) SIFT, 2) PANTHER, 3) MAPP, 4) PhD-SNP, 5) PolyPhen-1, 6) PolyPhen-2, 7) SNAP, and 8) MAPP. After assessing the performance of these tools, only the six best-performing ones were selected for consensus prediction, with a confidence score ranging from 0 to 100. Pathogenicity was classified as 'deleterious' or 'neutral' based on the consensus from these top six tools.

The approach for Predictsnp1 was similar to that of Predictsnp2, although Predictsnp2 was specifically used for predicting the pathogenicity of disease-related nucleotide variants. It employed six established tools GWAVA, Funseq2, CADD, FATHMM, Fitcons, and DANN to generate a consensus regarding the pathogenicity of these variants.

As with Predictsnp1, the pathogenicity was categorised as 'deleterious' or 'neutral' with a confidence score between 0 and 100. The polygenic risk score (PRS) for patients and controls was calculated using the previously established formula.¹² The PRS scores for both groups were divided into percentiles: 1%, 1-5%, 5-10%, 10-20%, 20-40%, 40-60%, 60-80%, 80-90%, 90-95%, 95-99%, and 99-100%.

RESULTS

Patients' clinical characteristics

Thirty patients diagnosed with young-onset myocardial infarction were recruited for this study, while 12 healthy subjects served as controls. The average age of patients was 37.47 ± 3.29 years, whereas the average age of controls was 34.67 ± 2.71 years. The mean age at first diagnosis of myocardial infarction among the patients was 34.47 ± 3.01 years. The age of patients ranged from 27 to 40 years, with half of them ($n=15$) aged between 30 and 35, and 46.7% ($n=14$) aged between 36 and 40. One patient was 27 years old at the time of first diagnosis. The myocardial infarction subgroups included non-STEMI in 10 patients (33.3%) and STEMI in 19 patients (63.3%). Most patients were smokers ($n=16$; 53.3%), while eight (26.7%) were former smokers and four (13.3%) had no history of smoking. Dyslipidemia, hypertension, and diabetes mellitus were observed in 14 (46.7%), 13 (43.3%), and 7 (23.3%) patients, respectively. Two patients (6.7%) had a family history of cardiovascular diseases, while six (20%) had a history of myocardial infarction. Nearly all patients ($n=29$; 96.7%) had ischaemic heart disease. No patients had a history of peripheral vascular disease and chronic liver disease.

Table I: Patients' clinical characteristics

Clinical characteristics	Frequency, n (%)
Age first diagnosed with MI	
<30 years	1 (3.3)
30-35 years	15 (50.0)
36-40 years	14 (46.7)
Subgroups of MI	
Non-stemi	10 (33.3)
Stemi	19 (63.3)
USA	1 (3.3)
Smoking status	
Smoker	16 (53.3)
Former smoker	8 (26.7)
Never	6 (20.0)
Aspirin intake	
Yes	5 (16.7)
No	25 (83.3)
Dyslipidemia	
Yes	14 (46.7)
No	16 (53.3)
Hypertension	
Yes	13 (43.3)
No	17 (56.6)
Diabetes mellitus status	
Yes	7 (23.3)
No	23 (76.7)
Insulin dependency	
Yes	1 (3.3)
No	29 (96.7)
Pharmacogenomics-guided treatment	
Yes	2 (6.7)
No	28 (93.3)
Family history of CVD	
Yes	2 (6.7)
No	28 (93.3)
History of MI	
Yes	6 (20)
No	24 (80)
Significant CAD	
Yes	4 (13.3)
No	26 (86.7)
New onset angina	
Yes	17 (56.7)
No	13 (43.3)
Chronic angina	
Yes	5 (16.7)
No	25 (83.3)
History of fractured neck of femor	
Yes	2 (6.7)
No	28 (93.3)
Cerebrovascular accident	
Yes	2 (6.7)
No	28 (93.3)
Chronic kidney disease	
Yes	2 (6.7)
No	28 (93.3)
Ischemic heart disease	
Yes	29 (96.7)
No	1 (3.3)

Abbreviations; MI:myocardial infarction; CVD: cardiovascular disease; CAD: coronary artery disease

Association of selected SNPs with myocardial infarction

Table I shows baseline characteristics of patients included in the study. Table II displays the association

of selected SNPs with myocardial infarction traits in 30 patients and 12 controls. Thirty-seven (37) SNPs were linked to myocardial infarction ($OR > 2$). The traits with the highest number of SNPs identified in the YOMI cohort were related to coronary heart disease (14 SNPs), followed by venous thromboembolism (10 SNPs), and atrial fibrillation (nine SNPs). Notably, the SNP rs13082914, located in the gene *KCNAB1*, was significantly associated with young myocardial infarction ($OR: 8.63$; $P < 0.05$).

Polygenic risk score (PRS) and patient risk

PRS scores for 20 myocardial traits were calculated for cases and controls. The PRS scores are shown in Table III. Scores for traits linked to Brugada syndrome, myocardial infarction in coronary artery disease, peripheral artery disease, and pulmonary arterial hypertension (without *BMPT2* mutations) were higher in cases than in the control group. Conversely, PRS scores for traits associated with atrial fibrillation, Behcet's disease, coronary heart disease, hypertension, intracranial aneurysm, ischemic stroke (cardioembolic and large artery atherosclerosis), large artery stroke, myocardial infarction (early onset), stroke, and sudden cardiac arrest were higher in controls than in cases.

SNP pathogenicity in myocardial infarction

We evaluated SNPs for pathogenicity, their genomic locations, mutation types, and confidence scores of pathogenicity using PredictSNP2. Out of the 37 SNPs examined, only two were predicted to be harmful, while the remaining were deemed neutral. The two SNPs predicted to be deleterious included rs11057401 (T>A: missense variant situated in the *CCDC92* gene, which is involved in DNA repair) and rs2296610 (G>T: missense variant located in the *NEBL* gene that encodes nebulin protein in cardiac muscle), with confidence scores of 82% and 89%, respectively.

Table II: List of high risk SNPs associated with young myocardial infarction in Malaysian population

SNP	Trait	Gene	Risk allele	Odds ratio	95% CI	P-value
rs7025486	Abdominal aortic aneurysm	<i>DAB2IP</i>	A	1.831	0.472-7.104	0.499
rs9316871	Abdominal aortic aneurysm	<i>AL136962.1 - AL512484.1</i>	G	1.5	0.39-5.768	0.732
rs602633	Abdominal aortic aneurysm	<i>CELSR2 - PSRC1</i>	A	2.167	0.405-11.601	0.387
rs6516091	Abdominal aortic aneurysm	<i>AL118505.1 - FERMT1</i>	A	2.167	0.405-11.601	0.387
rs6843082	Atrial fibrillation	<i>LINC01438</i>	G	1.667	0.329-8.434	0.668
rs17042171	Atrial fibrillation	<i>PITX2 - LINC01438</i>	A	1.143	0.299-4.364	1
rs2106261	Atrial fibrillation	<i>ZFHX3</i>	A	1.429	0.361-5.656	0.726
rs17059534	Atrial fibrillation	<i>AC093849.2 - HAND2</i>	A	14.5	1.415-148.569	0.018
rs7164883	Atrial fibrillation	<i>HCN4</i>	G	4	0.443-36.145	0.247
rs883079	Atrial fibrillation	<i>TBX5</i>	A	4	0.443-36.145	0.247
rs3903239	Atrial fibrillation	<i>AL023495.1</i>	C	1.522	0.268-8.653	1
rs76097649	Atrial fibrillation	<i>KCNJ5</i>	A	1.3	0.205-8.247	1
rs639652	Atrial fibrillation	<i>AL023495.1</i>	C	1.522	0.268-8.653	1
rs10821415	Atrial fibrillation	<i>AOPEP</i>	A	4	0.967-16.551	0.084
rs12044963	Atrial fibrillation	<i>KCND3</i>	T	1.234	0.314-4.840	1
rs10458660	Atrial fibrillation	<i>LRMDA</i>	G	1.375	0.323-5.847	0.715
rs7687819	Atrial fibrillation	<i>ALPK1</i>	A	1.692	0.169-16.912	1
rs133902	Atrial fibrillation	<i>MYO18B</i>	T	1.273	0.105-15.501	1
rs7616215	Behcet's disease	<i>CCR3</i>	C	1.643	0.378-7.134	0.699
rs7574070	Behcet's disease	<i>STAT4</i>	A	2.750	0.295-25.678	0.651
rs671	Coronary artery disease	<i>ALDH2</i>	A	4.667	0.67-32.488	0.131
rs1878406	Coronary artery disease	<i>PRMT5P1 - EDNR4</i>	T	1.529	0.377-6.207	0.731
rs2681472	Coronary artery disease	<i>ATP2B1</i>	C	1.071	0.275-4.176	1
rs2281727	Coronary artery disease	<i>SMG6</i>	C	3	0.736-12.227	0.175
rs13232179	Coronary heart disease	<i>WDR86-AS1 - AC005996.1</i>	A	5.5	0.62-48.817	0.133
rs11066280	Coronary heart disease	<i>HECTD4</i>	A	1.727	0.446-6.686	0.498
rs2123536	Coronary heart disease	<i>AC019055.1 - CISD1P1</i>	A	1.071	0.276-4.154	1
rs7808424	Coronary heart disease	<i>ASZ1, CFTR</i>	G	1.737	0.386-7.807	0.719
rs10933436	Coronary heart disease	<i>INPP5D, INPP5D</i>	A	2.895	0.534-15.689	0.282
rs4937126	Coronary heart disease	<i>ST3GAL4</i>	G	1.375	0.323-5.847	0.715
rs4387287	Hypertension	<i>STN1</i>	A	1.309	0.342-5.006	0.742
rs2398162	Hypertension	<i>NR2F2-AS1, AC012409.2</i>	A	1.818	0.325-10.157	0.696
rs11646213	Hypertension	<i>AC009117.2 - CDH13</i>	T	1.737	0.386-7.807	0.719
rs1735151	Hypertension	<i>IGSF5</i>	T	1.727	0.446-6.686	0.498
rs2066865	Venous thromboembolism	<i>FGA - FGG</i>	T	2	0.448-8.936	0.485
rs6088735	Venous thromboembolism	<i>EDEM2 - PROCR</i>	T	2.294	0.516-10.209	0.316
rs2296610	Atrial fibrillation	<i>NEBL</i>	T	3.3478	0.3654-30.6738	0.402
rs1152591	Atrial fibrillation	<i>ESR2, SYNE2</i>	T	2.1	0.5388-8.1852	0.322
rs6882776	Atrial fibrillation	<i>NKX2-5 - AC008412.1</i>	G	2.5	0.5375-11.6274	0.405
rs242557	Atrial fibrillation	<i>MAPT</i>	G	3.4286	0.7662-15.3428	0.124
rs13082914	Coronary artery disease	<i>AC091607.2, KCNAB1</i>	T	8.6364	1.5934-46.8086	0.015
rs4773144	Coronary artery disease	<i>COL4A2</i>	G	2.3469	0.564-9.7662	0.274
rs2244608	Coronary artery disease	<i>HNF1A, HNF1A-AS1</i>	C	3	0.7361-12.2271	0.17465
rs12936587	Coronary heart disease	<i>AC020558.5 - SMCR2</i>	G	2.636	0.151-45.91	0.495
rs2505083	Coronary heart disease	<i>JCAD</i>	C	1.5294	0.3769-6.2067	0.731
rs4773144	Coronary heart disease	<i>COL4A2</i>	G	3.2857	0.7998-13.4976	0.140519
rs7903146	Peripheral artery disease	<i>TCF7L2</i>	T	2.75	0.2945-25.6795	0.65137
rs2217560	Pulmonary arterial hypertension (without <i>BMPR2</i> mutations)	<i>AC069114.1 - CBLN2</i>	G	2.75	0.2945-25.6795	0.65137
rs687621	Venous thromboembolism	<i>ABO</i>	C	1.5	0.4077-5.5181	0.73755
rs7659024	Venous thromboembolism	<i>FGA - FGG</i>	A	2	0.4476-8.9363	0.48479
rs6536024	Venous thromboembolism	<i>FGG - LRAT</i>	C	2.333	0.59-9.2275	0.2919
rs2066865	Venous thromboembolism	<i>FGA-FGG</i>	T	2	0.4476-8.9363	0.4847986
rs8176749	Venous thromboembolism	<i>ABO</i>	A	2.1429	0.3886-11.8154	0.46377
rs2066865	Venous thromboembolism	<i>FGA-FGG</i>	T	2	0.4476-8.9363	0.484798
rs6088735	Venous thromboembolism	<i>EDEM2 - PROCR</i>	T	2.2941	0.5155-10.2092	0.31631

Table III: Polygenic risk score (case vs control)

	Case	Control
Abdominal aortic aneurysm	34.53	34.755
Atrial fibrillation	40.767	41.763
Behcet's disease	16.51	18.42
Brugada syndrome	27.971	25.641
Coronary artery disease	25.69	25.855
Coronary heart disease	49.81	54.81
Hypertension	44.748	45.9
Intracranial aneurysm	84.58	86.64
Ischemic stroke (cardioembolic)	31.11	34.66
Ischemic stroke (large artery atherosclerosis)	0	4.17
Large artery stroke	39.11697	42.54
Myocardial infarction	63.89333	64.47833
Myocardial infarction (early onset)	50.331	52.5625
Myocardial infarction in coronary artery disease	38.33333	33.33333
Peripheral artery disease	21.755	20.25
Pulmonary arterial hypertension (without <i>BMPR2</i> mutations)	13.33333	4.166667
Stroke	4.918667	5.333333
Stroke (ischemic)	25.63333	27.25
Sudden cardiac arrest	8.333333	12.5
Venous thromboembolism	18.77315	17.05794

DISCUSSION

The prevalence of YOMI is higher in Malaysia than in developed countries. The main factors contributing to the increased risk of developing myocardial infarction are individual lifestyle and diet. In recent decades, as Malaysia has moved towards urbanisation and industrialisation, the lifestyles of young adults have become more unhealthy, characterised by increased consumption of fast foods and physical inactivity. This has led to a high prevalence of obesity among Malaysians. An unhealthy lifestyle combined with genetic susceptibility elevates the risk of myocardial infarction. Therefore, we carried out this study to investigate the genetic risks that increase susceptibility to YOMI in Malaysia. We also calculated the polygenic risk score for the cases and controls to examine the differences in genetic scores between the groups.

We extracted 316 SNPs from the GWAS database associated with cardiovascular diseases. Of these, 37 SNPs were identified in our study. These 37 SNPs were linked to myocardial infarction with an OR of over 2.

We also identified two SNPs predicted to be harmful using an online bioinformatics tool. These SNPs are involved in DNA repair and cardiac muscle development. We calculated PRS scores for patients and controls to predict the risk of MI based on the individual's genetics.

To the best of our knowledge, our study is the first to attempt to find an association between the risks of young myocardial infarction and PRS scores in our population. Although we observed certain myocardial infarction traits to be higher in cases than in controls, these findings were not statistically significant. This may be due to the small sample size of patients in our study. Additionally, we derived PRS scores based on the GWAS database, which predominantly includes participants of European descent. The GWAS database is underrepresented by Asian populations, with 80% of the subjects reported in the database being from Europe.¹⁵ Malaysia is a multicultural country with diverse ancestry, which may influence the distribution of risk alleles. The results of this study highlight the need to establish our own population genomic database for future research on genetic variants associated with disease. According to the American Heart Association, seven criteria must be met by young adults to prevent cardiovascular disease: 1) at least 150 minutes of moderate physical activity per week, 2) body mass index below 25 kg/m², 3) serum cholesterol under 200 mg/dl, 4) blood pressure of 120/80 mmHg, 5) fasting plasma glucose under 100 mg/dl, 6) a balanced diet low in fat, salt and sugar, and rich in vegetables and fruits, and 7) never smoking or quitting smoking for over a year.¹⁶ Results from our study identified high-risk alleles for young myocardial infarction, and the information obtained will be valuable for screening individuals at high risk of developing early-onset myocardial infarction for early intervention. Interestingly, the control groups exhibited higher PRS for MI (young onset), suggesting that they carry genetic risks for MI but may not express traits due to healthier lifestyles.

LIMITATION

The small sample size and single-centre design of the study may restrict the ability to generalise the results to a broader population. We recognize that our SNP selection was limited to variants annotated against the GWAS database, which predominantly represents individuals of European ancestry. This reliance may have excluded population-specific variants relevant to the Malaysian multiethnic cohort. As this is a pilot study, our aim was to evaluate feasibility using an established international database.

CONCLUSION

Although the sample size in our pilot study was small, we observed a higher prevalence of several genetic traits associated with myocardial infarction among patients with young-onset myocardial infarction (YOMI) than among healthy controls. These findings highlight the potential of genetic risk prediction for identifying YOMI within the Malaysian population. However, our genetic risk prediction was based on the Genome-Wide Association Studies (GWAS) database, which primarily derived from populations of European ancestry and may not fully capture the genetic architecture of Malaysians. Therefore, there is a need to establish population-specific genomic databases to improve the accuracy and clinical applicability of genetic risk prediction in Malaysia. Future multicentre studies with larger and more ethnically diverse cohorts are warranted to better characterize the genomic landscape of the Malaysian population and validate these preliminary findings.

Competency in medical knowledge

The prevalence of young-onset myocardial infarction is higher in Malaysia than in developed countries. Finding innovative ways to prevent and lessen the severity of the disease at its onset is crucial. This includes screening for high-risk alleles linked to cardiovascular diseases. The study identified thirty-seven (37) SNPs associated with myocardial infarction. Most SNPs found in patients with young-onset myocardial infarction were related to genetic traits of coronary artery disease,

thromboembolism, and atrial fibrillation. The SNP rs13082914 in the *KCNAB1* gene demonstrated a significant association with young-onset myocardial infarction, highlighting its potential role as a genetic marker for cardiovascular risk assessment.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare

ACKNOWLEDGEMENT

This work was supported by the Higher Institution Centre of Excellence (HICoE) research grant 600-RMC/MOHE HICoE CARE-I 5/3 (01/2025) awarded to the Cardiovascular Advancement and Research Excellence Institute (CARE Institute), Universiti Teknologi MARA.

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The Relationship Between Social Support and Religious Coping Strategies Towards Quality of Life of Muslim Retirees in The East Coast Region in Malaysia

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ABSTRACT

INTRODUCTION: Quality of Life (QoL) is a multidimensional concept crucial for older adults, particularly as they experience physical decline, chronic diseases, and reduced social participation. This study examines the relationship between social support, religious coping, and QoL among older Muslims in the East Coast Region of Malaysia. **MATERIALS AND METHODS:** A positivist approach was employed, utilising an online survey distributed to Muslim retirees aged 60 and above. A self-administered questionnaire assessed demographic data, social support, religious coping strategies, and QoL. **RESULTS:** 150 responses were analysed using SPSS Statistics 29.0 and Smart PLS 4.0. Most respondents (97.3%) belonged to the young-old category. The findings revealed that religious coping was positively associated with quality of life (QoL) ($\beta=0.209$, $t=2.365$, $p<0.01$), and social support was also positively associated with QoL ($\beta=0.502$, $t=4.181$, $p<0.01$). **CONCLUSION:** These findings highlight the importance of social and religious support in enhancing older adults' well-being. Future research should explore qualitative approaches to gain deeper insights into the lived experiences of older Muslims. Understanding these factors can inform policymakers and healthcare providers in developing effective ageing interventions that promote healthy ageing, social participation, and autonomy.

Keywords

Quality of Life, Elderly; Social Support, Religious Coping, Gender

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Received: 5th June 2025; Accepted: 22nd July 2026

Doi:
<https://doi.org/10.31436/10.31436/imjm.v25i04/2989>

INTRODUCTION

Malaysia is on track to become an ageing nation, with the population aged 65 and above projected to reach 7.5% and rise to 14% by 2044.¹ This demographic shift highlights the urgent need to enhance social support systems and improve the quality of life (QoL) for older adults, particularly those at risk of social isolation and loneliness.

Malaysia's multicultural society, comprising Malays, Chinese, Indians, and indigenous groups, shares strong cultural values such as filial piety and care for ageing parents. However, this model is under strain due to social and demographic changes. The sandwich generation, caring for ageing parents and children, faces increasing financial, physical, and emotional pressure. Middle-income families, in particular, struggle as they do not qualify for public aid and often cannot afford private care.

While various government and NGO initiatives exist, many are short-term and lack sustainability. A key concern is the decline of family-based care, which has negatively impacted the QoL of older adults, especially among Muslims.² Healthcare and social services are often inadequate in meeting the complex needs of the ageing population.³ Social support is vital in promoting mental and physical well-being, especially for those living alone or far from family. However, research focusing on the East Coast of Malaysia, a region known for its strong religious and communal values, is limited. There is a pressing need to explore how factors like social support, access to healthcare, and religious coping affect the QoL of older Muslims in this region.

Religious coping has been linked to better mental health, emotional stability, and life satisfaction.⁴⁻⁶ Yet, its role in enhancing QoL among older Malaysian adults remains underexplored. Moreover, promoting independence and community-based programs that encourage physical activity and social engagement have shown positive outcomes.⁷ Combining social support with religious coping may offer a holistic approach to improving well-being in later life. Therefore, this study aims to explore the factors influencing the quality of life among older Muslims on the East Coast of Malaysia, focusing on the roles of social support and religious coping.

MATERIALS AND METHODS

This study employed a cross-sectional survey design, which enabled the observation of social support, religious coping, and quality of life among Muslim retirees in the East Coast Region without manipulating or controlling any variables. In this research, the selected population is limited to retirees who previously worked in the government and non-government sectors and are currently living as older adults aged 60 years and above. To be included in this study, the participants must meet the following criteria: (1) 60 years and above and (2) government or non-government retirees. This criterion focuses on retirees who have transitioned from a

professional or formal work environment, and (3) Muslims from the East Coast Region.

The study utilised convenience sampling to recruit participants during the COVID-19 pandemic, a period when public health protocols restricted traditional probability sampling and face-to-face data collection. While this approach facilitated data collection during a crisis, it necessitated a digital-first strategy. The survey was distributed via Google Forms and disseminated through WhatsApp groups and community networks. This approach required participants to possess smartphone access and basic digital literacy. The sample size calculation was conducted in G*Power, and the test used an alpha of 0.05, a power of 0.80, and a medium effect size ($f^2=0.15$). 80% is considered the minimum acceptable power in most social science studies, so the desired sample size was 85.⁸

INSTRUMENTATION

The questionnaire was distributed as an online survey via Google Forms to all participants, available in both English and Malay. A back-translation procedure was used to ensure the accuracy and consistency of the Malay version with the original English version. The survey link was disseminated through WhatsApp groups to facilitate easy access for participants. The questionnaire comprised four sections: demographic profile, quality of life, social support, and religious coping strategies. The QoL section was adapted from the Older People's Quality of Life Questionnaire (OPQOL-21).⁹ The social support section used the Multidimensional Scale of Perceived Social Support (MSPSS), comprising 12 items, to assess perceived support from family, friends, and significant others.¹⁰ Religious coping was measured using an adapted version of the Religious Coping Scale, a self-rated questionnaire consisting of 22 items, to assess the use of religion as a coping strategy in the face of difficulties, struggles, and adverse life events.¹¹ The items were derived initially from RCOPE.^{12\}

All items in the questionnaire were measured using a five-point Likert scale, ranging from 1 (Strongly Disagree) to 5 (Strongly Agree). In the final section, sociodemographic information was collected to characterise the sample. This section included 11 items covering gender, age, religion, ethnicity, highest educational level, marital status, source of income, monthly income, living arrangement, existing medical conditions, and locality. Given the different cultural context of the present study, content validity was first established through experts' evaluation to assess the relevance, clarity, and cultural appropriateness of the items. Based on the feedback, minor wording refinements were made to enhance contextual suitability while preserving the theoretical meaning of the constructs. The data were analysed using SPSS version 29.0 and SmartPLS 4.0.

RESULTS

One hundred fifty respondents participated in the study, comprising 61 males (40.7%) and 89 females (59.3%). Most were aged 60–74 years (90%), with a mean age of 65.4 years. Regarding education, 80% had a tertiary education, 19.3% had completed secondary school, and 0.7% had only a primary education. The majority were married (86%), while others were single (4.7%), widowed (6.7%), or divorced (2.7%). Most relied on earned income (92.7%), while others received support from family (1.3%), government (1.3%), or other sources (2.7%); 2% had no income. Monthly income ranged mainly from RM 4,500–10,500 (50%), followed by RM 2,500–4,500 (32%). Most lived with spouses and children (91.3%), while a few lived alone (4.7%) or with others (4%). Common chronic illnesses were hypertension (35.3%) and diabetes (30.7%). Regarding location, 62% lived in urban areas, 26.7% in suburban areas, and 11.3% in rural areas.

Table I: Demographic Profile of the Respondents

	Frequency (n)	Percentage (%)	Mean	Sd
<u>Gender</u>				
Male	61	40.7		
Female	89	59.3		
<u>Age</u>				
60–74 years old (young old)	135	90	65.41	3.605
75 years old and above (old-old)	15	10		
<u>Highest education</u>				
University or college	120	80.0		
Secondary school	29	19.3		
Primary school	1	0.7		
<u>Marital status</u>				
Married	129	86.0		
Single	7	4.7		
Widowed	10	6.7		
Divorced	4	2.7		
<u>Source of income</u>				
Support from the government (welfare department)	2	1.3		
Various sources (rent, interest, dividends and bonuses)	4	2.7		
Family-related income (remittance from sons, daughters and relatives)	2	1.3		
Earned income (salary, pension or income from agriculture and business)	139	92.7		
No income	3	2.0		
<u>Monthly income</u>				
Less than rm 2,500	19	12.7		
Rm 10,500 and above	8	5.3		
Rm 2,500 – rm 4,500	48	32.0		
Rm 4,500 – rm 10,500	75	50.0		
<u>Living arrangement</u>				
Living with spouse and children	137	91.3		
Living with others	6	4.0		
Living alone	7	4.7		
<u>Presence of chronic illness</u>				
Cataract/vision impairment	6	4.0		
Hypertension	53	35.3		
Arthritis	6	4.0		
Diabetic mellitus	46	30.7		
Heart diseases	14	9.3		
Neurological problems	2	1.3		
Asthma	8	5.3		
Chronic kidney disease	3	2.0		
Bone and muscle disorders	12	8.0		
Cancers	2	1.3		
Others	58	36.0		
<u>Local areas</u>				
Urban	93	62.0		
Rural	17	11.3		
Sub urban	40	26.7		

MEASUREMENT MODEL

Next, the data was further analysed using SmartPLS 4.0, following the two-stage approach.¹³ This process involved assessing the measurement model for reliability and validity before evaluating the structural model. Bootstrapping with 5,000 samples was used to test significance. The first step was measuring the internal consistency. Internal consistency was assessed using Cronbach's Alpha and Composite Reliability (CR). As shown in Table III, Cronbach's Alpha values ranged from 0.883 to 0.908, exceeding the recommended threshold of 0.7.¹⁴ Similarly, CR values were above 0.7, confirming the reliability of all constructs.¹⁵

Indicator reliability was assessed by examining outer loadings of each item. Following established PLS-SEM guidelines,^{14,16} Indicator loadings of 0.70 or higher are considered ideal, while loadings between 0.50 and 0.70 may be retained if construct reliability and convergent validity remain satisfactory. In the initial model, 12 items under the religious coping construct demonstrated loadings below the acceptable threshold. Consequently, the items were removed due to insufficient outer loadings (< 0.50) to improve measurement quality. The final model retained 10 religious coping items, with loadings ranging from 0.583 to 0.851. Next, convergent validity was assessed using Average Variance Extracted (AVE), with values above 0.5 indicating that each construct explained at least 50% of the variance in its indicators. The highest AVE value was 0.524 (social support), followed by 0.517 (religious coping), demonstrating adequate convergent validity. Table II presents only the retained indicators included in the final measurement model.

Next, discriminant validity was tested using the HTMT approach.¹⁷ All HTMT values were below 0.85, indicating no validity issues.¹⁸ Bootstrapping results further confirmed that confidence intervals did not include 1.00, supporting discriminant validity.¹⁴ The findings are presented in Table III.

Table II: Results Summary for Measurement Models

Constructs	Items	Indicator Reliability	Convergent Validity	Internal Consistency
		Outer loadings >0.60	AVE >0.50	Reliability Composite Reliability >0.7
Quality of Life	F19	0.528	0.501	0.945
	H3	0.669		
	HN11	0.856		
	HN12	0.802		
	HN13	0.845		
	HN14	0.735		
	I10	0.755		
	I9	0.680		
	L1	0.665		
	L2	0.760		
	P15	0.623		
	P16	0.528		
	R20	0.745		
	R21	0.685		
	SR4	0.696		
	SR5	0.587		
	SR6	0.696		
	SR7	0.662		
	SR8	0.662		
Religious Coping	R1	0.583	0.517	0.904
	R10	0.607		
	R2	0.851		
	R3	0.626		
	R4	0.822		
	R5	0.680		
	R6	0.731		
	R7	0.798		
	R8	0.743		
	R9	0.698		
Social Support	R10	0.607		
	SS1	0.658	0.524	0.913
	SS10	0.681		
	SS11	0.803		
	SS12	0.636		
	SS3	0.736		
	SS4	0.817		
	SS5	0.677		
	SS6	0.671		
	SS7	0.684		
	SS8	0.800		
	SS9	0.767		

Table III: Discriminant Validity

Variable	Religious Coping	Social Support	Quality of Life
Religious Coping	0.719		
Social Support	0.513	0.724	
Quality of Life	0.518	0.704	0.708

STRUCTURAL MODEL

After confirming reliability and validity, the structural model was assessed. The first step was the collinearity assessment. Variance Inflation Factor (VIF) values ranged from 1.361 to 2.616, below the recommended

threshold of 5, indicating no collinearity concerns.¹⁴ Bootstrapping with 5,000 resamples was performed at a 0.05 significance level to test the hypotheses. The results indicate that religious coping has a positive and statistically significant effect on quality of life ($\beta = 0.209$, $t = 2.365$, $p < 0.01$). Similarly, social support demonstrates a positive and significant relationship with quality of life ($\beta = 0.502$, $t = 4.181$, $p < 0.01$). Thus, both hypotheses are supported. These results highlight the importance of religious coping and social support in enhancing the QoL among older adults. The findings are presented in Table IV.

Table IV: Structural Model

Relationship	Path Coefficient (β)	Std. Error	t-value	P-value	Decision	R ²	f ²	Effect Size	VIF
Religious coping -> Quality of Life	0.209	0.088	2.365	$p < 0.01$	Supported	0.529	0.069	Small	1.364
Social support -> Quality of Life	0.502	0.120	4.181	$p < 0.01$	Supported	0.529	0.209	Moderate	2.616

The moderate R2 value of 0.529 suggests that social support and religious coping together account for more than 52.9% of the variance in quality of life, indicating a significant predictive relevance of the model beyond the findings reported.¹⁴ Although both predictors are statistically significant, social support appears to have a greater practical influence on quality of life than religious coping, as indicated by the small to moderate effect sizes (f^2).

DISCUSSION

This study investigated the relationship between religious coping, social support, and quality of life (QoL) among Muslim retirees in the East Coast region of Malaysia. The findings proved that religious coping and social support are significantly associated with quality of life in this population. These results offer valuable insights with important policy, practice, and future research implications.

Demographically, the study sample comprised predominantly older adults who were relatively well-

educated, financially stable, and reported strong social support networks. Despite these advantages, a significant proportion of participants faced chronic health issues, particularly chronic illnesses. This paradox highlights the complex interplay between physical health, social resources, and well-being. It suggests a critical need for targeted healthcare interventions that address chronic disease management while promoting healthy ageing strategies tailored to this population. Even among socially and economically advantaged older adults, chronic health conditions remain a key challenge to achieving optimal quality of life.¹⁹

The finding revealed a significant relationship between religious coping and QoL among the older people in the East Coast Region. Consistent with previous studies, religious coping was found to play a pivotal role in enhancing the quality of life among older adults in this study.^{20–23} A possible explanation is that in the East Coast region of Malaysia, where religious beliefs and practices are deeply ingrained in daily life, religious coping provides emotional comfort, a sense of purpose, and psychological resilience. Positive religious coping strategies such as prayer, seeking spiritual support, and engaging in religious rituals help older individuals manage stress, accept health challenges, and find meaning in life. These practices foster optimism, emotional stability, and mental well-being, ultimately improving quality of life.

This result implies that older persons gain more from concrete and emotional support from family, friends, and other members of society. Though still important, religious coping seems more of an emotional and spiritual buffer that accentuates other help. Reflecting the model's modest explanatory power, the R² value of 0.529 suggests that other factors, including mental health, physical activity, and access to healthcare, may also be necessary in influencing quality of life and should be investigated in future studies.

Similarly, social support emerged as a significant predictor of quality of life. Older adults who reported

strong support from family, friends, and communities experienced better physical health, emotional well-being, and greater life satisfaction. This finding aligns with socioemotional selectivity theory, which suggests that older adults prioritise emotionally meaningful relationships in later life.^{21,24} This could be explained by the fact that, on the East Coast, where kinship ties and communal interactions are culturally valued, strong social networks likely enhance the availability and effectiveness of social support, further contributing to positive well-being outcomes.

LIMITATION

Despite its contributions, this study has several limitations. First, the cross-sectional design prevents establishing causal relationships among social support, religious coping, and Quality of Life (QoL). Second, the use of self-reported measures may introduce social desirability bias, particularly regarding religious coping strategies.

Most significantly, the recruitment strategy introduced a systematic sampling bias. By utilising an online survey (Google Forms) distributed via WhatsApp, the study inadvertently excluded older adults with limited digital literacy, those without smartphones, and those residing in rural areas with poor connectivity. This is reflected in the participant profile, which is heavily skewed toward highly educated (80% tertiary) and financially stable individuals. Consequently, the findings may not be representative of the broader Muslim retiree population in the East Coast region, specifically the rural poor and those with lower literacy levels.

Future research should address these gaps by employing a hybrid recruitment strategy that combines digital surveys with face-to-face interviews in community centres or mosques to ensure a more inclusive socio-economic cross-section. Longitudinal studies are also recommended to understand how these variables evolve as health and social circumstances change in later life.

CONCLUSION

This study examined the influence of religious coping and social support on quality of life among Muslim retirees in the East Coast region of Malaysia. Both factors were significant predictors, with social backing demonstrating a greater practical effect. These findings reinforce the idea that quality of life in later life is not determined solely by physical health, but also by meaningful social connections and religiously embedded coping resources.

From a healthcare and policy perspective, the results support the need for integrated ageing strategies that incorporate psychosocial and spiritual dimensions alongside chronic disease management. Community-based initiatives that strengthen family involvement, peer engagement, and structured social interaction benefit older adults' well-being. In addition, recognising the role of religious coping in providing psychological comfort and resilience may enhance culturally sensitive care planning in predominantly Muslim populations.

Given Malaysia's ageing demographic profile, policymakers and healthcare providers should consider holistic eldercare approaches that combine medical management with social and spiritual support systems. Such multidimensional strategies may help sustain functional ability, emotional well-being, and overall quality of life among older adults.

ACKNOWLEDGEMENT

We thank all participants for their involvement in this study.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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Translation and Content Validation of the Dementia Communication Difficulties Scale (DCDS) in Bahasa Melayu

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ABSTRACT

INTRODUCTION: The impact of communication challenges on dementia patients' quality of life is profound and multifaceted. Originally designed in the English language, the Dementia Communication Difficulties Scale (DCDS) required translation and content validation to suit the diverse linguistic and cultural landscape of Malaysia, where culturally appropriate assessment tools are essential. **MATERIALS AND METHODS:** The translation of DCDS into Bahasa Melayu was done using a careful, methodical approach consisting of five stages: (1) forward translation, (2) synthesis, (3) backward translation, (4) expert review, and (5) cognitive debriefing. Cultural adaptation was done by a multidisciplinary team of professionals. The Content Validity Index (CVI) and Content Validity Ratio (CVR) were used by medical professionals to confirm and measure the content validity. **RESULTS:** The translated DCDS is evidenced to have excellent content validity by achieving an I-CVI score of 0.95 and 0.96 on relevance and clarity, respectively. The translation and its linguistic and cultural updates ensured the DCDS is suitable in a clinical setting and appropriately relevant for the multicultural Malaysian population. **CONCLUSION:** The DCDS in Bahasa Melayu has content validity in assessing communication problems among dementia patients in Malaysia. The DCDS has the potential to improve the quality of care and outcomes for patients, yet its clinical applicability is limited, and more psychometric assessments (reliability and construct validity) are needed to establish its true value.

Keywords

Dementia, communication difficulties, translation, content validation, cultural adaptation.

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Received: 29th October 2025; Accepted: 21st June 2026

Doi:
<https://doi.org/10.31436/10.31436/imjm.v25i04/3101>

INTRODUCTION

Expressing needs and understanding complex conversations are significant challenges for aging individuals, particularly those living with dementia. Research has shown that these communication difficulties have a negative impact on patients' social, psychological, and physical well-being.^{1,2} Communication difficulties involving speaking, understanding, reading, and writing have been shown to result in severe depression, loneliness, and social isolation.^{1,2} Several factors contribute to communication difficulties in older adults, including normal aging, loss

of cognitive function, oral frailty, and reduced oral muscular strength.^{3,4} Studies have demonstrated that communication difficulties, particularly in Alzheimer's disease, can begin to occur long before problems with episodic memory appear, highlighting the importance of early intervention.^{5,6}

Numerous intervention strategies have been investigated, including speech therapy, cognitive intervention, and the use of hearing aids, with varying degrees of accessibility and effectiveness.^{1,3} The

Dementia Communication Difficulties Scale (DCDS) was developed to help caregivers assess and manage communication challenges in dementia patients more effectively. However, many non-native English-speaking countries, such as Malaysia, have not yet adopted the DCDS and require a culturally appropriate version.⁹

This study aims to translate and validate the DCDS into Bahasa Melayu using a rigorous five-step cross-cultural adaptation process, followed by content validity evaluation. The study also examines potential cultural, sociolinguistic, and cross-linguistic challenges specific to the Malaysian context. The adaptation process consists of five steps: (1) forward translation, (2) synthesis, (3) backward translation, (4) expert review, and (5) cognitive debriefing. These steps are designed to produce a translated instrument that is free from linguistic errors and cultural biases.^{5,6}

MATERIAL AND METHODS

This study obtained ethical approval from the Universiti Putra Malaysia Ethics Committee for Research Involving Human Subjects (JKEUPM-2024-311). The linguistic and content validity of the translated tools was evaluated using established guidelines for the cross-cultural adaptation of quality-of-life instruments.⁵ A five-step process was implemented to translate and adapt the DCDS into Bahasa Melayu, followed by a content validation process.

TRANSLATION AND CULTURAL ADAPTATION

Step 1 -2: forward translation and synthesis

The original English DCDS was translated into Bahasa Melayu by two independent, bilingual native speakers: a speech therapist with a clinical background and a non-medical professional. While their initial versions presented minor linguistic variations, particularly regarding the phrasing of communication difficulties, the researchers harmonized the texts to balance conceptual fidelity with linguistic appropriateness.

This synthesis process resolved the discrepancies, yielding a unified draft.

Step 3: Backward Translation

During the back-translation phase, two independent, bilingual native Bahasa Melayu speakers translated the synthesized draft back into English. A multidisciplinary team then compared these versions against the original DCDS to identify any conceptual drifts. This review revealed three minor discrepancies, specifically regarding the colloquial wording for 'off-topic/ramble' and 'thingy.' The team iteratively revised these items to optimize semantic equivalence, ultimately achieving full alignment with the original instrument.

Step 4: Expert Review

A multidisciplinary team of seven clinicians (three speech therapists, two occupational therapists, one physiotherapist, and one audiologist, representing Malay, Chinese, and Indian ethnicities) reviewed the revised Bahasa Melayu version via teleconference. They discussed and recorded feedback on meaning, clarity, and cultural appropriateness, leading to a third revised version. The team identified five items needing cultural tweaks (e.g. Bendah alah) and clarified two ambiguous terms, resulting in a revised version.

Step 5: Cognitive Debriefing

Nine caregivers of dementia patients (three from each major Malaysian ethnicity: Malay, Chinese, and Indian; aged 35–46) participated in face-to-face interviews. Each spent 10–15 minutes completing the questionnaire and providing feedback on clarity, relevance, and cultural fit. Insights from these interviews were used to finalize the Bahasa Melayu DCDS. Caregivers reported high clarity (8/9 rated all items understandable) but suggested minor adjustments for two items (e.g., simplifying phrasing for non-Malay speakers). No items were deemed irrelevant; all feedback was incorporated into the final version.

Feedback Analysis: From Step 4 and Step 5

Feedback from the clinicians' review and cognitive debriefing was analyzed using consensus methods. A multidisciplinary team (including occupational therapists, speech and language therapists, audiologists, and caregivers) consolidated suggestions, which informed iterative revisions such as enhancing cultural applicability, modifying phrases, and clarifying ambiguous terms (a total of 9 revisions) as listed below in Table I.

