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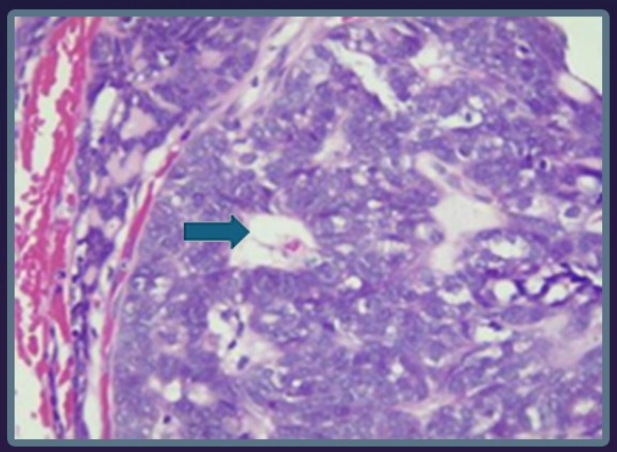

REVIEW ARTICLE

ORIGINAL ARTICLE

CASE REPORT

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CASE REPORT

EDITORIAL

Volume 24 Number 3, July 2025

Halimatussaadia Mother's Milk Centre (HMMC): A Unique Shariah Compliant Human Milk Bank with Single Donor Pools, Satiety Based Distribution

Human milk is widely acknowledged as the gold standard for infant nutrition, especially for preterm and low birth weight neonates. World Health Organization summarized a few factors in relation to the global implementation of human milk banking which include regulatory issues, quality criteria and management, data registries, ethical issues, and global coordination.[1] In Muslim majority countries where Islamic jurisprudence guides medical decisions, milk kinship often takes precedence over other clinical considerations. This is particularly relevant in the context of human milk banking, where milk kinship carries significant ethical and legal implications under Shariah law.[2]

Donor milk handling practices in human milk banks vary, pooling milk from a single donor to combining donations from multiple anonymous donors. For instance, the United Kingdom Association for Milk Banking (UKAMB) adopts a single donor pooling model, allowing traceability within a donor's milk while maintaining anonymity. In contrast, the Human Milk Banking Association of North America (HMBANA) allows pooling from multiple- donors, typically between two to six - resulting in fully anonymous mixed batches. While pooling improves efficiency and standardization, donor anonymity poses challenges in tracing milk kinship, which carries ethical and legal implications in certain cultural and Islamic contexts.[2]

In some Muslim-majority countries, human milk bank initiatives without prior endorsement by Islamic councils often face religious pushback and are either transformed or dismantled completely.[3] In Turkey, a pilot human milk bank was halted due to religious concerns over milk kinship, and hence absence of consensus with religious authorities can hinder implementation.[4]

The Halimatussaadia Mothers' Milk Centre (HMMC), officially established in July 2022 at the Sultan Ahmad Shah Medical Centre (SASMEC) @IIUM, Kuantan, Pahang, represents a significant milestone in Malaysia's advancement of Shariah-compliant donor milk services. As the country's first Islamic-compliant milk bank recognized by the Malaysia Book of Records, HMMC operates under stringent protocols that are reviewed annually by the Pahang State Religious Council, ensuring continuous adherence to Islamic bioethical principles.

Central to the operations of Shariah-compliant milk banks is the concept of milk kinship, which is established when a child receives breast milk from a woman other than the biological mother. In Malaysia, where the Shafii jurisprudence is followed, milk kinship can be formed through any method of feeding, including bottle, cup, or nasogastric tube not limited to direct breastfeeding. According to the Shafii and some Hanbali scholars, at least five separate satiety feedings are required to establish this kinship, regardless of the feeding method. This interpretation has significant implications for milk bank operations and legal parentage considerations under Islamic law.

However, assessing satiety in preterm and sick neonates can be difficult, as these infants may not consistently exhibit typical cues of fullness such as turning away or ceasing to suck that are readily observed in term infants.[5]

HMMC exemplifies a single-donor-pools, satiety based distribution model that integrates strict satiety based volume control to reduce the risk of milk kinship while ensuring the safe provision of high quality donor milk. In this model, "satiety feeding" refers to a controlled feeding volume intended to meet the infant's immediate needs

without exceeding the threshold that would establish kinship under Islamic law. At HMMC, satiety is operationally defined using a modified total fluid intake index tailored to each recipient's clinical needs. During non-satiety feeding, a recipient may receive repeated feeds from the same donor until their own mother's milk becomes available. In contrast, under satiety feeding protocols, infants may receive up to three satiety feedings from one donor. If further satiety feedings required and indicated while waiting for access to mother's own milk (MOM), milk from different donors should be used. Each feed is meticulously recorded to ensure traceability and compliance with Shariah principles.

This approach mitigates risks associated with multi donor pooled milk particularly the loss of donor recipient traceability while upholding both safety and religious integrity. It exemplifies operational excellence in Shariah-compliant neonatal nutrition, harmonizing biomedical ethics with Islamic jurisprudence through structured implementation and oversight.

Religious and Ethical Safeguards: Under Shafii jurisprudence, five or more feedings that induce satiety in infants under two years of age establish milk kinship. At HMMC, most donors prefer to avoid forming such ties. To accommodate this, the centre imposes strict volume limitations per donor. In rare cases where milk kinship may be unavoidable, informed consent is obtained from both the donor and the recipient's guardian before the threshold is met. Families are then formally introduced, fostering a lifelong commitment to honour the religious and social responsibilities associated with milk kinship. A milk kinship card is issued for transparency and lifelong documentation.

Comparative Ethical and Operational Considerations: Unlike conventional donor milk models relying on anonymous pooling, HMMC adopts a personalized, traceable approach grounded in religious and ethical accountability. Informal community milk sharing may support cultural values but often lacks institutional safeguards. HMMC bridges this gap by providing a regulated, safe, and Shariah-compliant alternative meeting both medical and religious standards.

Implications and Recommendations: The HMMC model establishes a meaningful benchmark for Shariah compliant donor milk systems in Sunni Muslim majority contexts. It offers an ethically sound alternative to anonymous single or multi-donors pooling, demonstrating that religious jurisprudence can be integrated with evidence-based neonatal care. Neonatal units in similar settings can replicate the HMMC framework to respect both faith and science.