Table I. Results of Cognitive Debriefing

Original Term/Phrase	Identified Issue	Suggested Improvement/Outcome
Berkembang	Associated with "progressive dementia," Latest guidelines recommend	Retain
Tidak masuk akal	positive, respectful words for caregivers; seen as negative.	Use alternatives like "bertukar-tukar," "lari daripada topic," or "keluar daripada topic" to describe off-topic or illogical speech empathetically.
Percakapan terlalu sedikit untuk dinilai	Describes insufficient conversation for evaluation.	Minor change on wording Suggestion : BERCAKAP TERLALU SEDIKIT UNTUK SAYA NILAI
Mengulangi percakapan apa orang lain katakan	Refers to echoing what others say. Supposed to be Refers to repeating recently said conversations.	No major change; focus on respectful context. Suggestion : mengulangi sesuatu apa yang orang lain telah perkatakan
Bendah alah	Not usual usage; consider Borneo regional dialects.	Adapt for cultural relevance, especially for Borneo audiences, to improve relatability Suggestion : Apa benda ?
Abstrak	Lacks examples, making it hard to understand.	Provide concrete examples to explain abstract concepts.
Kehilangan jejak	All participants understood it; possible reference to "jungle trek" for context.	Retain as it's comprehensible; consider contextual examples like "jungle trek" for illustration.
Bunyi	Refers to sound; may need clarification.	Replace or clarify with "sebutan" (pronunciation) for precision. Replaced
Item 13- Example	Provide the root words	Mengangguk-angguk, Senyumam-senyum Gelisah- bergelisah

CONTENT VALIDITY PROCESS

Content validation was conducted to assess the relevance, clarity, and necessity of items in the Bahasa Melayu DCDS after five step translation process.

STEPS FOR CONTENT VALIDATION

- Translation and Cultural Adaptation:** The five-step process described above was completed.
- Expert Panel Review for Content Validity Index (CVI):** A panel of 12 medical practitioners rated each item's relevance and clarity on a 4-point scale.
- Item-Level Content Validity Index (I-CVI):** The I-CVI is calculated as the proportion of experts who rate an item as relevant or clear. Specifically, it is the proportion of experts who rate an item as either "quite relevant/clear" (3) or "highly relevant/clear" (4) on a 4-point scale. This means that the I-CVI reflects the consensus among experts regarding the relevance and clarity of each item, rather than being based on the opinion of a single expert.
- Scale-Level Content Validity Index (S-CVI):** The S-CVI is the average of all I-CVIs across the items in the scale. It provides an overall measure of the content validity of the entire scale, indicating how well the items collectively meet the criteria for relevance and clarity as judged by the expert panel.
- Necessity Assessment for Content Validity Ratio (CVR):** A separate panel of 10 experts rated each item's necessity. CVR was calculated using the formula: $CVR = (n_e - N/2) / (N/2)$, where n_e is the number of experts rating the item as "necessary," and N is the total number of experts.
- Item Evaluation:** Items with low agreement in relevance, clarity, or necessity were reviewed, modified, or removed based on expert feedback.
- Cultural Re-alignment:** Specific items were adapted for Malaysian contexts (e.g., replacing idioms).
- Finalization:** The final Bahasa Melayu DCDS incorporated all feedback from experts and caregivers.

RESULTS

Linguistic Validation

Several major changes in the adaptation of the Dementia Communication Difficulties Scale (DCDS) in the translation and cultural adaptation to the Malay Language of Malaysia were made for cultural and contextual relevance and clarity purposes. The adjustments made involved the cultural idioms, terminology, and articulation.

Regional candidates for the expression, “Rome wasn’t built in a day”, include the phrase, “Katak Di Bawah Tempurung”. Also, the phrase “Their use of pronouns (e.g., 'he', 'she', and 'they') is poor”, from which the term “poor” was substituted with “weak”, was intended to eliminate any negative connotations. The phrase “bahasa mudah” was replaced with “ayat mudah”. “Menyimpang” was corrected to “bertukar-tukar”, “lari daripada topik”, “keluar daripada topik”, and “tukar” from which a plural or locative form is used to indicate some of the synonyms for the term “menyimpang” on a lesser scale. Minimal changes involved two words and two phrases, in addition to one word with several alternatives. The changes made to the DCDS scale were necessary to eliminate all cultural and linguistic prejudices to enhance the understanding and flexibility of the scale for the users.

Table II. Outcome of Linguistic Validation

Change Category	Original Phrase/Word	Modified Phrase/Word	Change Count
Cultural Idioms	"Rome wasn't built in a day"	"Katak Di Bawah Tempurung"	1 phrase
Terminology Adjustments	"poor" in "Their use of pronouns..."	"weak"	1 word
Language and Clarity	"bahasa mudah"	"ayat mudah"	1 phrase
Language and Clarity	"menyimpang"	Suggested alternatives: "bertukar-tukar," "lari daripada topik," "keluar daripada topik"	1 word with multiple suggestions

Outcome of Content Validity Process

A total of twelve and ten medical practitioners assessed the CVI of the translated Bahasa Melayu DCDS for relevance and clarity, and CVR for the necessity of questions, respectively. The practitioners included

medical doctors from a medical clinic, occupational and physiotherapists, optometrists, speech therapists, a pharmacist, and a dentist. The majority of DCDS questions demonstrated a high degree of content validity regarding relevance and clarity. I-CVI scores ranged from 0.83 to 1.00 (average S-CVI=0.92), indicating excellent relevance and clarity. CVR scores ranged from 0.60 to 1.00, with all items meeting the threshold for necessity (no items discarded).

Table III: Summary of content validity analysis for questionnaires

Item	Relevance (Number of Experts=12)		Clarity (Number of Experts=12)		CVR*** (Number of Experts=10)
	I-CVI**a	κ**a	I-CVI**a	κ**a	
1. They have difficulty coming up with words.	1.00	1.00	1.00	1.00	1.00
2. They are likely to repeat things that they have just said	0.92	0.91	0.92	0.90	1.00
3. They are likely to repeat things that other people have said	0.92	0.91	0.92	0.90	1.00
4. They tend to digress / to go off on a tangent	1.00	1.00	1.00	1.00	1.00
5. They use filler words (e.g. “thing”, “whatsit”) instead of content words (e.g. “pen”, “cooker”)	1.00	1.00	0.83	0.80	1.00
6. They have difficulty understanding simple language	1.00	1.00	1.00	1.00	1.00
7. They have difficulty understanding abstract language (e.g. “Rome wasn’t built in a day”)	1.00	1.00	0.92	0.90	0.80
8. They have problems understanding even single words	1.00	1.00	1.00	1.00	0.80
9. They lose track of what they are saying	1.00	1.00	1.00	1.00	1.00
10. They are difficult to understand	0.83	0.81	0.92	0.90	0.60
11. Their use of pronouns (e.g. “he”, “she”, “they”) is poor	0.83	0.81	1.00	1.00	1.00
12. Their speech makes little sense because they use the wrong words or sounds	0.92	0.92	1.00	1.00	1.00
13. They communicate nonverbally (e.g. nodding, smiling, agitation, striking-out)	0.92	0.91	0.92	0.90	1.00

DISCUSSION

The integrity of the original DCDS was fully maintained during its translation into Bahasa Melayu through a systematic, five-step adaptation process.^{5,6}

Incorporating forward-backward translation, expert reviews, pretesting, and cognitive debriefing ensured the final instrument is both culturally meaningful and methodologically sound for Malaysian dementia caregivers.^{5,6} The content validation phase confirmed that the items were both relevant and essential. This was reflected in the high Item-Content Validity Index (I-CVI) scores, which averaged 0.92, alongside strong Content Validity Ratio (CVR) values. Furthermore, the feedback indicated that the vast majority of items were highly comprehensible^{7,8}. Idiomatic phrasing was adjusted to maximize local relatability, following best-practice protocols for maintaining cross-cultural equivalence.^{5,6} The multidisciplinary expert panel, which included members from diverse ethnic backgrounds, addressed the varied communication challenges present in Malaysia's multiethnic population. This approach was consistent with the adaptation of the Montreal Cognitive Assessment into Malay (MoCA-BM).¹⁰ During cognitive debriefing, caregivers validated the practical usability of the tool while flagging a few minor linguistic ambiguities. We addressed these issues through iterative modifications, reflecting the standard feedback-driven refinement loops common in cross-cultural instrument validation.¹¹ Limitations of the study include the small sample size used in cognitive debriefing (n=9) and the absence of reliability testing, both of which should be addressed in future psychometric evaluation.^{1,3}

CONCLUSION

This adapted Bahasa Melayu DCDS represents a vital tool for assessing dementia-related communication difficulties in Malaysia's multicultural context, potentially improving clinical interventions and caregiver support. Future research should prioritize larger-scale psychometric testing, including reliability and validity assessments, to enhance its applicability across diverse populations and facilitate broader adoption in Southeast Asian healthcare settings.

INSTITUTIONAL REVIEW BOARD (ETHIC COMMITTEE)

Approval for ethics was obtained from the Universiti Putra Malaysia Ethics Committee for Research involving Human Subjects (JKEUPM-2024-311). Linguistic and Content Validation of the Stroke Impact Scale (SIS) 3.0 (Khaw et al., 2021) in Three Languages (HA Ainuddin, 2023) was used as references.

ACKNOWLEDGEMENT

We also extend our thanks to the multidisciplinary team from Malaysia's major ethnic groups, whose insights and feedback were crucial in ensuring the cultural and linguistic appropriateness of the translated tool. Additionally, we appreciate the support of the medical professionals who participated in the content validity assessment, as well as the caregivers and healthcare practitioners who provided valuable feedback during the cognitive debriefing sessions. Finally, we acknowledge the support of the Malaysian Research Institute On Ageing (MyAgeing®) at Universiti Putra Malaysia (UPM) and the Ministry of Health, Kuala Lumpur, Malaysia, for their assistance and resources throughout this study. This acknowledgment section pays tribute to Dr. Muhammad Hibatullah bin Romli's contributions while also recognizing the efforts of other individuals and organizations involved in the research.

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A CT-Based Comparative Analysis of Mandibular Morphology Across Dentofacial Classification

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ABSTRACT

INTRODUCTION: Anatomical variations of the posterior mandible have been an ongoing dialogue because of the importance of ensuring the safety of a vital structure that has a risk of damage in mandibular surgeries. Hence, this study aims to analyse the morphology of posterior mandibles across different dentofacial relationships. **MATERIAL AND METHODS:** A cross-sectional study was conducted utilizing CT scans of the head and neck. The recruitment of samples adhered to specified criteria, which were then categorised according to their skeletal pattern. The CT measurements include height of ramus (R), distance from lingula to sigmoid notch (LS), distance from lingula to inferior border (LI), vertical position of lingula in relation to occlusal plane (L-OP), ramus thickness at the crestal level (RT-C), and ramus thickness midway between sigmoid notch and lingula (RT-M). **RESULTS:** A total of 60 CT scans were evaluated and classified into Class I, II, and III. The LI and RT-C displayed noteworthy differences ($p < 0.05$) when compared across groups. Other variables showed no significant difference. Nonetheless, a marginal difference was observed in the ramus height ($p = 0.055$). Upon additional post hoc analysis for LI and RT-C, significant differences exist between Class II and III ($p = 0.019$, $p = 0.023$, respectively). **CONCLUSION:** Significant differences exist in the critical landmarks of the posterior mandible of different dentofacial patterns, where Class II mandibles portrayed a thicker ramus at the crestal level and a shorter distance from the lingula to the inferior border. These findings are crucial information in ensuring safe surgical practice involving the posterior mandible.

Keywords

Mandible, Morphology, Dentofacial, CT Scan

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Received: 16th November 2025; Accepted:
25th June 2026

Doi:
<https://doi.org/10.31436/10.31436/imjm.v25i04/3118>

INTRODUCTION

Dentofacial relationship refers to the alignment of the dental and skeletal components of the maxilla and mandible. Different dentofacial relationships can occur due to multiple developmental causes. One of them includes mandibular prognathism and retrognathism caused by overgrowth and undergrowth of the jaw, respectively¹. Patients with these mandibular anatomical variations may present with a different dentofacial relationship commonly categorised into Class I, Class II, and Class III dentofacial relationships.²

These significant anatomical variations in the posterior mandible can hinder various ramus osteotomy procedures, including sagittal split ramus osteotomy, inverted L ramus osteotomy, vertical ramus osteotomy, and ramus graft harvest. These are common orthognathic surgery procedures indicated in patients with deformities in their dentofacial relationship.³ Key anatomical considerations during the surgical procedure encompass the height and thickness of the ramus, the position of the lingula and coronoid notch, as well as the location of the mandibular foramen. This

anatomical information, which was believed to differ in different dentofacial relationships, is crucial in averting complications associated with mandibular osteotomies.⁴ Unfavourable fracture, also known as bad split, is a disastrous intraoperative complication in orthognathic surgery, with reported incidences ranging from 2% to 23%.⁵ These bad splits result in prolonged operation time to fix the unfavourable fractures while ensuring the planned movement for the orthognathic surgery is achieved intraoperatively. Postoperatively, this complication can exacerbate the morbidity with issues such as postoperative neurosensory disturbance, temporomandibular joint dysfunction, and instability.⁶⁻⁸ Previous studies have identified factors associated with bad splits in mandibular osteotomy, including variations in the mandibular anatomy, presence of third molars, age, and surgical technique.⁸ One particular factor that risks bad split complications is the variations in the mandibular anatomy of different dentofacial classes. It was thought that mandibular prognathism is associated with a longer and thinner ramus, while mandibular retrognathism is linked to a shorter and thicker ramus. An anatomical study of Thai cadaveric mandibles reported the variations in the distance between the coronoid and gonion, as well as the position of the lingula in various mandibular classes.⁹ Another retrospective Cone Beam Computed Tomography (CBCT) study found that shorter ramus and thinner mandible increase the susceptibility of bad splits during sagittal osteotomy.¹⁰

For these reasons, various imaging modalities have been employed and have become a prevalent tool for the preoperative evaluation of mandibular anatomy to aid the identification of gross anatomical features in the posterior mandible.¹¹ A panoramic radiograph will give an overview of the mandible, allowing for assessment of some landmarks in two dimensions. Meanwhile, a three-dimensional assessment of the mandibular anatomy would provide a more precise and accurate evaluation of the key landmarks of the mandible.^{12,13}

The current literature debates the mandibular anatomical differences in various dentofacial relationships due to the heterogeneous methodologies used and the diversity of ethnicity.¹⁰ Currently, there is insufficient evidence to confirm that the differences in the posterior mandibular anatomy in three dentofacial relationship classes do exist.

Therefore, the aim of this research was to evaluate the anatomical morphology of the posterior mandible using CT imaging in different dentofacial relationships concerning the key landmarks involved in various posterior mandibular surgeries. Secondly, this study also aims to compare the morphology between different dentofacial relationships. This information would be crucial for surgical decision-making and establishing a safe surgical reference for mandibular osteotomies.

MATERIALS AND METHODS

STUDY DESIGN

A cross-sectional study was conducted using computed tomography (CT) scans of the head and neck region obtained from the database of the radiology department, Sultan Ahmad Shah Medical Centre @IIUM.

STUDY SAMPLE

The sample consisted of CT scans of the head and neck region taken from the years 2016 to 2021, indicated on adult patients aged 18 and above for any clinical reasons. The CT scans were screened for any notable evidence of a history of jaw surgery, mandibular fracture, severe facial asymmetry, edentulous mandible, and presence of pathology in the maxillofacial region that will lead to deformity of the facial skeleton, such as fibrous dysplasia of the maxillofacial region, intra-bony tumour, and soft tissue tumour that is abutting on the mandible, were excluded. The medical records were carefully reviewed to exclude syndromic cases.

The sample was collected via convenience sampling. Sample size was obtained using G*Power analysis for one-way Anova F test (G*Power software version

3.1.9.7), with the alpha error set at 0.05 and the test power set at 80%. A medium effect size ($d = 0.66$) was assumed based on the magnitude of mean differences and the level of variability commonly reported in previous CBCT-based mandibular morphometric studies comparing different skeletal patterns.¹⁴ The minimum total required sample size for this study was 39. However, to improve the statistical analysis, a total of 60 CT scans of the head and neck were recruited and analysed.

IMAGING

The CT imaging of the head and neck was done with patients in the supine position and head placed at the midline, using Siemens Somatom (Siemens Healthcare, Erlangen, Germany) with the following technical specifications; collimation: 16 x 0.6 mm, tube settings: 130 kV, 26 mAs; scan time: 23.8 s. DLP: 110.6 mGy cm; scan length: 342 mm. CTDI vol: 3 mGy; rotation time: 1s. eff. The images were taken to allow multiplanar reconstruction with axial, coronal, and sagittal reformats at a slice thickness of at least 3mm. These DICOM images were then exported and transferred into the Picture Archiving and Communication System (PACS) for viewing and analysis.

DATA COLLECTION

The dependent variables consist of the posterior mandible landmarks on CT, while the independent variable was characterised by the different dentofacial relationships. The measurement and analysis of the CT images were done using PACS.

The CT scans were first evaluated, and skeletal classification was determined based on the ANB angle from lateral cephalometric analysis according to Steiner’s analysis, with 2-4° as Class I, >4° as Class II, and <2° as Class III.¹⁵ This step involved determining the points A, B, and Nasion at the mid-sagittal slice of the CT scan (see Figure 1). Using the ANB angles, the samples were then categorised according to the Angles skeletal classification. This step was analysed and

categorised by 2 researchers (W.N.Z. and I.N.I.) who underwent prior training to measure the landmarks. Secondly, the mandibular morphology was assessed and measured digitally using PACS by 2 researchers (S.A.Y. and N.N.S.). Both researchers also underwent prior training before their analysis. The posterior mandible anatomical landmarks and measurements were selected and measured according to protocol from a previous CT anatomical study.¹³ Table I represents the anatomical parameters and their descriptions. Figure 2 illustrates the method employed for the CT measurement of each individual landmark.

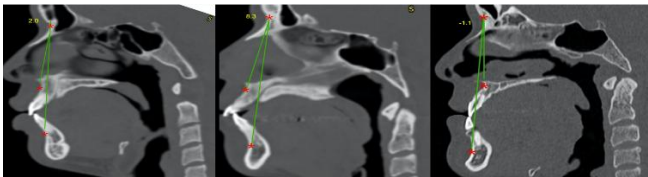


Figure 1. Determination of the $\angle$ ANB

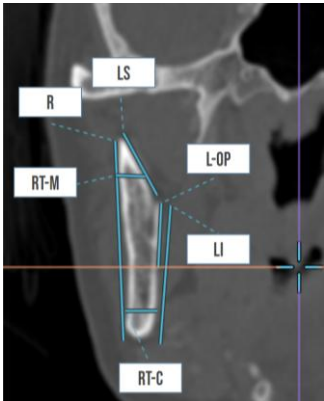


Figure 2. The measurement for the anatomical landmark

Table I. Description of the anatomical parameters

Parameters	Description
Point A	The point of deepest concavity anteriorly on the maxillary alveolus
Point B	The point of deepest concavity anteriorly on the mandibular apical base
Nasion	The most anterior point of the frontonasal suture
ANB	The angle formed by point A, Nasion and point B
R	Ramus height
LS	Lingula to sigmoid notch distance
LI	Lingula to inferior border distance
L-OP	Vertical position of lingula relative to the occlusal plane
RT-C	Ramus thickness at crestal level
RT-M	Ramus thickness midway between sigmoid notch and lingula

OUTCOME MEASURES

The primary outcome of this study was to determine the morphology of the posterior mandible in different dentofacial relationships and compare the morphology of the posterior mandible in different dentofacial relationships. All data collection and relevant statistical analyses were conducted using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). The Intraclass Correlation Coefficient (ICC) test was employed to assess intra-reliability and inter-reliability between two researchers for both CT measurements of the posterior mandible and the different dentofacial classes. Descriptive statistics of the variables were analysed for each category of dentofacial relationships. The normality test was done by using One-Sample Kolmogorov-Smirnov test. The comparison of the posterior mandible anatomical variables between the three groups was done utilizing One-Way ANOVA test for the normally distributed data and Kruskal Wallis test as the non-parametric test. The statistical significance is indicated by a p -value < 0.05 .

RESULTS

A total of 60 CT images were collected and categorised into Class I, Class II, and Class III, with each group consisting of 20 CT images. The mean age of the total sample was 54.5 years (SD: 18.66; range 19 - 84). The gender distribution was generally equally distributed with male and female 43.3% and 56.7%, respectively. The majority of the ethnicity of the CT images belonged to the Malay (N=54/60) with a small Chinese minority. The means for the ANB angle for each dentofacial relationship were in accordance with the Angles definition.

An inter-examiner reliability test was done for the first 10 patients involving every skeletal pattern class. The ICC was used as an inter-examiner reliability test and generally showed good inter-examiner reliability, with ICC ranging from 0.754 to 0.863. Variables LS and L-OP initially showed moderate reliability. However, after additional training and repeat measurements, the

reliability of these measures improved modestly, approaching the good agreement threshold.

Group comparisons were carried out using one-way ANOVA and Kruskal–Wallis tests, as appropriate, to compare the measured parameters across the different dentofacial groups.

PRIMARY OUTCOME

The posterior mandibular landmarks across the three dentofacial groups are summarised in Table II. Group comparisons demonstrated statistically significant differences in certain parameters, particularly LI and RT-C, while the remaining measurements did not differ substantially between the groups.

Table II. Results comparison of mandibular landmarks between different skeletal classes

Mandibular Landmark (mm)	Class I (Mean $\pm$ SD)	Class II (Mean $\pm$ SD)	Class III (Mean $\pm$ SD)	p -value
R ^a	48.8 $\pm$ 6.66	48.7 $\pm$ 4.40	51.3 $\pm$ 4.92	0.055
LS ^b	18.7 $\pm$ 3.04	19.5 $\pm$ 2.97	18.9 $\pm$ 3.76	0.233
LI ^a	32.4 $\pm$ 4.75	31.8 $\pm$ 3.61	34.5 $\pm$ 4.61	*0.017
L-OP ^a	17.2 $\pm$ 5.42	16.2 $\pm$ 6.12	15.7 $\pm$ 4.29	0.446
RT-C ^a	8.7 $\pm$ 1.87	8.8 $\pm$ 1.69	7.9 $\pm$ 1.33	*0.017
RT-M ^b	7.5 $\pm$ 1.36	7.2 $\pm$ 1.37	6.9 $\pm$ 1.58	0.511

^aOne Way ANOVA, ^bKruskal Wallis Test, * p -value <0.05

SECONDARY OUTCOME

Subsequent post hoc analysis was conducted for LI and RT-C to identify significant differences across Class I, Class II, and Class III skeletal patterns, as presented in Table III and Table IV. The results revealed that the statistically significant differences in LI and RT-C were mostly driven by comparisons between Class II and Class III skeletal patterns, while comparisons involving Class I did not demonstrate statistically significant differences for majority of measured parameters.

Table III. Post hoc analysis for LI

Skeletal Pattern	Skeletal Pattern	Mean Difference	Std. Error	Sig.	95% Confidence Interval	95% Confidence Interval
(I)	(J)	(I-J)			Lower Bound	Lower Bound
Class I	Class II	0.54	0.973	0.843	-1.76	2.85
Class I	Class III	-2.12	0.973	0.078	-4.43	0.18
Class II	Class III	-2.67	0.973	*0.019	-4.98	-0.36

*Tukey Honestly Significant Difference test with p -value <0.05

Table IV. Results of post hoc analysis for RT-C

Skeletal Pattern	Skeletal Pattern	Mean Difference	Std. Error	Sig.	95% Confidence Interval	95% Confidence Interval
					Lower Bound	Lower Bound
(I)	(J)	(I-J)				
Class I	Class II	-0.14	0.368	0.926	-1.01	0.73
Class I	Class III	0.85	0.368	0.059	-0.02	1.72
Class II	Class III	0.99	0.368	*0.023	0.11	1.86

*Tukey Honestly Significant Difference test with p -value<0.05

DISCUSSION

The key findings of this study revealed notable variations in the measurements of LI and RT-C across three classes of dentofacial deformity. Upon conducting the post hoc test, the comparison between Class II and Class III predominantly drives these significant differences in both parameters. This outcome suggests a discernible distinction in the mean values of the lingula position and ramus thickness, particularly when comparing the Class II and Class III skeletal patterns.

This study first evaluated the morphology of the posterior mandibular landmarks using CT imaging across different dentofacial relationships. The results demonstrated that patients with a class III skeletal pattern had higher LI, indicating a higher lingula level from the inferior border. A significant difference was noted when comparing class III and class II exclusively after conducting the post hoc test. This finding concurred with other recent studies that confirmed a higher position of the mandibular lingula in relation to the inferior border, the occlusal plane, and the internal oblique ridge.^{16–18} However, all the mentioned studies compared between class I and class III while excluding class II skeletal patterns.

The clinical relevance of having knowledge on the variations in the position of the lingula in different dentofacial patterns includes the ability to locate the inferior alveolar nerve that enters the mandibular foramen behind the lingula. This information provides crucial operative planning in various ramus surgeries, including the sagittal split osteotomy, inverted L osteotomy, and ramus graft harvest.^{18,19} Precise

localisation of the lingula allows the osteotomy to be placed higher, thereby reducing the risk of inferior alveolar nerve injury, a known consequence of mandibular osteotomies.^{20,21} Inferior alveolar nerve injury may result in neurosensory disturbances such as numbness, altered sensation, or persistent paraesthesia of the lower lip, chin, and mandibular teeth, which can adversely affect speech, mastication, and overall quality of life. In some cases, these sensory deficits may be permanent, emphasising the importance of comprehensive anatomical assessment prior to surgery.²⁰ Furthermore, when giving an inferior alveolar nerve block for skeletal class III individuals, adjustment needs to be considered, as they have a higher lingula level. Following the standard technique in locating the anatomical landmark for inferior alveolar nerve (IAN) block may lead to ineffective local anaesthesia.

Regardless, there is a limit on the extent to which the osteotomy or the vertical placement of the IAN block needle should be placed more superiorly. This depends on the vertical distance between the lingula and the sigmoid notch and between the lingual and the occlusal plane. Fortunately, this study found no significant difference between the dentofacial classes in the position of the lingula in relation to the sigmoid notch and occlusal plane. Current evidence also indicates that the morphology of the ramus further superior from the lingula becomes slenderer and thinner with minimal cancellous bone between the two cortical walls, thereby further risking complications such as bad splits.^{10,17}

Subsequently, posterior mandibular morphology was compared across Class I, Class II, and Class III dentofacial relationships. This study found a significant variation in the thickness of the mandibular ramus at the crestal level across different skeletal classes ($p=0.017$) with class II and class III having the most significant difference when a post hoc test was analysed ($p=0.023$). This finding is in agreement with other studies, which also found that Class III individuals have a thinner ramus.^{18,22} Similarly, other studies concluded that the class II skeletal pattern has a significantly thicker ramus

near the crestal and occlusal plane level.^{23,24} The clinical significance of this information is that it allows surgeons to determine the depth of the osteotomy, especially where cancellous bone is absent, to ensure a more predictable fracture propagation when the osteotomy is made, thereby preventing the incidence of unfavourable splits and damage to the IAN.^{18, 25}

This study has several methodological considerations that should be acknowledged. The use of convenience sampling may limit the generalisability of the findings to the wider population. However, this approach enabled the inclusion of comparable group sizes across skeletal patterns, thereby supporting balanced statistical comparisons and maintaining adequate analytical power. In addition, the effect size used for sample size calculation was derived from previously published CBCT-based mandibular morphometric studies rather than pilot data from the present population. As anatomical variability may differ according to population characteristics and imaging modalities, the true effect size in this cohort may not be identical to the estimated value. Nevertheless, the final recruited sample exceeded the minimum required number, which strengthens the robustness of the statistical analysis. Furthermore, although the CT scans were collected over a five-year period, all images were acquired using the same scanner and standardised imaging parameters, thereby enhancing reproducibility of the study. Future prospective studies with controlled sampling strategies and standardised imaging timelines may further validate and expand upon these findings.

CONCLUSION

The study highlighted notable distinctions in certain mandibular parameters, namely the lingula position in relation to the inferior border of the mandible and ramus thickness at the crestal level, between Class II and Class III dentofacial deformity. These findings contribute as a surgical reference for clinical applications in maxillofacial surgery, particularly surgeries involving the posterior mandible.

INSTITUTIONAL REVIEW BOARD (ETHICAL COMMITTEE)

Ethical clearance has been granted by the IIUM Research Ethics Committee (IREC 2023-089).

ACKNOWLEDGEMENT

This research was supported by the International Islamic University Malaysia, under the Research Initiative Grant Scheme (RIGS17-021-0596).

The authors also wish to express sincere gratitude to the radiographers, IT technicians, dental officers, and lecturers for their invaluable guidance, constructive feedback, and unwavering support throughout the research process. The authors would like to thank their family and friends for their encouragement and moral support during the writing and revision stages of this manuscript.

CONFLICT OF INTEREST

There is no conflict of interest to declare.

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Associated Factors of Parental Stress: Child Repetitive Behaviour and Cognitive Emotional Regulation in Parents of Children with Autism Spectrum Disorder in Kelantan

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ABSTRACT

INTRODUCTION: Restricted and Repetitive behaviour (RRB) is one of the main features in autism spectrum disorder (ASD). This behaviour may disrupt children's routines and adaptability, contributing to significant parental stress. Good coping strategies are important for parents in handling this stress. This study aims to study the parents' stress levels, children's restricted and repetitive behaviour, and cognitive-emotional regulation among parents of ASD children in Kelantan and its associations. **MATERIALS & METHODS:** A cross-sectional study was conducted from December 2023 to May 2024, involving 177 parents, selected through purposive sampling. Data were collected using the Malay versions of the Perceived Stress Scale, Repetitive Behaviour Scale-Revised, and Cognitive Emotional Regulation Questionnaire. Descriptive statistics and linear regression analyses were performed using SPSS to identify significant predictors. **RESULTS:** Among the respondents, 80.2% were mothers. The mean perceived stress score was slightly high at 16.86 (6.26). Positive Reappraisal had the highest cognitive strategy score with a mean 15.30 (3.89). The most common RRB was *Sameness* with a mean 7.95 (6.38). Factors significantly associated with parental stress included being a mother, having mental illness, *Rumination*, *Positive Refocusing*, *Positive Reappraisal*, *Stereotyped*, and *Sameness* behaviour (all $p < 0.05$). **CONCLUSION:** Parental stress was moderately high among those with ASD children in Kelantan. Major stressors included being a mother, having mental illness, *rumination*, and children's *stereotyped* and *sameness* behaviours, while *positive refocusing* and *reappraisal* acted as protective factors. These findings highlight the need to promote effective cognitive emotional regulation strategies to alleviate stress in parents of children with ASD.

Keywords

Autism Spectrum Disorder, Repetitive Behaviour, Stress, Parents, Emotional Regulation.

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Received: 12th December 2024; Accepted: 5th August 2026

Doi:
<https://doi.org/10.31436/10.31436/imjm.v25i04/2800>

INTRODUCTION

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterised by impairments in communication, behaviour and social functioning beginning in childhood¹. ASD affects approximately 0.6% of children worldwide.² Ministry of

Health Malaysia recorded that the prevalence of ASD was 1.6 in 1000 population. One of the key domains in diagnosing ASD in children is restricted and repetitive patterns of behaviour, interests, or activities.³

Caring for a child with ASD presents unique challenges that significantly impact the mental health and well-being of caregivers.⁴ The stress associated with these demands can be substantial and often leading to multiple mental health issues compared to caregivers with typically developed children.^{5,6} Xin Lee compared stress levels among Malaysian parents of typically developed children to parents of ASD children and found significant higher level of parenting stress among the latter group ($U=15.0$, $p<0.001$).⁷ A study by Adib et al found that 81.6% of parents with ASD children in Kelantan experienced moderate to high level of stress with mean perceived stress score of 16.96 ($SD=4.66$).⁸

Parental stress in families with children diagnosed with ASD significantly impacts the well-being of both parents and children, influenced by environmental, child-related, and parent-related factors.⁹ These include residing far from healthcare facilities, lack of personal transportation to treatment centres, children of younger age, children with comorbid intellectual disability and social impairment and parents poor coping strategies.^{8,9,10,11}

Restricted and repetitive behaviour (RRB) is thought to be a hallmark of ASD.¹² According to Esbensen et al., RRBs encompass a wide range of behaviours, from repetitive movements to more cognitively mediated symptoms like excessive interests or preoccupations.¹³ Restricted and repetitive behaviours can be particularly challenging for parents as they may interfere with daily routines and make transitions or unexpected changes more difficult for children. Managing these behaviours often requires additional time, attention, and flexibility from caregivers, which may contribute to increased parental stress. A study in Italy found that among the RRB subtype, Stereotype and Ritualistic/Sameness behaviour was the most frequent behaviour among ASD children.¹⁴ While a local study by Chua et al., found positive correlation between behavioural problems and caregiver burden.¹⁵

Often, parents of children with ASD employ maladaptive coping strategies, and this too increase their

susceptibility to stress exhibiting higher levels of anxiety and depression compared to parents with typically developed children.^{16,17} Cognitive emotional regulation (CER) is a process of integrating emotional and behavioural responses, allowing individuals to adapt their strategies in response to changing emotional contexts.¹⁸ Parents of children with ASD who had difficulty in managing emotions are linked to an increase perception of stress in their parenting roles.¹⁹

Existing research on ASD has focused on parental stress related to meeting children's needs, social factors, and general behaviours. Although studies such as Harrop et al. have reported associations between restricted and repetitive behaviours (RRB) and caregiver stress, evidence from Malaysia remains limited. Research examining the combined influence of children's RRB and parental cognitive emotional regulation (CER) strategies on parental stress is also scarce. Therefore, this study investigates the relationship between RRB, CER strategies, and parental stress, among parents of children with ASD in Kelantan.

MATERIALS AND METHODS

Design and Participants

This cross-sectional study was conducted from December 2023 to May 2024, employing purposive sampling to select participants from two populations: children attending the psychiatric clinic at Hospital Pakar Universiti Sains Malaysia (HPUSM), Kubang Kerian, Kelantan and those at the Kelantan Autism Care Centre (KACC), Kota Bharu, Kelantan. HPUSM offers multidisciplinary services, including Child and Adolescent Psychiatry, while KACC provides education and rehabilitation for children with ASD throughout Kelantan. This approach facilitated access to a larger and more diverse cohort of children with ASD by incorporating children from various districts in Kelantan.

All parents attending psychiatry clinic and KACC and met the inclusion and exclusion criteria were invited to

participate in this research. The inclusion criteria were parents with ASD children aged 2-12 years, who were diagnosed by psychiatrists or paediatricians. The exclusion criteria were parents who do not understand Malay or illiterate. Only one parent from each family was invited to participate. The participating parent was the one who met the inclusion criteria of spending more time with the child. Both parents or a parent-child dyad were not included to avoid duplication of data and to ensure consistency in reporting the child's experiences. The sample size was calculated using the single mean formula, and the total number of respondents required, after accounting for a 10% attrition rate (based on prior similar online surveys among parents in our setting, which showed minimal dropout when the questionnaire was concise and recruitment was via targeted networks; additionally, the questionnaire was designed to be completed in one sitting of approximately 10-15 minutes, reducing incomplete responses), was 195.

Four sets of questionnaires were distributed online to parents, with guidance from the researcher. In cases where both parents were present, the parent who spent more time with the child completed the questionnaires (defined as the parent who, on average, spent most the child's waking hours during a typical week, more than 50% of waking hours). The questionnaires used were i) sociodemographic data ii) Perceived Stress Scale-10 (PSS-10), iii) Repetitive Behaviour Scale-Revised RBS-R) and iv) Cognitive Emotional Regulation Questionnaire (CERQ). All the questionnaires used were the validated Malay versions. The sociodemographic section contained 19 questions, divided into parent and child data. It included information on sex and age of both parents and children, educational level, employment, monthly income, which were then categorized according to the Department of Statistics Malaysia in 2020, distance to the therapy centre, medical and psychiatric conditions in parents, number of children and number of children requiring special needs, participation in therapy, and whether the children had a disability card.²⁰

The Malay version of the PSS-10 consists of 10 items rated on a 5-point Likert scale (0-4), with higher total scores indicating greater perceived stress. Stress levels are categorized as: much lower (0-7), slightly lower (8-11), average (12-15), slightly higher (16-20), and much higher (>20).²¹ The Malay version of PSS-10 was validated by Sandhu et al., and had a Cronbach's alpha of 0.63 and an ICC of 0.8. Significant correlations were found with the DASS-21 stress component ($r=0.61$, $p<0.001$; $r=0.56$, $p<0.004$).²²

The RBS-R Malay version consisted of 43 items with 6 subdomains: i) stereotyped Behaviour; ii) Self-injurious Behaviour; iii) Compulsive Behaviour; iv) Ritualistic Behaviour; v) Sameness Behaviour; and vi) Restricted Behaviour. Items on the RBS-R were rated on a 4-point Likert scale ranging from 0 to 3. The higher the RBS-R scores, the more severe the behaviours. The Malay-validated RBS-R questionnaire has a good internal consistency with Cronbach's alpha ranging from 0.758 to 0.914. The internal consistency for the overall questionnaire scale gave Cronbach's alpha coefficient of 0.940, while the overall scale-level FVI was above 0.²³

The CERQ, a 36-item self-report questionnaire, measures nine cognitive emotional regulation strategies, both i) adaptive (i.e. *positive refocusing*, *positive reappraisal*, *putting into perspective*, *refocus on planning* and *acceptance*) and ii) the less-adaptive (i.e. *rumination*, *self-blame*, *blaming others* and *catastrophizing*). The Malay version, CERQ-M, demonstrated strong reliability ($\alpha = .891$) and satisfactory fit (CFI=0.80).²⁴

STATISTICAL ANALYSIS

Data were entered, cleaned, and analysed using statistical software Statistical Package for Social Study (SPSS) version 29. Descriptive statistics were used to analyse demographic data, with categorical data presented as frequencies and percentages, and numerical data as mean and standard deviation (SD). Simple and multiple linear regression were used to identify factors associated with perceived stress. Demographic, CERQ, and RBS-R scores were analysed as independent variables, while

PSS-10 scores were the dependent variable. Variables with a p-value <0.25 and clinically relevant variables were included in the multiple regression model. Significant variables (p<0.05) were checked for interactions and multicollinearity to determine the final model.

RESULT

Characteristics of the parents and children

A total of 177 caregivers participated in this study, with a mean age of 37.29 (5.16) years old. The majority were mothers 142 (80.2%), predominantly Muslims and Malay 169 (95.5%). Educational attainment indicated 72.3% with tertiary education, while only 68.9% were employed. The majority of the participants reside less than 25km away from the therapy centre. Only 27 (15.3%) of the parents reported having underlying chronic diseases, and 14 (7.9%) had underlying mental illness. On average, the participants had one disabled child.

Meanwhile, the children with ASD had a mean age of 6.45 (2.10) years old. The majority of the children were male, 140 (79.1%). The mean age at diagnosis was 4 (1.38) years old, with 169 (95.5%) receiving therapy and 150 (84.7%) own the disability card. Their sociodemographic characteristics are shown in **Table I**.

Table I Sociodemographic profile (n=177)

Variables	n(%)	Mean (SD)
<i>Parents' Information</i>		
Age		37.29 (5.16)
Sex		
Male	35 (19.8)	
Female	142 (80.2)	
Religion		
Islam	169 (95.5)	
Buddha	4 (2.3)	
Christian	4 (2.3)	
Race		
Malay	169 (95.5)	
Non-Malay	8 (4.5)	
Marital Status		
Married	167 (94.4)	
Divorced	10 (5.6)	
Education		
Tertiary level	128 (72.3)	
Secondary level	49 (27.7)	
Employment		
Employed	122 (68.9)	
Unemployed	54 (30.5)	
Retired	1 (0.6)	

Income (n=173)		
B40 (< RM 3030)	69 (39.9)	
M40 (RM 3030 – 6619)	53 (30.6)	
T20 (> RM 6620)	51 (29.5)	
Distance (n=170)		
< 25km	147 (86.5)	
> 25km	23 (13.5)	
Chronic disease		
Yes	27 (15.3)	
No	150 (84.7)	
Mental illness		
Yes	14 (7.9)	
No	163 (92.1)	
*Disabled children		1 (0)
Children's Information		
Child age		
2-4 years old	31 (17.5)	
5-6 years old	69 (39)	6.45 (2.1)
7-9 years old	62 (35)	
10-12 years old	15 (8.5)	
Child sex		
Male	140 (79.1)	
Female	37 (20.9)	
Age of diagnosis		
Therapy		4.00 (1.38)
Yes	169 (95.5)	
No	8 (4.5)	
Disability card		
Yes	150 (84.7)	
No	27 (15.3)	
*No of siblings		2 (1)

*Median (IQR) used for number of siblings

Level of Stress Among Parents with ASD Children in Kelantan

The mean total score on the PSS for the 177 caregivers of children with ASD was 16.86 (6.26), with item 5, “*felt that things were going your way*,” scoring the highest with a mean of 2.14 (1.11).

Types of Cognitive Emotional Regulation Among Parents with ASD Children in Kelantan

Positive reappraisal (attaching a positive meaning to a negative situation for personal growth) scored the highest among parents, with a mean score of 15.30 (3.89). On the other hand, *blaming others* (attributing the responsibility for one's experiences to others) scored the lowest with a mean score of 5.62 (2.54). The result is shown in Table II.

Table II Types of cognitive emotional regulation among parents with ASD children (n=177)

Cognitive Emotional Regulation	Mean	SD
Positive Reappraisal	15.30	3.89
Refocus on Planning	14.85	3.89
Rumination	12.70	4.63
Positive Refocusing	12.53	3.57
Putting into Perspective	12.25	3.48
Acceptance	10.95	3.19
Self-Blame	9.47	4.10
Catastrophizing	8.59	3.69
Blaming others	5.62	2.54

Types of RRB Among Children with ASD in Kelantan

Sameness behaviour (resistance to change, insisting that things stay the same) scored the highest with a mean score of 7.95 (6.38), followed by *compulsive behaviour* (behaviour that is repeated and performed according to a rule or involves things being done “just so”) with mean score of 6.73 (4.57). Self-injurious behaviour scored the lowest with a mean score of 2.59 (2.06). The result is shown in Table III.

Table III Level of RRB among children with ASD in Kelantan (n=177)

RBS-R Subscales	Mean (SD)
Sameness Behaviour	7.95 (6.38)
Compulsive Behaviour	6.73 (4.57)
Stereotype Behaviour	6.29 (3.58)
Ritualistic Behaviour	5.42 (3.84)
Restricted Behaviour	4.33 (3.00)
Self-injurious Behaviour	2.59 (2.06)

Factors associated with perceived stress among caregivers with ASD children

Variables with a p-value <0.25 from simple linear regression (Self-blame, Rumination, Catastrophizing, Blaming Others, Positive Refocusing, Refocus on Planning, Positive Reappraisal, Stereotyped Behaviour, Self-injurious, Compulsive, Ritualistic, Sameness, Restricted Behaviour, Parents' Sex, Religion, Mental Illness, and Number of Children) and clinically relevant variables (distance to therapy centre, household income, and Putting into Perspective) were further analysed using multiple linear regression. The results are shown in Table IV.

The result demonstrated that mothers exhibited higher perceived stress levels than fathers, increasing the PSS score by 2.13 (p=0.037, 95%CI 0.35 to 4.00). Caregivers with underlying mental illness experienced elevated perceived stress, illustrating an increment in the PSS score by 3.36 (p=0.019, 95% CI 0.55 to 6.16).

For cognitive emotional regulation, employing strategies such as *Rumination* led to an elevation in the PSS score by 0.61 (p<0.012, 95% CI 0.44 to 0.78), while *Positive Refocusing* and *Positive Reappraisal* demonstrated reductions in the PSS score by 0.40 (p=0.01, 95% CI -

0.71 to -0.09 and 0.36 (p=0.011, 95% CI -0.64 to -0.09) respectively.

Children's behaviour *Stereotypes* and *Sameness* affects parents' perceived stress by increment in PSS score of 0.40 (p=0.001, 95% CI 0.16 to 0.64) and 0.20 (p=0.012, 95% CI 0.04 to 0.35), respectively.

Table IV Associated factors of perceived stress among caregivers with ASD children

Variables	Simple Linear Regression			r	Multiple linear regression		
	b	95% CI	P-Value		b	95% CI	P-value
Mother vs Father	2.75	(0.45, 5.05)	0.019	0.03	2.127	(0.12, 3.76)	0.037
Experiencing Mental illness	7.75	(4.50,11.00)	<0.001	0.11	3.36	(0.55,6.16)	0.019
Rumination	0.56	(0.37, 0.74)	<0.001	0.17	0.61	(0.44, 0.78)	<0.001
Positive Refocusing	-0.3	(-0.56, -0.04)	0.024	0.03	-0.40	(-0.71, -0.09)	0.012
Positive Reappraisal	0.43	(-0.70, -0.20)	<0.001	0.07	-0.36	(-0.64, -0.09)	0.011
Stereotype	0.51	(0.26, 0.76)	<0.001	0.09	0.40	(0.16, 0.64)	0.001
Sameness	0.30	(0.16, 0.44)	<0.001	0.10	0.20	(0.04, 0.35)	0.012

DISCUSSION

Consistent with previous studies, the majority of the participants were mothers, as mothers spent more time caring for the children.^{25,26} The distribution in this study reflected the Kelantanese population, where 95% of them were Muslims. The majority of the participants were Malay and Muslims.²⁷

The level of perceived stress among parents of children with ASD in Kelantan was found to be slightly high. This is aligned with previous literature whereby parents caring for ASD children were experiencing more stress compared to those with typically developing children and those with Down Syndrome.^{4,5,6,10} This heightened stress is often attributed to the children's behaviours and community stigmatization, stemming from a lack of public awareness, and understanding about ASD.^{4,7,28}

Our study found that the most commonly used cognitive emotional regulation strategies among parents in our sample were positive reappraisal, refocus on planning, and rumination. These findings align with Isa et al., where cognitive reframing, which is conceptually similar to positive reappraisal, was among the most common coping strategies, alongside religion and acceptance.¹⁰

This suggests that adaptive strategies such as reframing and planning are commonly used by caregivers, while cultural and religious contexts may also influence coping behaviours. The predominance of Malay Muslim participants in the present study may partly explain the high use of positive reappraisal. Within the local context, concepts such as *redha* (acceptance of God's will) and gratitude may encourage parents to reinterpret caregiving challenges in a more positive and meaningful manner. Such religious coping mechanisms may complement positive reappraisal and help reduce the psychological impact of caregiving stress.

Sameness behaviour emerged with the highest mean score among RRBs, confirming a trend seen in other studies where it consistently appears as one of the top three most prevalent behaviours, alongside stereotypy, restricted, and ritualistic behaviours.^{14,29,30}

Our study found that mothers experienced higher stress levels than fathers, likely due to their greater involvement in parenting and social activities with their children, as supported by previous studies^{31,32}. In contrast, Adib et al. and Azamin Anuar et al. reported no significant gender differences in stress.^{8,26} This discrepancy may stem from differences in statistical models (logistic vs. linear regression), lower PSS cut-off points in previous studies, and differences in sample populations, as earlier studies focused on broader caregiver groups rather than parents specifically.

In our study, the heightened stress levels observed, particularly among parents with underlying mental illnesses, could be indicative of the role that mental well-being plays as a contributing factor. According to Teh et al., compromised mental well-being may exacerbate the perceived stress levels in parents of children with ASD, suggesting that mental health status significantly influences stress perception.³³ This underscores the importance of supporting mental health to mitigate stress among parents of children with ASD, highlighting a crucial area for intervention.

Our findings are consistent with previous research, showing that adaptive coping strategies, such as positive reappraisal and positive refocusing, are negatively associated with stress, reinforcing their role as protective buffers against parental stress.³⁴ These strategies help parents manage stress more effectively by promoting optimism and cognitive control. In contrast, maladaptive coping strategies such as rumination are positively associated with perceived stress, as rumination is believed to perpetuate the cycle of negative thoughts and emotions in parents. This aligns with previous studies which found that emotional dysregulation and maladaptive coping strategies increase parents' vulnerability to stress, highlighting the importance of adaptive emotional regulation.^{16,17,19}

Our study found that *stereotype* and *sameness* behaviours in children with ASD cause significant stress for parents. Stereotype behaviours in children with ASD are often inappropriate and unpredictable, causing disruptions in everyday routines and adding to parental stress.^{34,35} On the other hand, sameness behaviours make it difficult for children to adapt to changes, making transitions and unexpected events particularly challenging for parents to manage. A lack of awareness about ASD makes it harder for parents and others to understand these behaviours, adding to the stress.²⁵

While previous studies have not directly associated *sameness* behaviour with increased parental stress, our findings reveal a significant connection, suggesting that such behaviours can substantially stress parents. This new insight underscores the necessity for further detailed research to understand how sameness and other RRBs specifically affect parental stress in families with ASD, potentially informing targeted interventions to better support these families.

LIMITATION AND RECOMMENDATION

One major limitation of this study is its cross-sectional design, which limits the ability to determine causal relationships between mental health issues and perceived stress. While a strong association was found,

it's unclear whether pre-existing mental health conditions increase stress or if high stress leads to mental health disorders. Longitudinal studies are needed to clarify these dynamics over time, identifying key intervention points to reduce stress and prevent mental health problems in caregivers.

The use of purposive sampling and self-reported measures may limit the generalizability of the findings, as self-reporting can introduce biases like social desirability or recall errors. Future research should adopt more rigorous sampling methods and include objective measures to improve reliability and applicability across different populations, thus confirming and expanding upon these preliminary results.

We acknowledge the potential bias due to the predominance of mothers (80%) in our sample, which reflects their more active role in caregiving. While this provides valuable insights, we recognize the importance of capturing both parents' perspectives, as fathers may experience and manage stress differently. Fathers may experience stress differently from mothers, often focusing on financial responsibilities, future planning, and concerns regarding long-term care, whereas mothers are typically more involved in daily caregiving activities and behavioural management. These differing roles may influence both the nature and intensity of stress experienced by each parent. Therefore, we recommend future studies aim for a more balanced representation of both parents to gain a fuller understanding of parental stress. Despite the bias, our findings remain relevant, as mothers are often the primary caregivers in families with children with ASD.

The findings also underscore the importance of parental mental well-being and its impact on stress levels. Therefore, screening for mental health and coping strategies in parents is crucial and should be implemented in clinical settings to better support families. Proper interventions could improve family dynamics and enhance overall quality of life.

CONCLUSION

This study examined a range of environmental, parental, and child-related factors associated with parental stress among parents of children with ASD in Kelantan. The findings highlight the significant role of cognitive emotional regulation in shaping parental stress and underscore the influence of children's stereotyped and sameness behaviours on caregiver well-being.

INSTITUTIONAL REVIEW BOARD (ETHICAL COMMITTEE)

This study was approved by the Human Ethical Committee of the School of Medical Sciences (JEPeM), Universiti Sains Malaysia, with JEPeM ethical code of USM/JEPeM/KK/23050388.

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Attitude, Educational Needs, and Challenges Faced by Physicians in Managing End-of-Life Care for Critically Ill COVID-19 Patients in Critical Care Settings During the COVID-19 Pandemic

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ABSTRACT

INTRODUCTION: End-of-life (EOL) decision-making is particularly sensitive and complex, especially during the COVID-19 pandemic. This study aimed to assess the attitudes, educational needs, and challenges faced by doctors working in critical care settings in providing EOL care for critically ill COVID-19 patients during the pandemic. **MATERIALS AND METHODS:** A structured questionnaire comprising four sections was utilized to assess the attitudes of critical care unit doctors at the Hospital Universiti Sains Malaysia and Hospital Selayang, Malaysia. The questionnaire captured responses related to the attitudes, educational needs, and challenges of the physicians in the management of critically ill COVID-19 patients. **RESULTS:** The respondents generally agreed that EOL care is an essential clinical competency during the pandemic, with a mean score of 3.44 ± 0.87 . There was strong recognition of diverse educational needs related to EOL care, encompassing both clinical and ethical aspects, with average mean scores exceeding 3 across relevant items. The physicians also identified several significant barriers to delivering effective EOL care, including the absence of standardized protocols or dedicated services ($p=0.001$), insufficient training ($p=0.006$), and time constraints ($p=0.007$). **CONCLUSION:** Overall, doctors in critical care settings demonstrated a positive attitude toward the role of EOL care for critically ill COVID-19 patients during the pandemic. A clearer understanding of their attitudes, challenges, and educational needs can help inform strategies to enhance the development and integration of EOL care in critical care settings moving forward.

Keywords

COVID-19, pandemic, critical care, End-of-Life care, educational needs

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Received: 21st September 2025; Accepted:
12th February 2026

Doi:
<https://doi.org/10.31436/10.31436/imjm.v25i04/3074>

INTRODUCTION

The COVID-19 pandemic exposed how interconnected and delicate our support systems and economies are on a global scale. There were more than 7 million COVID-19 deaths reported to WHO as of April 2024.¹ The critical illness associated with COVID-19 has underscored the vital importance of end-of-life (EOL) care within the context of the pandemic. As the severity

of the COVID-19 disease became apparent, it brought into focus the need for comprehensive and compassionate care for those facing life-threatening situations. This has prompted a heightened awareness of the significance of providing support, comfort, and dignity to individuals nearing the end of their lives due to COVID-19, emphasizing the crucial role of EOL care

in managing the impact of the pandemic on human health and well-being.

The critical nature of the COVID-19 crisis has led healthcare professionals to initiate early and intentional conversations concerning values, objectives, and treatment preferences, particularly for patients facing severe illnesses who are susceptible to clinical decline. These exchanges were further constrained by social isolation due to strict visitation policies and the need to communicate remotely.²

In the critical care setting, particularly in the intensive care unit (ICU), decision-making is complex and highly stressful. Decisions on EOL pose sensitive and challenging issues, particularly when considering cultural, legal, religious, and social factors, especially amidst a pandemic.^{3,4,16} EOL care falls within the spectrum of palliative care and is applied towards the end of the disease trajectory. According to the United States National Quality Forum, EOL care applies when a chronic illness of patients is no longer curable and life-prolonging therapies are no longer appropriate indicated or desired.⁵ To put it in simpler terms, EOL care is palliative care that is delivered when death is imminent.⁶ The concept of EOL care originated in Western countries, and an established ethico-legal framework exists in many developed Western nations.^{4,7} However, there is limited data available on EOL in other regions of the world, including Asia, the Middle East, South America, and Africa.^{8,9} The recent pandemic makes the findings of this research more relevant.

The objective of this study was to evaluate the attitudes, educational needs, and problems faced by critical care setting doctors in providing end-of-life care management for critically ill Covid-19 patients during the COVID-19 pandemic. Certainly, this study has the potential to offer valuable insights for formulating recommendations to improve preparedness for similar future pandemics. It can provide useful information for organizations and authorities in developing guidelines and protocols for providing EOL care to critically ill

patients, particularly during pandemics. Additionally, it may contribute to enhancing education for both undergraduate and postgraduate doctors, empowering them with the skills and confidence needed to deliver effective EOL care.

MATERIALS AND METHODS

This study was a multicentre, cross-sectional questionnaire study. We collected data at the critical area in Hospital USM, Kelantan, Malaysia and Hospital Selayang (HS), Selangor, from April 2023 to August 2023 through the distribution of questionnaires to doctors who are currently working in a critical care setting which met the inclusion criteria. The inclusion criteria were doctors who have had experience in taking care of critically ill COVID-19 patients (Category 4 and 5) in a critical care setting. COVID-19 Category 4 patients are those who were symptomatic with pneumonia and requiring supplemental oxygen, while Category 5 patients are those critically ill with or without other organ failures.¹⁰ The exclusion criteria included house officers, doctors on extended leave (maternity, study, and unpaid leave), as well as those deployed doctors from departments other than Anaesthesiology and ICU who offered their service taking care of COVID-19 patients in the critical care setting during the pandemic.

The questionnaire used in this study was adapted from previously validated questionnaires^{11,12,13}. Permission for the use and adaptation of the questionnaire was duly obtained from the respective authors. The adapted questionnaire underwent expert review by a panel consisting of one intensivist, one anaesthesiologist, and one palliative care physician. The panel assessed each item for clarity, relevance, and cultural appropriateness within the Malaysian ICU setting, including replacement of “emergency department” with “ICU” and the addition of scenarios involving COVID-19 care. Face validity and content validity were assessed through expert consensus, while a pilot test involving 10 ICU doctors (excluded from the final sample) was conducted

to evaluate clarity, comprehensibility, and internal consistency. Minor adjustments in wordings were made based on pilot feedback to improve item clarity.

The required sample size was calculated using both single-proportion and single-mean formulae based on previous studies.¹² For assessing attitudes and challenges in EOL care, the expected proportion was set at 50% to maximize sample size, with a 95% confidence level and 10% precision, resulting in a minimum of 96 participants. For variables assessed using mean scores, the sample size for 90% power ($\alpha=0.05$, two-sided) was estimated at 113 participants. Allowing for a 20% non-response rate, the target recruitment was 145 participants.

The questionnaire consisted of two sections. Section 1 comprised the demographic characteristics of doctors in ICU, while Section 2 contains 15 questions to assess the attitudes and problems in providing EOL care during the COVID-19 pandemic and 11 questions on the items indicating for further educational needs. A 5-point Likert scale was used for each question for Section 2, which included the options strongly disagree, disagree, neutral, agree, strongly agree.

The validated questionnaire together with participation information sheet and consent were uploaded into Google Forms and distributed to the participants through the head of department in Hospital USM and HS via the WhatsApp Messenger application (app). Participants were provided with information on the intention of the study, research procedures, confidentiality guarantee, and their right to withdraw at any time. All the data selected and sent by the participants were recorded in Google Forms via an online platform. The Statistical Package for Social Science (SPSS) version 26.0 for Windows was used for the analysis of the data in this study. Mean, standard deviations (*SD*), frequency (*n*) and percentages (%) were used to classify data. Spearman's rank correlation coefficients were used to calculate each obstacle to evaluate problems and limitations in EOL care faced by

doctors. It was considered statistically significant if $p<0.05$.

RESULTS

A total of 145 participants were included in the final analysis, with a male-to-female ratio of 1:1.5. The demographic characteristics of the respondents are presented in Table I. The majority were Muslim (51%), followed by Buddhist (31.7%), Christian (11%), and Hindu (6.2%). Most had 6-10 years of working experience, while nearly half were Master Trainees (49.7%) and one-third Medical Officers (33.8%); specialists and consultants comprised 12.4% and 4.1%, respectively. More participants were from public hospitals (58.6%) than university hospitals (41.4%). EOL care was mainly on-the-job (60%), with fewer having short courses (22.8%), no training (12.4%), or specialist training (4.8%) (Figure 1). Most respondents reported only general knowledge of EOL care (90.3%) (Figure 2), and almost all had experience caring for terminal patients (93.8%) (Figure 3). Confidence in providing such care was modest (mean score 2.17 ± 1.08), and opinions were divided on the adequacy of support, with 60% feeling insufficiently supported.

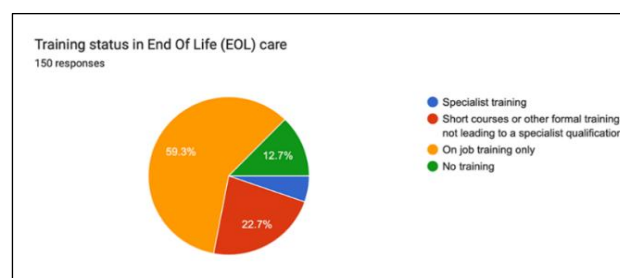


Figure 1: Training status in End of Life (EOL) care

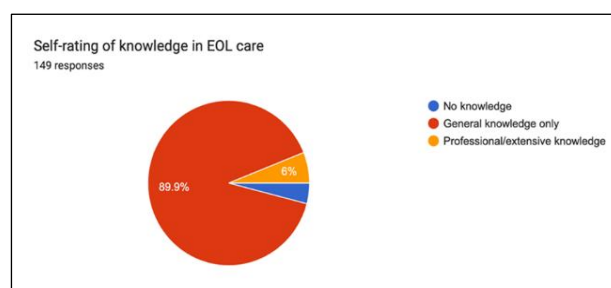


Figure 2: Self-rating knowledge in EOL

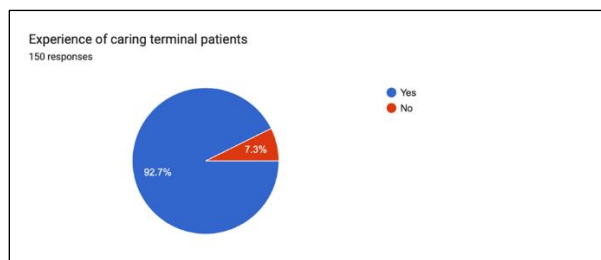


Figure 3: Experience in caring terminal patients

Table I: Demographic characteristics of the respondents (n=145)

Variable	Value
Gender	
Female	88 (60.7%)
Male	57 (39.3%)
Religion	
Islamic	74 (51.0%)
Buddhism	46 (31.7%)
Hinduism	9 (6.2%)
Christian	16 (11.0%)
Years of clinical experience (years)	
≤ 2	7 (4.8%)
3-5	36 (24.8%)
6-10	75 (51.7%)
≥ 10	27 (18.6%)
Position	
Master Trainee	72 (49.7%)
Medical Officer	49 (33.8%)
Specialist	18 (12.4%)
Consultant	6 (4.1%)
Which hospital do you work?	
KKM hospital	85 (58.6%)
University hospital	60 (41.4%)
Training status in End of Life (EOL) care	
No training	18 (12.4%)
On job training only	87 (60.0%)
Short courses or other formal training not leading to a specialist qualification	33 (22.8%)
Specialist training	7 (4.8%)
Self-rating of knowledge in EOL care	
No knowledge	1.01 (0.31)
General knowledge only	6 (4.1%)
Professional/extensive knowledge	131 (90.3%)
Experience of caring terminal patients	8 (5.5%)
Confidence in caring terminal patients	136 (93.8%)
Not at all	2.17 (1.08)
Undecided	7 (4.8%)
Somewhat	43 (29.7%)
Most of the time	22 (15.2%)
All the time	64 (44.1%)
Did you feel that you had enough support in caring for terminally ill patients?	9 (6.2%)
No	0.92 (0.94)
Don't know	69 (47.6%)
Yes	18 (12.4%)
	58 (40.0%)

Note: Data is presented as mean (standard deviation) or frequency (percentage).

According to Table II, respondents largely agreed that EOL care is an important competence for ICU doctors during the COVID-19 pandemic [mean 3.44 ± 0.87] and rejected the notions that it is not their responsibility [1.20 ± 1.10], that it should have lower priority in a busy ICU [1.08 ± 0.96], or that ICU doctors are solely trained to save lives [1.31 ± 1.12]. However, they expressed neutrality regarding the clarity of their role in EOL care during the pandemic [2.59 ± 0.89].

Table II. Attitude in providing EOL care

No	Statements	Value
1	EOL care is an important competence for an ICU doctor in COVID-19 pandemic	3.44 (0.87)
	Strongly Disagree	5 (3.45%)
	Disagree	1 (0.69%)
	Neutral	4 (2.76%)
	Agree	50 (34.48%)
	Strongly Agree	85 (58.62%)
2	I have a clear idea of the role of EOL care in COVID-19 pandemic	2.59 (0.89)
	Strongly Disagree	3 (2.07%)
	Disagree	9 (6.21%)
	Neutral	55 (37.93%)
	Agree	56 (38.62%)
	Strongly Agree	22 (15.17%)
3	ICU doctors are trained to save lives and not to manage death	1.20 (1.10)
	Strongly Disagree	42 (28.97%)
	Disagree	61 (42.07%)
	Neutral	18 (12.41%)
	Agree	19 (13.10%)
	Strongly Agree	5 (3.45%)
4	My workplace does not have protocols or services addressing EOL issues	2.17 (1.11)
	Strongly Disagree	11 (7.59%)
	Disagree	28 (19.31%)
	Neutral	49 (33.79%)
	Agree	39 (26.90%)
	Strongly Agree	18 (12.41%)
5	I feel comfortable providing EOL care in ICU during the pandemic	2.28 (0.98)
	Strongly Disagree	8 (5.52%)
	Disagree	16 (11.03%)
	Neutral	62 (42.76%)
	Agree	45 (31.03%)
	Strongly Agree	14 (9.66%)
6	EOL care should not be the responsibility of the ICU doctors	1.31 (1.12)
	Strongly Disagree	38 (26.21%)
	Disagree	54 (37.24%)
	Neutral	29 (20.00%)
	Agree	18 (12.41%)
	Strongly Agree	6 (4.14%)
7	EOL care should have a lower priority in the busy ICU especially during the pandemic	1.08 (0.96)
	Strongly Disagree	41 (28.28%)
	Disagree	68 (46.90%)
	Neutral	22 (15.17%)
	Agree	11 (7.59%)
	Strongly Agree	3 (2.07%)
8	There is lack of access to EOL care specialist /teams in ICU	2.30 (1.09)
	Strongly Disagree	8 (5.52%)
	Disagree	29 (20.00%)
	Neutral	37 (25.52%)
	Agree	54 (37.24%)
	Strongly Agree	17 (11.72%)
9	Having no access to communication with palliative care physician affects my ability to provide EOL care in ICU during COVID-19 pandemic	2.14 (1.08)
	Strongly Disagree	9 (6.21%)
	Disagree	37 (25.52%)
	Neutral	35 (24.14%)
	Agree	53 (36.55%)
	Strongly Agree	11 (7.59%)
10	I have difficulty discussing EOL issues with patients and/or their families	1.89 (1.06)
	Strongly Disagree	13 (8.97%)
	Disagree	43 (29.66%)
	Neutral	44 (30.34%)
	Agree	37 (25.52%)
	Strongly Agree	8 (5.52%)
11	I cannot identify patients who may need palliative and EOL care in the ICU	1.39 (0.86)
	Strongly Disagree	18 (12.41%)
	Disagree	69 (47.59%)
	Neutral	42 (28.97%)
	Agree	15 (10.34%)
	Strongly Agree	1 (0.69%)

<i>Cont.</i>		
12	My lack of training in EOL care affects my ability to provide this service	2.19 (1.03)
	Strongly Disagree	9 (6.21%)
	Disagree	28 (19.31%)
	Neutral	44 (30.34%)
	Agree	54 (37.24%)
	Strongly Agree	10 (6.90%)
13	Fear of lawsuits leads me away from offering EOL care to potential candidates in the COVID-19 pandemic	1.92 (0.99)
	Strongly Disagree	9 (6.21%)
	Disagree	42 (28.97%)
	Neutral	54 (37.24%)
	Agree	32 (22.07%)
	Strongly Agree	8 (5.52%)
14	I do not have sufficient time during my shift to provide EOL care in ICU during the COVID-19 pandemic	2.24 (1.13)
	Strongly Disagree	7 (4.83%)
	Disagree	38 (26.21%)
	Neutral	32 (22.07%)
	Agree	49 (33.79%)
	Strongly Agree	19 (13.10%)
15	ICU is not the best place for EOL discussions	1.20 (1.08)
	Strongly Disagree	45 (31.03%)
	Disagree	50 (34.48%)
	Neutral	30 (20.69%)
	Agree	16 (11.03%)
	Strongly Agree	4 (2.76%)

Note: Data is presented as mean (standard deviation) or frequency (percentage). Likert scale: 0: strongly disagree, 1: disagree, 2: neutral, 3: agree, 4: strongly agree.

Correlation analysis demonstrated that all obstacle items showed poor to moderate correlations with negative attitudes toward EOL care in the ICU (Table III). Among these, the most significant perceived obstacle was the lack of access to communication with palliative care physicians, which respondents felt strongly limited their ability to provide adequate EOL care during the COVID-19 pandemic. In contrast, the lack of access to specialized EOL care teams within the ICU was rated as the least significant obstacle.

Table III. Obstacles (statements 4, 8, 9, 11 to 14) correlated with overall impression (statement 15)

No	Statement	r	P value
4	My workplace does not have protocols or services addressing EOL issues	0.270	0.001*
8	There is lack of access to EOL care specialist /teams in ICU	0.160	0.052
9	Having no access to communication with palliative care physician affects my ability to provide EOL care in ICU during COVID-19 pandemic	0.339	0.000*
11	I cannot identify patients who may need palliative and EOL care in the ICU	0.273	0.001*
12	My lack of training in EOL care affects my ability to provide this service	0.227	0.006*
13	Fear of lawsuits leads me away from offering EOL care to potential candidates in the COVID-19 pandemic	0.203	0.014*
14	I do not have sufficient time during my shift to provide EOL care in ICU during Covid-19 pandemic	0.222	0.007*

Note: Spearman correlation; a P value less than 0.05 indicates statistical significance.

Physicians and clinicians recognized multiple educational needs in EOL care, particularly in both clinical and ethical aspects (Table IV), with mean scores

above 3, indicating agreement on the importance of training. The highest priority was ethics-related education, including DNR orders, advance directives, and decision-making capacity, while the lowest priority was training on feeding management in EOL care.

Table IV. Educational need pertaining to EOL care in critical care setting

Education Needs	Data
Pain assessment and management	3.03 (0.97)
Strongly Disagree	6 (4.14%)
Disagree	5 (3.45%)
Neutral	15 (10.34%)
Agree	71 (48.97%)
Strongly Agree	48 (33.10%)
Management of terminal delirium	3.14 (0.92)
Strongly Disagree	7 (4.83%)
Disagree	1 (0.69%)
Neutral	7 (4.83%)
Agree	80 (55.17%)
Strongly Agree	50 (34.48%)
Management of dyspnoea	3.10 (0.95)
Strongly Disagree	6 (4.14%)
Disagree	4 (2.76%)
Neutral	11 (7.59%)
Agree	73 (50.34%)
Strongly Agree	51 (35.17%)
Management of death rattle	3.10 (0.93)
Strongly Disagree	6 (4.14%)
Disagree	2 (1.38%)
Neutral	14 (9.66%)
Agree	73 (50.34%)
Strongly Agree	50 (34.48%)
Management of feeding in EOL care	3.01 (0.91)
Strongly Disagree	6 (4.14%)
Disagree	2 (1.38%)
Neutral	17 (11.72%)
Agree	80 (55.17%)
Strongly Agree	40 (27.59%)
Management of psycho-social aspect of EOL	3.11 (0.88)
Strongly Disagree	6 (4.14%)
Disagree	0 (0.00%)
Neutral	13 (8.97%)
Agree	79 (54.48%)
Strongly Agree	47 (32.41%)
Management of spirituality and cultural aspects in EOL	3.10 (0.88)
Strongly Disagree	6 (4.14%)
Disagree	0 (0.00%)
Neutral	13 (8.97%)
Agree	81 (55.86%)
Strongly Agree	45 (31.03%)
Grief and bereavement support	3.23 (0.90)
Strongly Disagree	6 (4.14%)
Disagree	2 (1.38%)
Neutral	4 (2.76%)
Agree	74 (51.03%)
Strongly Agree	59 (40.69%)
Communication skills - breaking bad news, talking with family, discussing prognosis, discussing various treatment options	3.23 (0.96)
Strongly Disagree	7 (4.83%)
Disagree	2 (1.38%)
Neutral	5 (3.45%)
Agree	67 (46.21%)
Strongly Agree	64 (44.14%)
EOL care ethics: DNR orders, advanced directives, decision-making capacity	3.26 (0.94)
Strongly Disagree	7 (4.83%)
Disagree	2 (1.38%)
Neutral	2 (1.38%)
Agree	70 (48.28%)

<i>Cont.</i>	
Strongly Agree	64 (44.14%)
Last office and ritual arrangement	3.02±1.01
Strongly Disagree	8 (5.52%)
Disagree	4 (2.76%)
Neutral	12 (8.28%)
Agree	74 (51.03%)
Strongly Agree	47 (32.41%)

Note: Data is presented as mean (standard deviation) or frequency (percentage). Likert scale: 0: strongly disagree, 1: disagree, 2: neutral, 3: agree, 4: strongly agree.

DISCUSSION

End-of-life (EOL) decision-making in the intensive care unit (ICU) is inherently complex, requiring the integration of medical, ethical, cultural, and emotional considerations.^{14,15} The COVID-19 pandemic further amplified these challenges by presenting unprecedented uncertainty, resource limitations, and heightened patient vulnerability. Our study highlights important insights into perspectives of physicians on EOL care during this period, underscoring both strengths and areas requiring further development.

The generally positive attitude toward EOL care among ICU physicians reflects an increasing recognition that critical care encompasses not only life-sustaining interventions but also the provision of compassionate and dignified care at the end of life. This aligns with global trends emphasizing palliative integration into ICU practice, particularly during health crises where mortality risk is elevated. Nevertheless, the uncertainty observed regarding the precise role of EOL care during the pandemic suggests a persisting gap in institutional clarity and structured guidance. It is important to note that the reported uncertainty regarding the precise role of EOL care reflects both institutional ambiguity and individual confidence among doctors. Decisions and declarations related to EOL care are not the sole responsibility of the treating physician; rather, they require input from multiple stakeholders. A multidisciplinary approach, involving collaboration with nurses, allied health professionals, and family members of patients, is essential, as their perspectives contribute significantly to holistic and patient-centred EOL. Recognizing and addressing these layers of uncertainty can enhance the quality and consistency of EOL decision-making in critical care settings

Clearer policies, protocols, and role delineation may therefore be necessary to support healthcare professionals in navigating these ethically sensitive situations. The reported barriers that particularly limited access to palliative care specialists, lack of standardized training, and institutional time constraints are consistent with challenges documented internationally. These systemic gaps likely contribute to variability in practice and may compromise the consistency of EOL care delivery. Targeted interventions such as formal training programs, development of institutional protocols, and expansion of multidisciplinary collaboration could mitigate these issues and improve both clinician confidence and patient outcomes.

An encouraging finding from this study is the relative comfort of ICU physicians in discussing EOL issues with patients and families. This may reflect accumulated experience during the pandemic, where communication regarding prognosis and goals of care became an essential part of daily practice. However, the fact that comfort levels remained only moderate highlights the importance of further strengthening communication skills training, with particular emphasis on culturally sensitive and ethically challenging discussions such as do-not-resuscitate (DNR) orders and advance care planning. Importantly, the identified educational needs, especially in relation to ethical and legal dimensions, underscore that improving knowledge and confidence in EOL decision-making remains a priority. Investment in structured educational programs tailored to ICU clinicians could not only enhance professional competence but also reduce variability in practice, support ethical decision-making, and ultimately improve the quality of care for critically ill patients and their family members.

In summary, this study reinforces the need for greater institutional support, specialized training, and integration of palliative care expertise within ICU practice. Addressing these gaps is essential to strengthen the capacity of doctors working in ICU to deliver

holistic, patient-centred EOL care, both during pandemics and beyond.

LIMITATIONS

This study contributes valuable insights into perspectives of physicians on end-of-life (EOL) care during the COVID-19 pandemic. However, several limitations should be acknowledged. Firstly, the study was conducted only in Malaysia, which may limit the generalizability of findings to regions with different cultural, legal, or healthcare contexts. Secondly, data were collected through self-reported questionnaires, which may be subject to recall bias or social desirability bias. Further, the cross-sectional design captures physician perspectives at one point in time, without accounting for potential changes in attitudes or practices as the pandemic evolved. Finally, the study focused on physicians in ICU and anaesthesiology settings; perspectives from nurses, allied health professionals, or family members of patients were not included, which may limit the holistic understanding of care delivery in EOL.

CONCLUSION

To the best of our knowledge, this is the first study in Malaysia to research the attitudes of doctors in critical care settings toward EOL care management for critically ill COVID-19 patients. The findings identified several challenges in implementing EOL care during the pandemic. Addressing these issues requires a comprehensive strategy, including stronger institutional support, enhanced educational initiatives, and better integration of palliative care services within the ICU. Such efforts are essential to improve the delivery of holistic, high-quality EOL care that upholds patient dignity and comfort while supporting clinicians in their vital roles.

INSTITUTIONAL REVIEW BOARD (ETHICAL COMMITTEE)

The study was conducted after receiving approval from the Ethics Committee of Universiti Sains Malaysia (USM/JEPeM/22120818), and the Medical Research

and Ethics Committee of the Ministry of Health Malaysia NMRR ID-22-02917-S3L (IIR).

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The Prevalence and Risk Association of Cardiovascular Disease Among Offshore Male Workers in Peninsular Malaysia

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ABSTRACT

INTRODUCTION: Offshore workers are exposed to occupational and lifestyle factors that may increase cardiovascular disease (CVD) risk. Limited data are available regarding cardiovascular risk profiles among offshore personnel in Malaysia. This study aimed to determine the prevalence of cardiovascular disease risk levels and associated factors among offshore male workers in Peninsular Malaysia. **MATERIAL AND METHODS:** A cross-sectional study was conducted among 241 offshore male workers between January and February 2025. Data were collected using structured questionnaires and clinical assessments, including body mass index, blood pressure, and lipid profiles. Participants were categorized into low, moderate, and severe CVD risk groups using Malaysian CVD risk scoring guidelines. Chi-square tests and binary logistic regression were performed to identify associated factors. **RESULTS:** Among the participants, 22.4% were classified as low risk, 47.3% as moderate risk, and 30.4% as severe risk. Overall, 77.7% fell within the moderate-to-severe CVD risk categories. Significant predictors of elevated risk included increasing age (OR=1.046, $p=0.003$), higher BMI (OR=1.094, $p=0.001$), smoking (OR=3.320, $p=0.008$), shift work (OR=2.663, $p=0.017$), high job stress (OR=4.530, $p=0.003$), hypertension (OR=5.930, $p=0.011$), and dyslipidaemia (OR=3.860, $p=0.011$). **CONCLUSION:** A high prevalence of moderate-to-severe cardiovascular risk was observed among offshore workers. Occupational health interventions, regular screening, and lifestyle modification programs are recommended to reduce cardiovascular risk in this population.

Keywords

Cardiovascular disease (CVD), Offshore workers, Risk factors.

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Received: 12th August 2025; Accepted:
16th August 2026

Doi:
<https://doi.org/10.31436/10.31436/imjm.v25i04/3051>

INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality worldwide, accounting for approximately 17.9 million deaths annually. The burden of CVD continues to increase, particularly among individuals in the economically productive age group, largely driven by modifiable risk factors such as physical inactivity, unhealthy dietary patterns, tobacco use, obesity, and psychosocial stress.

Offshore workers represent a unique occupational group exposed to multiple cardiovascular risk factors,

including long working hours, shift work, psychosocial stress, irregular sleep patterns, and limited access to healthy lifestyle options. These occupational demands may contribute to the development of cardiometabolic abnormalities and increased cardiovascular risk over time.

Despite the importance of occupational health surveillance, limited data are available regarding cardiovascular risk profiles among offshore workers in Malaysia. Therefore, this study aims to determine the

prevalence of cardiovascular disease risk levels among male offshore workers in Peninsular Malaysia and to examine the associations between socio-demographic, lifestyle, and occupational factors and CVD risk categories.

MATERIALS AND METHODS

Study Design and Setting

A cross-sectional study was conducted among offshore male workers in Peninsular Malaysia. A total of 241 participants were recruited based on inclusion criteria, including male offshore workers aged 18 years and above who consented to participate.

Study Population

The study population consisted of male offshore workers aged 20 years and above who had been actively employed offshore for at least six months. Workers with incomplete data or with diagnosed chronic illnesses unrelated to cardiovascular conditions were excluded.¹¹ Participation was voluntary, and informed consent was obtained from all respondents before data collection.

Sample Size and Sampling

The sample size was calculated using the single population proportion formula: $n = Z^2 P(1-P)/d^2$, where $Z=1.96$ for a 95% confidence level, P represents the expected prevalence based on previous studies, and $d=0.05$ margin of error. The calculated minimum sample size was achieved, and 241 participants were included. Participants were recruited using purposive sampling.¹³

Data Collection Procedures

Data collection consisted of two components: a structured questionnaire and clinical assessments. Data were collected during routine offshore medical screenings to ensure feasibility and minimize disruption to work operations.

Structured Questionnaire

A structured questionnaire adapted from standardized occupational health screening components and

Malaysian cardiovascular risk assessment variables was used. The questionnaire collected information on sociodemographic characteristics, lifestyle behaviours, dietary habits, occupational factors, psychosocial indicators, and medical history. The questionnaire was reviewed by occupational health experts before data collection.¹⁴ Research personnel were available to clarify questionnaire items when necessary.

Clinical and Biometric Measurements

Anthropometric and clinical measurements, including body mass index, blood pressure, and laboratory investigations, were recorded. Standard measurement procedures were followed.¹⁶

Cardiovascular Risk Classification

Ten-year cardiovascular risk was estimated using the Framingham General Cardiovascular Disease (FRS-General CVD) Risk Score, as recommended for risk stratification in the Malaysian Clinical Practice Guidelines on Management of Dyslipidaemia.^{17,18,19} The sex-specific score incorporates age, total cholesterol, high-density lipoprotein cholesterol (HDL-C), systolic blood pressure, treatment for hypertension, current smoking status, and diabetes status. The calculated 10-year CVD risk was classified as low risk (<10%), intermediate/moderate risk (10–20%), or high risk (>20%). In this manuscript, the term “moderate” is used for the guideline’s intermediate category.