To expand HMMC's impact, scaling its principles across Malaysia and other Muslim majority countries is imperative. Integrating digital tracking systems will enhance donor-recipient traceability and safety protocols. Continuous collaboration between neonatologists and Islamic scholars remains vital for refining protocols as religious guidance evolves. Additionally, research into satiety thresholds in preterm infants is needed to support clinical standardization and strengthen the scientific foundation of Shariah-compliant feeding protocols.

The Halimatussaadia Mothers' Milk Centre exemplifies how Islamic bioethics can shape and guide modern neonatal care. Through its single-donor-pools model with strict satiety based volume control, HMMC offers a replicable, ethically sound, and Shariah-compliant model for human milk banking setting a pioneering precedent for Muslim-majority healthcare systems worldwide.

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EXPERT OPINION

Bioethics and Biobanking in Biomedical Research in Malaysia

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In the rapidly evolving domain of biomedical research, bioethics is a critical pillar that ensures the alignment of scientific advancements to ethical principles, societal values and human rights. The systematic collection of biological samples, processing and storage involved in precision medicine, epidemiological research and genetic studies are in need of a robust ethical governance and careful navigation in the biobanking practice. Addressing bioethical concerns is crucial, as Malaysia progresses to become one of the leaders in biomedical innovation. Discussions and the establishment of various ethical frameworks and national guidelines throughout the years have demonstrated Malaysia's commitment towards improving ethical oversights, regulatory clarity, and public trust in biomedical research and biobanking practices. However, challenges in areas such as informed consent, data privacy, equitable sharing of benefits and public trust in research institutions persist.

Biobanking, the storage of biological samples, is considered a cornerstone in biomedical research and it has revolutionised the study of human biology to an unprecedented scale. In this technology, biological specimens such as blood, tissue and DNA are collected, managed and stored in repositories to enable better understanding of disease mechanisms, identification of biomarkers and development of new treatments for diseases through original and pioneering research studies. In Malaysia initiatives to foster a robust biobanking infrastructure has led to the establishment of a Biobank Unit under the purview of the Institute for Medical Research (IMR) under the Ministry of Health in Malaysia (MOH) in 2019. Despite this, the ethical implications of biobanking are far-reaching and issues related to consent, sample ownership, secondary data use and fair distribution of research benefits are still being debated. A foundational guidance can be found in '*The Malaysian Guidelines on the Use of Human Biological Samples for Research*', published in 2015 by the MOH[1], but the ensuing ethical dilemmas that emerged in modern biobanking suggest the need for more comprehensive and updated regulations.

In light of these challenges and concerns surrounding ethical practices in research, some of the most pressing issues related to biobanking are discussed below.

Informed Consent

During the process of obtaining consent, it is important that donors-participants understand what will be done to the biological samples that they contribute. A valid informed consent is complex and Malaysia has currently adopted the *broad consent model*, which allows researchers to use biological samples for future research that are not specified but still within the ethical boundaries.[2] Apart from giving voluntary consent, it is important that donors -participants clearly understand the potential uses of their samples. A broad consent therefore poses a challenge as the validity of the consent can be questioned.

Genetic modification and commercial exploitation of biological samples in controversial research has always been the cause of fear and public apprehension. The proposal of a more stringent and ethical consent process is the *dynamic consent model* which allows donors-participants to continually update their preferences with regard to the use of their samples.[3] This alternative process may foster transparency and thus build trust between donors-participants and researchers including the biobank authorities. However, it is apparent that important infrastructure such as specific digital platforms for real-time donor-participant engagement including secure technology would be required in the implementation of this type of consent.

Data Privacy and Ownership

The privacy of data is a significant concern as biobanking is increasingly linked to genomic and genetic research. Re-identification of anonymised genetic data poses risks to donors-participants such as genetic discrimination, for instance, by insurance companies and employers. Issues of data security have notably become a barrier to public participation in biobanking initiatives. Thus, to prevent unauthorised access to private data and to preserve data integrity, secure data-sharing frameworks, blockchain or privacy technology driven by artificial intelligence (AI) would be required. Ownership rights are also imperative to ensure that donors-participants consent is obtained prior to third party sharing.

The recent amendment to the Personal Data Protection Act (PDPA) in Malaysia in 2024[4] is not only timely but necessary. The key changes made in areas such as data privacy, security and governance, have direct impact on bioethics and biobanking in research. The PDPA (Amendment) 2024, has now introduced crucial practices in the protection of personal data and some of them include mandatory data breach notifications to enhance transparency and accountability, and appointment of Data Protection Officers in research institutions. Biobanks handling large volumes of genetic or health data need to oversee compliance to data protection laws and expansion of definitions of sensitive personal data which now includes DNA, fingerprints and facial recognition data.[5]

Governance, Regulations and the Role of Ethics Committees

The biobanking landscape in Malaysia is in need of a clear, dedicated guideline and legislative framework. Donors-participants information is protected by the PDPA (Amendment) 2024 but issues pertaining to practices in biobanking are not specifically addressed. Groundwork has commenced for a National Biorepository Policy to establish standardised governance that will address challenges in storage of biological samples, access, privacy including commercialisation (National Sub-Committee for Laboratory Biosafety & Biosecurity, 2023).[6] At present, multiple biorepositories in the country are managed by government agencies, universities and private companies. The biobanks in most of these institutions and facilities have been operating under general laws such as Human Tissue Act 1974[7] that governs the use of human tissues and the previous PDPA 2010 to cover privacy and confidentiality aspects. The current Malaysian Guidelines on the Use of Human Biological Samples for Research (2015) are not legally binding and consent under the Human Tissue Act 1974 only applies to samples of deceased individuals and not living donors. There are concerns from the public that biological samples are being commercialised without donor-participant consent and exploitation of donated biological samples for financial gain.[8,9] Enforcement in the form of a dedicated biobank legislation, improved ethical guidelines and sustainable biobank models for research, diagnosis and public health are therefore vital.

Across the board, decisions from Institutional Review Boards (IRB) or Ethics Committees are sometimes delayed and there can be inconsistencies in the procedures used. Standardisation of ethical assessments and an efficient biobank governance that adhere to international ethical standards are crucial. Reviewers for ethical applications must also be trained to be well-versed in ethical considerations that are unique to biorepositories, genomic data privacy and storage of samples.

Standardisation

For purposes of universal standardisation of global biobanking, ISO 20387:2018 was developed by integrating guidelines from national and international biobank standards such as from the United Kingdom, Brazil, France and the Organisation for Economic Co-operation and Development (OECD). This ISO standard focuses on quality assurance of biological materials, data management and governance, standardisation of procedures for sample collection to distribution as well as risks assessments and sustainability of biobanks. With standardisation of processing protocols including rigorous quality control and regulatory compliance, it is now hoped that research using the biological samples can be reproducible, in turn promoting international

collaborations for advancements in the field of study while at the same time increasing stakeholder confidence in biospecimen-based research.[10]

Artificial Intelligence (AI) and Biobanking Governance

The Ministry of Science, Technology and Innovation (MOSTI), published a guideline, 'National Guidelines on AI Governance & Ethics' in 2024, to ensure responsible application of artificial intelligence (AI) across healthcare and multiple sectors.[11] The use of AI in biobanking is no doubt necessary as it brings efficiency in data analysis but this also raises concerns on algorithmic bias, security vulnerabilities, and ethical accountability. Key ethical principles pertaining to biobanking as outlined in the guideline by MOSTI include fairness and non-discrimination (AI-driven analyses to be free from bias so as not to disadvantage certain populations), transparency and explainability (AI-generated results in genomic research to be interpretable for accountability in clinical decision-making), privacy and data protection (AI algorithms to adhere to strict privacy measures, preventing unauthorised access and data misuse) and most importantly, human oversight (AI to only enhance ethical and scientific rigor but must not replace human-decision making).

From the Islamic bioethics perspective, the use of human biological materials in research is regulated by principles that emphasises on consent, overall benefit to the society and the prevention of harm. With reference to 'Kompilasi Muzakarah MKI 2016' by Jabatan Kemajuan Islam Malaysia, the utilisation of biological samples e.g., adult stem cells, umbilical cord blood and residual embryos from *in vitro* fertilisation (IVF) treatments is allowed under Shariah law with the condition that informed consent has been obtained from the donor or guardian.[12] However, the commercialisation of those samples for non-therapeutic or business purposes is strictly prohibited, a stance that expresses the strong ethical position against exploitation. Biomedical research must have scientific rationale, have undergone ethical scrutiny and should only be performed by qualified researchers. These legal pronouncements affirm the conformity of Islamic Jurisprudence with universal standards of ethics and they provide the cultural and theological frameworks for regulation of biobanking and biomedical research in a Muslim-majority country like Malaysia.

The future of biobanking in Malaysia must ultimately prioritise transparency, ethical stewardship and public trust. Confidence in the biobanking governance can be nurtured by raising ethical literacy among the public, improving engagement with donors, participants and researchers as well as educating the larger society. An ethically robust and sustainable biobanking ecosystem can be achieved by bridging regulatory gaps and embracing technological innovations, propelling medical advancements, improvements to public health and precision medicine on both national and global scales.

As biomedical research advances, the 'Malaysian Guidelines on the Use of Human Biological Samples for Research' is currently being updated by the Biobank Secretariat at the National Institutes of Health, MOH, as a critical move toward ethical modernisation, instilling principles of dynamic consent, data sovereignty and fair benefit-sharing in national practice. This effort will ensure the harmonisation of Malaysia's biobanking environment with global standards and guidelines, ultimately strengthening trust, transparency, and scientific integrity in this age of precision medicine.

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REVIEW ARTICLE

Injury Prevention Program among Athletes in Malaysia: A Systematic Review

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ABSTRACT

Sport is responsible for the significant occurrence of acute and overuse injuries among athletes. The injuries during sport can result in long-term negative consequences that reduces the performance of sports. The burden of sport-related injuries is substantial, and there is a lack of studies assessing the effectiveness of injury prevention strategies. To date, cumulative information regarding injury prevention strategies is limited in Malaysia. This study aims to identify the characteristics of injury prevention programs among athletes in Malaysia. This research was systematically conducted utilising the electronic databases of Web of Science (WoS), Scopus, ClinicalKey, Cochrane Library, PubMed, SPORTDiscus, and Google Scholar. Two reviewers, MIS and HAY, independently selected articles based on the established inclusion criteria from 1st January 2015 to 31st December 2024. The study followed PRISMA guidelines and was registered with PROSPERO under registration number CRD42024513383.Nine eligible papers were included in the study and scored at least five points on the 11-point checklist of the CASP appraisal tool. Injury prevention programs, including neuromuscular training and sport-specific interventions, enhance strength, flexibility, and balance, reducing injury risk among athletes. It is recommended that injury prevention programs be adopted in every sport, especially during warm-up periods of training sessions. Future research should focus on individualised programs and technology for real-time feedback injury prevention strategies.

Keywords
Sports injury, Injury prevention strategies, Athlete, Malaysia

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INTRODUCTION

Sporting activity is responsible for the significant impact of injuries on adults and children.[1,2] Previous studies show that athletes suffer acute and overuse injuries in individual and team sports.[3,27] The combined prevalence of injuries in individual and team sports was 42.0% and 33.0%, respectively.[3] Several studies demonstrate that acute and overuse injuries can have detrimental long-term effects that impair an athlete's performance, resulting in pain and dysfunction and, in certain situations, possibly ending an athlete's career.[4,5,28] The prevalence of sport-related injuries is significant, and there is a shortage of research evaluating the efficacy of injury prevention techniques across all sports and age demographics in Malaysia.[2] Hence, evidence-informed injury prevention interventions, especially among athletes, are necessary to mitigate injury risk.