For binary logistic regression, the moderate and high CVD risk categories were combined into a single “moderate-to-high CVD risk” outcome and compared with the low-risk category, because age, smoking, systolic blood pressure/antihypertensive treatment, and lipid measures are components of the FRS-General CVD calculation, associations involving these variables may partly reflect their mathematical contribution to the derived risk score and should not be interpreted as independent causal predictors. BMI is not a component of the lipid-based FRS-General CVD score.^{20,21}

Hypertension history and dyslipidaemia history were analysed as clinical variables; however, they are related to blood-pressure and lipid parameters used in the score.²²

Statistical Analysis

Data were analysed using appropriate statistical software. Descriptive statistics were used to summarize participant characteristics. Associations between categorical variables and CVD risk categories were examined using Chi-square tests. Variables with significant associations were further analysed using multivariate logistic regression to identify independent predictors of moderate-to-severe CVD risk. Statistical significance was set at $p < 0.05$.

Data Analysis

Data were analysed using SPSS software. Descriptive statistics were used to summarize participant characteristics. Chi-square tests were performed to identify associations. Binary logistic regression was conducted to determine predictors of moderate-to-severe CVD risk. Statistical significance was set at $p < 0.05$.

RESULT

A total of 241 offshore male workers participated in the study. Among the participants, 22.4% were classified as low risk, 47.3% as moderate risk, and 30.4% as severe risk. Overall, 77.7% fell within the moderate-to-severe CVD risk categories.

Increasing age, higher BMI, smoking status, shift work, high job stress, hypertension, and dyslipidaemia were significantly associated with moderate-to-severe cardiovascular risk. Logistic regression analysis identified age, BMI, smoking, job stress, shift work, hypertension, and dyslipidaemia as independent predictors.

Table I. Sociodemographic, Occupational, Lifestyle and Clinical Characteristics of Participants (n = 241)

Variable	Frequency (n)	Percentage (%)
Age Group (years)		
25–34	131	54.4
35–44	75	31.1
45–54	28	11.6
55–60	7	2.9
Marital Status		
Married	191	79.3
Single/Other	50	20.7
Education Level		
Secondary	213	88.4
Tertiary	28	11.6
Shift Work		
Yes	87	36.1
No	154	63.9
Work Experience (years)		
≤5	74	30.7
6–10	128	53.1
>10	39	16.2
Smoking Status		
Non-smoker	25	10.4
Light smoker	50	20.7
Moderate smoker	165	68.5
Heavy smoker	1	0.4
Physical Activity		
Active	217	90.0
Inactive	24	10.0
BMI Category		
Normal	143	59.3
Overweight	44	18.3
Obese	28	11.6
Underweight	26	10.8
Hypertension (History)	31	12.9
Dyslipidaemia (History)	49	20.3
Abnormal LDL	194	80.5
Elevated Blood Pressure	49	20.3
CVD Risk Category		
Low	54	22.4
Moderate	114	47.3
Severe	73	30.4

Note: Chi-square test applied. Significance set at $p < 0.05$.

Table II. Bivariate Associations Between Selected Variables and Moderate-to-Severe CVD Risk

Variable	χ^2	p-value
Age group	28.34	<0.001
Smoking status	9.88	0.020
Shift work	5.79	0.016
Physical inactivity	7.12	0.028
Hypertension (history)	8.96	0.003
Dyslipidaemia (history)	6.12	0.013
Family history of CVD	4.56	0.033
BMI category	16.12	0.001
Elevated blood pressure	20.47	<0.001
Work-related stress	7.24	0.027
Anxiety/depression symptoms	9.78	0.008
Poor sleep quality	6.35	0.042
Self-rated fair health	6.18	0.045

Note: OR: Odds Ratio; CI: Confidence Interval. Logistic regression adjusted for significant covariates. Significance set at $p < 0.05$.

Table III: Multivariate Logistic Regression Analysis for Predictors of Moderate-to-Severe CVD Risk

Variable	B	OR (95% CI)	p-value
Age (per year)	0.045	1.046 (1.016–1.077)	0.003
BMI (per unit)	0.090	1.094 (1.041–1.150)	0.001
Smoking (yes vs no)	1.200	3.320 (1.360–8.100)	0.008
Shift work (yes vs no)	0.980	2.663 (1.190–5.960)	0.017
High job stress	1.510	4.530 (1.650–12.450)	0.003
Hypertension	1.780	5.930 (1.480–23.750)	0.011
Dyslipidaemia	1.350	3.860 (1.350–11.020)	0.011
Sleep disturbance	0.700	2.010 (0.920–4.400)	0.080

Note: OR: Odds Ratio; CI: Confidence Interval. Logistic regression adjusted for significant covariates. Significance set at $p < 0.05$.

DISCUSSION

This study examined cardiovascular risk and associated factors among offshore male workers in Peninsular Malaysia. The findings revealed that 77.7% of participants were classified within the moderate-to-high CVD risk categories, indicating a substantial burden of cardiovascular risk in this occupational group.

The observed associations reflect a combination of demographic, behavioural, clinical, occupational, and psychosocial characteristics. Increasing age and higher BMI were associated with elevated CVD risk.

Smoking and shift work were also associated with the combined moderate-to-high risk category, while high job stress highlighted the potential relevance of psychosocial factors in this workforce.

Clinical characteristics, including hypertension and dyslipidaemia, were associated with moderate-to-high CVD risk. However, interpretation of these findings requires caution because the FRS-General CVD score itself incorporates age, smoking, systolic blood pressure, antihypertensive treatment, total cholesterol, and HDL-C.

Therefore, associations for variables that directly or indirectly overlap with score components may partly reflect the construction of the outcome measure rather than independent causal effects. BMI, shift work, and job stress are not components of the lipid-based FRS-General CVD score and therefore represent conceptually distinct factors examined in this analysis.

This study has several limitations. Its cross-sectional design does not permit causal inference. In addition, purposive sampling was used to recruit participants, which may introduce selection bias and limits the generalisability of the findings to the wider offshore worker population in Peninsular Malaysia or Malaysia as a whole.

The findings should therefore be interpreted within the characteristics of the sampled workforce. Future studies should consider probability-based sampling, broader recruitment across offshore installations, and longitudinal designs to improve external validity and evaluate temporal relationships.

CONCLUSION

This study identified a high prevalence of moderate-to-high 10-year cardiovascular risk among offshore male workers in Peninsular Malaysia, with 77.7% of participants classified in the combined moderate-to-high risk categories. The findings support the importance of regular cardiovascular risk assessment and workplace-based health promotion in offshore settings.

Occupational health programmes should continue to emphasise cardiovascular screening, smoking cessation, healthy weight, blood pressure and lipid management, fatigue and shift-work management, and psychosocial wellbeing. Further longitudinal studies using more representative sampling approaches are warranted

List of abbreviations

CVD: Cardiovascular Disease

BMI: Body Mass Index

BP: Blood Pressure

HDL: High-Density Lipoprotein (Good Cholesterol)

LDL: Low-Density Lipoprotein (Bad Cholesterol)

OR: Odds Ratio

CI: Confidence Interval

SOB: Shortness of Breath

SPSS: Statistical Package for the Social Sciences

r: Pearson Correlation Coefficient

χ^2 : Chi-Square

SE: Standard Error

B: Beta Coefficient (Regression Coefficient)

P: p-value (Statistical Significance)

%: Percentage

n: Sample Size

Availability of data and material

The datasets generated and analysed during the current study are not publicly available due to confidentiality agreements and data protection regulations involving the offshore workforce. However, data may be made available from the corresponding author on reasonable request and with permission from the relevant institutional and organizational authorities.

Author contributions

A.H.M. (Amin Hamzah Mustafha) conceptualized the study, developed the research design, and oversaw data collection.

A.H.M. also performed the data analysis and interpretation, drafted the manuscript, and coordinated revisions.

All authors contributed to the review of the manuscript for intellectual content and approved the final version for submission.

FUNDING

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

CONFLICT OF INTEREST

The authors declare no conflict of interest.

INSTITUTIONAL REVIEW BOARD (ETHICS COMMITTEE)

This study was conducted following the ethical standards of the Faculty of Medicine, University of Sultan Zainal Abidin (UniSZA). Ethical approval was obtained from the Jawatankuasa Etika Penyelidikan Manusia UniSZA (UHREC), UniSZA Human Research Ethics Committee, with approval reference number: UniSZA.100-6/2/7 Jld. 2 (47).

All participants were provided with detailed information regarding the purpose, procedures, potential risks, and

benefits of the study. Written informed consent was obtained from each participant before data collection.

Participation was voluntary, and participants were assured of confidentiality and the right to withdraw from the study at any time without any consequences.

ACKNOWLEDGEMENTS

The authors would like to thank all offshore workers who participated in this study and the management teams who facilitated data collection.

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A Malay Version of the Dementia Attitude Scale (DAS-M) Questionnaire: Its Adaptation, Validation, and Reliability among Malaysian Informal Dementia Caregivers

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ABSTRACT

INTRODUCTION: Dementia is an increasing public health concern globally and in Malaysia, where informal caregivers, mainly family members, provide most care. Caregivers' attitudes may influence the quality of care and outcomes of people living with dementia (PLwD). However, no validated Malay questionnaire is available to assess dementia-related attitudes. This study aimed to translate, cross-culturally adapt, and evaluate the psychometric properties of the Malay Dementia Attitude Scale (DAS-M) among Malaysian informal dementia caregivers. **MATERIALS AND METHODS:** This cross-sectional study involved 355 informal caregivers recruited from geriatric clinics at Hospital Kuala Lumpur and Universiti Malaya Medical Centre between March and July 2025. The DAS underwent forward-backward translation, expert content validation, and pilot testing for face validity. Construct validity was evaluated using exploratory factor analysis (EFA) with principal axis factoring and Promax rotation. Internal consistency and test-retest reliability were assessed using Cronbach's alpha and the intraclass correlation coefficient, respectively. **RESULTS:** The DAS-M demonstrated excellent content validity (I-CVI=1.00; S-CVI/Ave=1.00) and strong face validity (S-FVI/Ave=0.995). EFA supported a two-factor structure comprising Social Comfort and Knowledge, which explained 40.2% of the total variance. Three items were removed due to low factor loadings and communalities, resulting in a 17-item scale. The final scale showed good internal consistency (Cronbach's α =0.825) and moderate-to-good test-retest reliability. **CONCLUSION:** The DAS-M demonstrated acceptable validity and reliability for assessing dementia-related attitudes among Malaysian informal caregivers. These findings support its potential use in research, caregiver training programmes, and public health interventions in Malaysia.

Keywords

Dementia, Caregivers, Attitude, Validation, Malaysia.

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Received: 4th April 2025; Accepted: 20th July 2026

Doi:
<https://doi.org/10.31436/10.31436/imjm.v25i04/3236>

INTRODUCTION

Dementia is a global public health priority, precipitating significant disability, dependency, and diminished quality of life. The World Health Organisation (WHO) estimates that over 55 million people live with dementia (PLwD) worldwide, with 10 million new cases annually,

primarily in low- and middle-income countries.^{37,39} As prevalence climbs alongside global population ageing, the socioeconomic burden increasingly shifts towards informal caregivers, most of whom are family members.³⁸

In Malaysia, these challenges are intensified by an accelerated demographic transition. The nation is projected to reach an aged status by 2030, with over 15% of the population aged 60 and above. The National Health and Morbidity Survey (NHMS) 2018 reported a prevalence of probable dementia of 8.5% among older adults, a figure expected to more than double by 2050.^{1,18} Despite this rising burden, negative attitudes towards PLwD remain prevalent at the global level and in Malaysia, highlighting the need for valid and culturally appropriate questionnaires to assess caregiver attitudes.^{1,22,23,38}

A caregiver's attitude is a fundamental determinant of caregiving behaviour, resilience, and the quality of care provided. Attitudes are conceptualised using the tripartite model, comprising cognitive beliefs, affective reactions, and behavioural components.^{4,9,15} Literature demonstrates that negative attitudes, such as fear, social discomfort, and therapeutic pessimism, are associated with higher caregiver burden and psychological distress. Conversely, positive attitudes characterised by empathy, acceptance and person-centredness are associated with better quality of life for both the caregiver and PLwD.^{4,6-7,9,15,35,42}

Several questionnaires have been developed to assess attitudes towards dementia, although they differ in their conceptual scope. The Approaches to Dementia Questionnaire (ADQ) primarily measures hope and person-centred attitudes, providing a narrower assessment of dementia-related attitudes.²⁶ In contrast, the Dementia Attitude Scale (DAS), developed by O'Connor and McFadden in 2010, offers a broader multidimensional framework grounded in the tripartite model of attitudes. It assesses cognitive (Knowledge) and affective and behavioural (Social Comfort) dimensions of attitudes towards PLwD, providing a more comprehensive evaluation of dementia-related attitudes.²⁸ The DAS has also demonstrated good psychometric properties across diverse populations, making it particularly suitable for cross-cultural adaptation and use among Malaysian informal dementia caregivers.²⁸

The DAS has demonstrated robust psychometric properties across healthcare professionals and family caregivers globally.²⁸ Cross-cultural adaptation and validation studies in Greece, Turkey, Indonesia, Croatia, and China have further confirmed its reliability while identifying culturally specific nuances in attitudinal expression.^{7,9,15,27,43}

Although the DAS has been successfully validated in several countries, a validated Malay version remains unavailable. This represents a significant research gap in Malaysia, where family-based care is deeply influenced by cultural frameworks such as filial piety, religious beliefs, and localised stigma. The absence of a validated Malay questionnaire limits the assessment of dementia-related attitudes among Malaysian caregivers and the evaluation of dementia-related educational or psychosocial interventions.

This study addresses this gap by cross-culturally adapting and translating the original DAS into Malay (DAS-M). It also aims to evaluate the psychometric properties of the DAS-M, including its validity and reliability, among Malaysian informal dementia caregivers. By providing a culturally appropriate and psychometrically sound questionnaire, this study supports research, clinical practice, and the evaluation of dementia-related interventions, ultimately contributing to improved dementia care in Malaysia.

MATERIALS AND METHODS

Study Design and Setting

A cross-sectional study was conducted between March and July 2025 among informal dementia caregivers recruited from geriatric clinics at Hospital Kuala Lumpur (HKL) and Universiti Malaya Medical Centre (UMMC). HKL and UMMC are tertiary referral hospitals in the Klang Valley, receiving referrals from both urban and rural populations across Kuala Lumpur and Selangor, thereby providing a diverse pool of caregivers for the validation study.

The study was guided by established recommendations for cross-cultural adaptation and psychometric validation of questionnaires, including forward and backward translation, expert review, content validation, face validation, pilot testing, exploratory factor analysis (EFA) to assess construct validity, and assessment of internal consistency and test–retest reliability.^{3,5,24}

Participants

Eligible participants were caregivers aged ≥ 18 years who provided at least 4 hours of unpaid care daily and were able to understand Bahasa Malaysia. Professional (formal) caregivers were excluded.

The Dementia Attitude Scale (DAS)

The DAS is a 20-item questionnaire grounded in the tripartite model of attitudes towards PLwD. It comprises two 10-item subscales: Social Comfort, reflecting affective and behavioural responses, and Dementia Knowledge, representing cognitive beliefs. Items are rated on a 7-point Likert scale (1 = “strongly disagree” to 7 = “strongly agree”), with six items (Items 2, 6, 8, 9, 16, and 17) reverse-scored. Total scores are summed, with higher values indicating more positive attitudes. The DAS has demonstrated robust psychometric properties, including Cronbach’s α ranging from 0.83 to 0.85 and strong construct validity.²⁸

Questionnaire Translation and Adaptation

The original Dementia Attitude Scale (DAS) was translated into Malay using a standard forward–backward translation procedure.^{3,5,31} Two independent forward translations from English into Malay were performed by a bilingual linguist and a medical doctor. Subsequently, two independent backward translations into English were carried out by another bilingual linguist and a medical doctor, both of whom were blinded to the original questionnaire. The two back-translated versions were then compared with the original English DAS by the research team together with the expert panel, comprising two public health medicine specialists, two geriatricians, one linguist, and one

experienced dementia caregiver. Any discrepancies identified between the backward translations and the original version were discussed until consensus was reached, with emphasis on preserving semantic, conceptual, and cultural equivalence rather than literal wording.

Cross-cultural adaptation extends beyond literal translation to ensure semantic, idiomatic, experiential, and conceptual equivalence between the original and adapted questionnaires. This process helps to ensure that questionnaire items are interpreted consistently within the target population while preserving the validity of the underlying construct. It is particularly important for attitude measures because perceptions and beliefs about dementia are influenced by sociocultural norms and may vary across cultural settings.³

Content Validity

Content validity was evaluated by a six-member expert panel comprising two public health medicine specialists from a public university and the Ministry of Health, two geriatricians from the Ministry of Health and a university hospital, one linguistics expert, and one dementia caregiver with over a decade of caregiving experience. The experts independently assessed each item for relevance, clarity, simplicity, and ambiguity. Any comments, discrepancies, or suggested amendments were reviewed by the research team and discussed with the expert panel until consensus was achieved. Revisions were made with emphasis on preserving item relevance, clarity, cultural appropriateness, and conceptual equivalence with the original DAS. Based on the experts’ feedback regarding translation accuracy and cultural appropriateness, the questionnaire was further refined to ensure clinical and contextual relevance.^{31,40}

Face Validity and Pilot Testing

The questionnaire then underwent a face validity assessment in March 2025 among 30 dementia caregivers aged 18 years and above at the HKL geriatric clinic. These participants met the study’s eligibility

criteria but were excluded from the final analysis. Cognitive debriefing was subsequently conducted as part of the face validation process to assess the clarity, comprehensibility, and cultural appropriateness of the pre-final Malay version among the target population.^{31,41}

Sample Size Determination for Construct Validity and Reliability

The required sample size for exploratory factor analysis (EFA) was determined using a participant-to-item ratio of at least 10:1, a widely recommended threshold for construct validation studies to ensure stable factor solutions.^{10,21} For the 20-item DAS-M, this required a minimum of 200 participants. After allowing for a potential 20% non-response rate, the target sample size was increased to 240 participants. Ultimately, 355 caregivers were recruited, corresponding to approximately 18 participants per item, thereby exceeding the recommended sample size for EFA.^{10,21} For test–retest reliability, a subsample of 30 caregivers from a similar population was reassessed after a two-week interval.²⁰

Sampling

Convenience sampling was employed because recruitment was conducted in geriatric outpatient clinics, where a relatively small number of eligible informal dementia caregivers attended each clinic session. Consecutive eligible caregivers who met the inclusion criteria were invited to participate throughout the study period until the required sample size was achieved.

Statistical Analysis

Data analysis was conducted using IBM SPSS Statistics version 30 and Microsoft Excel. Descriptive statistics were used to summarise the sociodemographic and caregiving characteristics of the participants. Psychometric evaluation of the 20-item DAS-M encompassed content and face validation, construct validation, and reliability testing.²⁹

Content validity was quantified through the Content Validity Index (CVI), including item-level CVI (I-CVI)

and scale-level CVI (S-CVI). According to established benchmarks, an item-level CVI (I-CVI) ≥ 0.78 was required for item retention, while a scale-level CVI (S-CVI/Ave) ≥ 0.80 indicated robust overall validity.^{30,31,40}

Face validity was subsequently assessed via the Face Validity Index (FVI), including item-level FVI (I-FVI) and scale-level FVI (S-FVI), with a pilot group of 30 respondents. Items were accepted if they achieved I-FVI and S-FVI values ≥ 0.80 ; those that failed to meet this threshold were refined based on participant feedback to improve linguistic clarity and comprehensiveness.^{31,41}

Construct validity was examined using EFA with Principal Axis Factoring (PAF) and Promax rotation to account for potential correlations between factors. Factor retention was guided by eigenvalues greater than 1.0, inspection of the scree plot, theoretical interpretability, and consistency with the original DAS factor structure. Items with factor loadings < 0.32 or communalities < 0.20 were considered to have poor structural contribution. Items with weak loadings, low communalities, or loading patterns inconsistent with the original theoretical framework were qualitatively reviewed before final decisions on retention or exclusion were made.^{8,10,21}

Reliability was established by evaluating internal consistency and test-retest stability for the finalised factor structure. Internal consistency was measured using Cronbach's alpha (α), with a threshold of ≥ 0.70 considered acceptable.³⁴ Test-retest reliability was assessed via the Intraclass Correlation Coefficient (ICC) and interpreted as poor (< 0.50), moderate (0.50 – 0.75), good (0.75 – 0.90), or excellent (> 0.90).²⁰

RESULTS

Sociodemographic and Caregiving Characteristics of Participants

Of the 363 caregivers recruited, 355 completed the questionnaire, giving a response rate of 97.8%. The participants had a mean age of 51.96 ± 15.73 years. Most were female, Malay, Muslim, married, and had tertiary

education. Care was provided mainly by children of PLwD, followed by other family members and spouses. Most caregivers lived in urban areas, and more than half cohabited with the PLwD. Caregiving intensity was high, with the majority providing care for 1–5 years and spending more than 9 hours per day on caregiving. The sociodemographic and caregiving characteristics are summarised in Table I.

Table I: Sociodemographic and Caregiving Characteristics of Participants

Characteristics	Mean (SD)	Range
Age (years)	51.96 (± 15.73)	18–86
Characteristics	n=355	Percentage (%)
Gender		
• Male	87	24.5
• Female	268	75.5
Ethnicity		
• Malay	247	69.6
• Chinese	55	15.5
• Indian	43	12.1
• Others	10	2.8
Religion		
• Islam	254	71.5
• Buddha	38	10.7
• Hindu	34	9.6
• Christian	25	7.0
• Others	4	1.1
Marital status		
• Married	226	63.7
• Single	75	21.1
• Divorced/separated	54	15.2
Educational level		
• Primary education	53	14.9
• Secondary education	140	39.4
• Tertiary education	162	45.7
Working status		
• Working	163	45.9
• Not working/retired	192	54.1
Relationship with PLwD		
• Spouse	45	12.7
• Children	162	45.6
• Others	148	41.7
Co-inhabitant		
• Yes	198	55.8
• No	157	44.2
Housing area		
• Urban	225	63.4
• Rural	130	36.6
Monthly household income (RM)		
• < 2,000	184	51.8
• 2,000 – 5,000	128	36.1
• 5,001 – 10,000	33	9.3
• > 10,000	10	2.8
Financial support		
• Yes	89	25.1
• No	266	74.9
Family/social support		
• Yes	225	63.4
• No	130	36.6

Length of caregiving (years)		
• 1–5 years	283	79.7
• > 5 years	72	20.3
Daily caregiving time (hours)		
• 4–6 hours	115	32.4
• 7–9 hours	24	6.8
• > 9 hours	216	60.8
Dementia severity of PLwD		
• Mild dementia	134	37.7
• Moderate dementia	102	28.7
• Severe dementia	39	11.0
• Unsure	80	22.5

Content and Face Validity

Content validity was evaluated by six experts who assessed the items across four domains: relevance, clarity, simplicity, and ambiguity. The four-point rating scale was dichotomised, with scores of 3 (quite) and 4 (highly) recoded as 1 (acceptable), and scores of 1 (not) and 2 (somewhat) recoded as 0 (unacceptable). All 20 items achieved an item-level I-CVI of 1.00, reflecting undisputed expert agreement. Both the scale-level Content Validity Index based on the average method (S-CVI/Ave) and the universal agreement method (S-CVI/UA) were 1.00.^{30,40}

Face validity was subsequently assessed by 30 raters to determine the linguistic clarity and comprehensibility of the translated items. Nineteen of the 20 items achieved an I-FVI of 1.00. Item 20 recorded an I-FVI of 0.90, which remains above the recommended threshold of 0.80.⁴¹ The S-FVI/Ave was 0.995, and the S-FVI/UA was 0.95. Therefore, all items were retained for subsequent testing.

Construct Validity and Factor Analysis

The construct validity of the Malay version of the DAS-M was evaluated using EFA on responses from 355 participants. The sampling adequacy was confirmed as meritorious, with a Kaiser–Meyer–Olkin (KMO) measure of 0.863 and a statistically significant Bartlett’s Test of Sphericity ($\chi^2=2396.369$, $p<0.001$), indicating that the correlation matrix was well-suited for factor extraction.^{13,17}

Although the Kaiser criterion (eigenvalues >1) initially suggested a five-factor solution, visual inspection of the scree plot (Figure I) supported retention of a two-factor solution, which also represented the most parsimonious and interpretable factor structure.^{10,13} This solution was theoretically consistent with the original Dementia Attitude Scale (DAS), comprising the Social Comfort and Knowledge domains.²⁸

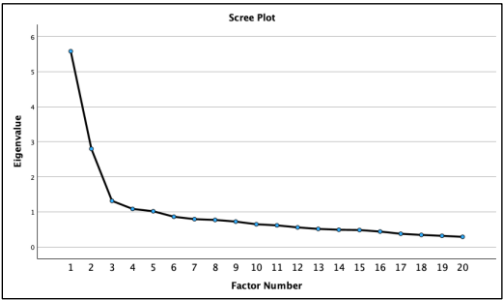


Figure I. Scree plot of the DAS-M.

Of the 20 items, 17 were retained. Three items were removed from the final model because of poor psychometric performance. Item 3 demonstrated a low factor loading of 0.249 and a communality of 0.066. Item 16 demonstrated a factor loading of 0.290 and a communality of 0.173. Item 20 showed a communality of 0.117 despite a marginal factor loading of 0.361. These findings indicated that the three items contributed weakly to the underlying factor structure and were therefore excluded from the final 17-item DAS-M (see Table II).

The initial 20-item two-factor solution explained 36.7% of the total variance, with Factor 1 accounting for 25.5% and Factor 2 accounting for 11.2%. After removal of Items 3, 16, and 20, the final 17-item two-factor solution explained 40.2% of the total variance, with Factor 1 accounting for 28.2% and Factor 2 accounting for 11.9%, based on the extraction sums of squared loadings. A moderate correlation between factors ($r=0.32$) supported the use of oblique rotation, with interpretation based on the pattern matrix.

The final solution comprised two factors. Factor 1 (Social Comfort) consisted of 10 items (Item 1, 2, 4-6, 8, 9, 13, 17-18), reflecting ease and confidence in interacting with PLwD. Factor loadings ranged from 0.455 to 0.753, with Item 9 contributing the highest loading of 0.753. Communalities ranging from 0.272 to 0.540 indicated good representation of the construct. Factor 2 (Knowledge) included 7 items (Item 7, 10-12, 14, 15, 19), reflecting beliefs and understanding of PLwD. Factor loadings ranged from 0.563 to 0.669, with Item 15 demonstrating the highest loading of 0.669. Communalities ranged from 0.293 to 0.575, indicating adequate shared variance. Overall, the refined 17-item, two-factor DAS-M demonstrated good construct validity and provided a coherent framework for assessing dementia-related attitudes among Malaysian caregivers (see Table II).

Reliability Analysis

Item Selection, Internal Consistency, and Test-Retest

Following EFA, internal consistency was assessed using Cronbach's alpha. The 17-item DAS-M showed good reliability ($\alpha=0.825$), comparable to the original DAS ($\alpha=0.83-0.85$). The Social Comfort subscale (10 items) demonstrated acceptable reliability ($\alpha=0.756$), which, although slightly lower than that of the original ($\alpha=0.82$), remained acceptable. Conversely, the Knowledge subscale (7 items) showed strong reliability ($\alpha=0.869$), notably exceeding the originally reported range of 0.75–0.78.²⁷ The removal of Items 3, 16, and 20 did not reduce reliability and improved the overall psychometric performance of the scale (see Table III).

Table III. Internal Consistency of the Items

Construct	N Items	Cronbach's α	Interpretation	Original α
Overall	17	0.825	Good	0.83–0.85
Social Comfort	10	0.756	Acceptable	0.82
Knowledge	7	0.869	Good	0.75–0.78

Test–retest reliability among 30 caregivers over a two-week interval indicated moderate-to-good temporal stability, with item-level ICC values ranging from 0.678 (95% CI: 0.390-0.838) to 0.859 (95% CI: 0.705-0.933), supporting the stability of DAS-M items over time.

Table II. Exploratory Factor Analysis (EFA) of the Items

No. of Item	Items	Mean (SD)	Factor 1 (Social Comfort)	Factor 2 (Knowledge)	Communalities	Interpretation
1	It is rewarding to work with people who have ADRD. Bekerjasama dengan penghidap demensia dapat memberikan kepuasan.	4.85 (1.674)	0.594	0.137	0.425	Retained
2	I am afraid of people with ADRD. Saya berasa takut dengan penghidap demensia.	4.92 (1.719)	0.650	0.116	0.484	Retained
3	People with ADRD can be creative. Penghidap demensia boleh menjadi kreatif.	4.17 (1.625)	0.249	0.023	0.066	Removed
4	I feel confident around people with ADRD. Saya berasa yakin berada dalam kalangan penghidap demensia.	4.29 (1.536)	0.455	0.312	0.396	Retained
5	I am comfortable touching people with ADRD. Saya berasa selesa menyentuh penghidap demensia.	4.81 (1.543)	0.481	0.233	0.358	Retained
6	I feel uncomfortable being around people with ADRD. Saya berasa kurang selesa berada dalam kalangan penghidap demensia.	4.96 (1.605)	0.651	0.022	0.434	Retained
8	I am not very familiar with ADRD. Saya tidak begitu biasa dengan penyakit demensia.	4.27 (1.710)	0.671	-0.100	0.417	Retained
9	I would avoid an agitated person with ADRD. Saya akan mengelak daripada penghidap demensia yang resah gelisah.	4.58 (1.708)	0.753	-0.065	0.540	Retained
13	I feel relaxed around people with ADRD. Saya berasa tenang berada di samping penghidap demensia.	4.56 (1.519)	0.588	0.086	0.385	Retained
16	I feel frustrated because I do not know how to help people with ADRD. Saya berasa kecewa apabila saya tidak tahu cara untuk membantu penghidap demensia.	2.85 (1.601)	0.290	-0.046	0.173	Removed

17	I cannot imagine taking care of someone with ADRD. Saya tidak dapat membayangkan n diri saya menjaga penghidap demensia.	3.79 (1.730)	0.546	-0.242	0.272	Retained
18	I admire the coping skills of people with ADRD. Saya mengagumi kemampuan yang dimiliki penghidap demensia dalam menghadapi cabaran.	5.15 (1.455)	0.563	0.034	0.330	Retained
7	Every person with ADRD has different needs. Setiap penghidap demensia mempunyai keperluan berbeza.	5.53 (1.367)	-0.205	0.604	0.327	Retained
10	People with ADRD like having familiar things nearby. Penghidap demensia berasa selesa jika barang-barang mereka berada dekat dengan mereka.	5.39 (1.449)	-0.232	0.569	0.293	Retained
11	It is important to know the past history of people with ADRD. Adalah penting untuk mengetahui sejarah hidup penghidap demensia.	5.68 (1.301)	-0.196	0.661	0.392	Retained
12	It is possible to enjoy interacting with people with ADRD. Saya masih boleh berasa seronok bergaul dengan penghidap demensia.	4.98 (1.486)	0.238	0.647	0.575	Retained
14	People with ADRD can enjoy life. Penghidap demensia boleh menikmati kehidupan.	5.29 (1.487)	0.033	0.615	0.392	Retained
15	People with ADRD can feel when others are kind to them. Penghidap demensia boleh merasai kebaikan orang lain terhadap mereka.	5.21 (1.539)	-0.040	0.669	0.432	Retained

19	We can do a lot now to improve the lives of people with ADRD. Banyak yang boleh kita lakukan untuk menambah baik kehidupan penghidap demensia.	5.63 (1.298)	0.026	0.601	0.372	Retained
20	Difficult behaviors may be a form of communication for people with ADRD. Tingkah laku yang sukar (seperti kerap lupa dan agresif), mungkin merupakan satu bentuk komunikasi bagi penghidap demensia.	5.40 (1.333)	-0.137	0.361	0.117	Removed

DISCUSSION

The present study demonstrates that the DAS-M retains the core two-factor structure of Social Comfort and Knowledge, consistent with the original Dementia Attitude Scale and several cross-cultural validations.^{9,15,27,28} This structural stability reinforces the DAS's theoretical robustness across diverse populations. However, important cross-cultural variations were observed at both the factor and item levels.

The two-factor structure of the DAS-M is consistent with validations in Greece, Croatia, and Indonesia, where the original domains of Social Comfort and Dementia Knowledge were preserved.^{9,15,27} In contrast, several studies reported deviations from the original structure. The Turkish validation identified a three-factor model comprising supporting, accepting, and exclusionary attitudes, whereas a European multi-country analysis showed a three-factor structure comprising social comfort, social discomfort, and knowledge.^{6,7} Similarly, validation in Mandarin Chinese populations revealed three components, comprising cognitive, affective, and experiential.⁴³ These findings suggest that while the DAS demonstrates core structural stability, cultural variation exists in how attitudes are conceptualised.

While the overall two-factor structure of the original instrument was preserved, the DAS-M exhibited specific item-level deviations. In the original scale, Item 3 and Item 18 were associated with the Knowledge factor; however, in the present analysis, these items aligned more closely with the Social Comfort domain. Item 18 demonstrated a stronger loading on Social Comfort (loading = 0.563; communality = 0.330) and was consequently retained under this factor. In contrast, Item 3 exhibited poor psychometric performance (loading = 0.249; communality = 0.066) and was excluded from the final 17-item model. Similar findings have been reported in Croatian, European, and Mandarin Chinese validations, in which several items exhibited different loading patterns or failed to align with the original domains, reflecting cultural differences in the interpretation of dementia-related attitudes.^{6,9,43}

Item-level variability is commonly reported in cross-cultural studies.^{6,7,9,43} The poor performance of Items 3, 16, and 20 may reflect differences in how dementia-related attitudes are understood within the Malaysian caregiving context. Item 3, which states that PLwD can be creative, may be less intuitive to caregivers who primarily associate dementia with memory loss, cognitive decline, dependency, and functional deterioration. In local caregiving settings, the concept of creativity among PLwD may be less commonly recognised, particularly when caregivers' daily experiences are centred on supervision, safety, and assistance with daily activities.^{22,38,39}

Item 16, which refers to feeling frustrated because of not knowing how to help PLwD, may reflect caregiver self-efficacy, emotional strain, or caregiving burden rather than attitude alone.^{35,42} Among Malaysian families, caregiving is often shaped by family obligation, filial responsibility, and religious or moral expectations.²² As a result, caregivers may interpret frustration differently, either as a personal emotional response, a lack of caregiving skill, or a sensitive feeling that may not be openly acknowledged.^{22,35,42}

Item 20, which describes difficult behaviours as a form of communication, may require a more specific understanding of behavioural and psychological symptoms of dementia.^{35,38} Caregivers with limited dementia education may interpret agitation, aggression, or repetitive behaviour as part of disease severity, personality change, or intentional behaviour rather than as unmet needs or communication.^{35,38} Therefore, this item may depend more on dementia literacy and caregiving experience than on the general attitude domains measured by the DAS-M.^{35,38}

The expert panel reviewed the retained factor structure and agreed that removal of these three items did not compromise the conceptual representation of the Social Comfort and Knowledge domains. The retained 17-item DAS-M continued to adequately capture the core constructs measured by the original instrument while remaining culturally appropriate for use among Malaysian caregivers.

The reduction from 20 to 17 items has both advantages and limitations. A shorter questionnaire reduces respondent burden, shortens completion time, and may improve feasibility in both clinical practice and research. However, removing items may reduce the breadth of content covered by the original instrument and may limit comparability with studies using the full 20-item DAS. Nevertheless, because the retained items continued to represent both the Social Comfort and Knowledge domains and demonstrated satisfactory validity and reliability, the 17-item DAS-M remains a comprehensive and culturally appropriate instrument for assessing dementia-related attitudes among Malaysian caregivers.

The DAS-M demonstrated good internal consistency ($\alpha=0.825$), comparable to the original and versions from other countries. Similar reliability was reported in the Turkish ($\alpha=0.84$), Indonesian ($\alpha=0.779$), and Greek ($\alpha\approx0.74$) validations.^{7,15,27} These findings suggest that despite structural differences and item removal, the DAS maintains stable internal coherence across cultures,

supporting its use as a global measure of dementia-related attitudes.

During cross-cultural adaptation, one notable change was replacing the term “ADRD” with “dementia” in the Malay version. This decision was made because “dementia” is more commonly understood by Malaysian informal caregivers, whereas “ADRD” may be less familiar outside academic or specialist clinical settings. This modification aimed to improve comprehensibility while maintaining conceptual equivalence with the original DAS.

The observed cross-cultural differences reflect broader sociocultural influences on perceptions of dementia. Studies from Europe and China show that attitudes are shaped by knowledge, exposure, education, and healthcare systems.^{6,43} In Malaysia, attitudes may be more influenced by family responsibility, religious beliefs, and social norms. These cultural factors may shape the distinction between cognitive (knowledge) and affective and behavioural (comfort) domains, as reflected in item reallocation within the DAS-M. In contrast, Western populations may show clearer distinctions between positive and negative attitudes or between comfort and discomfort dimensions.

The validated DAS-M has several practical implications. First, in clinical settings, it may be used as a brief screening tool to identify caregivers with less favourable dementia-related attitudes, particularly those who may feel uncomfortable, fearful, or uncertain when interacting with PLwD. This may help healthcare providers identify caregivers who could benefit from additional counselling, psychoeducation, or referral to caregiver support services.

Second, in caregiver education, the DAS-M can help identify specific attitudinal gaps before training and guide the development of culturally appropriate educational modules. For example, low scores in the Knowledge domain may indicate the need for education on dementia symptoms, communication strategies, and

behavioural management, whereas lower Social Comfort scores may indicate the need for practical exposure, communication skills training, and stigma reduction.

Third, in future intervention studies, the DAS-M can be used as an outcome measure to evaluate whether caregiver education, psychosocial interventions, or dementia awareness programmes improve attitudes over time. Its use may also support the assessment of programme effectiveness across clinical, community, and public health settings in Malaysia.

This study has several strengths. It involved a relatively large sample ($n=355$), exceeding recommended requirements for factor analysis, and involved multi-centre recruitment from two tertiary referral hospitals, enhancing representativeness. A comprehensive validation process, including content validity, face validity, construct validity, and reliability testing, further supports the DAS-M's psychometric robustness.

However, some limitations should be acknowledged. Convenience sampling may introduce selection bias and limit generalisability. Additionally, confirmatory factor analysis (CFA) was not conducted, which could have further strengthened validation of the factor structure.

CONCLUSION

The DAS-M demonstrated acceptable validity and reliability for assessing dementia-related attitudes among Malaysian informal caregivers. The findings support its potential use in research, caregiver training programmes, and public health interventions within similar clinical and caregiving contexts. However, further studies using confirmatory factor analysis and validation in larger, more diverse community-based samples, including caregivers from different regions and care settings, are recommended to strengthen its generalisability and confirm its factor structure.

The DAS-M demonstrated acceptable validity and reliability for assessing dementia-related attitudes among Malaysian informal caregivers. The findings support its potential use in research, caregiver training programmes, and public health interventions within similar clinical and caregiving contexts. However, further external validation in larger and more diverse community-based populations is recommended. In particular, confirmatory factor analysis should be conducted in an independent sample to verify the factor structure identified in the present study. Future validation should also include caregivers from different geographical regions and care settings to further establish the generalisability and robustness of the DAS-M.

DECLARATION OF AI USE

Generative AI tools (ChatGPT and Gemini) were used solely for language editing and improving clarity.

FUNDING

This study was conducted without any specific external financial support or grants from any public, commercial, or not-for-profit funding agencies.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

INSTITUTIONAL REVIEW BOARD (ETHICAL COMMITTEE)

The study adhered to the Declaration of Helsinki and received ethical approval from multiple boards. Primary approval was obtained from the UiTM Faculty Ethics Research Committee (7 November 2024; Ref: REC/11/2024 [PG/MR/549]), followed by the Ministry of Health Malaysia Medical Research and Ethics Committee (16 December 2024; NMRR ID: 24-03494-W6I [IIR]) and the UMMC Medical Research Ethics Committee (21 May 2025; Ref: 2025122-14637). Operational permissions were granted by HKL and UMMC, and formal authorisation to use the study instruments was obtained from the original developers and copyright holders.

ACKNOWLEDGEMENT

The authors thank the Director-General of Health Malaysia for permission to publish this article. Special appreciation is extended to Dr Rizah Mazzuin binti Razali and Madam Saadah binti Hassan for their invaluable guidance and contributions. The authors also thank the nursing and administrative staff of the Geriatric Clinics at Hospital Kuala Lumpur (HKL) and Universiti Malaya Medical Centre (UMMC), as well as members of Persatuan Usiamas, for their assistance with participant recruitment. The institutional support provided by the Faculty of Medicine, Universiti Teknologi MARA (UiTM), Sungai Buloh Campus, and the Faculty of Medicine, Universiti Malaya (UM), is gratefully acknowledged. The authors further express their sincere gratitude to UiTM Cawangan Selangor for funding the journal article publication fee through the Pembiayaan Bayaran Penerbitan Jurnal. Finally, the authors extend their heartfelt thanks to all caregivers who participated in this study, whose time and valuable insights were essential to the validation of the DAS-M.