The four-step model is the basis for creating and assessing sport injury prevention programs. It involves gathering data on injuries in a specific population using surveillance systems and identifying the risk factors contributing to these injuries.[6,7] This process leads to developing and validating injury prevention strategies using suitable surveillance systems to measure their impact on injury incidence. Thus, randomised controlled trials (RCTs) represent the most effective means to assess the success of a preventative plan, although they are not always practical or ethical. Other study designs, including quasi-experimental, cohort, and case-control, are employed to assess the effectiveness and efficacy of injury prevention programs. However, these designs possess intrinsic methodological limitations that induce biases and constrain the interpretation of study results to a certain degree.[8]

Players, coaches, and athletic organisations can readily adopt and sustain the best injury prevention program. Consequently, a significant focus has been on incorporating injury prevention studies into real-life environments.[9,10] Injury prevention measures have demonstrated efficacy in lowering the frequency and severity of injuries.[7,11] An increasing number of epidemiological studies have evaluated the effectiveness of injury prevention strategies among athletes, particularly in relation to musculoskeletal injuries. This evidence-based approach includes three primary themes: 1) Training strategies, 2) Enhancements to sports regulations and policies, and 3) Suggestions for equipment.[7] Many of these strategies emphasise training modification that includes strength, endurance, and balance through exercise interventions such as neuromuscular training.[7] To date, cumulative information regarding injury prevention strategies is limited in Malaysia. This study aims to identify the characteristics of injury prevention programs intervention among athletes in Malaysia. The findings can provide helpful insight to athletes, coaches, and healthcare practitioners in minimising the risk of injuries and effectively managing sports-related injuries.

MATERIALS AND METHODS

Search strategy

Eligible articles were systematically identified for inclusion in this study through electronic databases, including Web of Science (WoS), Scopus, ClinicalKey, Cochrane Library, PubMed, SPORTDiscus, and Google Scholar. The articles were identified by typing keywords using the primary search term (injury prevention program OR injury prevention strategies). The search strategy continued with the individual search terms (general OR sport specific), (athlete OR sports person) AND (Malaysia OR Malaysian). Articles will be chosen according to the inclusion criteria outlined in Table I. The criteria stipulate full-text articles authored in English and published within the last decade, specifically from 1st January 2015 to 31st December 2024. Articles must include athlete participants who participated in the competition within the past year. The studies should detail injury prevention programs implemented in Malaysia.

Table I: Criteria for the article's selection

1. An athlete who has participated in competitions at the school, university, district, state, or national level within the past year.
2. Studies published over the ten years (2015-2024)
3. Full-text articles written in English
4. Study conducted in Malaysia
5. Subject participates in general OR Sport specific Injury Prevention Program (IPP)

Data selection & extraction

Two reviewers, MIS and HAY, independently selected articles based on the established inclusion criteria. The analysis comprised screening titles and abstracts of articles, followed by a detailed examination of the full texts of eligible articles for inclusion and subsequent review. Excluded articles comprise abstracts, narrative reviews, non-English publications, commentaries, and studies lacking descriptions of injury prevention programs for athletes. The articles were compared during a consensus meeting among researchers. Articles were included based on mutual agreement between both reviewers, with disagreements resolved through discussion. The research followed the PRISMA guidelines for systematic reviews and meta-analyses.[12] The study was registered with PROSPERO (International Prospective Register of Systematic Reviews) under registration number CRD42024513383. Information from the chosen articles was collected based on structured sheets that included demographic data such as age, total number of participants, and study locations. Furthermore, the research encompassed intervention details, assessment tools, study results and recommendations.

Study Evaluation

The methodological quality of the selected article was evaluated using the Critical Appraisal Skills Programme (CASP) appraisal tool to systematically assess the quality of the randomised control trial studies. The checklists consist of 11 questions encompassing three primary components: bias associated with selection and allocation, administration of intervention/exposure, and the assessment, detection, and measurement of outcomes, as well as participant retention in randomised control trial

studies.[13] The articles that meet the reviewer team's predetermined weight will be included.

RESULTS

Study selection

The analysis of the computerised bibliographic database identified a total of 211 articles. Following the elimination of duplicate articles, commentaries, and conference proceedings, a total of 200 articles underwent additional screening, resulting in the identification of ten articles based on their titles and abstracts. After a comprehensive evaluation and screening of the full-text articles based on the inclusion criteria, nine eligible papers were identified for the study. All nine articles scored at least five points on the 11-point checklist of the CASP appraisal tool. Figure 1 is a PRISMA flowchart that outlines the process of selecting studies. Results are summarised in Table II, which includes a comprehensive overview of the nine articles, providing details regarding the type of sports involved, participants, the assessment tools, intervention details, outcomes, and study recommendations.

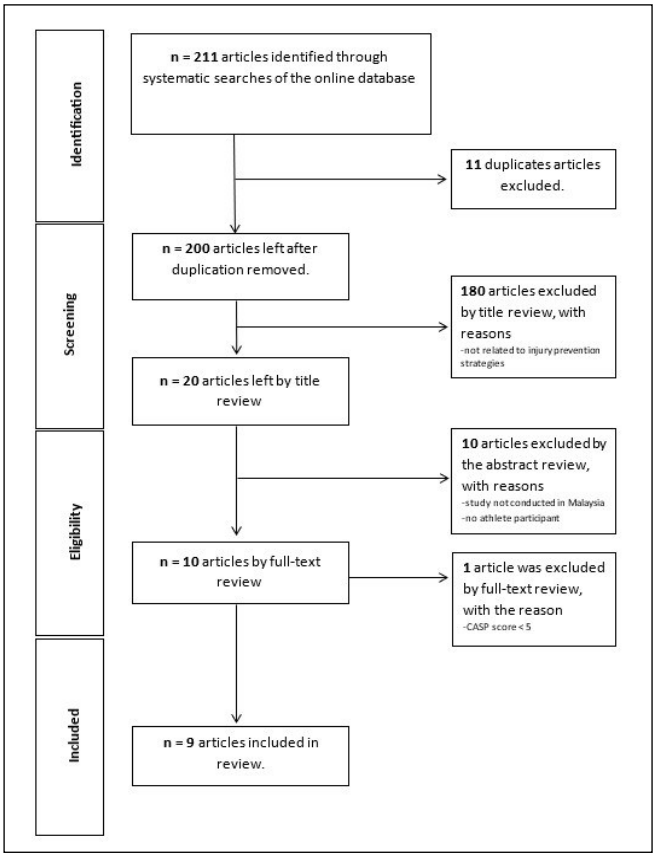

Figure 1: Flowchart illustrating the selection process of published articles from 1st January 2015 to 31st December 2024.

Type of sport

This section provides information regarding the type of sports involved in injury prevention programs. The results indicate that three studies reported injury prevention programs that involve a single type of sport, football[16], volleyball[21] and netball.[32] Four studies[14,15,18,19] reported injury prevention programs for multiple sports ranging from volleyball, futsal, football, basketball, hockey, netball, rugby, tennis, and athletics. The last two studies did not specify the type of sport in which the participants were involved in the injury prevention program.[17, 20]

Demographic information

The number of participants varies between studies, from as low as 10 to as high as 50. Four studies reported fewer than 20 participants,[15,17,18,20] four studies had 20 or more participants,[14,19,21,32] and one study reported a substantial amount of 50 participants.[16] The studies have participants between 13 and 35 years old. Most of the studies reported mean average ages above 20 years old.[14,15,17-19,21,32] Three studies were conducted at rehabilitation clinics,[14,15,17] and the remaining were conducted at academic institutes.[16,18-21,32]

Assessment tools

The findings indicate that most studies reported physical performance tests as assessment tools[14,15,17-21], and two studies reported the outcome using only a questionnaire.[16,32] The physical performance test includes but is not limited to the standing long jump test,[14,21] balance test,[14,17–20] agility test,[18] strength test[14,15] and flexibility.[20] Four studies reported using questionnaires,[14,16,20,32] one study involved a lab test on antioxidant enzymes' activity,[15] a study in neuromuscular activity using surface electromyography (sEMG)[20] and a study implementing a pain rating scale using the visual analogue scale (VAS).[20]

Intervention details

Sport-specific injury prevention programs were conducted in three studies.[14,16,32] and the remaining six studies reported on conducting general injury prevention

Table II: Injury Prevention Program among Athletes in Malaysia

No	Author	Article title	Type of Sports	Participant (N, Age, Location)	Assessment Tools	Intervention Details	Outcomes	Recommendations
1.	(Teichmann et al., 2016)	Unexpected-Disturbance Program for Rehabilitation of High-Performance Athletes	Multiple sports backgrounds	n=24; 16 male and 8 female Age 22.1 ± 4.10. Location Sports Medicine and Rehabilitation Clinic at the National Sports Institute of Malaysia	**Physical Performance Test:** Single-leg press (1-repetition maximum [1RM]), Standing long jump test, 20m sprint test, single leg balance test, **Questionnaire:** Perceived-Recovery Questionnaire.	**Intervention group** Each subject will undergo six to seven weeks of UDP, with a training volume of 8 to 10 weekly sessions, each lasting around two hours. Sport-specific Unexpected-Disturbance Program (UDP) encompasses exercises such as executing low and overhead shuttle shots in badminton, performing headers with hops or one-touch passing in football, executing kicking sequences in Tae Kwon Do, and engaging in shooting or rebound recovery in basketball.	**Single-Leg 1RM Strength**: Improved significantly (22%, P < .05) in male and f (29%, P < .05) in female subjects. **Standing Long Jump: S**ignificant improvements by 4% in male subjects. **20-m Sprint:** Time was markedly reduced by 3% in males and 4% in females. **Single-Leg Balance:** Minor yet inconsequential reduction in average anteroposterior and mediolateral sway**.** **Perceived Recovery:** Substantially elevated levels of bodily confidence	Training that resembles the nature of competitive sports helps elevate the fear of movement and reinjury and enhances neuromuscular firing properties and functions.
2.	(Lai et al., 2016)	Effect Of Platelet-Rich Plasma Treatment on Antioxidant Enzymes' Activity Following Hamstring Injury Among Malaysian Athletes	Multiple sports backgrounds (athletics, football, basketball, hockey, netball, rugby, tennis)	n=10; 7 male and 3 female Age Intervention: 22.8±4.03 Control: 24.8±6.42 Location Sport Medicine Clinic of the University of Malaya Medical Centre	**Lab Test: (Primary)** Antioxidant enzymes' activity of the erythrocyte CAT and superoxide dismutase (SOD) **Physical Performance Test (Secondary)** Criteria for return to play (RTP) (Hamstring palpation; isometric hamstring contraction, active knee extension test and isokinetic dynamometer)	**Intervention group** Platelet-rich plasma treatment (PRP-T) with a rehabilitation program, including progressive agility and trunk stabilization (PATS) exercises weekly for four weeks. **Control group** Progressive agility and trunk stabilisation (PATS) exercises weekly for 4 weeks. Progressive agility and trunk stabilisation (PATS)**:** Exercises that include **s**ide-stepping, grapevine stepping, forward and backwards stepping, single leg stand, prone abdominal body bridge, side bridges, icing in a sitting position, push-up stabilisation with trunk rotation, fast feet in the ground, proprioceptive neuromuscular facilitation trunk-pull downs, symptoms-free practice, icing if any symptoms of pain.	**Primary outcomes measure:** Week 2: The CAT activity in the control group was about the same as in the intervention group. There was a reduction in SOD activity (from W0 to W4) in both groups and no statistically significant difference between groups throughout the reference time frame. **Secondary outcome measure:** The mean time to RTP was 27.6±14.99 and 42.2±17.3 days for the intervention and control groups.	It was thought that PRP could be used as an extra treatment for injuries to shorten the time it takes to get back to playing (RTP).