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Warning Signs and Communication Effects: The Influence of Pictorial Health Warnings on Smoking-Related Knowledge, Attitudes, and Practices among Student Athletes

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ABSTRACT

INTRODUCTION: Pictorial health warnings (PHWs) on cigarette packaging are a widely recognised tobacco control strategy that aims to increase awareness of smoking-related health risks and discourage tobacco use. Although PHWs have demonstrated effectiveness in the general population, evidence regarding their impact on athletic populations remains limited. This study examined the relationship between responses to pictorial health warnings on cigarette boxes (PHWCB) and smoking-related knowledge, attitudes, and practices (KAP) among university student athletes. **MATERIALS AND METHODS:** A cross-sectional study was conducted among 68 university student athletes selected through convenience sampling. Data were collected using a self-administered online questionnaire assessing participants' cognitive and emotional responses to PHWCB and their smoking-related KAP. Descriptive statistics and Spearman's rank correlation were used to analyse the associations between PHWCB responses and KAP. **RESULTS:** Significant positive correlations were found between PHWCB responses and smoking-related knowledge ($p < 0.05$) and attitudes ($p < 0.05$), indicating that stronger responses to PHWCB were associated with greater awareness of smoking hazards and more negative attitudes toward smoking. However, no significant association was observed between PHWCB responses and smoking practices ($p > 0.05$). PHWCB effectively enhanced knowledge and influenced attitudes toward smoking but did not significantly affect smoking practices among student athletes. This intention-behaviour gap may be explained by factors beyond awareness, including social influences, nicotine dependence, and athlete-specific motivations. **CONCLUSION:** PHWCB improves smoking-related knowledge and attitudes but has limited influence on smoking behaviour among university student athletes. Athlete-specific tobacco control interventions emphasising the immediate effects of smoking on physical performance are recommended.

Keywords

anti-smoking campaign, athletes, cigarette box, KAP, pictorial health warning

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Received: 3rd March 2026; Accepted: 31st August 2026

Doi:
<https://doi.org/10.31436/10.31436/imjm.v25i04/3221>

INTRODUCTION

Tobacco smoking remains a major global public health concern, affecting individuals across diverse populations, including athletes. The World Health Organisation (WHO) reports that tobacco use is the

leading preventable cause of death worldwide, killing well over 8 million people each year.^{1,2} There were about 1.25 billion people aged 15 and up who used tobacco in 2022.³ In Malaysia, the Ministry of Health revealed that

the Malaysian National Health and Morbidity Survey⁴ found a smoking prevalence of 19% among adults over 15 years old, which includes 35.7% of males and 0.9% of females, while the prevalence of vaping was 5%.⁴

Athletes, despite their active lifestyles and knowledge of health's importance, are susceptible to the temptations of smoking, especially to relieve competitive anxiety and stress from expectations of their team and fans. Studies have shown that smoking prevalence among athletes varies across different sports and countries, with some athletes using tobacco products to manage weight, stress, or as a social habit.⁵ Although the epidemiology of smoking among athletes in Malaysia lacks extensive documentation, it remains a significant issue. Smoking among athletes presents unique challenges and behaviours that differ from those in the general population.⁵ These challenges and behaviours are influenced by various factors, including the nature of their sports, social environments, and the specific demands of their profession, especially performance and health awareness, peer influences, stress, coping mechanisms, weight management, cultural role models, policies, and regulations. The study among adolescent athletes found that smoking prevalence was significantly higher among football and basketball players compared with swimmers, who showed the lowest smoking rates.⁶

Differences in smoking prevalence between individual and team sports may be explained by variations in perceived responsibility and performance contribution, with athletes in team sports potentially experiencing less direct accountability for individual performance outcomes compared to those in individual sports.⁶ Malaysia has not extensively studied the effect of PHWs on cigarette boxes among athletes. Athletes, with their heightened awareness of health and body maintenance, might be more responsive to the graphic nature of PHWs.⁷ The warnings could serve as a constant reminder of the potential health risks that could impair their performance and overall well-being. Athletes are supposed to be more worried about smoking because damaged their lungs and affects their peak physical performance. Because of this, pictorial health warnings

(PHWs) may have an even greater effect on athletes' perception that smoking affects their performance and endurance.

Indeed, the social and professional environment of athletes, where health and fitness are paramount, might amplify the impact of PHWs. Peer influence and the need to maintain a certain image could make athletes more susceptible to the messages conveyed by the warnings.⁸ However, further research is needed to understand the specific impact of PHWs on athletes' KAPs in relation to smoking and to tailor interventions that effectively leverage the unique context of athletic communities.⁹

Implementation of pictorial health warnings (PHWs) on cigarette packaging is a strategy adopted by many countries, including Malaysia, to deter smoking. Malaysia has been proactive in implementing policies and interventions to achieve the Tobacco Endgame, particularly through the use of Pictorial Health Warnings (PHWs) on cigarette packaging. Malaysia introduced PHWs in 2009, and these warnings have since been revised to include more graphic images and messages in line with the Framework Convention on Tobacco Control (FCTC) guidelines.¹⁰ These warnings feature graphic images and strong messages to convey the health risks associated with smoking.^{11,12} Designed to be highly visible, the PHWs occupy at least 40% of the principal display areas of cigarette packs.

Pictorial health warnings have been established as a cost-effective tool for educating the public about the dangers of smoking, demonstrating superior comprehensibility compared to text-only warnings in raising awareness about the health consequences of tobacco consumption.¹³ Relative to text-only warnings, pictorial labels garner stronger cognitive and emotional reactions, eliciting more negative pack attitudes and smoking attitudes while effectively increasing intentions to quit.¹⁴ Despite these established benefits, the efficacy of health warning labels varies significantly across different demographics and cultural contexts, with specific evidence suggesting that young adults may respond

differently to standardised messaging due to unique social motivations and risk perceptions.¹⁵

In contrast, the effectiveness of these PHWs in influencing knowledge, attitude, and practice towards smoking habits has been reported in studies.^{16–18} A study by the Institute of Public Health (IPH) explored the impact of PHWs on cigarette boxes among Malaysian adults.¹⁸ The findings indicated that the majority of respondents noticed the PHWs, and there was a significant association between exposure to PHWs and increased knowledge about the health risks of smoking. The study also found that PHWs were more effective in influencing non-smokers' attitudes towards avoiding smoking than smokers.¹⁶ However, the practice of smoking was less affected, suggesting that while PHWs can raise awareness,^{14,18} There may not be sufficient evidence to change behaviour among established smokers,¹⁹ while another study shows a significant reduction in tobacco consumption.¹⁵

The effect of pictorial health warnings (PHWs) on cigarette packages in shaping smoking-related knowledge, attitudes, and behaviours among athletes in Malaysia has received limited attention. Evidence from the general population may not fully reflect the experiences of athletes, who may face different levels of performance demands, competitive stress, and sport-related environments. Thus, it is important to examine how PHW interventions affect athletes. Understanding their responses to these warnings can help determine whether current tobacco control strategies are effective for this group. Such evidence is important to guide the development of more targeted approaches to support smoking cessation and reduce smoking among athletes in Malaysia.

MATERIALS AND METHODS

Study design

We employed a cross-sectional study design to investigate the relationship between PHWs and KAP related to smoking among university athletes.

Sampling method

A convenience sampling method was used to recruit participants. This non-probability sampling technique involved selecting participants who were willing to participate in the study.

Participants' characteristics

They must be current UiTM Shah Alam students and athletes at least at the university level before or during the data collection. We collected the data from January 2024 to August 2024.

Study procedures

We initiated this study after receiving ethical approval from the Faculty of Sport and Recreation (FSR) ethical committee (FREC/04/2023/ (UG/MR/ 0146). We collected data by distributing a structured questionnaire via an online survey platform (Google Forms). The questionnaire consists of consent to participate, demographic details, and PHW and KAP questionnaires in Malay.

Study instruments

This study used the PHW and KAP questionnaires.¹⁷ The PHW Questionnaire consists of 22 items designed to assess various aspects of feeling fear (3 items), warning credibility (7 items), influence on perception (7 items), and picture content (5 items). Each item is rated on a 5-point Likert scale ranging from 1 (Strongly Disagree) to 5 (Strongly Agree). The PHW questionnaire has been validated with a Cronbach's alpha of more than 0.80.¹⁷ For KAP, questions were adapted from a previous study.²⁰ The questions were translated into the Malay language by an expert. The questionnaire contains 10 items to measure knowledge, 5 items to measure attitude, and 5 items to measure practice.

Data screening and cleaning

A total of 134 responses were collected. After screening the inclusion criteria, 68 university student-athletes were included in the final analysis.

Statistical analysis

The data were analysed using IBM SPSS Statistics version 30. Descriptive statistics were used to summarise the study variables. Spearman's rank correlation coefficient was used to examine the associations between pictorial health warnings (PHW) and knowledge, attitude, and practice (KAP). The Mann–Whitney U test was performed to compare PHW and KAP domain scores between smokers and non-smokers. Statistical significance was set at $p < 0.05$.

RESULTS

A total of 68 university athletes participated in the study, with most being male (69.1%), aged 18–25 years, and from the Faculty of Sports and Recreation (FSR). Nearly half (44%) were pursuing a bachelor's degree, while the rest had diploma or lower qualifications. Most participants were non-smokers (66.2%), whereas 33.8% were smokers. The majority competed at the national level. Participant characteristics are presented in Table I.

Table I. Participants' characteristics

Demographic	n(%)
<i>Gender</i>	
Male	47(69.1)
Female	21(30.9)
<i>Age</i>	
18-21	28(41.2)
22-25	28(41.2)
26-29	10(14.7)
>30	2(2.9)
<i>Races</i>	
Malay	50(95.6)
Indigenous Malay	3(4.4)
<i>Faculties</i>	
Sport science	40(58.8)
Non-sport science	28(41.2)
<i>Education level</i>	
SPM	5(7.4)
Matriculation/A level	2(2.9)
Diploma	30(44.1)
Degree	30(44.1)
Other	1(1.5)
<i>Smoking status</i>	
Smoker	23(33.8)
Non-smokers	45(66.2)
<i>Highest Competitive Level</i>	
University level	16(23.5)
National level	48(70.6)
International level	4(5.9)

Table II. The PHW domains showed moderate responses, with mean scores ranging from 2.57 to 3.21, indicating varying perceptions of fear, credibility, influence, and picture content. For KAP, participants demonstrated relatively higher mean knowledge (3.47)

and attitude levels (3.37), while practice scored lower (2.15).

Table II. Domain characteristics for PHW and KAP

Measures	Domain	Mean (SD)
PHW	Feeling Fear	
	Smoker	1.84 (0.92)
	Non-smoker	3.06 (0.87)
	Warning Credibility	
	Smoker	2.80 (0.82)
	Non-smoker	3.42 (0.59)
	Perception of influence	
	Smoker	2.88 (0.88)
	Non-smoker	
	Picture Content	
	Smoker	2.86 (0.99)
	Non-smoker	3.19 (0.70)
KAP	Knowledge	
	Smoker	3.21 (0.61)
	Non-smoker	3.60 (0.45)
	Attitude	
	Smoker	3.05 (0.60)
	Non-smoker	3.53 (0.59)
	Practice	
	Smoker	2.25 (0.34)
	Non-smoker	2.11 (0.58)
	Perception of influence	
	Smoker	1.96 (0.96)
	Non-smoker	2.88 (0.88)
	Picture Content	
	Smoker	2.86 (0.99)
	Non-smoker	3.19 (0.70)

Table III shows correlations between the PHW domains and KAP. Knowledge was significantly positively correlated with all PHW domains ($p < 0.05$). Attitude was significantly correlated with all except picture content. No significant correlations were found between any PHW domain and practice

Table III. Correlation between PHW and KAP

	Feeling fear	Warning credibility	Perception on Influence	Picture content
PHW				
KAP				
Knowledge	$r = 0.390^*$	$r = 0.570^*$	$r = 0.452^*$	$r = 0.456^*$
Attitude	$r = 0.447^*$	$r = 0.432^*$	$r = 0.385^*$	$r = 0.220$
Practice	$r = -0.097$	$r = -0.102$	$r = 0.147$	$r = -0.017$

* $P < 0.05$ = significant difference

Table IV compares pictorial health warning (PHW) domains between smokers and non-smokers using the Mann–Whitney U test. Significant differences were found for fear, warning credibility, perception of influence, knowledge, and attitude, with non-smokers reporting higher mean ranks than smokers ($p < .05$). Fear showed the largest effect size ($r = 0.57$). In contrast, no

significant differences were observed for picture content ($p=.202$) or practice ($p=.793$).

Table IV. Mann-Whitney test between smoking athletes and non-smoking athletes

Variables	Smoking status	Mean Rank	Median (IQR)	Mann-Whitney (U)	Z	p-value	Effect size (r)
Fear	Smoker	19.15	2.00(1.00)	870.50	4.704	<0.001	0.57
	Non-smoker	42.34	3.00(1.50)				
Warning Credibility	Smoker	23.96	3.00(1.00)	760.00	3.207	0.001	0.39
	Non-smoker	39.89	3.42(1.00)				
Perception of influence	Smoker	22.00	2.00(1.17)	805.00	3.742	<0.001	0.45
	Non-smoker	40.89	3.00(1.33)				
Picture Content	Smoker	36.66	3.00(1.33)	614.50	1.275	0.202	0.15
	Non-smoker	30.28	3.16(1.25)				
Knowledge	Smoker	25.61	3.00(1.10)	722.00	2.732	0.006	0.33
	Non-smoker	39.04	3.80(0.95)				
Attitude	Smoker	25.26	3.00(1.00)	730.00	2.843	0.004	0.34
	Non-smoker	39.22	3.80(1.00)				
Practice	Smoker	35.37	2.20(0.60)	497.50	-0.263	0.793	0.03
	Non-smoker						

DISCUSSION

Health information improves health literacy and helps people understand the risks of smoking. Studies have shown that pictorial health warnings (PHWs) on cigarette packages increase awareness and knowledge of the harmful effects of smoking. In Malaysia, most people noticed PHWs, which were associated with greater awareness of smoking-related health risks.¹⁹ Graphic images and strong messages can evoke emotional responses and create negative attitudes towards smoking, as well as prevent smoking initiation among non-smokers and encourage quitting for smokers. Research in Malaysia indicates that PHWs are more effective in influencing non-smokers' attitudes than smokers.¹⁶

Athletes, who are generally more health-conscious and informed about their bodies, may be even more receptive to the information provided by PHWs, potentially leading to heightened awareness of the specific impacts of smoking on athletic performance.²¹ Smokers had significantly lower muscle strength in the

shoulder and lower limb compared to non-smokers, while smokers showed less agility and speed than non-smokers. However, there are no significant differences in muscle endurance and flexibility between the two groups.²¹ Research suggests that these visual warnings enhance awareness of health risks, fostering more negative attitudes towards smoking. Smokers often report heightened motivation to quit, whereas non-smokers tend to perceive smoking as harmful. However, this perception may not significantly influence smoking habits.^{11,16,19} Studies in Malaysia suggest that, although PHWs can raise awareness and negatively influence attitudes, they may not be enough to change the smoking behaviour of established smokers.¹⁸ The study in Indonesia also reported that the same PHW is inadequate to reduce cessation rather than induce desensitisation to the PHW.¹⁵ Athletes who are already smokers may exhibit greater resistance to altering their habits due to nicotine dependence or the social norms prevalent within their sport. However, the distinctive environments of athletes, which emphasise health and performance, could provide additional motivation for them to quit smoking. In addition, smoking among elite athletes has become part of a coping mechanism to help them cope with the high pressure of high-profile competition.⁶

Graphic health warnings can enhance public awareness, encourage cessation, and promote concern about the emotionally charged messages. The value of graphic warnings lies in their ability to make the potential health risks associated with smoking more tangible for the smoker, thereby enhancing the likelihood that they will contemplate taking action to mitigate this risk.¹⁶ In addition, due to our predominantly Malay-Muslim participants and the lack of non-Malay participants in this study, some opinions, i.e., attitudes, may be shaped by participants' sociocultural and religious beliefs.²² The present study showed PHWs have an impact on knowledge and awareness about the harm of smoking, as also reported previously. However, the findings indicate that PHWs were more effective among non-smokers than smokers. Non-smokers reported significantly higher levels of fear, warning credibility,

perceived influence, knowledge, and positive attitudes, with fear showing the largest effect size. In contrast, smokers may be less responsive to PHWs due to cognitive dissonance or optimistic bias, reducing the impact of the warnings.

PHWs failed to influence the practices among athletes; thus, it was similar to the previous study in the general population. The previous study also showed that greater exposure to the truth anti-smoking campaign is significantly associated with reduced intention and current use of e-cigarettes among young people. This study showed that PHWs were positively associated with increased knowledge among participants and awareness about the harms of smoking among athletes, consistent with previous findings.¹⁸ However, similar to patterns seen in the general population, these improvements did not translate into changes in smoking-related practices. Evidence from broader health communication research demonstrates that behavioural change is more likely when individuals experience frequent and repeated exposure to health messages.¹⁴ The anti-smoking campaign showed that higher weekly exposure significantly reduced both intentions and current use of e-cigarettes among young people. Additionally, findings from randomised controlled trials have shown that repeated exposure to graphic health warnings can increase quit-related thoughts and strengthen cessation intentions over time, reinforcing the importance of sustained message repetition.¹⁴

In the context of this study, most participants were non-smokers, meaning their exposure to cigarette boxes, and therefore, to PHWs was minimal. This limited and inconsistent contact with the warnings reduces the likelihood of behavioural influence, helping explain the non-significant relationship between PHWs and practice. Taken together, these findings suggest that while PHWs can effectively shape knowledge and attitudes, meaningful changes in smoking behaviour depend heavily on the frequency, duration, and context of exposure to these health messages. However, we can hypothesise that the insignificant effects due to a few of the existing PHWs were misunderstanding or inability to

understand PHWs deeply or collectively, such as displaying gangrene, premature birth, etc., as reported in a previous study.¹¹ As recommended from an Australian perspective, the issues regarding the design of PHW, such as the usage of pictures and the potential adverse outcome, are very critical.¹⁸ This aspect might be a factor that should be further evaluated in the Malaysian athlete context to relate the PHW to health and performance.

This study also revealed that there was an insignificant difference in the practices between smoking athletes and non-smoking athletes, similar to the previous study by Amirah et al.²³ Mustafa et al. found that good knowledge about the harmful effects of smoking was associated with a low prevalence of tobacco.²⁴ However, a previous study indicated that among medical students who recognised the dangers of smoking, 35.17% still identified as smokers.²⁵ This finding highlights the complexity of smoking behaviour, where awareness alone may not be sufficient to deter individuals from smoking. Therefore, it is essential to implement comprehensive interventions that educate and address the underlying factors contributing to smoking habits among athletes and other populations. Knowledge of smoking was also associated with gender and educational status.^{23,24} Poor knowledge might lead to increased use of cigarettes.²⁶ Thus, it is difficult to conclude that knowledge and attitude can affect the practice in the smoking context either in the general population or in athletes' populations.

Feeling fear, warning credibility, and perception of influence differed significantly between smokers and non-smokers, whereas picture content did not. These findings indicate that non-smoking athletes exhibited significantly higher knowledge and more favourable attitudes towards pictorial health warnings than smoking athletes. In addition, non-smokers reported stronger emotional reactions, greater perceived credibility, and stronger perceived influence of the warning labels.¹² In addition, a study conducted in Cyprus found that smokers rarely noticed the pictorial health warnings (PHWs) on cigarette packages, although approximately 59.4% considered the health warnings to be effective.²⁷

Non-smokers manifested more awareness and positive opinions about the warnings. Furthermore, pictures illustrating the most aggressive health conditions became the most effective of the warnings. This study also showed that most smokers were very concerned with the premature birth compared to other health warning pictures. The findings are in support of the role of pictorial warnings as a method of tobacco control and quitting smoking. A similar study found that anti-smoking advertisements create fear toward smoking.²⁸

The findings of this study underscore the superior effectiveness of pictorial health warnings over text-only formats in eliciting adaptive cognitive and emotional responses.²⁹ Specifically, pictorial warnings have been shown to attract and hold attention better while communicating health risks more effectively than text-only alternatives.²⁹ Research indicates that these visual warnings generate greater fear, harm perception, and intentions to quit compared to standard text labels, particularly when themes emphasise specific consequences such as harm to others or comparative risks.³⁰ However, the effectiveness of these warnings is not uniform across all populations, as demographic and cultural factors play a significant role in shaping smoking behaviours and responses to anti-smoking campaigns.^{5,15,31} In China, messages emphasising the harm of second-hand smoke to family members and children received the highest evaluations, particularly in terms of credibility and perceived effectiveness for smoking prevention, and were regarded as more credible by smokers than messages focused on self-harm.³²

Thus, the PHW also needs to consider athletic aspects for targeting athletes or a physically active population. This aligns with evidence from waterpipe and e-cigarette-specific research, which demonstrates that tailored pictorial warnings elicit greater attention, negative affect, and cognitive elaboration than generic text warnings.^{30,33} Such targeted messaging is particularly salient for athletes, who may be more responsive to information highlighting the direct impact of tobacco use on athletic performance and physical capacity rather

than general health outcomes.³⁴ Therefore, interventions that frame tobacco risks in terms of compromised endurance, reduced oxygen efficiency, and slower recovery times may resonate more strongly with this demographic than generic warnings emphasising long-term morbidity or mortality.³⁵

The limitations of the study were acknowledged. First, the sample size was somewhat small because the study was of limited duration, and few responses were excluded during the data cleaning process as participants were not eligible for athletic-level inclusion requirements. Second, the unbalanced distribution of smokers and non-smokers may have created a floor effect and lowered statistical power to detect group differences. This discrepancy is representative of the difficulties of recruiting smokers in athletic populations where rates of smoking are often low. Finally, the generalisability of the findings is limited by the use of a convenience sample drawn from a single institution. The cross-sectional design precluded causal inference and did not allow the intention-behaviour gap to be examined. Future studies should recruit larger and more diverse samples from multiple universities to improve statistical power, identify potential confounders, and improve the generalisability of the findings.

CONCLUSION

Pictorial health warnings on cigarette boxes have the potential to be effective in influencing athletes' knowledge and attitudes, but not their practices, in Malaysia. Thus, these findings were similar to those reported in the general population. The health-conscious nature of athletes and the emphasis on performance in their professional and social environments could make them particularly receptive to PHWs' messages. However, further research is needed to understand the specific impact of PHWs on athletes and how it would affect practices towards smoking cessation. Further exploration is necessary to develop targeted interventions that leverage the unique context of athletic communities.

FUNDING

This study was funded by Universiti Teknologi MARA (UiTM) under the Geran Penyelidikan MyRA Lepas PhD (Grant No. 600-RMC/GPM LPHD 5/3 (100/2022)).

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

INSTITUTIONAL REVIEW BOARD (ETHIC COMMITTEE)

This study obtained ethical approval from the Universiti Teknologi MARA (UiTM) Ethics Committee (Approval No. FERC/04/2023/(UG/MR/0146)).

ACKNOWLEDGEMENTS

The authors thank all participants and contributors to this study.

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Ethical and Shariah Considerations in Contemporary Genetic Practices: Where Should the Limits Be? A Thematic Analysis

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ABSTRACT

INTRODUCTION: Rapid advances in genetic technology have improved the diagnosis and treatment of genetic diseases but also raise ethical and *Shariah* concerns, particularly regarding human intervention in *fitrah*, genetic manipulation, and unclear *fiqh* guidance. This study explored the ethical and *Shariah* considerations in contemporary genetic practices based on the views and experiences of respondents involved in genetic issues within the context of Muslims in Malaysia. **MATERIALS AND METHODS:** A qualitative approach using semi-structured interviews was employed, with data analysed through inductive thematic analysis. **RESULTS:** Three themes were identified: *Shariah* limits in genetic technology, ethical concerns regarding genetic manipulation, and the need for contemporary *fiqh* guidelines. Acceptance of genetic practices was influenced by legal clarity, concerns about exceeding human *fitrah*, uncertainty regarding long-term consequences, and the potential misuse of genetic technology. **CONCLUSION:** The findings highlight the need for greater integration of genetic science, ethics, and *Shariah* in addressing contemporary genetic issues. This study provides empirical insight into gaps in practical *fiqh* guidance and offers a foundation for developing context-sensitive ethical and *Shariah* frameworks aligned with ongoing scientific developments.

Keywords

genetic ethics, *Shariah*, genetic manipulation, contemporary *fiqh*, thematic analysis

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Received: 2nd February 2026; Accepted: 27th
July 2026

Doi:
<https://doi.org/10.31436/10.31436/imjm.v25i04/3188>

INTRODUCTION

Rapid advances in genetic science have improved the diagnosis, prevention, and treatment of genetic diseases, with technologies such as genetic screening, prenatal diagnosis, and gene manipulation offering substantial clinical benefits.¹⁻³ However, interventions that alter fundamental aspects of human life raise complex ethical and moral concerns.^{4,5} In the context of Muslims, their acceptance is assessed not only by clinical effectiveness but also through *Shariah* and religious values.^{6,7}

Central to this evaluation are two related concepts: *taghyir khalqillah* (changing God's creation), which concerns the legitimacy of altering creation, and

exceeding *fitrah*, which concerns whether biotechnology may distort divinely endowed human nature.^{8,9} The treatment–enhancement distinction further differentiates therapeutic from non-medical interventions, together forming ethical limits on genetic manipulation.^{9,10} As *fitrah* is regarded as divinely endowed and stable, excessive alteration may threaten the intended material-spiritual human constitution.^{8,9} Yet the boundary between permissible therapeutic restoration and illegitimate enhancement remains poorly defined in classical *fiqh* and contemporary scholarship.^{3,10,11}

In Malaysia, *fatwa* governance operates at national and state levels through the National Fatwa Committee of the National Council for Islamic Religious Affairs Malaysia (MKI) and respective state *fatwa* committees.^{12,13} MKI coordinates expert deliberation under the Department of Islamic Development Malaysia.^{13,14} Existing biomedical *fatwas* remain largely case-specific: embryonic stem-cell research is permitted only up to 14 days post-fertilisation,¹³ while the 120-day ensoulment threshold guides abortion decisions for severe foetal anomalies, although late detection can create clinical uncertainty.^{5,15} Genetic modification is generally accepted for therapeutic purposes but not cosmetic enhancement or selection of socially desirable traits.^{3,6} MKI rulings on genetically modified food similarly involve weighing benefit (*maṣlaḥah*) and harm (*mafsadah*).^{16,17} Nevertheless, specific operational guidance for emerging technologies such as CRISPR-Cas9 and polygenic testing remains limited.^{16,18}

Global Islamic discourse on genetics remains dominated by normative legal analysis using *Maqāṣid al-Shari'ah* and "five rulings" (*al-aḥkām al-khamsa*), with limited philosophical engagement with scientific transformation.^{9,10} The International Islamic Fiqh Academy has been criticised for a technical medical outlook,⁹ while its 2019 CRISPR-Cas9 resolutions were largely reactive rather than providing a proactive distinction between germline and somatic editing.¹⁹ Similarly, *Dār al-Iftā' al-Miṣriyyah* rulings emphasise therapeutic potential but leave concepts such as *ḍarar* and *maṣlaḥah* insufficiently defined.⁹ Key gaps include limited scientific literacy in juristic assessment,⁹ insufficient clinical specificity regarding the treatment-enhancement distinction,^{3,10} and weak methodological integration between jurists and scientists.⁹ These gaps contribute to uncertainty in cases such as severe foetal anomalies detected beyond 120 days.¹⁵ Global discourse also insufficiently addresses challenges relevant to Malaysian Muslims, including consanguinity and uneven healthcare training.^{20,21} Addressing these limitations requires empirical attention to stakeholder experiences

in specific clinical and cultural settings,^{3,9} particularly in Malaysia, to support interdisciplinary bioethical frameworks and dialogue among medical, scientific, and religious authorities.^{3,22} Such integration is needed for proactive guidance responsive to local social and religious requirements.²²

Accordingly, this study examines the ethical and *Shariah* dimensions of contemporary genetic practices in the Malaysian Muslim community by: (1) defining *Shariah* boundaries between therapeutic treatment and genetic enhancement; (2) examining clinical and operational challenges arising from the absence of proactive *fiqh* guidance for CRISPR-Cas9 and prenatal screening beyond the 120-day threshold; and (3) identifying requirements for an integrated interdisciplinary bioethical framework linking scientific innovation with *Shariah* principles in Malaysia.

MATERIALS AND METHODS

Study Design

This study used a qualitative design to explore ethical and *Shariah* considerations in genetic practices and to understand the meanings and interpretations of respondents regarding complex genetic issues.²³⁻²⁵ This design enabled contextual examination of their experiences and concerns in relation to *Shariah* limits, ethical dilemmas of gene manipulation, and the need for contemporary *fiqh* guidance.²⁶⁻²⁸

Thematic Analysis Approach

Inductive thematic analysis was used to identify recurring patterns of meaning in the interview data without imposing a pre-established theoretical framework. Explicit and implicit meanings were systematically examined to develop themes reflecting the ethical and *Shariah* dimensions of genetic practices.²⁹

Study Respondents

The study included 23 respondents (n=23), purposively selected for relevant professional, scholarly, policy, advocacy, or lived experience in contemporary genetic

practices and their ethical or *Shariah* dimensions within the context of Malaysian Muslims. Respondents represented medical practitioners, clinical geneticists, one genetic counsellor, *Shariah* scholars and *fatwa*-related experts, patient/NGO and parent advocacy representatives, and policymakers. This diversity captured clinical, religious, ethical, policy, and lived-experience perspectives. Clinical geneticists were distinguished from general medical practitioners because of their specialised expertise in genetic counselling, diagnosis, and genomic analysis. Table I presents the demographic and professional characteristics of the respondents in aggregated form to preserve confidentiality.

Table I. Characteristics of the Study Respondents (n = 23).

Characteristic	Category	n
Stakeholder category	Medical practitioners	5
	Clinical geneticists	4
	Genetic counsellor	1
	<i>Shariah</i> scholars, Muftis and <i>Fatwa</i> officers	7
	Policymakers	2
	Representatives from patient associations, non-governmental organisations (NGOs), and parent advocacy groups	4
Professional experience (years)	10–19	5
	≥ 20	18
	Universities	7
	Hospitals	4
Institution type	Religious authorities	5
	Government agencies	2
	Patient organisations / NGOs	4
	Private genetic services	1

Note. Respondents were purposively selected to represent key stakeholder groups involved in contemporary genetic decision-making within the Malaysian Muslim context. Respondent characteristics are presented in aggregated form to preserve confidentiality. Gender and detailed institutional affiliations were not reported because they were not relevant to the study objectives and, when combined with specialised stakeholder groups, could increase the risk of indirect respondent identification. *n* = number of respondents.

The adequacy of the 23-interview sample was assessed using information power, whereby sample sufficiency depends on the relevance, specificity, and richness of information rather than a fixed numerical target.³⁰ Given respondents' specialised expertise and the focused study aims, the interviews provided sufficient information power to identify recurring patterns and meaningful

variations.³⁰ This supported a holistic interpretation of the complex socio-religious discourse surrounding genetics.³¹

Data Collection

Data were collected through semi-structured interviews conducted face-to-face or via digital platforms according to respondent preference. Researchers experienced in qualitative inquiry used an open-ended interview guide to explore genetic technology, ethical concerns, and *Shariah* considerations.³² Interview duration varied according to discussion depth and respondent availability. Interviews were conducted in Malay, English, or both, recorded with consent, and transcribed verbatim before analysis.

Data Analysis Process

Data analysis involved repeated reading of transcripts, identification of meaningful units, and grouping related codes into subthemes and broader themes. Themes and subthemes were repeatedly reviewed against the original data to ensure interpretive accuracy, and theme names were selected to reflect respondents' shared meanings. Selected quotations requiring translation were translated into English while preserving meaning, tone, and contextual nuance. Where necessary, translations were checked against the original transcripts and thematic analysis table for consistency. No qualitative data-analysis software was used; coding, theme development, and review were conducted manually.

RESULTS

Thematic analysis of interviews with 23 respondents identified three themes concerning ethical and *Shariah* considerations in genetic practices: boundaries of genetic technology, ethical dilemmas of manipulation, and gaps in contemporary Islamic jurisprudence.²⁹ Despite the small sample, the specialised exposure of respondents to genetic ethics provided sufficient information power to capture recurring patterns and meaningful variations relevant to the focus of the study.³⁰

Shariah Limits in Genetic Technology

This theme reflects respondents' view that advances in genetic science require *Shariah* guidance, as technological feasibility does not necessarily imply moral permissibility when interventions affect the sanctity and dignity of human creation.

Need for Shariah Boundaries in the Use of Genetic Technology

Respondents viewed genetic technology as requiring systematic regulation to prevent arbitrary application.³³ A central concern was preserving the "physical and functional boundaries of human agency."³⁴ Without religious guidance, such interventions may risk violating the "best form" (*absan taqwim*) intended by Allah.⁹ As one respondent stated in File 2-07: "*Genetic technology cannot be used arbitrarily; there must be boundaries from the Shariah perspective.*"

Concerns about Departing from Human Fitrah

Respondents expressed concern that departing from *fitrah* could move genetic intervention beyond therapeutic restoration, distorting the spiritual essence and the "uniqueness of human creation."^{9,35} Excessive intervention was also perceived as risking forms of human existence that diverge from the divinely intended material-spiritual constitution.⁹ As one respondent noted in File 1-04: "*I am worried if this genetic technology ends up changing the original human creation.*"

Legal Assessment as the Basis for Technology Acceptance

Respondents' acceptance of genetic technology depended on clear *Shariah*-based determinants (*dawabit Shar'iyah*).⁹ Confidence was linked to benefit-harm assessment (*maslahah-mafsadah*), rather than scientific feasibility alone, as a basis for ensuring interventions remain within Islamic legal objectives.³ As stated in File 3-03: "*If the law is clearly permitted, then I feel confident to accept that technology.*"

Ethical Doubts Regarding Gene Manipulation

This theme reflects the uncertainty of the respondents about the ontological and clinical implications of human genome manipulation, particularly the tension between therapeutic potential and preserving human nature.

Uncertainty of Long-Term Implications of Gene Manipulation

Respondents voiced concern about the "remote and unpredictable consequences" of genetic editing.³⁹ They perceived that a single genetic alteration could have wider effects on biological and spiritual integrity, making long-term uncertainty both a scientific and moral concern.³⁶ As stated in File 2-04: "*The long-term effects of this gene manipulation we ourselves do not yet know.*"

Conflict between Treatment Needs and Moral Considerations

Respondents distinguished therapeutic restoration from enhancement.¹⁰ They were generally open to treating disease but resisted interventions targeting non-medical or socially desirable traits.^{3,34} This tension reflected a balance between clinical benefit and concerns about "tampering" with divine creation.³ As one respondent in File 3-03 noted: "*From a treatment perspective, it may help, but from a moral perspective, I am still doubtful.*"

Concerns about the Misuse of Genetic Technology

Beyond clinical use, respondents raised concerns about the commercial or political misuse of genomics and its implications for the "security of peoples."⁹ Inadequate ethical control could enable uses that conflict with humanitarian and religious values and undermine human dignity.³⁵ These concerns highlight the need to prevent weaponised or exclusionary applications. As stated in File 1-04: "*Afraid that this genetic technology will be misused for unethical purposes.*"

Need for Contemporary Fiqh Guidelines

The final theme highlights substantive and methodological gaps in contemporary Islamic discourse, particularly the lack of specific and authoritative *fiqh*

references responsive to rapid biotechnological developments.

Lack of Specific Fiqh References on Genetics

Respondents noted that existing juristic rulings (*ahkām fiqhīyya*) often address immediate questions without providing a comprehensive philosophical perspective on genetics.⁹ The lack of specific, codified guidance contributes to uncertainty regarding emerging technologies such as polygenic testing,^{3,10} while the absence of a unified reference complicates ethical and legal navigation. File 2-07 similarly indicated that specific *fiqh* guidelines on genetics remain absent.

Reliance on Individual Opinions without Official Guidelines

In the absence of clear institutional *fatwas*, respondents described reliance on personal interpretations as inconsistent and risky. Such “instrumental considerations,” focused mainly on body and disease, may overlook broader dimensions of *maslahah* and *ḍarar* (harm), which are integral to Islamic bioethics.⁹ Without official guidance, subjective bias in clinical decision-making may increase.³⁷ As noted in File 2-04: “*Sometimes decisions are made based on one's own opinion because there is no clear guidance.*”

Need for New Ijtihad Aligned with Scientific Developments

Respondents supported a dynamic and contextual approach through collective *ijtihad* (*al-ijtihād al-jamāʿī*).⁹ Given the complexity of genomics, multidisciplinary deliberation between religious scholars and biomedical experts was considered necessary to ensure that new rulings are scientifically informed and grounded in *Shariah* principles.⁹ As one respondent in File 3-03 stated: “*This genetic issue requires new ijtihad that aligns with current scientific developments.*”

DISCUSSION

Summary of Main Findings

This study identified three central considerations in genetic practices: *Shariah* boundaries, ethical concerns regarding gene manipulation, and the need for clearer contemporary *fiqh* guidance. Acceptance was shaped by clinical benefit, legal clarity, compatibility with human *fiṭrah*, and concerns about misuse.

Interpretation of Findings

Respondents viewed genetic technology through religious and moral principles rather than as value-neutral. Concerns about *fiṭrah* reflected ontological and theological dimensions beyond clinical considerations, while uncertainty over gene manipulation highlighted tensions between therapeutic benefit and long-term harm.

Comparison with Previous Studies

The findings are consistent with Islamic bioethics scholarship applying *Maqasid Shariah* to contemporary biotechnology. *Maqasid*-based frameworks have been used to evaluate biotechnological dilemmas through intention, methodology, consequences, benefits, and risks.³⁸ In biotechnology and genetically modified food, these principles emphasise health, preservation of life, and avoidance of harm.³⁹ Their application to genetically modified crops further encompasses the preservation of religion, life, progeny, intellect, and wealth,⁴⁰ while germline editing has been considered permissible for therapeutic purposes when safety and *Shariah* objectives are fulfilled.⁴¹ The present study extends this predominantly normative literature by providing empirical evidence of respondents’ experiences and perceptions of gaps in practical *fiqh* guidance for contemporary genetics.

Implications of the Study

From a professional practice perspective, the findings support explicit ethical and *Shariah*-compliant guidance for genetic decision-making. Robust ethical regulation is

needed to preserve human dignity and prevent premature or inappropriate use of genetic technologies,⁶ while the absence of universally applicable religious guidance may create uncertainty in clinical decision-making.¹⁵ *Shariah*-based assessment before genetic research or therapy, complemented by *Maqasid Shariah* frameworks, may provide a structured basis for addressing such dilemmas.^{9,42}

At the level of policy, Muslim-majority settings require contemporary *fiqh*- and *ijtihad*-informed guidance responsive to developments such as CRISPR-Cas9 and genomics.⁴³⁻⁴⁵ Regulatory gaps across Islamic contexts further reinforce the need for oversight that protects human dignity, fulfils *Maqasid Shariah*, prevents misuse, and enables therapeutic benefit.^{6,15,41}

Education and training should also strengthen engagement with Islamic ethics to improve public understanding and professional competence. *Shariah*-informed awareness and genetic counselling education may help address religious and cultural misconceptions and support principled decision-making in genomics and precision medicine.⁴⁶

Islamic Legal and Bioethical Interpretation of the Findings

The findings from 23 specialised respondents provide substantial information power by extending beyond normative legal analysis to the lived complexities of genetic technology.³⁰ Interpreted through Islamic legal theory, these findings highlight the interplay between preserving human nature, preventing biological harm, and promoting public interest in the context of genomics among Muslims in Malaysia.

Maqasid al-Shariah and the Preservation of Human Fitrah

The concern about departing from human *fitrah* can be interpreted through *Maqasid al-Shariah* as relating to the protection of *al-Din* (religion) and *al-Nafs* (life).^{48,49} Preservation of *al-Din* includes safeguarding the divinely intended human form described as the “best form”

(*absan taqvim*).³ *Fitrah* has also been characterised as a stable ontological disposition distinct from *tabi'ah*, or biological traits open to alteration.⁸ This distinction helps explain respondents' concern that genetic manipulation could affect the spiritual and material constitution associated with *fitrah*,⁸ including fears of changing the “original human creation” (File 1-04), which aligns with protecting the individual's spiritual essence.⁵⁰

Islamic bioethical permissibility likewise depends on fulfilling these higher objectives.⁴⁰ Accordingly, interventions perceived to threaten the “uniqueness of human creation” may challenge the sanctity of life as a divinely endowed trust,³⁵ reinforcing the need for *Shariah* boundaries in genetic practice.