cont'd

No	Author	Article title	Type of Sports	Participant (N, Age, Location)	Assessment Tools	Intervention Details	Outcomes	Recommendations
3..	(Ahmed F Farhan et al., 2017)	Prevention Of Soccer-Related Ankle Injuries in Youth Amateur Players: A Randomized Controlled Trial	Football	n=50 male Age 13.34±0.47 Location Sport School, Malaysia	**Questionnaire:** Incidence of injury and exposure time in a year.	**Intervention group** Football-specific training exercises, 15-20 minutes per session, five times weekly, for 12 weeks. Football-specific training: Core stabilisation, eccentric exercise of the thigh muscles, proprioceptive training, dynamic stabilisation, and plyometrics. **Control group** Continue regular training regime.	**Prevalence of injury for the intervention group:** Ankle: 31% **Prevalence of injury for the control group**: Ankle: 69% **Total injuries per 1000 hours of exposure. Intervention group**: 0.96 **Control group**: 2.16	The injury prevention program can be integrated into the training regimen and the pre-participation assessment of athletes to mitigate risk factors associated with injuries.
4.	(Saha et al., 2016)	Effectiveness of Neuromuscular Training Program in Young Athletes Suffering from Lower Lateral Ankle Ligament Injury	not reported	n=18 Age 23.2± 2.46 Location Hospital of Universiti Sains Malaysia	**Physical Performance Test:** Y-balance test and proprioception assessment utilising Biodex 4 Isokinetic Equipment	**Intervention group** 12 sessions; 30 min/ day; two days/week for six weeks. Neuromuscular training program: Level 1: squats, heel raises, and toe raises. Levels 2 and 3: unilateral exercises on stable surfaces. Levels 4 and 5: intricate unilateral workouts on both stable and unstable surfaces.	Neuromuscular therapy utilising a bosu-ball balance trainer is recommended to enhance proprioception in athletes with lateral ankle injuries.	Neuromuscular controlled exercise training perhaps helped restore lost proprioception.
5.	(Baharudd in & Junaid, 2018)	Effect of Neuromuscular Training to Prevent Anterior Cruciate Ligament Injury Among Female Athletes	Multiple sports backgrounds (volleyball, futsal and basketball)	n=16 Age 23.2± 2.46 Location Universiti Pendidikan Sultan Idris	**Physical Performance Test:** Star Excursion Balance Test (SEBT) for dynamic balance. T-Test for agility.	**Intervention group** Four weeks; two sessions every week of neuromuscular training. Neuromuscular training program: Double leg jumps forward; lunges step; side-to-side box; knee lift on the box; single jump forward; lunges step forward; unilateral leg side-to-side box jump; squat jump; lateral bound. **Control group** Continue regular training.	The intervention group exhibited a substantial difference in dynamic balance and agility performance before and after four weeks of neuromuscular training.	Neuromuscular training is advisable for female athletes to improve dynamic balance and agility performance while preventing ACL injuries.
6.	(Sankarav el et al., 2016)	Effect Of Neuromuscular Training on Balance Among University Athletes	Non-contact sports,	n=20 Age 20.9± 0.85 Location Universiti Pendidikan Sultan Idris	**Physical Performance Test:** Balance error scoring system (BESS).	**Intervention group** Three sessions weekly for six weeks of progressive neuromuscular training. Progressive neuromuscular training is an ideal performance training strategy encompassing stability, strength, and power through a three-tiered progression from simple to more complex exercises. **Control group** Continue regular training.	The principal finding reveals a notable enhancement in static balance within the intervention group.	The early commencement of proprioceptive neuromuscular training may enhance balance and safeguard young athletes against potential reinjury.

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No	Author	Article title	Type of Sports	Participant (N, Age, Location)	Assessment Tools	Intervention Details	Outcomes	Recommendations
7.	(Ramalingam et al., 2020)	Effect of Neuro-Dynamic Technique on Repetitive Inward Ankle Rolls among Young Malaysian Athletes - A Randomized Controlled Trial	Not reported	n=18 Age 17-35 years old. Location National Sports Institute of Malaysia and Physiotherapy Centre, International University Malaysia (INTI)	**Physical Performance Test:** Dynamic equilibrium was assessed via the Y Balance Test, and the range of motion was evaluated using a dual-axis electro-goniometer. **Neuromuscular activity:** Peroneus longus and tibialis anterior muscle activation using wireless surface electromyography (sEMG). **Pain rating scale:** Visual analogue scale (VAS) **Questionnaire:** Functional Ankle Disability Index (FADI).	**Intervention group** Three sessions per week for six weeks of neurodynamic technique and Standard Physiotherapy (SP). Neurodynamic Technique (NDT): Technique that mobilise the peroneal nerve was carried out without producing pain symptoms. **Control group** Standard Physiotherapy (SP) Management.	The study's findings indicate enhancements in dynamic balance, pain scores, peroneal longus and tibialis anterior muscle activation responses, knee range of motion (ROM), and the functional ankle disability index (FADI) for both the intervention and control groups.	The neurodynamic approach and conventional physiotherapy intervention demonstrate comparable and safe outcomes across variables. The neurodynamic approach is also advised to prevent recurrent inversion ankle sprains.
8.	(Baharuddin, Mohd et al., 2020)	Effect of Plyometric Training on Anterior Cruciate Ligament Injury among Female Volleyball Players	Volleyball	n=20 Age Intervention: 21.9± 1.27 Control: 20.9± 1.9 Location Universiti Pendidikan Sultan Idris (UPSI	**Physical Performance Test:** Standing Long Jump	**Intervention group** Twice a week for six weeks of plyometric training. Plyometric training: Bilateral two-foot ankle hops, unilateral jumps, and jump trucks. **Control group** Routine training.	The intervention group exhibited a notable difference between the pre-test and post-test results for the standing long jump, whereas the control group did not.	Plyometric training enhances lower limb strength and may mitigate the risk of anterior cruciate ligament (ACL) injuries in female athletes.
9	(Zulkarnain & Khairullina 2019)	The pilot study on Down to Earth (D2E) injury prevention program among varsity netball players	Netball	n=42 Age Intervention: 21.2± 1.8 Control: 20.9± 1.9 Location University Malaya Sports Centre, Kuala Lumpur	**Questionnaire:** Incidence of injuries on the lower extremity.	**Intervention group** Thrice a week for six weeks of *The Down to Earth* (D2E) training. **Control group** Routine training.	The results indicate a lower rate of lower extremity injuries in the intervention group than in the control group.	*Down to Earth* (D2E) training reduces netball players' risk of lower extremity injury. Increasing the training hours is also beneficial for athletes in minimising injury risk.

programs.[15,17–21] In sport-specific injury prevention programs, one study conducted polymetric training[21] , one study conducted the Down to Earth training (D2E)[32] and the remaining on football-specific training.[16] General injury prevention programs indicate that three studies conducted neuromuscular training[17–19] and the remaining studies conducted on progressive agility and trunk stabilisation (PATS),[15] Neurodynamic Technique (NDT)[20] and Unexpected-Disturbance Program (UDP).[14]

The training frequency varies, and many studies were conducted about six weeks of intervention.[14,17,19–21,32] The lowest frequency is about four weeks of intervention conducted in two studies[15,18] and 12 weeks is the highest frequency of intervention indicated in a study among football players.[16] There was primarily a twice-a-week intervention,[17,18,21] three studies were conducted three times per week,[19,20,32] and the remaining study is conducted once a week,[15] five times per week[16] and more

than eight times per week.[14] Three studies reported that hours per training ranged from 15 to 30 minutes per session.[16,17,32]