Applying the Maxim 'Al-Darar Yuzal' to Ethical Uncertainty

Concerns about long-term biological consequences and technological misuse can be interpreted through the *Shariah* maxim *al-darar yuzal* (“harm must be eliminated”).³⁹ *Shariah*-based assessment requires consideration of benefit (*maslahah*) and harm (*mafsadah*),¹⁸ making uncertain and potentially irreversible effects of genetic manipulation ethically significant.⁹ Such uncertainty also relates to the avoidance of *gharar* in matters affecting life and progeny.⁹ Until sufficient clinical certainty (*yaqin*) is established regarding germline modification, a precautionary approach is therefore consistent with protecting future generations from harm.^{3,41}

In Malaysia, the unresolved regulatory and ethical status of CRISPR-Cas9-mediated human germline editing reinforces respondents' concerns about the absence of an operational *fatwa* framework.⁶ Existing scholarship similarly calls for robust ethical guidance and regulation to preserve human dignity and prevent premature use or misuse of the technology.⁶

Collective *Ijtihad* as a Mechanism for *Maslahah*

The findings identify collective *ijtihad* (*al-ijtihad al-jamā'i*) as an important mechanism for realising *maslahah* while addressing tensions between treatment and enhancement. Respondents supported permissible restoration for disease but remained concerned about enhancement (File 3-03), reflecting the need for a dynamic and contextual treatment–enhancement assessment.¹⁰ Collective *ijtihad* enables multidisciplinary deliberation in which scientific expertise informs juristic determinants (*dawābiṭ*).⁹ Similar interdisciplinary dialogue among scientists, medical practitioners, and religious communities has been advocated in the broader regional Muslim context to balance genetic innovation with Islamic ethical values.²² Such deliberation prevents *maslahah* from being reduced to a merely technical medical outlook⁹ and supports structured benefit–harm assessment (*maslahah–mafsadah*) within an interdisciplinary bioethical framework.¹⁸

Synthesis with Global Academic Discourse

The findings extend global Islamic bioethics discourse by empirically supporting reported gaps in interdisciplinary engagement and the treatment–enhancement debate.^{9,10} Respondents' lack of specific *fiqh* references and reliance on individual opinions demonstrate how these gaps arise in practice.¹⁵ International resolutions may therefore remain insufficient for context-specific clinical complexities.⁹

Accordingly, this study proposes an Integrated Ethical and *Shariah* Decision-Making Framework for contemporary genetic practices in Malaysia. Emerging technologies are assessed against ethical concerns and *Shariah* principles, including *Maqāṣid al-Shari'ah*, *Ḥifẓ al-Naṣl*, *Fitrah*, *Maṣlahah*, *Ḍarar*, justice, and responsibility.^{9,35} Through *al-ijtihad al-jamā'i* involving clinical, genetic, counselling, *Shariah*, policy, and patient stakeholders, the framework links multidisciplinary deliberation with clinical practice, religious guidance, and policy development.

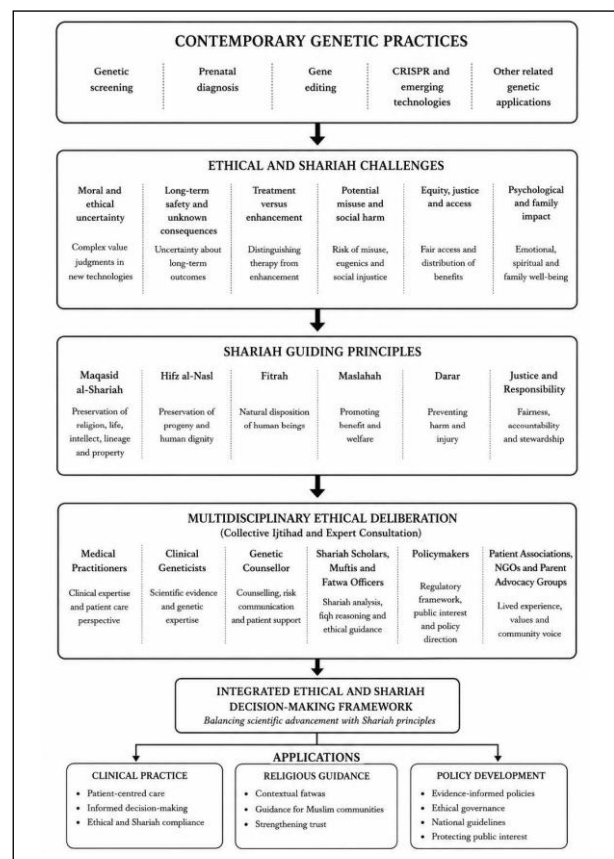


Figure 1: Integrated Ethical and *Shariah* Decision-Making Framework for contemporary genetic practices in the Malaysian Muslim context.

Abbreviations: CRISPR, clustered regularly interspaced short palindromic repeats; NGOs, non-governmental organisations.

STRENGTHS AND LIMITATIONS OF THE STUDY

This study's focused qualitative and thematic approach enabled in-depth exploration of ethical and *Shariah* considerations in genetic practices. Themes and subthemes supported by verbatim quotations enhance analytical transparency and credibility while providing empirical insight into gaps in contemporary *fiqh* guidance. Limitations include the small number of respondents and a scope confined to ethical and *Shariah* dimensions without detailed clinical or technical analysis. Accordingly, the findings are not intended for generalisation but provide a conceptual and empirical basis for future research and development of more comprehensive ethical and *Shariah* guidelines in genetics.

CONCLUSION

Genetic practices in the Malaysian Muslim context require evaluation not only in terms of scientific and clinical benefit but also through ethical and *Shariah* considerations. The findings highlight the importance of *Shariah* boundaries, concerns about genetic manipulation that may exceed human *fiṭrah*, uncertainty regarding long-term consequences, and gaps in contemporary *fiqh* guidance. These gaps may contribute to inconsistent decision-making and reinforce the need for contextual *ijtihad* responsive to scientific developments.

To address these concerns, this study proposes an Integrated Ethical and *Shariah* Decision-Making Framework that links emerging genetic technologies with *Maqāṣid al-Shari'ah*, *Hijz al-Nasl*, *Fiṭrah*, *Maṣlaḥah*, *Ḍarar*, justice, and responsibility through *al-ijtihad al-jamā'i* involving relevant clinical, religious, policy, and patient stakeholders. The framework provides a conceptual pathway for clinical practice, religious guidance, policy development, and future research. Although not intended for generalisation, the findings offer an empirical and conceptual basis for developing practical *Shariah*-informed guidance for contemporary genetics.

INSTITUTIONAL REVIEW BOARD (ETHIC COMMITTEE)

Ethical approval was obtained from the Human Research Ethics Committee of Universiti Sains Malaysia (USM/JEPeM/15100402). Respondents were informed of the study purpose, data collection procedures, and their rights before providing informed consent. Confidentiality was maintained through coded identifiers without disclosure of personal information. Participation was voluntary, and respondents could withdraw at any time without adverse consequences. No respondents withdrew after providing consent.

ACKNOWLEDGEMENTS

The authors would like to express their sincere appreciation to Ahmad Fakhurrazi Yahya for his valuable assistance in the data collection process. This study was supported by the Ministry of Higher Education (MOHE), Malaysia, under the Fundamental Research Grant Scheme (FRGS), project code FRGS/1/2017/SKK06/USM/02/6.

ARTIFICIAL INTELLIGENCE (AI) STATEMENT

ChatGPT (version 5.2) was used infrequently to improve the grammar and fluency of the text, without contributing to the content or ideas.

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Impact of Chronic Low Back Pain (CLBP) On Quality of Life (QOL) of Parents with Physically Handicapped Children

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ABSTRACT

INTRODUCTION: Parents of physically disabled children are susceptible to chronic low back pain (CLBP) due to sustained physical demands and psychosocial stress associated with caregiving. However, data on the prevalence of CLBP and its impact on quality of life (QOL) among parental caregivers in Malaysia remain limited. This study aimed to determine the prevalence of CLBP among parents of physically disabled children and to examine its relationship with children's functional level and parental QOL. **MATERIALS AND METHODS:** A retrospective analysis of data from a cross-sectional survey was conducted among 94 parents of physically disabled children aged 2-14 years in Bandar Puncak Alam, Selangor. Participants were primary caregivers aged 18 years and above who lived with the child and reported low back pain (LBP) lasting more than three months. Data collected included demographic characteristics, children's functional level, pain-related disability, and QOL. Descriptive and inferential analyses were performed to examine prevalence and associations. **RESULT:** CLBP was reported by 70% of parents (n=66). No significant association was found between children's functional level and the prevalence of CLBP ($\chi^2=3.47$, $p=0.48$). Pain-related disability showed significant negative correlations with QOL domains, including role limitations due to physical health ($p=0.002$), fatigue ($p=0.001$), pain ($p=0.002$), general health ($p=0.001$), and perceived health change ($p=0.004$). **CONCLUSION:** Our findings reveal a high prevalent of CLBP among parents of physically disabled children and are associated with substantial impairments in QOL.

Keywords

Handicapped, Musculoskeletal, Pain, Physiotherapy, Rehabilitation

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Received: 23rd December 2025; Accepted: 3rd September 2026

Doi:
<https://doi.org/10.31436/10.31436/imjm.v25i04/3147>

INTRODUCTION

Chronic low back pain (CLBP) is a major global public health concern and a leading contributor to years lived with disability across all age groups.¹⁻³ Epidemiological evidence consistently demonstrates that CLBP affects a substantial proportion of the adult population worldwide, with increasing prevalence attributed to aging populations, sedentary lifestyles, and cumulative occupational and caregiving demands. Beyond its clinical

implications, CLBP imposes considerable socioeconomic burdens through healthcare utilization, work absenteeism, reduced productivity, and long-term disability, underscoring its significance as a priority condition in public health planning.

Informal caregivers represent a high-risk subgroup within the population burdened by CLBP, particularly parents of physically disabled children who provide

long-term, unpaid care. From an epidemiological perspective, caregiving-related musculoskeletal disorders are increasingly recognized as a neglected public health issue, as caregivers are routinely exposed to repetitive biomechanical loading, manual handling tasks, and prolonged static or awkward postures. These exposures substantially elevate the risk of developing low back pain that may transition into chronicity.⁴⁻⁵ The cumulative nature of these physical stressors, compounded by psychosocial strain and limited access to preventive healthcare services, positions caregiver CLBP as both a clinical and population-level concern.

The public health implications of CLBP among parents of physically disabled children extend beyond individual morbidity. Persistent pain in caregivers is associated with reduced functional capacity, diminished workforce participation, increased healthcare-seeking behaviour, and impaired quality of life (QOL).⁷⁻⁹ Importantly, caregiver health directly influences caregiving quality and continuity, with potential downstream effects on child health outcomes and broader family well-being. Despite these implications, epidemiological data on CLBP among parental caregivers remain limited in low- and middle-income countries, including Malaysia, where community-based prevalence estimates are scarce, particularly in rapidly developing regions such as Selangor.^{6,10,11}

From a population health perspective, identifying factors associated with CLBP in caregivers is essential for informing targeted preventive strategies. The functional severity of a child's physical disability, commonly classified using the Gross Motor Function Classification System (GMFCS), may serve as an important exposure variable influencing caregiving intensity and musculoskeletal load. However, the relationship between GMFCS levels and parental CLBP has not been sufficiently examined, limiting the ability to stratify risk and allocate resources effectively within caregiver support programs.

Therefore, this study aimed to determine the prevalence of CLBP among parents of physically disabled children in Bandar Puncak Alam, Selangor, Malaysia. In addition, the study examined the association between children's GMFCS levels and the occurrence of CLBP, as well as the relationship between CLBP and QOL among parents. By providing localized epidemiological evidence, the findings of this study may inform public health policies, caregiver health surveillance, and the development of context-specific interventions aimed at reducing the burden of CLBP and improving quality of life among parental caregivers.

MATERIALS AND METHODS

Study Design

The current study employed a retrospective study design, which aimed to analyse data collected from a cross-sectional survey.

Study Setting and Participant Recruitment

The study was conducted at Universiti Teknologi MARA Selangor, Bandar Puncak Alam, Selangor. The retrospective data were drawn from a cross-sectional survey conducted among parents with physically disabled children within Bandar Puncak Alam from November 2022 until March 2023.

Only data that met the following inclusion criteria were included: i) experienced CLBP lasting more than 3 months, ii) age above 18 years old (≥ 18 years old), iii) having a physically handicapped child aged between 2 and 14 years old, iv) being the main caregiver responsible for the daily provision of care to the child, and v) living with the child in the same place.

Data were excluded if the parent had the following criteria: i) need to care for more than one physically disabled child, ii) have additional caregiving responsibilities apart from their usual parenting care, iii) caregivers of children with other conditions like Down syndrome, Leukodystrophy and Autism are excluded, and iv) caregivers who has chronic illnesses

like diabetes mellitus, chronic obstructive pulmonary disease, hypertension, carcinoma, or a history of chronic psychological disorder or depression.

Size Calculations

One of the aims of the current study is to explore the prevalence of CLBP incidence among parents with physically disabled children. Hence, the sample size was calculated based on parents attending physiotherapy services and Community Rehabilitation Centre at Puncak Alam. The known population of parents with physically disabled children is 148. The following steps were used to calculate the sample size.¹⁵⁻¹⁶

The infinite sample size calculation was identified using the following formula

$$n = \frac{Z^2 \cdot p \cdot (1 - p)}{E^2}$$

Where, **n** is the required sample size.

Z is the Z-value corresponding to the desired confidence level (e.g., 1.96 for 95% confidence).

p is the estimated prevalence of the condition.

E is the margin of error.

$$n = \frac{(1.96)^2 \cdot 0.20 \cdot (1 - 0.20)}{(0.05)^2}$$

$$n = 246$$

Since the known population is 150, the Finite Population Correction (FPC) calculation was applied based on the infinite calculation to adjust for the smaller population size.

$$n_{adj} = \frac{n}{1 + \frac{n-1}{N}}$$

Where, **n** is the initial sample size from the infinite population formula.

n_{adj} is the adjusted sample size for the finite population.

N is the total population size (150).

$$n_{adj} = \frac{246}{1 + \frac{246-1}{148}}$$

$$n_{adj} = 92.5$$

$$n_{adj} \approx 93$$

Based on the calculation, with an estimated prevalence of 20%, a 95% confidence level, and a 5% margin of error, the required sample size after applying the finite population correction was a total of 93 data was needed for the study.

Data Collection

Data were retrospectively collected from previous surveys conducted in November 2022 until March 2023. The parameters of interest are demographic details (age, gender, marital status, the number of physically disabled children, history of low back pain, child's functional level), the Oswestry Low Back Pain Disability Questionnaire total score, and the 36-Item Short Form Survey (SF-36) total score. Data screening was performed by a research assistant who was not involved with the previous survey. All data were anonymously screened to maintain participants' confidentiality. Once data were available, the research team entered and organized it.

Statistical Analysis

Data were analysed using IBM Statistical Package for the Social Sciences (SPSS) Statistics 29.0.2.0. The descriptive statistics (frequency, percentage, minimum, maximum, mean $\pm$ SD) were used to report the prevalence of CLBP, participant's demographic data, Oswestry total score, and SF-36 total score. The Shapiro-Wilk test yielded that the p-value is greater than 0.05 ($p=0.08$). Hence, the Oswestry and SF-36 data is considered not significantly to deviate from normality and can be assumed to have a normal distribution. The Chi-Square test for independence was conducted to explore the association between GMFCS level with CLBP incidence. Next, the Spearman Correlation Coefficient was used to identify the relationship between Oswestry and SF-36 score. Significance values were set a p is less than 0.05

($p < 0.05$) to indicate that CLBP (Oswestry score) has significantly affected the parents' QOL (SF-36 scores).

RESULTS

The prevalence of CLBP among parents of physically disabled children in Bandar Puncak Alam, Selangor
Overall, 94 data (21 male / 73 female) of parents with physically handicapped children were included. Most of the parents were aged between 26 to 44 years old ($n = 62$), with an average age is 41.6 ± 7.1 years old. Around 70% of the participants declared that they have CLBP. The majority of children have a high level of impairment. Around 65% of children have GMFC level IV ($n = 21$; 22.3%) and level V ($n = 44$; 46.8%). Of 94 children, 67 (71.3%) of them are underweight, 13 (13.8%) have normal BMI, 8 (8.5%) are pre-obese, and 6 (6.4%) children have BMI Obesity Class I (Table I).

Association Between GMFCS Level and CLBP Incidence

The Chi-Square test for independence revealed that there was no significant association between the child's GMFC level and CLBP prevalence ($\chi^2(1) = 3.468$, $p = 0.483$).

The Impact of CLBP on QOL of Parents with Physically Disabled Children

The Spearman Correlation analysis reveals that CLBP has significantly affected 5 QOL domains of the parents ($p < 0.05$) (Table II), which are role limitations due to physical health, fatigue, pain, general health, and health change.

Table I: Parents' and children demographic characteristic

Characteristics	(n) %	Min	Max	Mean $\pm$ SD	Chi-Square (p)
Parent's detail					
Age (years old)	94	25	56	41.6 ± 7.1	
18 -25	1 (1.1)				
26-44	62 (66)				
45-59	31 (33)				
Gender					
Male	21 (22.3)				
Female	73 (77.7)				
Ethnicity					
Malay	87 (92.6)				
Indian	4 (4.3)				
Chinese	3 (3.2)				

Cont.

Incidence of CLBP					
Yes	70 (74.5)				
No	24 (25.5)				
Duration of CLBP (months)		0	18	4.6± 4.0	
Child's detail					
Age		2	22	9.1± 4.4	
GMFCS level					0.483
I	4 (4.3)				
II	10 (10.6)				
III	15 (16.0)				
IV	21 (22.3)				
V	44 (46.8)				
Gender					
Boy	53 (56.4)				
Girl	41 (43.6)				
Height (meter)		0.60	1.76	1.2± 0.6	
Weight (kilogram)		6.80	70	26 ±14	
Body Mass Index (BMI) (kg/m2)		4.70	34.60	17.3 ±6.0	

Table II: Impact of CLBP on Quality of Life

Questionnaire	Min	Max	Mean $\pm$ SD	p
Oswestry	0	100	9.7 ± 7.9	
SF-36				
Physical function	10	100	74.9 ± 21.6	0.58
Role limitation due to physical health	0	100	81.8 ± 23.7	0.002*
Role limitation due to emotional	0	100	81.3 ± 23.8	0.171
Fatigue	0	100	58.1 ± 22.5	0.001*
Emotional wellbeing	28	100	71.9 ± 16.4	0.25
Social function	25	100	78.8 ± 15.5	0.557
Pain	12.5	100	71.2 ± 20.2	0.002*
General Health	20	100	64.7 ± 23	0.001*
Health Change	25	100	61.0 ± 25.7	0.004*

($p < 0.05$)*

DISCUSSION

The present study found that 70% of parents caring for physically disabled children experienced chronic low back pain (CLBP), indicating a substantial burden of musculoskeletal morbidity within this caregiving population. This prevalence is comparable to that reported in previous studies involving caregivers of children with disabilities, which consistently demonstrate high rates of CLBP attributable to

sustained physical demands and caregiving-related biomechanical stressors.^{17,18} Activities such as repetitive lifting, manual transfers, prolonged forward-flexed postures, and continuous physical support have been identified as key contributors to lumbar spine overload and the development of chronic pain.^{19,20} From a public health perspective, these findings underscore caregiving as an occupational-like exposure that warrants greater recognition in musculoskeletal health surveillance.

Previous literature suggests that the severity of a child's motor impairment, as classified by the Gross Motor Function Classification System (GMFCS), is associated with increased caregiver physical burden and higher prevalence of CLBP, particularly among parents of children classified at GMFCS levels IV and V.^{19,21} However, contrary to these findings, the present study did not demonstrate a significant association between GMFCS level and CLBP prevalence. This discrepancy may be partly explained by contextual factors within the studied population, such as the relatively low body mass index (BMI) of the children, even among those with severe functional limitations.¹³ Lower child body weight may reduce the absolute mechanical load experienced by parents during caregiving tasks, potentially attenuating the relationship between GMFCS level and CLBP.²⁸ Additionally, variability in caregiving techniques, use of assistive devices, and informal coping strategies may further moderate this relationship.^{6,19} Nonetheless, the high overall prevalence of CLBP observed highlights the need for targeted preventive interventions regardless of GMFCS level, including ergonomic training and caregiver-focused musculoskeletal health programs.

The present study also demonstrated significant correlations between CLBP and multiple domains of quality of life (QOL), particularly role limitations due to physical health, fatigue, pain, general health perception, and perceived health changes. These findings are consistent with existing evidence showing that chronic musculoskeletal pain substantially compromises caregivers' functional capacity and well-being.^{17,22} Role limitations related to physical health emerged as a

prominent concern, reflecting caregivers' reduced ability to perform daily activities, occupational responsibilities, and caregiving tasks. Such limitations may lead to psychological distress, including frustration, guilt, and perceived inadequacy, which can further exacerbate pain and emotional burden.^{23,24}

Fatigue was also significantly associated with CLBP, highlighting the multidimensional impact of chronic pain on caregiver health. CLBP is known to disrupt sleep quality and recovery, contributing to persistent fatigue and reduced energy levels. For parents of physically disabled children who already experience heightened physical and emotional demands this fatigue may significantly impair caregiving capacity and overall functioning. These findings align with previous studies reporting elevated fatigue levels among caregivers with chronic musculoskeletal pain, reinforcing the interrelationship between pain, sleep disturbance, and diminished QOL.¹⁷⁻¹⁸

Pain severity demonstrated a significant association across all assessed QOL domains, underscoring pain as a central determinant of caregiver well-being. Chronic pain not only limits physical activity but also restricts social participation and contributes to emotional distress, including symptoms of anxiety and depression.²⁵⁻²⁷ Psychological distress, in turn, may amplify pain perception, creating a bidirectional cycle that further deteriorates QOL.^{17,25} These findings emphasize the importance of comprehensive pain management strategies that address both physical and psychosocial dimensions of CLBP in caregivers.

Furthermore, caregivers with CLBP reported poorer perceptions of general health and negative health changes over time, reflecting a broader decline in self-rated health status. This observation is consistent with prior research indicating that prolonged caregiving responsibilities combined with chronic pain contribute to cumulative health deterioration among caregivers.^{27,28} Negative health perceptions may reduce motivation to seek healthcare or engage in preventive behaviours,

thereby perpetuating poor health outcomes and increasing long-term healthcare utilization.^{10,24,27}

Overall, the findings of this study align with the growing body of literature demonstrating the detrimental impact of CLBP on the quality of life of caregivers of children with disabilities.²⁹ While some studies have reported inconsistent associations between pain severity and caregiving intensity, such variability may reflect differences in caregiving environments, access to support systems, individual coping mechanisms, and cultural expectations surrounding caregiving roles.²⁷⁻³⁰ These factors highlight the need for a holistic, context-sensitive approach to caregiver health that integrates ergonomic, physical, and psychosocial interventions.

From a public health perspective, the high prevalence of CLBP and its significant association with reduced QOL among parents of physically disabled children indicate an urgent need for caregiver-focused musculoskeletal health policies. Early screening, ergonomic education, access to rehabilitation services, and structured caregiver support programs should be incorporated into disability and family health services to mitigate long-term health consequences and sustain caregiving capacity.⁶⁻⁷

CONCLUSION

This study provides evidence that chronic low back pain (CLBP) is highly prevalent among parents of physically disabled children and is significantly associated with poorer quality of life, particularly in relation to role limitations, fatigue, pain, and perceived general health. These findings reinforce the need to recognize parental caregiving as a significant risk context for chronic musculoskeletal conditions. Addressing CLBP in this population requires integrated, caregiver-centred approaches that combine musculoskeletal health management with psychosocial support. Future research should focus on longitudinal and intervention-based studies to inform evidence-driven strategies that promote caregiver health, functional capacity, and caregiving sustainability.

INSTITUTIONAL REVIEW BOARD (ETHIC COMMITTEE)

Ethical approval for the cross-sectional survey was gained from the university Research Ethics Committee (FERC/FSK/MR/2022/0283).

ACKNOWLEDGEMENT

This research was not funded by any grant.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work, the author(s) used ChatGPT to draft the manuscript text. The author(s) subsequently reviewed, revised, and approved all content, and accept full responsibility for the final manuscript

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Reduced Urinary Endothelin-1 Levels Are Associated with Elevated Blood Pressure in Young Adults: A Cross-Sectional Study

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ABSTRACT

INTRODUCTION: Urinary biomarkers offer practical and non-invasive advantages for clinical screening, including early cardiovascular risk assessment. While endothelin-1 (ET-1) is a recognised serum biomarker for hypertension, its role in urine, particularly among young adults, has not been fully explored. Therefore, this study aimed to evaluate the association between urinary ET-1 levels and elevated blood pressure (BP) among young adults. **MATERIALS AND METHODS:** In this cross-sectional study, 117 adults aged 18-45 years were recruited: normotensive (n=44; systolic blood pressure (SBP) <120 and diastolic blood pressure (DBP) <80 mmHg), prehypertensive (n=40; SBP 120-139 and/or DBP 80-89 mmHg), and newly diagnosed hypertensive (n=33; SBP≥140 and/or DBP≥90 mmHg). Pregnant women, individuals who were receiving antihypertensive therapy, or those diagnosed with underlying renal disease were excluded from the study. Plasma and urinary ET-1 levels were measured via enzyme-linked immunosorbent assay (ELISA). Urinary ET-1 was normalised to urinary creatinine to adjust for hydration status. **RESULTS:** Creatinine-normalised urinary ET-1 concentrations decreased progressively across the normotensive, prehypertensive, and hypertensive groups; median (25th-75th percentile) 26.39 (22.19-48.82) pg/mmol, 20.61 (14.72-38.55) pg/mmol and 13.49 (9.69-27.27) pg/mmol, respectively ($p=0.002$). Hypertensive participants exhibited significantly lower normalised urinary ET-1 levels compared to normotensive controls ($p=0.001$). In contrast, plasma ET-1 levels showed neither significant intergroup differences nor a significant correlation with urinary ET-1 levels. **CONCLUSION:** Reduced urinary ET-1 levels are significantly associated with elevated BP in young adults. However, prospective longitudinal studies are required to establish causality and clarify its mechanistic role in the development of young-onset hypertension.

Keywords

Young Adults, Hypertension, Prehypertension, Creatinine-normalised Urinary Biomarker, Cross-sectional Study

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Received: 5th May 2026; Accepted: 8th
September 2026

Doi:
<https://doi.org/10.31436/10.31436/imjm.v2.5i04/2944>

INTRODUCTION

Hypertension remains the strongest modifiable risk factor for global premature mortality and morbidity, causing approximately 10.8 million avoidable deaths annually.¹⁻³ Crucially, emerging evidence suggests that

cardiovascular risk begins to accumulate well before the formal clinical threshold for hypertension is met.⁴⁻⁸ Individuals classified as prehypertensive, defined by a systolic blood pressure (SBP) of 120-139 mmHg or a

diastolic blood pressure (DBP) of 80–89 mmHg, exhibit a significantly higher predisposition toward progressing to clinical hypertension, developing overt cardiovascular disease, and suffering premature death.^{9–11} This prehypertensive phase represents a pivotal transitional state in blood pressure (BP) regulation.⁹ If left unaddressed, this persistent elevation may trigger metabolic and vascular derangements that facilitate adverse myocardial remodelling.⁹

Additionally, elevated BP during early adulthood also substantially contributes to long-term cardiovascular morbidity and mortality.^{12–15} The rising incidence of both hypertension and prehypertension in the younger population underscores the need for timely identification of early BP abnormalities.¹⁵ However, despite this urgency, early detection efforts remain challenging and often inadequate. In Malaysia, for instance, the highest proportion of undiagnosed hypertension cases (80.4%) occurs among young adults aged 18–29, highlighting a critical gap in current screening and preventive strategies.¹⁶

Several factors contribute to this gap, including poor health awareness and a lack of engagement with preventive services among the young, alongside the inherent limitations of traditional diagnostics.^{12,17} Conventional office-based BP measurements using sphygmomanometers are inadequate as the sole diagnostic tool, given that hypertension is a multifactorial and heterogeneous condition shaped by the complex interplay of genetic, environmental, and behavioural factors.¹⁸ Furthermore, office measurements are susceptible to confounding by natural BP variability, white-coat and masked hypertension, and potential measurement errors, which may hinder accurate detection in younger populations.^{18–22}

Consequently, identifying and utilising early-stage biomarkers that can reflect the initial pathophysiological changes associated with young-onset hypertension are critically important. While various plasma and serum

biomarkers show promise, their utility is often hampered by the invasive nature of venepuncture. This can induce procedure-related anxiety, potentially deterring young adults from participating in screening programmes.²³ Conversely, urine, once considered a waste product, is gaining increasing interest in clinical applications for early detection, risk stratification, and disease monitoring, particularly in cardiovascular and renal conditions.^{24–26} Urinary biomarkers offer further advantages in young populations, in which the absence of polypharmacy, pre-existing renal diseases, or other comorbidities such as chronic diseases minimises confounding influences.²⁷

Among the potential urinary biomarkers for the early development of hypertension in young adults is endothelin-1 (ET-1). Plasma ET-1 is a potent vasoconstrictor peptide, and its levels have been shown to be strongly associated with SBP in young adults.²⁸ Meanwhile, urinary ET-1, predominantly produced locally by renal cells, contributes to the regulation of fluid balance by promoting the renal excretion of sodium and water.^{29–30} Previous studies investigating urinary ET-1 in hypertension have primarily focused on older populations and cohorts with secondary hypertension, such as patients with chronic kidney disease or diabetes mellitus. These studies have yielded inconsistent findings, with some reporting elevated levels, others lower levels, and some showing no significant difference.^{31–35}

Furthermore, prior studies investigating urinary ET-1 have primarily compared established hypertension with normotension, largely overlooking the prehypertensive stage.^{31–35} Evaluating ET-1 during prehypertension is critical, as subclinical pathophysiological changes during this window offer a vital target for early intervention, particularly in young adults.⁹ To address this gap, this study investigated urinary ET-1 levels among normotensive, prehypertensive, and hypertensive young adults to determine the relationship between urinary ET-1 levels and early BP elevation.

MATERIALS AND METHODS

Calculation of Sample Size

The required sample size was determined based on a mean difference analysis using OpenEpi software (Version 3.01), following the parameters described by Raina et al.²⁹ With a two-sided confidence level of 95% and a statistical power of 95%, a 1:2 allocation ratio was applied. This calculation indicated a minimum requirement of 32 participants per group to ensure sufficient power to detect significant differences in biomarker concentrations.

Study Design and Subject Recruitment

This was a comparative cross-sectional study comprising 117 young adults aged 18–45 years: 44 participants in the normotensive group, 40 participants in the prehypertensive group, and 33 participants in the hypertensive group. All participants, including hypertensive participants, were recruited from a health-screening programme conducted at a local tertiary education institution. BP was measured across two separate visits. During the initial health screening, three BP readings were taken and averaged. Eligible subjects were then invited to participate in the study and scheduled for a sample collection visit. During the second visit, another three BP measurements were obtained and averaged. Participants were classified as hypertensive only if they consistently met the diagnostic criteria for hypertension across both visits.

Pregnant women, participants with chronic illnesses, including diabetes mellitus, previously diagnosed hypertension, neoplasm, an infection during the preceding four weeks, autoimmune diseases, and anxiety disorders, and/or on long-term medications, such as antihypertensive medications, steroids, nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase 2 (COX-2) inhibitors, and combined oral contraceptive pills (COCP), were excluded from the study to minimise confounding factors. Prior to the sample collection appointment, participants were instructed to fast for at least eight hours specifically for the fasting blood investigations. They were also advised to refrain from

physical exercise, smoking, and caffeine consumption for at least 30 minutes before BP measurement.

Upon arrival at the appointment, all participants were given at least 10 minutes to rest in a seated position in a quiet room before BP was measured. BP was measured using an automated upper-arm oscillometric monitor (HEM-7120; Omron Healthcare Co., Ltd., Japan). An appropriately sized cuff was selected such that the bladder length encircled at least 80% of the arm circumference and the bladder width was at least 40% of the arm circumference. A standard cuff (HEM-CR24, Type B; 22–32 cm) was used for participants with arm circumferences of 22–32 cm, whereas a wide-range cuff (HEM-RML31, Type B; 22–42 cm) was used for those with arm circumferences greater than 32 cm and up to 42 cm. The device was factory-calibrated by the manufacturer and has been clinically validated for accuracy in accordance with the European Society of Hypertension International Protocol (ESH-IP / ISO 81060-2). Three BP measurements were performed at 10-minute intervals for all participants in a sitting position, with their arms and backs supported. Participants were categorised as normotensive, prehypertensive, or hypertensive based on the average of three BP measurements, adhering to the Joint National Committee (JNC) guidelines on BP categories.³⁶ Normotensive participants were defined as healthy individuals with an average SBP of less than 120 mmHg and DBP of less than 80 mmHg. Prehypertensive participants were defined as individuals with an average SBP of 120–139 mmHg and/or a DBP of 80–89 mmHg. Hypertensive participants were defined as individuals with an average SBP $\geq$ 140 mmHg and/or a DBP $\geq$ 90 mmHg in both screening and sample collection visits.

Urine and Blood Samples Collection

Data and sample collection were standardised between 8:00 a.m. and 10:00 a.m. Each participant was provided with a urine container and instructed to collect approximately 30 mL of midstream urine. The collected urine samples were centrifuged at $10,000 \times g$ for 15 minutes at 4°C. The supernatant was collected and

stored at -80°C for further analysis. For blood collection, approximately 10 mL of venous blood was drawn from the antecubital vein of each participant. Then, 8 mL of blood was dispatched for biochemical profile analysis, including full blood count (FBC), renal profile (RP), liver function test (LFT), fasting lipid profile (FLP), and fasting blood sugar (FBS) at Innoquest Pathology Sdn. Bhd. The remaining 2 mL of blood was centrifuged for 10 minutes at $1,000 \times g$ at 4°C , and the plasma sample was collected and stored at -80°C for future analysis. To prevent observer bias, urine and plasma samples were anonymised with unique code numbers prior to analysis. Consequently, laboratory personnel remained strictly blinded to the participants' BP classifications during ELISA testing.

Enzyme-linked Immunosorbent Assays (ELISA) Analysis

An ELISA kit (Elabscience, United States) with Catalogue Number: E-EL-H0064 for human ET-1 (sensitivity: 0.75 pg/mL; detection range: 1.25–80 pg/mL) was used to quantify the concentrations of ET-1 in urine and plasma samples. The microplate was pre-coated with an antibody (Ab) specific to the target protein, ET-1. First, 100 μL of standards or samples were added to the microplate wells, where the target proteins were bound to the antibody. The protein-antibody complex was detected using a biotinylated detection antibody specific to the target protein and was further recognised by an Avidin-Horseradish Peroxidase (HRP) conjugate. The optical density (OD) of the enzyme-substrate reaction was measured using a microplate reader Infinite 200 PRO (TECAN, Switzerland) at a wavelength of 450 nm. Standard curves for urinary and plasma ET-1 levels were constructed, and the actual protein concentration for each sample was determined using the corresponding standard curve equations.

Prior to processing the study cohort, pilot optimisation experiments were performed to determine the optimal sample dilution and evaluate potential matrix interference. The OD values for neat (undiluted) urine (OD=0.186) and plasma (OD=0.328) fell within the

dynamic linear range of the standard curve (Lowest Standard OD=0.133; Highest Standard OD=1.171). Meanwhile, a two-fold dilution of urine resulted in an OD of 0.148, approaching the lower boundary of detection. Therefore, neat (undiluted) samples were selected for downstream clinical analyses to maintain maximum quantitative accuracy and analytical sensitivity. Samples were analysed in duplicate, adhering to a strict duplicate acceptance criterion of coefficient of variation (CV) less than 10%. The assay demonstrated a mean intra-assay %CV of 0.33% (range: 0.1%–1.38%) across all samples analysed.

To account for variations in urine dilution and hydration status, absolute urinary ET-1 concentrations (pg/mL) were normalised to urinary creatinine concentrations. Urinary creatinine was first converted from $\mu\text{mol/L}$ to mmol/L, and normalised ET-1 values were calculated by dividing absolute ET-1 (pg/mL) by creatinine (mmol/L), expressed as pg/mmol. Urinary creatinine concentrations were determined by an accredited central diagnostic laboratory at Innoquest Pathology Sdn. Bhd.

Statistical Analysis

Baseline sociodemographic characteristics and cardiovascular risk factor profiles were analysed using appropriate statistical tests based on the data distribution. Categorical variables were expressed as numbers and percentages. Normally distributed continuous variables were analysed using standard one-way analysis of variance (ANOVA), followed by Games–Howell post-hoc tests for pairwise comparisons when equal variance was not assumed. Data are presented as mean (standard deviation [SD]). Non-normally distributed continuous variables and ordinal data were evaluated across the three independent groups using the Kruskal–Wallis test, with post-hoc pairwise comparisons conducted via the Mann–Whitney U test. Non-parametric data are presented as median (interquartile range [IQR]) or (25th–75th percentile). Correlations between plasma and urinary concentrations of ET-1 in prehypertension and hypertension were

assessed using Spearman's rank-order correlation analysis.

RESULTS

Sociodemographic and Risk Factor Profiles

The baseline sociodemographic characteristics and cardiovascular risk profiles of the participants are presented in Table I. Participant age, gender distribution, and smoking status did not differ significantly across the normotensive, prehypertensive, and hypertensive groups. As expected, mean systolic and diastolic BP demonstrated significant progressive increases across the clinical categories ($p < 0.001$). Meanwhile, post-hoc pairwise analyses indicated that both hypertensive and prehypertensive participants had significantly higher mean arterial pressure and body mass index (BMI) than normotensive participants ($p < 0.005$). Additionally, hypertensive participants exhibited significantly higher waist circumference and pulse rate compared to normotensive controls ($p < 0.01$). Interestingly, the fasting blood glucose levels were significantly highest in the prehypertensive group compared to other cohorts ($p = 0.032$).

Table I: Sociodemographic characteristics and cardiovascular risk factor profiles of all participants.

Variables	Normotensive (n=44)	Prehypertensive (n=40)	Hypertensive (n=33)	p-value
Age (years)	35.2 ± 5	35.1 ± 6	37.0 ± 6	0.204 [#]
Male, n (%)	19 (43)	21 (52)	22 (67)	0.123 [‡]
Female, n (%)	25 (57)	19 (48)	11 (33)	
Smoking status, n (%)				
Active smoker	7 (15)	11 (28)	5 (15)	0.305 [‡]
Non-smoker	37 (85)	29 (72)	28 (85)	
Systolic blood pressure (mmHg)	109 ± 7.25	^a 127 ± 6.18	^{a, b} 142 ± 13.24	<0.001[#]
Diastolic blood pressure (mmHg)	74 ± 5.7	^a 83 ± 6.4	^{a, b} 97 ± 9.9	<0.001[#]
Mean arterial pressure (mmHg)	84 ± 7.7	^a 95 ± 6.1	^a 106 ± 12.9	<0.001[#]
Body mass index (kg/m ²)	25.1 ± 5.2	^a 29.9 ± 6.8	^a 31.5 ± 8.1	0.020[#]
Waist circumference (cm)	88.3 ± 13.8	95.3 ± 16.1	^a 99.0 ± 14.7	0.008[#]
Pulse rate (beats per minute)	72 ± 12	78 ± 12	^a 81 ± 13	0.007[#]
Fasting blood sugar* (mmol/L)	4.69 (0.41)	[‡] 5.01 (0.55)	4.93 (0.73)	0.032[‡]
Total cholesterol (mmol/L)	5.39 ± 0.77	5.61 ± 0.78	5.42 ± 0.83	0.429 [#]

Notes: Data are expressed as n (%), Mean ± Standard Deviation (SD), or

[‡]Median (Interquartile Range, IQR).

[#]Analysed using One-Way ANOVA across groups.

^{*}Analysed using Kruskal-Wallis test across groups.

[‡]Analysed using Pearson Chi-Square test across groups (for categorical variables).

^a $p < 0.05$ when compared to the Normotensive group using Games-Howell post-hoc pairwise comparison.

^b $p < 0.05$ when compared to the Prehypertensive group using Games-Howell post-hoc pairwise comparison.

^c $p < 0.05$ when compared to the Normotensive group using Mann-Whitney U post-hoc test.

Urinary and Plasma Concentrations of Endothelin-1

The concentrations of absolute and creatinine-normalised urinary ET-1, urinary creatinine, and plasma ET-1 among the normotensive, prehypertensive, and hypertensive groups are summarised in Table II. Absolute urinary ET-1 levels decreased across the groups, with the highest median concentration observed in the normotensive group [2.51 (1.48–6.01) pg/mL], followed by the prehypertensive group [1.81 (1.08–3.09) pg/mL], and the lowest in the hypertensive group [1.28 (0.75–2.46) pg/mL, $p = 0.023$]. Post-hoc pairwise analysis revealed that absolute urinary ET-1 levels were significantly lower in the hypertensive group than in the normotensive group ($p = 0.011$). Similarly, creatinine-normalised urinary ET-1 levels demonstrated a significant progressive reduction across the groups: [26.39 (22.19–48.82)] pg/mmol in the normotensive group, [20.61 (14.72–38.55)] pg/mmol in the prehypertensive group, and [13.49 (9.69–27.27)] pg/mmol in the hypertensive group ($p = 0.002$). Furthermore, creatinine-normalised ET-1 levels were significantly lower in the hypertensive group than in the normotensive group ($p = 0.001$). In contrast, no statistically significant differences were observed across the three groups for urinary creatinine or plasma ET-1 levels.

Table II: Absolute and creatinine-normalised urinary endothelin-1 (ET-1), urinary creatinine, and plasma ET-1 concentrations in normotensive, prehypertensive and hypertensive groups.

Biomarker	Normotensive (n=44)	Prehypertensive (n=40)	Hypertensive (n=33)	p-value
Absolute urinary ET-1 (pg/mL)	2.51 (1.48-6.01)	1.81 (1.08-3.09)	1.28 (0.75-2.46) ^a	0.023[*]
Urinary creatinine (μmol/L)	70.34 ± 15.07	74.98 ± 17.17	74.36 ± 16.68	0.372 [#]
Creatinine-normalised ET-1 (pg/mmol)	26.39 (22.19-48.82)	20.61 (14.72-38.55)	13.49 (9.69-27.27) ^b	0.002[*]
Plasma ET-1 (pg/mL)	2.86 (1.70-4.24)	2.89 (2.00-10.17)	2.36 (1.75-6.01)	0.513 [*]

Notes: Data are expressed as Median (25th–75th percentile) or Mean ± Standard Deviation (SD).

[#]Analysed using One-Way ANOVA across groups.

^{*}Analysed using Kruskal-Wallis test across groups.

^aPairwise difference between Normotension and Hypertension is statistically significant via Mann-Whitney U post-hoc test, $p = 0.011$

^bPairwise difference between Normotension and Hypertension is statistically significant via Mann-Whitney U post-hoc test, $p = 0.001$

Correlations Between Plasma and Urinary Endothelin-1 Levels

Correlation analysis revealed no significant association between plasma and urinary ET-1 concentrations in either the prehypertensive or hypertensive groups (Table III). In the prehypertensive group, there was no

meaningful correlation between plasma and urinary ET-1 levels ($r=0.040$, $p=0.788$). Similarly, although a weak inverse correlation was observed in the hypertensive group, it did not reach statistical significance ($r=-0.244$, $p=0.201$).

Table III: Correlation between plasma and urinary endothelin-1 in prehypertensive and hypertensive groups.

Subject groups	Spearman's rho	p-value
Prehypertensive	0.04	0.788
Hypertensive	-0.244	0.201

Note: $p<0.05$ was considered statistically significant.

DISCUSSION

In the present study, both absolute and creatinine-normalised urinary ET-1 levels demonstrated a progressive decline from normotensive to hypertensive in young adults, with significantly lower concentrations observed in the hypertensive group than in their normotensive counterparts. This finding is consistent with previous reports suggesting that reduced renal ET-1 synthesis or excretion may contribute to sodium and water retention, thereby increasing the blood volume and promoting the development of hypertension, particularly in salt-sensitive individuals.^{32,34} Urinary ET-1 primarily reflects local intrarenal synthesis rather than filtration from systemic circulation.^{29,37-38} In this study, to account for variations in urine hydration status and volume, urinary ET-1 concentrations were normalised to urinary creatinine. This ratio ensures that differences in ET-1 excretion are not due to the concentration of the urine itself.³²

Renally derived ET-1 primarily acts through local autocrine and paracrine mechanisms, exerting diuretic effects by inhibiting vasopressin-induced cyclic adenosine monophosphate (cAMP) accumulation in the collecting ducts, which leads to reduced aquaporin-2 channel insertion into the apical membrane and thus diminished water reabsorption.³⁰ Moreover, reduced renal ET-1 levels can impair sodium excretion by attenuating several natriuretic pathways within the nephron.³⁰ Under physiological conditions, intrarenal ET-1 production is upregulated in response to high sodium intake and acts via endothelin receptor subtype

B (ETB) receptors in the thick ascending limb and collecting duct to enhance nitric oxide (NO) production, inhibit chloride transport, and reduce epithelial sodium channel activity, thereby suppressing sodium reabsorption.³⁰

Renal ET-1 also induces vasodilation of the vasa recta, thereby augmenting medullary blood flow and promoting natriuresis.³⁰ Additional actions include suppression of sodium-potassium adenosine triphosphatase (Na^+/K^+ -ATPase) activity in the proximal tubule and inhibition of renin secretion from the juxtaglomerular apparatus.³⁰ Consequently, a decline in renal ET-1 synthesis can diminish the diuretic and natriuretic effects, leading to sodium and water retention, volume expansion, and elevated BP.³⁰

In contrast, the plasma ET-1 concentrations in this study did not differ significantly among the three groups. This finding contradicts a previous study that reported significantly higher mean serum ET-1 levels in patients with essential hypertension than in the control group.³⁹ However, other studies have found normal plasma ET-1 concentrations in individuals with essential hypertension, while noting elevated local ET-1 expression within the vascular wall.⁴⁰⁻⁴²

The inconsistencies in reported plasma ET-1 levels among patients with hypertension may be attributed to several factors. First, ET-1 has an extremely short plasma half-life of approximately 1-2 minutes, resulting in rapid clearance from circulation.⁴³ Second, ET-1 secretion by endothelial cells is predominantly directed towards adjacent vascular smooth muscle cells (VSMCs), resulting in minimal increases in measurable plasma ET-1 concentrations.⁴³ Additional factors that may account for these discrepancies include variability in assay antibody specificity, the degree of cardiovascular damage, salt intake, obesity, diabetes, and ethnic background.⁴³

This study showed that the correlation between plasma and urinary ET-1 concentrations was negligible in the

prehypertensive group and weakly negative in the hypertensive group, with no statistical significance. These results indicate that urinary ET-1 levels do not directly reflect plasma concentrations in young adults with elevated BP, suggesting that urinary ET-1 may be regulated by independent renal mechanisms. The absence of a significant correlation between urinary and plasma ET-1 levels observed in this study is consistent with the findings of previous studies, supporting the notion that urinary ET-1 is predominantly derived from local renal synthesis rather than from systemic filtration, with less than 1.0% of urinary ET-1 originating from filtered plasma load.^{29, 33, 35} Consequently, urinary ET-1 concentrations may not reliably reflect plasma ET-1 levels.

Our study showed that hypertensive young adults demonstrated elevated levels of key cardiometabolic risk indicators, including BMI, waist circumference, total cholesterol, mean arterial pressure, and pulse rate, compared to their normotensive counterparts. These findings align with previous local studies in Malaysia reporting that hypertension in young adults frequently co-occurs with features of metabolic syndrome.⁴⁴⁻⁴⁵ Metabolic syndrome is defined by the Harmonised Joint Interim Statement of 2009 as a constellation of central obesity, dyslipidaemia, insulin resistance, and elevated BP.⁴⁶

Nevertheless, the observed clustering of these cardiometabolic risk factors introduces potential residual confounding that could influence urinary ET-1 levels. While multivariable regression analysis to adjust for these cardiometabolic covariates would ideally isolate the independent association between hypertension and urinary ET-1, formal statistical adjustment was not conducted in the present study. Given our modest sample size across sub-groups, fitting a complex multivariable model with multiple interrelated covariates risked severe model over-fitting, loss of statistical power, and unstable parameter estimates. Consequently, these findings should be interpreted with caution as unadjusted associations, and future larger-scale cohort

studies with sufficient statistical power are warranted to perform multivariable-adjusted analyses to confirm whether urinary ET-1 serves as an independent marker or an unadjusted surrogate of cardiometabolic dysfunction.

Several other limitations of this study warrant consideration. First, the cross-sectional design and modest sample size preclude causal inferences, requiring larger longitudinal cohorts to track young-onset hypertension. Second, BP was measured in a clinic setting, raising the potential for white-coat or masked hypertension. Future studies incorporating 24-hour ambulatory blood pressure monitoring (ABPM) would provide a more precise characterisation of BP phenotypes. Third, salt sensitivity was not formally evaluated using controlled sodium-loading protocols, which is pertinent given renal ET-1's role in natriuresis. Lastly, a single-centre recruitment from a university health screening and the exclusion of comorbidities may introduce selection bias, limiting generalisability to broader young-adult populations.

CONCLUSION

In summary, these findings demonstrate that reduced urinary ET-1 excretion is associated with early BP elevation in young adults, potentially reflecting subclinical renal endothelin signalling dysregulation. Although these observations elucidate early pathophysiological mechanisms, urinary ET-1 should be conceptualised as a novel candidate biomarker rather than a definitive diagnostic tool. Translating these insights into clinical practice will require rigorous validation in larger, longitudinal, multi-centre cohorts to establish the predictive and clinical utility of urinary ET-1.

ACKNOWLEDGEMENT

This research has been funded by SRG25-138-0138, Sultan Ahmad Shah Medical Centre @IIUM (SASMEC @IIUM).

INSTITUTIONAL REVIEW BOARD (ETHIC COMMITTEE)

Written informed consent was obtained from all participants prior to recruitment. Ethical approval for this study was granted by the IIUM Research Ethics Committee (IREC 2024-339).

CONFLICT OF INTEREST

There is no conflict of interest.

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Primary Total Knee Arthroplasty with Tibial Tubercle Advancement Osteotomy in a Young Adult with Severe Deformity: A Case Report

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ABSTRACT

Keywords

total knee arthroplasty, tibial tubercle advancement, valgus deformity, patella baja, young adult

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Received: 3rd May 2025; Accepted: 5th
November 2025

Doi:
<https://doi.org/10.31436/10.31436/imjm.v25i04/2948>

Total knee arthroplasty (TKA) in young patients with complex deformities and prior surgical interventions presents unique technical challenges. We report the case of a 32-year-old male with post-traumatic arthritis, fixed valgus deformity, patella baja, and limited motion secondary to previous femoral and patellar fractures with subsequent infection. He underwent primary TKA with tibial tubercle advancement (TTA) osteotomy. Intraoperative findings included severe scarring and patellar maltracking. A non-constrained implant was used with good intraoperative balance. The patient maintained good function at a five-year follow-up with no pain or instability. This case highlights the feasibility of non-constrained TKA with TTA in young patients when guided by thorough preoperative planning and soft tissue management.

INTRODUCTION

Total knee arthroplasty (TKA) is an effective and dependable management strategy for advanced knee osteoarthritis, yielding reproducible functional outcomes.¹⁻³ However, a subset of patients presents with complex issues that complicate surgery and may lead to poorer outcomes. Outcomes may be less predictable due to deformities, joint stiffness, and involvement of the extensor mechanism.^{1,3-6} Tibial tubercle advancement (TTA) osteotomy, while rarely used in primary TKA, may be necessary to address exposure difficulty, patella baja, or extensor tensioning.⁷ This report details a challenging case of TKA in a young male with a history of trauma, knee joint infection, and multiple surgeries, necessitating TTA to improve patellar alignment.

CASE REPORT

A 32-year-old man presented with pain, stiffness, and a multi-axial deformity of the left knee. Ten years earlier, he sustained a closed supracondylar femoral fracture

with an intercondylar split and a closed fracture of the ipsilateral patella following a motor vehicle accident. These were treated with internal fixation at another facility. His recovery was complicated by deep peri-prosthetic infection requiring implant removal, serial debridement, and prolonged antibiotics. Although the infection resolved, the fracture united with malalignment, and no further intervention has been done for the last eight years.

Upon presentation, he ambulated with a single crutch due to lateral knee pain. Clinical assessment revealed a non-correctable valgus deformity of 25° and limited knee motion (30°-70°). Scarring from previous surgeries, including a long lateral para-patellar scar and two smaller anterior scars, was evident. There was mild effusion, but no clinical signs of active deep-seated infection were present. The patella was low-seated and laterally subluxated. Pre-operative investigations showed normal blood counts and negative synovial fluid assays for

infection. Weight-bearing radiographs indicated severe osteoarthritis, femoral condyle deformity, and patella baja (Figure 1). MRI confirmed significant osteochondral defects, absent lateral meniscus, a partially torn anterior cruciate ligament, and extensive soft tissue fibrosis (Figure 2).

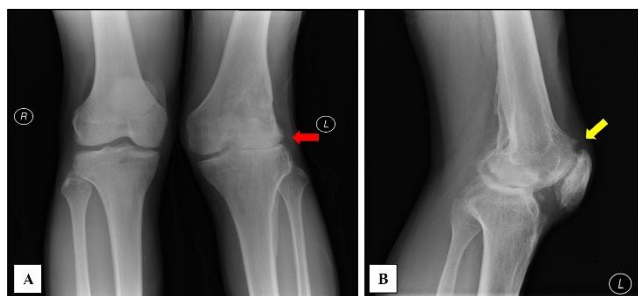


Figure 1: Preoperative plain radiographs. (A) Anteroposterior (AP) view of the bilateral knees demonstrates valgus deformity of the left knee with a malunited lateral femoral condyle and severe osteoarthritis in the lateral compartment (indicated by the red arrow). (B) Lateral view of the left knee reveals severe osteoarthritis in the left patellofemoral compartment with patella baja (indicated by the yellow arrow).

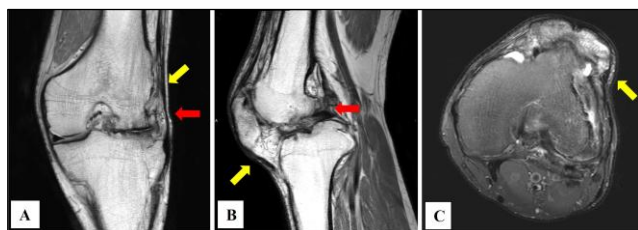


Figure 2: MRI of the left knee. (A) T1-weighted image (coronal plane) showing contracture and fibrosis at the lateral aspect of the knee, including involvement of the lateral collateral ligament (yellow arrow) and presence of a chondral defect in the lateral compartment (red arrow). (B) T1-weighted image (sagittal plane) showing patella baja with patella ligament contracture (yellow arrow). The lateral femoral condyle is deformed with an extensive chondral defect in the posterior aspect of the joint (red arrow). (C) T2-weighted image (axial plane) showing a deformed patella, which is laterally subluxated (indicated by the yellow arrow).

The patient, a young businessman with a family, strongly desired a painless and mobile knee. Given the patient's goals, TKA was recommended, with discussions about potential outcomes and the necessity for a semi-constrained or fully constrained implant depending on intra-operative findings. Key surgical concerns included fixed flexion deformity, patellar maltracking, extensive fibrosis, and valgus malalignment. The main goal was to achieve a functional, pain-free, and mobile knee rather than full anatomical correction of deformities. Objective measurement of patellar height (e.g., Insall-Salvati index) could not be reliably performed due to the patient's

limited flexion and distorted bony anatomy on lateral radiographs. Additionally, long-leg radiographs were not available at our institution at the time, and mechanical alignment was assessed intraoperatively and on standard AP radiographs.

The surgery was performed with a tourniquet, utilizing the existing lateral parapatellar scar to preserve anterior skin vascularity and facilitate valgus deformity correction. The patellar tendon was thin and contracted, contributing to patella baja and lateral subluxation. Extensive fibrosis was observed posteriorly and laterally. Intraoperative cultures were taken due to the infection history; all returned negative.

A 3° valgus distal femoral cut with an additional 2 mm resection was made. A standard tibial cut accommodated a 10 mm insert. To correct the extensor mechanism and improve patellar tracking, a 2-cm TTA was performed and fixed with cancellous screws after confirming intraoperative flexion of 120° (Figure 3). Grafting or tendon lengthening procedures were avoided due to the prior infection risk and the fragile nature of the patellar tendon. The goal of TTA was to optimize tracking and exposure, not necessarily to fully restore patellar height. Soft tissue balancing included posterolateral release and pie-crusting of the lateral collateral ligament and iliotibial band. This achieved a well-balanced knee without releasing the popliteus. A non-constrained implant was used with satisfactory intraoperative stability.

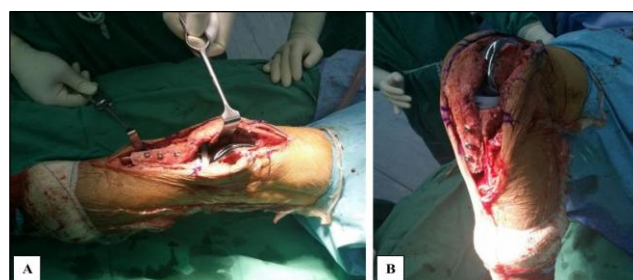


Figure 3: Intra-operative images of the left knee with completed TKA and TTA osteotomy. (A) The knee in full extension. (B) The knee in 120° of flexion with the patella fully relocated.

Postoperatively, the patient used a hinged knee brace and remained non-weight-bearing for 12 weeks. Flexion

was restricted to 60° for 6 weeks (Figure 4(A)), then progressed with physiotherapy. At six months, the range of motion (ROM) improved to 5°-115°. The tibial tubercle screws were later removed due to local tenderness after union was confirmed. At the five-year follow-up, the patient remained pain-free and functional with no instability and maintained ROM. The Knee Society Score (KSS) improved from 35 (pre-operation) to 85 (five-year follow-up). Radiographs showed a small area of tibial radiolucency, but there were no symptoms or signs of loosening or infection (Figure 4(B) and (C)).



Figure 4: Plain radiographs of the left knee. (A) Lateral and AP views at six weeks post-operation show stable fixation of the unconstrained primary TKA implant alongside the TTA osteotomy construct (indicated by the yellow arrows). (B) AP view and (C) lateral view at five years post-operation reveal a healed TTA osteotomy construct, with cortical screws removed and good fixation of the primary TKA component (red and yellow arrows), demonstrating no signs of loosening. The TTA osteotomy construct has successfully achieved union (indicated by the yellow arrow).

DISCUSSION

TKA is a well-established procedure for managing severe osteoarthritis and related deformities, typically yielding highly satisfactory long-term outcomes and improved patient lifestyles.^{1,2,8} While many primary TKAs can be successfully performed with non-constrained implants, complex cases involving prior trauma, infection, or deformity necessitate tailored strategies, meticulous planning, and intraoperative adaptability to optimize results. These patients often have less predictable outcomes and should not be

evaluated by the same expectations as typical primary TKA cases.⁵⁻¹⁰

Patella baja, commonly encountered in revision TKA, is rarely addressed in primary cases unless it compromises function or exposure. In this case, a TTA was performed to realign the extensor mechanism and improve patellar tracking. Full correction of patellar height was not achieved, but this was not the primary objective. Due to limited preoperative flexion and distorted anatomy, standard indices such as the Insall-Salvati ratio could not be reliably calculated from lateral radiographs. Similarly, long-leg radiographs to assess mechanical alignment were not available; however, clinical and intraoperative assessments confirmed satisfactory alignment postoperatively. TTA is not routinely used in primary TKA but can be an effective adjunct when addressing challenges such as patella baja, difficult exposure, limited flexion, and extensor mechanism tensioning.^{6,7} Though associated with complications like skin necrosis or fracture, its use is justified when essential, and success depends heavily on preoperative planning and careful execution.

This case exemplifies the challenges posed by a deformed patella and extensive soft tissue scarring, including lateral subluxation due to prior fractures and contracted patellar tendons leading to patella baja. The malunited supracondylar left femur resulted in a severe fixed valgus deformity, further compounded by deep fibrosis from previous surgeries. In revision or post-infective cases, patella baja and poor exposure are significant challenges. In this patient, TTA enhanced exposure and corrected patellar maltracking and extensor alignment. Soft tissue balancing was achieved through targeted posterolateral release and pie-crusting of the iliotibial band and lateral collateral ligament. This allowed for the successful correction of the valgus deformity without compromising ligament function. A constrained implant was avoided, as sufficient stability was achieved with a non-constrained component. While young age is a relative contraindication for TKA due to higher lifetime revision risks, realistic counselling and

shared decision-making can facilitate functional restoration.

To maintain knee stability, additional procedures on the patellar tendon were avoided to prevent weakening the extensor mechanism, especially since TTA had already been incorporated. Post-operative care, including bracing and physiotherapy, was pivotal in protecting the osteotomy site and optimizing functional recovery, particularly given the patient's youth and concerns regarding implant longevity and increased lifetime revision risk.¹ At 5 years, the patient demonstrated stable implant fixation, a functional ROM, and a substantial improvement in KSS. There were no signs of infection or instability. However, the case also highlights potential shortcomings, including incomplete correction of patella baja and reliance on clinical rather than radiographic alignment assessment. These limitations were accepted in favour of minimizing surgical risk in a previously infected and structurally compromised knee.

CONCLUSION

This case illustrates that even in complex scenarios, TKA with adjunct procedures like TTA can yield durable, satisfying results in young patients when guided by sound surgical principles. The successful outcome was attributed to meticulous planning, effective communication between the patient and the managing team, utilization of existing surgical scars, and intraoperative adaptability.

ACKNOWLEDGEMENT

The authors would like to thank 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 the report.

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Beyond the Lungs: Presumptive Tuberculous Dacryoadenitis Associated with Latent Tuberculosis Infection

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ABSTRACT

We report a case of a 30-year-old woman working in a tuberculosis laboratory who presented with a two-week history of right periorbital swelling, pain, and redness. Examination revealed right eye dacryoadenitis with scleritis. Given her occupational exposure, strongly positive tuberculin skin test (TST) and positive Interferon-gamma Release Assay (IGRA) results, a presumptive diagnosis of orbital tuberculosis was made, despite the absence of microbiological or histopathological confirmation. The patient received anti-tuberculosis therapy, resulting in complete resolution of symptoms. This case highlights that dacryoadenitis with scleritis, though uncommon, should be considered in the differential diagnosis of atypical orbital presentations, particularly in endemic settings.

Keywords

Dacryoadenitis, scleritis, orbital tuberculosis

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Received: 17th July 2025; Accepted: 18th
February 2026

Doi:
<https://doi.org/10.31436/10.31436/imjm.v25i04/2993>

INTRODUCTION

Tuberculosis (TB) is a communicable infection caused by *Mycobacterium tuberculosis* (MTB), an obligate aerobic acid-fast bacillus. It can affect various organs and result in a broad spectrum of disease.¹ Although TB typically affects the lungs, it can also affect other sites including the eye, resulting in ocular TB, with reported incidence rates ranging from 1.4% to 5.74%.² TB of the lacrimal gland is a rare entity; it is more commonly found in India and other endemic areas.³ Remarkably few cases of tubercular dacryoadenitis have been documented in the literature. Agrawal et al. reported only one case of lacrimal gland involvement out of 14 cases of orbital TB in India, over a period of 5 years.⁴ In another retrospective case series conducted in Malaysia, 34 ocular TB cases were observed over a period of 6 years in a tertiary hospital with no reported cases of tuberculous dacryoadenitis.⁵ We report a case of TB presenting as dacryoadenitis in a 30-year-old healthcare worker in Malaysia. In the absence of microbiological or

histopathological confirmation, the diagnosis of orbital tuberculosis was presumptive, based on clinical presentation, radiological findings, immunological evidence of tuberculosis exposure, and therapeutic response.

CASE REPORT

A 30-year-old woman with underlying polycystic ovary syndrome presented with a two-week history of right periorbital swelling. The swelling had gradually worsened in size and redness, associated with right-sided headache, diplopia on up gaze, pain on eye movement, and photophobia. There was no associated eye discharge or visual acuity impairment. She denied systemic symptoms such as fever, dry cough, weight loss, or night sweats, as well as any history of insect bites or ocular trauma. She was employed as a laboratory assistant in an Infectious Unit Laboratory, handling tuberculosis-related specimens.

Upon examination, best corrected visual acuity in both eyes was 6/9 with no relative afferent pupillary defect. There was diffuse right periorbital swelling involving the upper and lower eyelids (Figure 1). Tenderness was noted over the right lacrimal fossa with no palpable mass. Right eye conjunctiva showed dilated tortuous vessel temporally (Figure 2) which was tender upon palpation and the vessels did not blanch with topical phenylephrine 2.5%. There was no pulsatile exophthalmos or bruits on auscultation. The patient had restricted dextrolevation and elevation over the right eye resulting in diplopia (Figure 3). Right eye intraocular pressure was 14 mmHg. Fundoscopy showed pink, well-defined optic disc, clear vitreous with no vasculitis or retinitis. Left eye examination was unremarkable. Systemic examination was normal; there was no cervical, axillary or pelvic lymphadenopathy.

Complete haematological profile, liver function tests, renal function tests and chest radiography were done and found to be within normal limits. The erythrocyte sedimentation rate was raised to 20 mm/Hr with positive TST measuring 30 mm of induration. Interferon-gamma release assay (IGRA) test was positive. Other infective markers were negative. The patient did not have diabetes mellitus or HIV infection. Contrast-enhanced computed tomography of the brain and orbit showed a well-defined hypodense lesion located at the lateral wall of the right orbit without any bony erosion or periostitis was seen, indicating right lacrimal gland enlargement (Figure 4). The patient was initially managed with intravenous amoxicillin-clavulanate (Augmentin) 1.2 g three times daily for seven days, in combination with oral ibuprofen 400 mg daily and topical Maxitrol administered every four hours to the right eye. This regimen resulted in minimal clinical improvement, suggesting the low likelihood of a pyogenic bacterial dacryoadenitis.

The lacrimal gland enlargement demonstrated a progressive course and occurred within a TB-endemic context. The lack of response to broad-spectrum antibiotic therapy raised suspicion for an atypical or granulomatous aetiology and contributed to the decision to escalate treatment. This patient was co-managed by a Chest Physician. Given the absence of microbiological confirmation and in accordance with national guidelines, the patient was treated as having latent tuberculosis infection with a short-course anti-tuberculous regimen, including Akurit-2 (Isoniazid 75 mg and Rifampicin 150 mg) 5 tablets daily and Pyridoxine 20 mg daily. During follow-up one month later, complete regression of right periorbital swelling and conjunctival redness were seen. Bilateral eye ocular motility was full and diplopia resolved.



Figure 1: Clinical photograph showing diffuse swelling of the right periorbital region involving both the upper and lower eyelids, consistent with inflammatory orbital involvement.

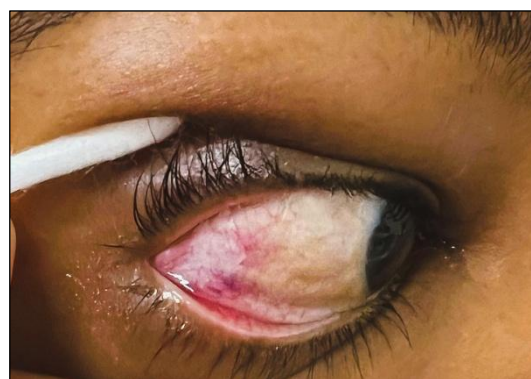


Figure 2: Clinical photograph demonstrating dilated and tortuous conjunctival vessels in the right eye, non-blanching with topical phenylephrine, supporting the presence of associated scleritis.

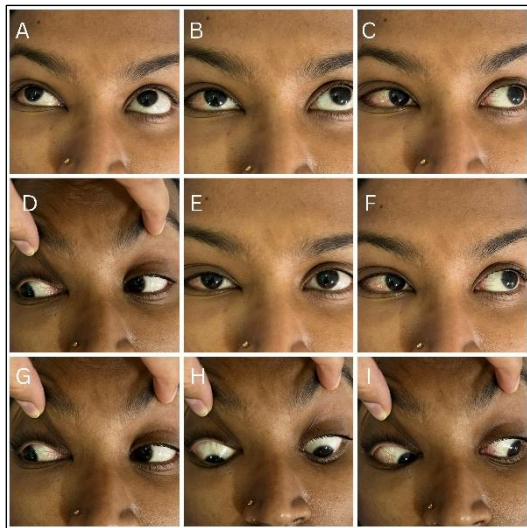


Figure 3: Ocular motility examination showing limitation of right eye movement during dextro-elevation (A) and elevation (B), correlating clinically with orbital inflammation resulting in diplopia.

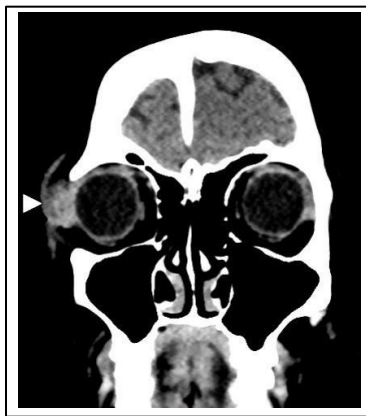


Figure 4: Computed tomography of orbit (coronal cut) shows well-defined hypodense lesion located at the lateral wall of the right orbit (arrowhead) without any bony erosion or periostitis.

DISCUSSION

Orbital tuberculosis (OTB) represents a rare extrapulmonary manifestation of TB. Despite its rarity, it is highly recognized for its potential to cause devastating outcomes due to pathological damage to various structures of the eye. The incidence of OTB ranges from 1.4% to 5.74%.² Fewer than 25 cases with similar clinical and radiological features have been reported, with over 50% of patients of Indian descent.³

OTB is classified as (i) classical periostitis; (ii) orbital soft tissue tuberculoma or cold abscess, with no bony destruction; (iii) orbital TB with evidence of bony involvement (iv) orbital spread from the paranasal

sinuses; and (v) tuberculous dacryoadenitis.⁶ Tuberculous dacryoadenitis typically manifests as eyelid swelling, often mimicking dacryoadenitis of a bacterial entity or benign mixed tumours of the lacrimal gland. Proptosis secondary to mass effect, ophthalmoplegia due to restricted extraocular muscle movement, and diplopia were found in most cases.

This case highlights similar clinical manifestations, as the patient developed preseptal cellulitis and ophthalmoplegia resulting in diplopia. Involvement of the orbit as seen in our case suggests a hematogenous source of infection. However, examination and investigations did not reveal any systemic involvement. TB is one possible infectious cause of scleritis and among other ocular inflammatory manifestations as depicted in the case report. The two pathogenic mechanisms involved in the development of infectious scleritis are direct invasion of MTB resulting in the destruction of the tissue as well as the immune reactions triggered by the infective agent.⁷

Diagnosing OTB is often challenging to ophthalmologists. While the isolation of *M. tuberculosis* remains the gold standard, positive cultures from lacrimal gland secretions, biopsy or fine needle aspirations are extremely rare. The detection of acid-fast bacilli (AFB) with Ziehl-Neelsen or auramine-rhodamine stain shows low yield, and MTB cultures, though definitive, require 6-8 weeks to provide results.⁸ Madge et al. obtained only 18 positive MTB cultures out of 59 cases with typical histologic features and systemic confirmation of TB.⁶ Histopathological examination requires a sufficiently large amount of sample, which is not feasible in this case as the lacrimal gland swelling is not clinically visible and it imposes additional risk in the already inflamed orbit. In the reported case, the patient showed positive response to topical steroid and oral anti-inflammatory drugs, negating the need for tissue biopsy.

Imaging modalities are pivotal in the evaluation of orbital tuberculosis, particularly given that chest radiographs may be normal in up to 70% of cases. In this patient, CT of the brain and orbit demonstrated preseptal cellulitis with mild enlargement of the right lacrimal gland, while coronal CT revealed a well-defined hypodense lesion along the lateral orbital wall without bony erosion or periostitis. Such findings of lacrimal gland enlargement and a discrete hypodense orbital lesion in the absence of bone involvement are consistent with manifestations of orbital tuberculosis.⁹

The diagnosis of OTB is presumptive in most of the reported cases. Positive tuberculin skin test (TST), Interferon-gamma release assays (IGRA), and lesion imaging findings play important roles in establishing the diagnosis. Both TST and IGRA involve the principle of cell-mediated immunity. While TST detects skin hypersensitivity to MTB antigens, the IGRA measures the interferon- γ release after in vitro stimulation of patients' lymphocytes with MTB specific antigens. Unlike TST, IGRA is unaffected by *Bacillus Calmette-Guérin* (BCG) vaccination or exposure to atypical MTB, making it more specific for MTB infection or prior exposure. Other possible diagnoses such as bacterial or viral infections, and orbital tumours were considered and excluded based on clinical presentation, laboratory results, and imaging characteristics.

The patient was co-managed with a chest physician in accordance with the Malaysian Clinical Practice Guidelines (CPG) for the Management of Tuberculosis (2021).¹⁰ The patient was a healthcare worker with significant occupational exposure, a strongly positive tuberculin skin test, and a positive interferon-gamma release assay, but showed no evidence of active pulmonary tuberculosis. There was no microbiological or histopathological evidence to confirm active extrapulmonary tuberculosis. Based on the Malaysian CPG, the case was classified as latent tuberculosis infection (LTBI), and a three-month anti-tuberculous treatment regimen was recommended. The patient

demonstrated clinical improvement, with no evidence of disease progression during subsequent follow-up.

CONCLUSION

Orbital inflammation, including dacryoadenitis and scleritis, can be an uncommon manifestation associated with tuberculosis, particularly in TB-endemic regions. Establishing a diagnosis of orbital tuberculosis can be challenging, necessitating a complete workup to exclude other causes. Although presumptive tubercular dacryoadenitis is very rare, it is crucial to have a high index of clinical suspicion, especially in patients with occupational or epidemiological risk factors. Prompt recognition and early commencement of ATT in carefully selected cases are crucial for good clinical outcomes, as reported in our case.

KEY MESSAGES

This case illustrates a rare presentation of tuberculosis-associated orbital inflammation, characterized by concurrent dacryoadenitis and scleritis in a healthcare worker. The absence of pulmonary involvement and initial microbiological confirmation highlights the diagnostic challenges inherent to isolated ocular tuberculosis. Clinicians should maintain a high index of suspicion for atypical ocular manifestations in patients with relevant epidemiological risk factors.

DECLARATION OF PATIENT CONSENT

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published, and due efforts will be made to conceal the identity, but anonymity cannot be guaranteed.

FINANCIAL SUPPORT AND SPONSORSHIP

Nil

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interests related to this paper.

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Scrotal Hernia or Castleman Disease? A Diagnostic Pitfall in an Unusual Presentation of a Rare Entity

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ABSTRACT

Castleman disease (CD) is a rare, non-neoplastic lymphoproliferative disorder with varied clinical presentations and uncertain etiology. It is classified into unicentric (UCD) and multicentric (MCD) forms, and histologically into hyaline vascular, plasma cell, or mixed subtypes. While CD typically affects the mediastinum or neck, scrotal involvement is exceedingly rare and can mimic more common conditions. We report a case of a 65-year-old man with a painless, enlarging scrotal mass initially diagnosed as a reducible hernia. Imaging and histopathology revealed a large lymphoid mass, diagnosed as UCD with mixed hyaline vascular and plasma cell subtypes. This case highlights the importance of including CD in the differential diagnosis of scrotal masses and underscores the critical role of histopathological examination in diagnosis and treatment planning. The patient had a favorable outcome after surgical excision, reinforcing that early recognition and proper management of UCD typically result in an excellent prognosis.

Keywords

Unicentric Castleman disease, scrotal mass, histopathology, surgical excision, mixed subtype

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Received: 22nd April 2025; Accepted: 14th
February 2026

Doi:
<https://doi.org/10.31436/10.31436/imjm.v25i04/2943>

INTRODUCTION

Castleman disease (CD) is a non-neoplastic lymphoproliferative disorder first described by Benjamin Castleman in 1954. Although considered benign, CD poses a diagnostic challenge due to its highly variable presentation and unclear etiology. CD is clinically classified into two main forms: Unicentric Castleman Disease (UCD), which involves a single lymph node region, and Multicentric Castleman Disease (MCD), which affects multiple lymph node regions with systemic manifestations. Histopathologically, CD is categorized into three subtypes: hyaline-vascular, plasma cell, and mixed type, with the hyaline-vascular variant being the most common.^{1,2}

CD most frequently arises in the mediastinum (31%), the neck (42%), the abdomen (18%), and the retroperitoneum (5%). Involvement of the scrotal region

is extremely rare and scarcely reported in the literature, making it a diagnostic challenge that can be easily mistaken for a more common condition, such as scrotal hernia.³ CD may present as a reducible mass, clinically resembling a hernia, thus necessitating a thorough differential diagnosis in such presentations.

While UCD predominantly occurs in the mediastinum, cervical, abdominal, or retroperitoneal nodes, scrotal involvement is exceedingly rare and scarcely documented. This rarity contributes to frequent misdiagnosis, particularly as inguinal or scrotal hernia-conditions far more common in clinical settings. Hernias, particularly of the indirect type, account for a lifetime risk of 27% in men.⁴ The overlapping clinical features, such as a reducible mass in the groin, further complicate diagnostic accuracy. Unlike typical hernias,

CD does not transilluminate and may not reduce fully, though these distinctions may be subtle.

The case presented here is a rare instance of UCD with a mixed histological subtype (hyaline-vascular and plasma cell), manifesting as a scrotal mass in a patient with no systemic symptoms. The unusual anatomical location and histological variant underscore the novelty of this case, highlighting the importance of considering CD in atypical scrotal masses. Histopathological examination remains the gold standard for diagnosis and therapeutic planning, with complete surgical excision typically curative in UCD cases.^{5,6}

CASE REPORT

A 65-year-old male with a history of previously treated pulmonary tuberculosis presented with a progressively enlarging scrotal mass, which he had first noticed approximately one year prior. The swelling was bilateral, painless, and gradually increased in size over time. Notably, he did not report any systemic symptoms such as fever, weight loss, or night sweats.

Initially, the patient consulted a general practitioner who suspected a bilateral, reducible scrotal hernia based on the partially reducible nature of the mass on physical exam. There were no gastrointestinal or genitourinary complaints. The patient had no prior significant surgical history, and baseline laboratory investigations, including complete blood count, renal and liver function tests, as well as tumor markers (AFP, β -HCG, LDH), were within normal limits.

Physical Examination, on inspection, bilateral scrotal enlargement was observed, with the left side more prominently affected. There was no palpable swelling above the pubic tubercle, a non-tender mass without transillumination, and the upper border of the mass could be clearly identified. This clinical finding was what initially led to the suspicion that the mass might not be a simple indirect hernia. Partial reducibility on examination reinforced the initial suspicion of an inguinal hernia.

Scrotal ultrasonography showed a heterogeneous mass with internal vascularity, suggesting a solid lesion rather than herniated bowel content. The ultrasound was performed to differentiate the atypical mass from a standard hernia by ruling out solid tumors or other scrotal pathologies. Despite this, the clinical team maintained a working diagnosis of incarcerated hernia and scheduled the patient for elective surgical exploration and herniotomy.

Intraoperatively, the surgical team encountered unexpected large lymphadenopathy within the left inguinal canal. No bowel herniation was found. The lymph nodes appeared firm and white on the cut surface. Macroscopic tissue mass is three pieces of enlarged lymph node, dimensions 8x7,7x8,5 cm; 3,5x3x2 cm; 4,5x2,5x1,5 cm, firm and white cut surface (figure 1). A standard herniotomy was performed as planned. Notably, the mass adhered to the spermatic cord, requiring meticulous dissection to avoid damage to adjacent structures. No frozen section was available, so the tissue was submitted for formal histopathological evaluation.

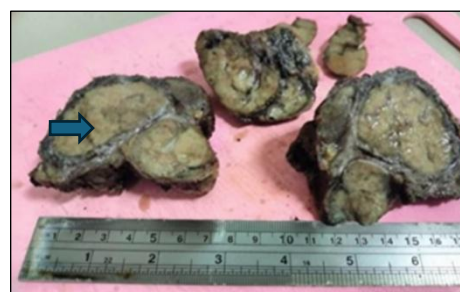


Figure 1: Macroscopic Mass in CD

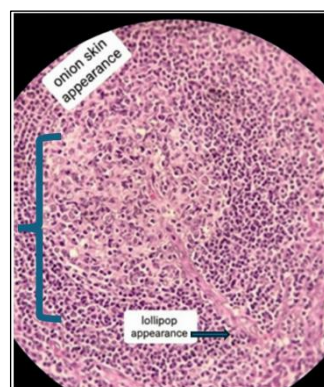


Figure 2: Onion skin appearance and lollipop appearance in CD

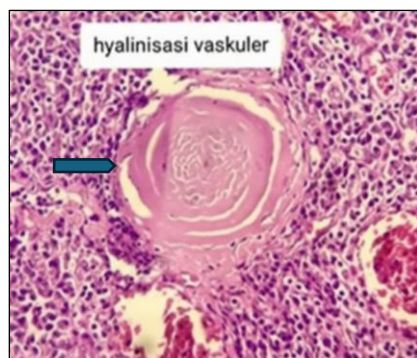


Figure 3. Hyalin Vascular in CD

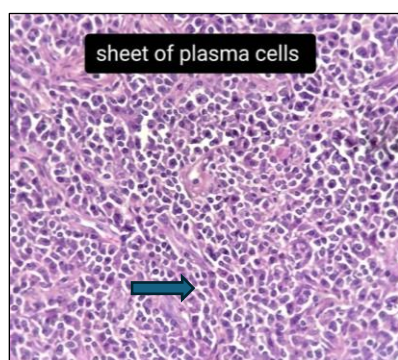


Figure 4. Plasma cell in CD

Histopathology and Final Diagnosis, microscopic examination revealed features diagnostic of Castleman disease, mixed hyaline vascular and plasma cell type. Histological hallmarks included: thickened fibrous capsule and marked follicular hyperplasia, hyalinized and sclerotic blood vessels traversing involuted germinal centers, producing a characteristic “lollipop” appearance, Concentric layering of lymphocytes in the mantle zones (“onion-skinning”) (figure 2) Interfollicular areas rich in mature plasma cells (figure 3), with prominent vascular proliferation and perivascular hyalinization (figure 4).