Outcomes and recommendations

The intervention group indicates positive and significant results in all studies for the physical performance test,[14,15,17–21] questionnaire,[14,16,20,32] neuromuscular activity,[20] pain rating scale[20] and lab test.[15] A study suggested that an injury prevention program tailored to the characteristics of the competitive sport could reduce injury risk and enhance overall athletic performance.[14] Injury prevention programs should be incorporated into training to mitigate injury risk.[16] Besides that, incorporating platelet-rich plasma (PRP) treatment in injury prevention programs has been shown to hasten the time to return to play.[15] Three studies recommended neuromuscular training in the injury prevention program for improving athletes' proprioception, dynamic balance, agility, and injury prevention.[17–19] A study suggested a neurodynamic technique to prevent recurrent ankle sprain.[20] Besides that, polymetric training also helps to strengthen the lower extremities and prevents ligamentous injury.[21]

DISCUSSION

The main findings of the study on the characteristics of injury prevention programs in Malaysia shows that neuromuscular training programs are the most widely adopted.[17–19] This is primarily because numerous studies have demonstrated that neuromuscular training is highly effective in reducing the risk of injuries among athletes.[41–43] In neuromuscular training, athletes were subjected to multi-intervention programs involving several types of balance, weight training, plyometric exercises, agility drills, and sport-specific exercises.[39,40] This comprehensive approach to injury prevention ensures that athletes are better equipped to maintain proper biomechanics during training or competition, thereby mitigating the risk of injuries. These findings underline the importance of neuromuscular training as a cornerstone of injury prevention strategies in Malaysian programs and support its inclusion as an evidence-based approach.

Alternative injury prevention strategies, such as Progressive Agility and Trunk Stabilization (PATS), have also effectively prevented re-injuries, especially in athletes recovering from previous injuries. However, it is worth noting that while PATS can help reduce the risk of re-injury, it may not significantly shorten recovery time. This limitation highlights the need for complementary strategies to optimise both prevention and rehabilitation processes.[46]

In addition to PATS, the Unexpected-Disturbance Program (UDP) has shown promising results. UDP involves exposing athletes to more challenging stimuli that engage the sensorimotor, vestibular, and proprioceptive systems, enhancing their ability to respond to unpredictable situations. Compared to conventional rehabilitation methods, UDP has been found to improve balance and unilateral strength, which are crucial for injury prevention and recovery.[47] These alternative strategies provide a multifaceted approach to injury prevention, ensuring that athletes are equipped with the physical and neuromuscular capabilities to reduce injury risks and enhance overall performance.

Sport-specific injury prevention programs have demonstrated significant efficacy in reducing injury rates and enhancing athletic performance across various disciplines. In volleyball, targeted injury prevention initiatives have shown promise in minimising injury risks among athletes. These programs typically incorporate exercises to optimise jump mechanics, strength, and flexibility-key factors in mitigating injury risks in the sport.[35] The integration of plyometric training into injury prevention programs has demonstrated notable improvements in athletic performance and injury reduction. A systematic review highlighted the benefits of combining plyometric training with balance and strengthening exercises, making it a comprehensive approach to injury prevention. [44]

In football, sport-specific interventions such as the FIFA 11+ program have been widely acknowledged for their effectiveness in injury prevention.[26] This program has been evaluated and shown to reduce injuries among

athletes, including semi-pros, amateurs, and professional athletes of both genders.[37,38] Furthermore, a systematic review identified five core strategies for injury prevention in football: pre-activation exercises, foam rolling, strength training, the FIFA 11+ program, and core stability training.[11]

Similarly, netball has benefited from tailored programs such as the Down to Earth (D2E) initiative, emphasising safe landing techniques during training. Safe landing mechanics are crucial in netball, as jumping and landing are frequent actions with a high risk of lower-limb injuries. This program has been particularly effective in reducing injury risks during both training and competition.[45] These sport-specific programs demonstrate the importance of tailored approaches to injury prevention. Addressing each sport's unique demands and movement patterns provides targeted strategies to reduce injuries and enhance athletic performance.

Injury prevention programs can be broadly categorised into general and sport-specific injury prevention strategies. Both approaches are essential for reducing the risk of injuries in athletes, but they differ in their scope, target population, and application. In Malaysia, these strategies are applied based on the population's needs, with general programs being more common in recreational and grassroots sports and sport-specific programs being implemented at the elite and competitive levels.[30,36] The implementation of injury prevention programs faces various challenges, including perceived barriers such as the potential cost of implementation, coaches' lack of knowledge and confidence to implement, perceived time burden, lack of importance placed on the program, confusing exercises, lack of motivation and flexibility of the program especially among different skills level athletes. [29,31,33,34] Addressing these issues by improving resource availability and enhancing coach training and awareness, Malaysia can further strengthen its approach to injury prevention, ensuring better safety and performance for its athletes.

In this review, one of the limitations identified was the small number of studies that met the inclusion criteria, with only nine studies being selected. This limitation arose from the specific focus of the criteria, which only included studies with athlete participants and articles published in the last decade to ensure relevance to current practices in injury prevention programs in Malaysia. Additionally, prospective injury prevention studies face several challenges, such as high financial costs, the need for lengthy training durations, and the requirement for skilled and competent coaches to implement the programs effectively.[22,23] These constraints can limit the feasibility and scalability of injury prevention programs, highlighting the need for further research to overcome these barriers while maintaining cost-effectiveness and broad applicability.

Another limitation of this review is that half of the relevant articles did not specify the type of sports in which the athletes participated. The lack of sport-specific information may hinder the ability to tailor injury prevention programs to match different sports' specific demands and risks. Research has shown that training programs designed to mirror the characteristics of competitive sports can effectively reduce injury risks while improving overall physical performance.[14,48] Furthermore, many studies included in this review involved fewer than 20 participants, raising concerns about the results' statistical power. A small sample size may not provide enough power to detect meaningful differences between groups, potentially leading to false negative results and Type II errors, as noted in prior research on statistical validity.[49] Nonetheless, the prospective nature of the studies ensures a more accurate representation of how injury prevention programs influence athletes over time.[50]

CONCLUSIONS

An injury prevention program has demonstrated promising results in minimising injuries and enhancing overall physical performance among athletes. Many of the studies adopted on neuromuscular training and general injury prevention programs, including the Unexpected Disturbance Program (UDP), Progressive Agility, Trunk Stabilisation (PATS), and sport-specific programs such as volleyball (plyometric training), football-specific training,

and netball (Down to Earth). These programs are typically conducted twice a week for six weeks, with 15–30 minutes per session, to improve strength, flexibility, balance, and neuromuscular control, which are critical factors in reducing injury risk. It is recommended that injury prevention programs be adopted in every sport, especially during warm-up periods of training sessions. Additionally, future research could focus on developing tailored exercise programs based on individual unique risk factors and incorporating technology to provide real-time feedback and enhance monitoring of injury prevention efforts. These advances could significantly improve the effectiveness of injury prevention strategies for athletes.