The final diagnosis was Unicentric Castleman Disease (UCD) of mixed histopathological subtype, involving the scrotal region an exceedingly rare anatomical location for this condition.

DISCUSSION

Scrotal hernia is among the most common conditions encountered in surgical practice, with an estimated lifetime risk of 27% in men and approximately 3% in

women. Indirect inguinal hernias occur twice as frequently as direct types, and right-sided hernias are more prevalent than left-sided ones. A significant male predominance is well-documented, with a male-to-female ratio of 7:1.^{7,8} Given its frequency and clinical familiarity, a scrotal hernia is often the initial diagnosis when encountering reducible scrotal masses.

However, Castleman disease (CD), a rare and poorly understood lymphoproliferative disorder, may masquerade as more common scrotal pathologies, including hernias. CD is clinically classified into unicentric (UCD), often presenting as a localized mass (commonly hyaline-vascular type), and multicentric (MCD), which is associated with systemic symptoms and typically plasma-cell histology.^{2,9} Most UCD cases involve the mediastinum (31%), neck (42%), abdomen (18%), or retroperitoneum (5%). While over 500 cases of CD have been reported globally, documented scrotal involvement remains extraordinarily rare, with fewer than two cases described in the English literature to date.³

Unicentric Castleman disease typically affects mediastinal or thoracic lymph nodes, with patients often being asymptomatic and cured following complete surgical excision. In contrast, MCD presents with generalized lymphadenopathy, constitutional symptoms (fever, night sweats, weight loss), and elevated inflammatory markers, and requires systemic therapy rather than surgery.¹⁰

The etiopathogenesis of CD remains elusive, though dysregulated cytokine production particularly interleukin-6 (IL-6) has been implicated. HHV-8 infection is commonly associated with MCD, especially in immunocompromised patients.⁹⁻¹⁰

In this case, a scrotal mass presumed to be a hernia revealed itself intraoperatively as enlarged lymph nodes, which were histologically confirmed as UCD of mixed hyaline-vascular and plasma-cell subtype. Pain and activity-related discomfort, uncommon in localized CD

added to the diagnostic confusion. These atypical features underscore the need for high clinical suspicion and comprehensive evaluation of scrotal masses, particularly when standard imaging or physical findings are incongruent. The scrotum remains an exceptionally unusual site, often leading to misdiagnosis, as symptoms and physical findings may resemble those of more common conditions such as hernias, hydrocele, or testicular tumors.

Complete surgical excision remains the definitive treatment for UCD, offering an excellent prognosis with minimal recurrence. In contrast, MCD typically requires systemic treatment such as corticosteroids, antiviral agents (e.g., ganciclovir), monoclonal antibodies (rituximab, tocilizumab), or immunomodulatory therapy due to its more aggressive clinical course.^{2,9,10}

CONCLUSION

This case highlights a rare presentation of UCD in the scrotal region, initially suspected as a bilateral reducible scrotal hernia. When a scrotal mass presents with atypical clinical signs, early imaging evaluation is crucial to avoid diagnostic pitfalls. Intraoperative findings revealed isolated lymphadenopathy in the inguinal canal, confirmed by histopathology as a mixed hyaline-vascular and plasma cell variant of CD. Notably, pain and activity-dependent discomfort unusual for UCD were present, further complicating the clinical picture. These findings underscore the importance of including rare etiologies such as Castleman disease in the differential diagnosis of atypical scrotal masses.

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Fulminant *Bacillus Cereus* Endogenous Panophthalmitis and Flood Water: A Case Report and Literature Review

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ABSTRACT

Bacillus cereus is a spore-forming Gram-positive bacillus found in soil and water that can cause severe ocular infections. This is a case of a 53-year-old woman with uncontrolled diabetes who developed sudden, painful vision loss in her left eye after flood exposure. Examination revealed no light perception, ophthalmoplegia, and elevated intraocular pressure (IOP) of 52 mmHg. Within eight hours, her condition worsened with severe proptosis, chemosis, and IOP rising to 87 mmHg, requiring emergency canthotomy and cantholysis. Blood cultures confirmed *B. cereus*, and blood tests showed leucocytosis and elevated C-reactive protein. Imaging revealed necrotizing infection with orbital gas. Despite intravenous antibiotics, the eye ruptured and evisceration was performed. She completed two weeks of antibiotics and recovered without systemic or intracranial spread. This case underscores the fulminant progression of *B. cereus* pan-ophthalmitis, the need for early intervention, and the importance of PPE during post-flood clean-up to prevent serious infections, particularly in vulnerable individuals.

Keywords

bacillus cereus panophthalmitis,
bacillus cereus infection, *bacillus cereus* and
floodwater, fulminant panophthalmitis

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Received: 9th June 2025; Accepted: 11th
August 2026

Doi:
<https://doi.org/10.31436/10.31436/imjm.v25i04/2992>

INTRODUCTION

A 53-year-old woman with suboptimal controlled type 2 diabetes mellitus (HbA1c: 7.1%) was referred to the ophthalmology team for sudden-onset painful vision loss in the left eye (OS) on the seventh day of hospitalisation. She was initially admitted for lethargy, bilateral upper limb numbness, and tremors, which were diagnosed as electrolyte imbalances secondary to poor oral intake. At the time of admission, she was afebrile and hemodynamically stable, although hyperglycaemic with a capillary blood glucose of 16 mmol/L. Initial investigations revealed a normal full blood count, but confirmed significant biochemical derangements: fasting blood sugar of 15 mmol/L, hyponatremia (128 mmol/L), hypokalaemia (2.8 mmol/L), and hypomagnesemia (0.45 mmol/L). Chest radiography

was deferred as the patient lacked respiratory symptoms. Upon further history, the patient revealed she was a recent flood victim and had waded through floodwaters to reach an evacuation centre. Physical examination noted a small, healing ulcer on her leg, though the patient denied any history of chronic or non-healing ulcers.

Ocular examination of the left eye: her vision was no perception of light (NPL) with a positive relative afferent pupillary defect. There was eyelid swelling with complete ophthalmoplegia but no obvious proptosis initially. Her conjunctiva was injected with a clear cornea and no anterior chamber activity (Figure 1). Fundoscopy examination showed the presence of vitreous haemorrhage (VH) obscuring the optic disc with

superior preretinal haemorrhages. The right eye was sound. The intraocular pressure (IOP) was 52mmHg OS and 10mmHg right eye (OD). B-scan ultrasound showed scleral thickening (2.35mm), presence of VH, and intact retina with no sign of loculation. Based on the initial clinical findings, she was treated as orbital cellulitis with scleritis and central retinal vein occlusion (CRVO) secondary to ocular hypertension.

She was treated with intravenous (IV) ceftriaxone 2g STAT and 1g twice a day and IV metronidazole 500mg thrice a day with topical pressure-lowering drugs including prostaglandin analogue, acetazolamide, alpha agonist and beta blocker. She was also given oral acetazolamide 500mg stat followed by 250mg QID. Despite this treatment, she developed left orbital compartment syndrome within eight hours of initiation of treatment. She developed sudden worsening periorbital swelling, conjunctival chemosis, and non-axial proptosis with corneal exposure (Figure 1). There was also presence of total hyphema, and the IOP shot up to 87 mmHg. Emergency canthotomy and cantholysis were done to release the pressure; her IOP remained high at 69 mmHg. Chloramphenicol ointment QID and a moist chamber were applied to protect the exposed cornea.

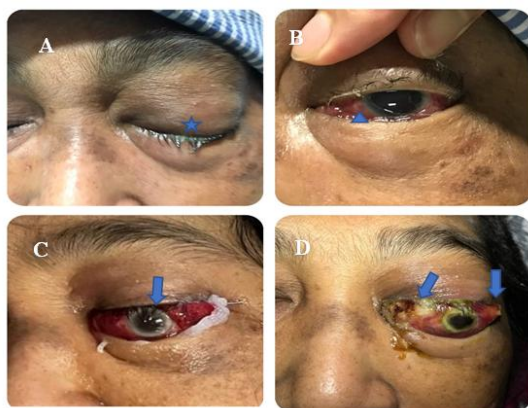


Figure 1: (A, B) shows swollen left upper and lower lids (star) with thick mucus discharges and injected conjunctival with shallow chemosis with clear cornea (triangle). (C) shows proptosis 8 hours later with severe lagophthalmos exposing whole cornea after lateral canthotomy and cantholysis procedure (arrow). (D) Shows deformed left eye globe after sclera perforation at temporal and medial region (arrow).

Laboratory investigations and imaging performed on day seven following the onset of ocular symptoms revealed leucocytosis and an elevated C-reactive protein. Blood cultures confirmed the presence of *Bacillus cereus*, which was sensitive to ciprofloxacin, meropenem, penicillin, and vancomycin, but resistant to metronidazole. Chest radiography subsequently revealed bilateral lower lobe consolidation (Figure 2). A computed tomography (CT) scan of the orbit and brain demonstrated left eye proptosis with orbital cellulitis, the presence of an intraocular gas bubble, and vitreous haemorrhage, with no intracranial or cavernous sinus involvement (Figure 2). Based on the blood culture result (Figure 3) and the rapid progression of the disease, the patient was diagnosed with *B. cereus* panophthalmitis complicated by orbital compartment syndrome. The infectious disease team initiated broad-spectrum antimicrobial therapy with intravenous vancomycin and ceftriaxone. However, due to an allergic reaction to vancomycin, the regimen was adjusted to oral linezolid 600 mg twice daily.

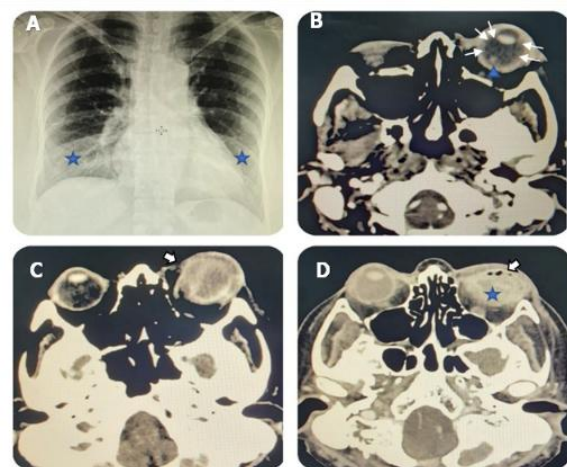


Figure 2: (A) Shows inferior lower lobes consolidation (star), (B) CT scan Brain and Orbit showed left eye proptosis. Presence of intraocular gas bubble (arrow), focal of hyperdensity at the vitreous region, suggestive of hemorrhage (triangle). No definite collection or subperiosteal collection seen. (C) Non contrasted CT scan brain and orbit on day seventh after onset of the infection showed distorted left eye globe with irregular wall and presence of crescent-shaped collection (arrow) at medial posterosuperior which communicating with discontinuity of lateral wall, suggestive of globe ruptured. (D) Non contrasted CT scan brain and orbit post evisceration showed small rim-enhancing collection (arrow) at preseptal region and associated with multiple air pockets within.

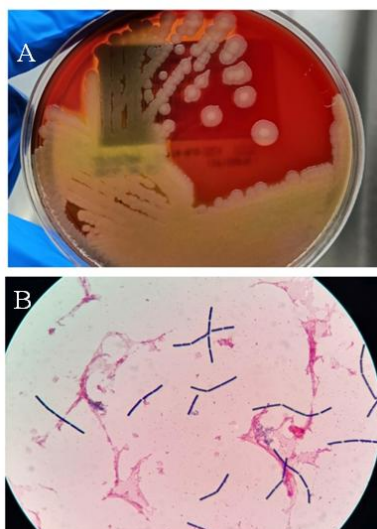


Figure 3: (A) shows large rounded dry looking grey-white, weakly haemolytic bacterial colony on blood agar. (B) microscopically *B. cereus* appears as gram-positive, rod-shaped bacilli.

Clinically, her ocular condition showed slight improvement, but her leucocyte level and inflammatory markers improved drastically. The patient remained afebrile, and repeated blood cultures showed no growth on day-6 post initiation of treatment. However, despite responding well to systemic antibiotics, her left eye perforated on day-7 (Figure 1D and Figure 2C, D). Emergency evisceration was done. Postoperatively, serial CT Scan brain and orbit showed resolution of the preseptal pus collection and air pocket (Figure 2D). She was then given a two-week course of ceftriaxone and linezolid, achieving full systemic recovery without contralateral eye involvement or septic complications. Her pneumonia was clinically resolved. She is currently fitted with a left ocular prosthesis and remains under follow-up for the right eye.

DISCUSSION

Bacillus cereus is a Gram-positive, spore-forming, rod-shaped aerobic bacterium that is commonly found in soil and water.¹ Its ability to form spores allows it to survive in harsh environmental conditions, including contaminated floodwater. The bacterium produces multiple virulence factors such as phospholipases, hemolysins, and enterotoxins that damage cell membranes, induce tissue necrosis, and cause intense

inflammation, making *B. cereus* infections particularly aggressive and destructive.² Its ability to form biofilms further enhances survival and antibiotic resistance.

In ocular infections, *B. cereus* can rapidly invade intraocular structures. Enzymes like collagenases and proteases damage the cornea, sclera, and vitreous, often leading to fulminant panophthalmitis.³ In our case, a 53-year-old diabetic patient developed sudden painful vision loss and orbital compartment syndrome following flood exposure. Her immunocompromised status and exposure to contaminated floodwater made her highly susceptible.⁴ The diagnosis of *B. cereus* panophthalmitis relies on clinical suspicion and microbiological confirmation. Hallmarks include rapid progression, typically within hours⁵, and profound ocular inflammation. In our case, the patient presented with no light perception, high IOP, and chemosis. Within hours, her IOP rose to 87 mmHg, necessitating emergency canthotomy and cantholysis. Imaging revealed the presence of intraocular gas bubbles on CT scan, an important diagnostic clue, as gas formation within the globe is highly suggestive of infection with gas-producing organisms such as *B. cereus*.⁶ This finding reflects rapid intraocular tissue necrosis and anaerobic metabolic activity. Culture of blood samples confirmed *B. cereus*. Microscopic examination revealed Gram-positive rods. While definitive diagnosis is made through culture, PCR and next-generation sequencing are also valuable for rapid identification. Clinically, *B. cereus* panophthalmitis often presents with severe ocular pain, chemosis, proptosis, hypopyon, vitreous haze, and loss of vision. The infection may extend to the orbit, causing cellulitis or abscess formation.⁷ In some cases, systemic spread to the central nervous system can occur. Our patient showed bilateral lower lobe consolidation, possibly from inhalation of spores during post-flood clean-up. Although she remained afebrile, she developed sepsis-like changes with elevated white cell count and C-reactive protein. Foot examination revealed a healing diabetic foot ulcer, suggestive of suboptimal glycaemic control rather than an active infectious source, as there was no evidence of purulent discharge, foul odour, or

necrotic tissue indicative of ongoing infection. Nosocomial transmission was excluded due to the absence of an epidemiological link to concurrent cases within the ward during the same period of admission, supported by a negative ward screening conducted by the hospital infection control team. The patient's significant history of exposure to contaminated floodwater prior to the manifestation of systemic and ocular symptoms instead suggests a community-acquired environmental aetiology.

It is worth noting that while most *B. cereus* ocular infections present within 12 to 24 hours, delayed onset of up to 48 hours has been documented, and in hematogenous cases the eye may appear unremarkable during the early bacteraemia phase, making unexplained systemic signs such as electrolyte disturbances, particularly hyponatremia, an important early warning that should prompt urgent blood cultures and close ophthalmic surveillance even before overt ocular symptoms emerge.^{5,8,9} The uncontrolled diabetic status of our patient likely contributed to this delayed yet fulminant presentation, as chronic hyperglycaemia is well established to impair neutrophil chemotaxis, phagocytosis, and complement activation, thereby blunting the early host response and allowing subclinical bacteraemic seeding to progress silently until intraocular invasion had already occurred, a pattern that has been

previously documented in fatal *B. cereus* bacteraemia in a diabetic patient.¹⁻⁴

Panophthalmitis is an ocular emergency. Although systemic antibiotics are the mainstay of treatment, *B. cereus* produces beta-lactamases, making it resistant to many beta-lactam antibiotics. In our patient, empirical intravenous ceftriaxone and metronidazole were started, but adjusted once *B. cereus* was identified in the blood culture. Vancomycin, typically used for Gram-positive coverage, was contraindicated due to allergy, so oral linezolid was initiated alongside continued ceftriaxone. The infection rapidly progressed despite timely antibiotic escalation, leading to globe perforation. Emergency evisceration was performed to control the infection and prevent systemic spread. This outcome is frequently reported in *B. cereus* ocular infections due to their aggressive, necrotizing course and poor response to medical therapy alone.¹⁰ Regarding the pneumonia, as it served as a potential source of ocular infection via septicaemia, the antibiotic regimen was aligned with that used for panophthalmitis as described above. The patient was treated with oral linezolid and ceftriaxone, demonstrating a favourable clinical response, evidenced by resolution of lung consolidation on imaging, clearance of bacteraemia on repeat blood cultures, and stable hemodynamic parameters without progression to respiratory distress requiring intensive care support.

Table I: Literature review on cases of *B. Cereus* Endophthalmitis and Panophthalmitis from 1974 until 2021s

Author(s), Year	Gender, Age	Eye(s)	Route of Infection	IOFB ¥	Culture Sample	Organism Grew	Antibiotic Treatment	Eviscerated	Presenting Vision	Final Vision
Current case report	Female, 53	Left	Floodwater exposure and endogenous	No	Blood culture	Bacillus cereus	Linezolid, Ceftriaxone	Yes	NPL	NPL
Shamsuddin et al. 1974	Female, 25	Right	Intravenous drug use	No	Intraocular content	Bacillus cereus	Vancomycin, Chloramphenicol	Not specified	Not specified	Not specified
Hatem et al. 1979	Male, 32	Left	Intravenous drug use	No	Vitreous humor	Bacillus cereus	Clindamycin, gentamicin	Yes	Not specified	NPL
Bouza et al. 1979	Male, 43	Right	Intravenous vitamin injection	No	Vitreous humor	Bacillus cereus	Not specified	Yes	Not specified	NPL
Young et al. 1980	Male, 23	Left	Intravenous drug use	No	Vitreous humor and blood	Bacillus cereus	Cefazolin -> Clindamycin, Gentamicin	Yes	Not specified	NPL
Ho P et al. 1982	Male, 30	Left	Soil-contaminated injury	Yes	Vitreous humor	Bacillus cereus	Clindamycin, gentamicin	Yes	PL €	NPL
Cowan et al. 1987	Female, 28	Right	Intravenous drug use	No	Vitreous humor	Bacillus cereus	Vancomycin, gentamicin	Yes	Not specified	NPL
Wai-Man Chan et al. 2015	Male, 72	Left	Post-cataract surgery	No	Vitreous humor	Bacillus cereus	Vancomycin, Cefuroxime	Yes	PL €	NPL
Donovan S. et al. 2021	Male, 39	left	Intravenous drug use	No	Blood culture	Bacillus cereus	Not specified	Yes	NPL	NPL

¥ Intraocular Foreign Body
€ Perception of light

Although early diagnosis and prompt antibiotic therapy can be sight- and life-saving in *B. cereus* panophthalmitis, preventive measures remain crucial, as *B. cereus* infections can lead to severe morbidity and potentially fatal outcomes. In this case, the lady likely acquired the infection via hematogenous spread from pneumonia after contact with contaminated floodwater. Spores can aerosolize during clean-up and be inhaled. Given that flooding is common in Malaysia during the monsoon season, this case highlights the need for strengthened public health guidance emphasizing the use of personal protective equipment (PPE), including gloves, N95 masks, goggles, and boots during flood recovery efforts. In addition, raising awareness of proper hand hygiene, avoiding eye contact with contaminated water, and ensuring adequate ventilation in enclosed spaces is equally important to reduce the risk of infection.

CONCLUSION

B. cereus panophthalmitis is a rapidly progressing ocular emergency. Prompt recognition, aggressive antibiotic therapy, and early surgical intervention are key to preventing systemic spread and mortality. Public health strategies focusing on prevention and awareness are crucial in post-flood scenarios, particularly for high-risk groups.

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From Intubation to Tracheal Resection: Navigating Severe Airway Complications in a Post-COVID-19 Patient with Comorbidities

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ABSTRACT

Laryngotracheal stenosis (LTS) is a significant complication post-intubation in COVID-19 patients, with incidence rates between 12.7% and 40%, exacerbated by comorbidities like diabetes and obesity. We report a 44-year-old female with type II obesity (BMI=39.8 kg/m²), diabetes mellitus, and hypertension, who developed LTS after 8 days of intubation for severe COVID-19. Her condition rapidly progressed from grade 3 to grade 4 LTS, requiring emergency tracheostomy, Shian-Yann-Lee procedure, and tracheal resection with anastomosis (TRA). Complications included anastomotic dehiscence, sepsis, and deep venous thrombosis. Serial dilatations and intralesional steroid injections (SILSI) were needed to manage restenosis. This case highlights the complexity of LTS management in patients with significant comorbidities, emphasising the need for early intervention, tailored strategies, and meticulous postoperative care to prevent complications like Critical Illness Weakness (CIW) and thromboembolic events.

Keywords

Tracheal resection, Tracheal anastomosis, Laryngotracheal stenosis, Open airway surgery

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Received: 9th February 2025; Accepted: 5th May 2026

Doi:
<https://doi.org/10.31436/10.31436/imjm.v25i04/2856>

INTRODUCTION

The incidence of LTS in COVID-19 patients post-intubation is significant (12.7% to 40%), with rapid progression observed in severe cases despite multiple interventions.^{1,2} Recommendations for TRA are: severe mature stenoses (grade III-IV) with a cranio-caudal length between 1 cm and 5.5 cm, and/or impairment of the laryngo-tracheal structure, or if multiple endoscopic procedures failed to yield a response.³ This case is highlighted due to its complex and severe progression of LTS following COVID-19 in a patient with diabetes and obesity, necessitating extensive surgical interventions including TRA, complicated by anastomotic dehiscence and significant complications due to prolonged mechanical ventilation post-surgery and hospitalization.

CASE SUMMARY

A 44-year-old female with type II Obesity (BMI = 39.8 kg/m²), diabetes mellitus, and hypertension was intubated for 8 days following Covid-19 Category 5. A month later, she developed hoarseness and biphasic stridor. An emergency tracheostomy was performed. Tracheoscopy revealed 80% LTS, Cotton-Meyer 3 (CM 3), in the form of a mature fibrotic semicircular segment, 4 cm from the free edge of the vocal cord and 1.8 cm in length. She was referred to another hospital for expert airway management, but the stenosis had progressed rapidly to CM 4. The Shian-Yann-Lee procedure was performed, followed by insertion of the Montgomery T-Tube. During planned decannulation 19 months later, suprastomal granulation tissue was noted, creating a ball-valve effect that caused immediate dyspnoea, requiring re-insertion of the tracheostomy tube.

Two direct laryngoscopies, SILSI, excision of suprastomal granulation tissue, and dilatation were performed, one month apart, but 70% restenosis was noted after the second procedure (Figure 1). TRA was performed with a total of 2.2 cm of tracheal segment removed (1.5 cm above the tracheal stoma and 0.7 cm below). Her neck was placed in a flexed position and secured by chin-to-chest stay sutures. She was intubated for 20 days and hospitalized for 2 months. During the intensive care period, she had anastomotic dehiscence and massive subcutaneous emphysema due to severe coughing after the first attempt at extubation on postoperative day 4 (Figure 2). The dehiscence was confirmed by CT scan and repaired immediately with a sternocleidomastoid flap. Post-extubation, unilateral vocal palsy was noted. She also suffered from multiple episodes of sepsis, severe extensive fungal skin lesions, and deep venous thrombosis due to prolonged immobilization and diabetes. Serial dilatations and SILSI were performed at 8, 10, and 14 weeks post-TRA due to restenosis, resulting in 20% mature, non-progressing stenosis. To date, she is rehabilitating well with normalised vocal cord mobility, good voice, and airway.



Figure 1: 70% tracheal stenosis after removal of T-tube and multiple dilatations.



Figure 2: Tracheal dehiscence was evident by bubbles from the anastomotic area.

DISCUSSION

The incidence of LTS in patients intubated due to COVID-19 may be related to the SARS-CoV-2 virus affecting the tracheal epithelium, causing structural weakness due to oedema and tracheitis.^{4,5} Prolonged intubation, large endotracheal tubes, and high cuff pressures contributed to tracheal injury. Lesions form when the endotracheal tube (ETT) pressure exceeds mucosal capillary pressure, leading to ulceration and cartilage necrosis, which results in fibrotic scarring visible 3 to 4 weeks post-extubation.²

Tracheostomy may exacerbate tracheal injury by causing suprastomal collapse and stenosis.⁶ Our patient experienced rapid progression from CM grade 3 to grade 4 LTS, highlighting the aggressive nature of the disease. Repeated interventions, such as multiple direct laryngoscopies, SILSI, and dilations, indicated persistent and recurrent airway issues. After various attempts, the patient met the criteria for TRA.

Postoperative anastomotic complications are more common in patients with comorbidities, previous tracheal appliances, reoperations, long segment resections, and prolonged ICU stays.⁷ The presence of diabetes and obesity increased the complexity of both the initial COVID-19 management and the postoperative complications. Diabetes adversely affects microcirculation, impairing wound healing at the anastomotic site. Additionally, obesity is associated with prolonged mechanical ventilation and ICU stays.⁸

In patients with LTS, diabetes is a significant risk factor for anastomotic complications.⁹ No major perioperative complications in a series of post-COVID-19 patients with similar comorbidities who underwent TRA.³ Dehiscence may be managed conservatively or surgically using surrounding tissues, as in our case. For restenosis patients, further dilatation can stabilise the airway.¹⁰ Prolonged mechanical ventilation, as in this case, can result in Critical Illness Weakness (CIW), which affects

over 50% of ICU patients. Early mobilisation is crucial to prevent CIW and thromboembolic complications.⁸

CONCLUSION

This case exemplifies the complexities of managing severe airway complications following COVID-19 in patients with significant comorbidities. Advanced surgical interventions, repeated procedures, and meticulous post-operative care highlight the need for a multidisciplinary approach. Patient selection and optimisation of comorbidities, such as weight loss programs and diabetic control, are essential prior to TRA.

INFORMED CONSENT

Written informed consent was obtained from the patient.

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A Rare Case of *Solobacterium moorei* Bacteraemia Secondary to Necrotising Fasciitis in a Patient with Chronic Elephantiasis

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Keywords

Solobacterium moorei, bacteraemia, necrotising fasciitis, immunocompromised

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Received: 16th May 2025; Accepted: 25th
September 2026

Doi:
<https://doi.org/10.31436/10.31436/imjm.v25i04/2964>

ABSTRACT

Solobacterium moorei is an anaerobic Gram-positive bacillus, part of the normal oral and intestinal microbiota, and is infrequently implicated in systemic infections. We report a rare case of *S. moorei* bacteraemia in a 64-year-old man with chronic right lower limb elephantiasis and multiple metabolic comorbidities. The patient presented with necrotising fasciitis of the right foot, necessitating urgent surgical intervention. Blood culture yielded *S. moorei*, while other significant cultures demonstrated mixed growth of aerobic and anaerobic organisms. The patient responded well to intravenous antibiotic therapy and was discharged in stable condition. This case underscores the potential pathogenicity of *S. moorei* in immunocompromised individuals and highlights the importance of considering rare anaerobic organisms in severe soft tissue infections.

INTRODUCTION

Solobacterium moorei is a non-spore-forming, gram-positive and an obligate anaerobic bacillus. Although part of the normal flora of the oral cavity and gut, it is rarely isolated in clinical settings and has been historically linked to halitosis.¹ Recent evidence has implicated *S. moorei* in a variety of opportunistic and invasive infections, including bacteremia, liver abscesses, oral infection including skin and soft tissue infections particularly in immunocompromised individuals.¹⁻⁴

The identification of *S. moorei* in blood cultures remains rare, and it is often underreported due to limitations in anaerobic culture methods and challenges with conventional identification systems. Newer diagnostic technologies such as MALDI-TOF MS and 16S rRNA gene sequencing have enhanced recognition of this organism in clinical practice.³

Necrotising fasciitis is a rapidly progressing, life-threatening soft tissue infection that is frequently polymicrobial and commonly affects individuals with predisposing factors such as diabetes, obesity, or chronic lymphoedema. The association between *S. moorei* and necrotising fasciitis has not been well established, and there are only a few published reports describing its presence in systemic infections of this nature.⁴

We present a case of *S. moorei* bacteremia secondary to necrotising fasciitis in a patient with chronic right leg elephantiasis and multiple metabolic comorbidities. This case adds to the growing recognition of *S. moorei* as a potentially invasive pathogen in vulnerable hosts.

CASE REPORT

A 64-year-old male presented to the emergency department with a 2-week history of right foot pain and swelling. The condition acutely worsened on the day of

presentation with new-onset fever and foul-smelling purulent discharge from the plantar aspect of the right foot. He was referred by a general practitioner who had noted signs suggestive of severe infection during a routine wound dressing visit after a progressive, painful swelling of the plantar aspect of the foot following a puncture wound which subsequently ruptured with purulent discharge.

He had multiple significant medical histories of Type 2 diabetes mellitus, hypertension, chronic kidney disease (CKD Stage 3), dyslipidaemia, ischemic heart disease, and obstructive sleep apnoea (OSA). He also had chronic dermatologic conditions, including bilateral stasis eczema, tinea pedis, and lymphostasis verrucosa cutis or elephantiasis nostras verrucosa (ENV), with a history of leg reduction surgery in 2011.

Clinical examination revealed that he was obese with a BMI of 52.6 kg/m². On admission, he was febrile with temperature of 38.0°C and the vital signs were stable. There were chronic skin changes consistent with elephantiasis, which were thickened and cracked skin over the calf, sloughy and swelling of the dorsum and sole of the right lower limb.

Physical examination of the right lower limb revealed massive, brawny, non-pitting oedema extending from the mid-thigh to the toes, with complete obliteration of the malleoli and normal anatomical contours. These findings are diagnostic of International Society of Lymphology (ISL) Stage III lymphedema (lymphostatic elephantiasis). The overlying skin exhibited pathognomonic features including severe pachydermia, diffuse hyperkeratosis, and verrucous papillomatosis prominent over the distal leg and dorsum of the foot, alongside a positive Stemmer's sign. Furthermore, deep transverse skin folds at the ankle and interdigital maceration with superficial fissures were present. Wet gangrene of the right fifth toe with surrounding oedema and slough was evident. The dorsalis pedis and posterior tibial pulses were not appreciable.

An X-ray of the right foot showed gas shadows over the fourth and fifth toes, suggestive of soft tissue gas-forming infection. Plain radiographs of the right lower extremity demonstrated features classic for severe chronic lymphostasis. There was massive expansion of the soft tissue compartment exhibiting a prominent reticular 'honeycomb' pattern, consistent with extensive fibrous septal thickening and oedema. The cutaneous silhouette was markedly thickened and lobulated. Superimposed on these changes, tracking gas dissecting along the deep fascial planes of the forefoot was observed, highly suspicious for an acute necrotising infection. No MRI or ultrasound was performed for lymphatic assessment in this acute setting.

He was immediately started on empirical intravenous piperacillin-tazobactam plus clindamycin, and underwent emergency debridement and Ray's amputation of the fourth and fifth toes. Blood culture was taken prior to antibiotic initiation. Intraoperative samples from bone, tissue, and pus were sent for culture and sensitivity.

The patient presented with a baseline haemoglobin of 11.3 g/dL.

The postoperative drop to 9.0 g/dL was primarily attributed to surgical blood loss following extensive wound debridement and Ray's amputation. The team managed subsequent decreases in haemoglobin with appropriate blood product transfusions (fresh frozen plasma and packed cells). On Day 13, haemoglobin levels decreased to 6.9 g/dL; notably, this occurred in the absence of active surgical bleeding or clinical signs of sepsis. Given the clinical stability, occult gastrointestinal blood loss was suspected; consequently, the patient has been scheduled for outpatient endoscopic investigation to determine the definitive aetiology.

Blood culture yielded growth after 24 hours of incubation in an anaerobic bottle. Direct Gram staining from the anaerobic bottle revealed gram-positive bacilli.

Subcultures were performed on MacConkey agar, and chocolate agar; however, no growth was observed after 48 hours under standard incubation conditions. Pure growth of tiny grey colonies was only seen on blood agar incubated under strict anaerobic conditions anaerobically after 48 hours (see figure 1). These colonies were sensitive to metronidazole. Identification was initially done by VITEK®system which was identified as 99% *Terrisporobacter glycolicus*, However, in view of the microbiology characteristics discrepancy, further identification was done via MALDI-TOF revealed *Solobacterium moorei*. Antibiotic susceptibility was evaluated by the E-test method in accordance with CLSI guidelines demonstrated sensitivity to ceftriaxone (MIC: 0.125 µg/mL), penicillin (MIC: 0.016 µg/mL), and piperacillin-tazobactam (MIC: 2 µg/mL).

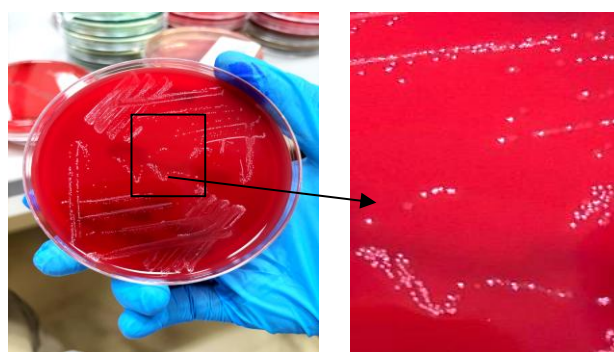


Figure 1: (a) Anaerobic blood agar plate showing pure growth of tiny grey colonies of *Solobacterium moorei* after 48 hours of incubation. (b) Higher magnification of the colonies.

There was no growth detected from the aerobic blood culture bottle. Mixed growth of more than three types of organisms which include three types of gram positive cocci and two types of gram negative bacilli were isolated from pus swabs, bone, and tissue samples.

Throughout the admission, C-reactive protein (CRP) levels demonstrated a steady downward trajectory, falling from 233.2 mg/L at presentation to 203.0 mg/L on Day 2, 124.5 mg/L on Day 4, 55.1 mg/L on Day 6, and 20.1 mg/L on Day 11, eventually normalizing to 11.4 mg/L at discharge on Day 13. Total White Cells (TWC) trends normalized (Admission: 17.1×10^9 to 8.7×10^9 /L at discharge).

Empirical antibiotic therapy was initiated with intravenous piperacillin-tazobactam (4.5 g QID) and clindamycin (600 mg TDS), with clindamycin subsequently discontinued after a 10-day course. Following an Infectious Disease consultation, intravenous piperacillin-tazobactam was continued to complete a total 14-day course. Surveillance blood cultures were deemed unnecessary by the Infectious Disease team in light of the patient's rapid clinical improvement and significant inflammatory marker clearance. Throughout the hospital stay, the patient maintained hemodynamic stability, with the exception of an isolated febrile episode (38.0°C) on admission that resolved within 24 hours of initiating targeted antimicrobial therapy. Leukocytosis showed marked improvement, decreasing from 17.1×10^9 /L at presentation to 8.7×10^9 /L at discharge, while the surgical site consistently demonstrated healthy granulation tissue.

Following that, antibiotics continued for 15 days, and the infection resolved without further complications. Postoperative recovery was uneventful. By day 15 post surgery, the patient was afebrile, hemodynamically stable, and his surgical site demonstrated healthy granulation tissue with no residual pus. The vital signs remained stable throughout the admission. Inflammatory markers and hematological trends showed significant improvement during the course of hospitalization: the C-reactive protein (CRP) level decreased from 233.2 mg/L on admission to 11.4 mg/L at discharge, while the total white cell count (TWC) normalized from 17.1×10^9 /L to 8.7×10^9 /L. He was mobilizing with a wheelchair and was deemed fit for discharge

DISCUSSION

Although traditionally associated with oral microbiota, *Solobacterium moorei* has increasingly been reported in invasive infections, including bacteraemia (Table I).² In a recent review of clinical cases, *S. moorei* was isolated from blood cultures, abscesses, and surgical wounds in

both immunocompromised and critically ill patients.¹⁻⁴ However, its involvement in necrotising fasciitis remains exceedingly rare and poorly documented in the literature.

Table I: Summary of Previously Reported *S. moorei* Infection Cases²

Study Focus	Reported Cases	Key Demographics	Primary Infection Source
Retrospective Analysis	~27	Immunocompromised and critical care patients	Bacteraemia, Abscesses, Surgical Wounds

This case highlights the potential for *S. moorei* to contribute to polymicrobial infections in high-risk patients with chronic limb disease, poor skin integrity, and metabolic diseases. Isolation of this organism in blood cultures indicates haematogenous spread, likely originating from infected necrotic foot tissue. Chronic tinea pedis, elephantiasis (ENV), and diabetes further compromised the skin barrier, predisposing the patient to rapid progression of soft tissue infection. In addition, chronic dermatological breaches, specifically deep transverse skin folds at the ankle and interdigital maceration with superficial fissures combined with local lymphostasis in this patient, served as the primary predisposing portal of entry facilitated the translocation of this oral or intestinal commensal into the systemic circulation.⁵ Consequently, these factors facilitated the subsequent development of the necrotising fascial infection. Elephantiasis is a rare disease which leads to chronic lymphoedema in these patients. It has been documented to increase susceptibility to cellulitis or recurrent skin infections significantly.⁶

Identification was initially attempted using the VITEK® 2 system, which misidentified the isolate as *Terrisporobacter glycolicus* (99% probability). However, in view of the microbiological characteristics, which were non-spore-forming Gram-positive bacilli, further identification was performed via matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS), which definitively identified the isolate as *S. moorei*. While 16S rRNA gene sequencing was not performed in this case, the MALDI-TOF MS

identification was consistent with the clinical presentation and morphological findings. Misidentification of *S. moorei* as *T. glycolicus* (formerly known as *Clostridium glycolicum*) occurred because *S. moorei* was not present in the VITEK® 2 database, highlighting the limitations of automated systems and the need for advanced molecular techniques like MALDI-TOF MS. Thus, *S. moorei* infection is likely underreported due to previous identification limitations before the widespread use of MALDI-TOF. As a fastidious obligate anaerobe, *S. moorei* may present with a metabolic profile that overlaps sufficiently with *T. glycolicus* in the limited biochemical tests performed by the VITEK® 2 system. A study has documented that commercially available systems such as the VITEK® 2 system have failed to identify *S. moorei*.⁵

Anaerobic bacteria are often underdiagnosed in necrotizing soft tissue infections because of the inherent limitations of culture-based methods, particularly in polymicrobial infections.⁷ *S. moorei* may be overlooked in mixed cultures if colony isolation on primary plates is suboptimal. The isolation of *S. moorei* as a pure isolate from the anaerobic blood culture, distinct from the polymicrobial wound environment, strongly supports its role as the causative agent of the patient's bacteraemia.^{1,2} Diagnostic confirmation proved challenging, as initial testing via the VITEK®2 system misidentified the organism, a known limitation documented in previous studies.⁷ Consequently, reliance on advanced diagnostic techniques like MALDI-TOF MS was essential to identify *S. moorei* and guide targeted therapy.³

This highlights the value of advanced diagnostic techniques for the accurate detection of fastidious anaerobes, which can ultimately inform targeted antimicrobial therapy.³

Despite his high-risk clinical profile, the patient responded favourably to prompt surgical debridement, culture-guided antimicrobial therapy, and supportive care. This outcome underscores the imperative for early

surgical intervention and broad-spectrum empirical coverage in severe necrotizing soft tissue infections.

CONCLUSION

This report emphasizes the emerging clinical significance of *Solobacterium moorei* as a potential opportunistic pathogen in necrotising soft tissue infections. Clinicians should be aware of its ability to cause systemic infections, particularly in immunocompromised individuals or those with compromised skin barriers. Appropriate anaerobic cultures and multidisciplinary care remain essential for optimizing outcomes in complex infections such as necrotising fasciitis.

ACKNOWLEDGMENTS

The authors would like to thank the multidisciplinary care team involved in the management of this patient.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this case report. All authors have read and approved the final manuscript.

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