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Authors' contributions

M.I.S – Conceptualization, Methodology, Data Curation and Writing - Original Draft
H.A.Y – Validation, Writing - Review & Editing, Supervision and Project administration

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REVIEW ARTICLE

Barriers to Physical Activity Among Stroke Survivors: A Scoping Review

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ABSTRACT

Barriers to physical activity (PA) experienced by stroke survivors may contribute to low PA participation. This review aims to update the existing review report on barriers to PA among stroke survivors. We conducted electronic searches across three databases (PubMed, Scopus, and Web of Science) between January 2011 and January 2023. Keywords related to barriers, physical activity, and stroke survivors were used to identify relevant studies. Eighteen studies were included. The identified barriers to PA among stroke survivors were physical impairments, fatigue, and issues with training venues and facilities. These barriers were categorized using the Theory Domain Framework, revealing nine domains, with environmental context and resources being the most common. Clinicians can develop individualized programs to address barriers, improving adherence to PA among stroke survivors and contributing to a better quality of life while reducing the risk of stroke recurrence.

INTRODUCTION

Stroke causes 143 million disability-adjusted life years (DALYs).[1] The majority of stroke survivors experience a disability that results in deconditioning, reduced fitness, and decreased functional capacity.[2,3] Complications such as muscle weakness, spasticity, and a lack of cardiovascular fitness contribute to the decline.[4] In recent studies, stroke survivors are 75% sedentary and engage in low physical activity (PA), averaging 1389 to 7379 steps per day, which is below recommended levels.[5–7] This sedentary lifestyle can lead to secondary health problems such as cardiovascular disease, obesity, and diabetes. As a result, enhancing PA is critical for improving stroke survivors' health and quality of life.

PA is an umbrella term for functional activities and community participation.[8] PA and exercise have been proven to be effective in enhancing physical fitness and functional capacity in stroke. The American Heart Association/American Stroke Association suggests at least 150 minutes of moderate-intensity aerobic activity each week, as well as strength, neuromuscular, and flexibility exercises 2-3 times per week.[3,9] This recommendation is supported by a systematic review conducted by Saunders et al. (2016), which found that physical fitness training for stroke increased cardiovascular fitness, muscle strength, and walkability.[10] Promoting PA should prioritise low-to-moderate intensity aerobic activity, muscle strengthening, minimising sedentary behaviour, and risk management to avoid secondary problems. However, stroke survivors often face barriers to PA, including personal, social, and environmental factors.[11] Understanding those barriers and developing effective models of behaviour changes can help promote PA and exercise among stroke survivors.

Stroke survivors often face barriers in PA due to various factors. Those barriers include physical deconditioning, lack of motivation, fear of injury, and many more.[3] Not only that, they also might have experienced post-stroke neuropsychiatric disorders such as post-stroke depression, anxiety, and stress.[12] These problems are the common complications experienced by most stroke survivors. Additionally, stroke survivors may encounter

personal and social barriers, such as lack of social support, transportation issues, and financial constraints.[11] Those barriers can hinder stroke survivors from participating in regular PA and exercise, which are crucial for improving their well-being.

Adherence to physical activity (PA) among stroke survivors is closely linked to their behaviours. The Theory Domain Framework (TDF) integrates various psychological theories to help understand these behaviours.[13] Hence, using the TDF is a successful approach in several scenarios such as stroke survivors' behaviour towards PA. This study used the TDF to identify PA barriers because it covers a wide range of domains, including individual factors like knowledge and skills, social factors like support, and environmental factors like treatment costs. A study that was conducted to identify the barriers to PA using the TDF found that the commonly reported domains were belief about capabilities, environmental context and resources, and social influence.[13]

Barriers to PA among stroke survivors were reported by a systematic review.[14] The review results showed that the most common barriers were environmental barriers (such as access, transport, and cost), health problems, impairments, embarrassment, and fear of a stroke recurrence.[14] However, the previous review covered papers from 2006 to 2010, which may not reflect the current situation regarding the topic. Additionally, the previous review did not thoroughly examine the stroke-specific questionnaires used to identify barriers to PA among stroke survivors. [14] Therefore, this scoping review aimed to provide an update on barriers to PA among stroke survivors. This scoping review would also update practitioners' knowledge regarding the barriers commonly experienced by stroke survivors and help understand their preferences regarding PA at home.

MATERIAL AND METHODOLOGY

This review protocol was registered on the Open Science Framework (https://osf.io/wvk5g). This scoping review utilized the updated methodology presented by Peters et al. (2020).[15] No quality assessment of individual studies was required, as the review aimed to scope the barriers to PA among stroke survivors. The primary research question was, "What are the barriers to PA among stroke survivors?" The sub-questions addressed were: (i) "What are the TDF domains based on the identified barriers?" and (ii) "What are the outcome measures used to identify barriers to PA among stroke survivors?"

Electronic searches were conducted across three databases (PubMed, Scopus, and Web of Science) from January 2011 to January 2023 to identify barriers to PA among stroke survivors. Medical Subject Headings (MeSH) terms and keywords such as 'barriers', 'obstacle', 'limitations', 'physical activity', 'exercise', 'physical exercise', 'leisure time physical activity', 'stroke survivor', 'community-dwelling stroke survivor', 'individual with post-stroke, and 'post-stroke population' were employed in the search process. Boolean operators such as 'AND' and 'OR' were used to separate the keywords.

For inclusion in this review, studies should have involved stroke survivors and discussed barriers or inhibitors to PA. All types of quantitative or qualitative studies were considered, whereas review articles, opinion articles, and editorials were excluded. Studies that were not written in English were also excluded. All identified studies from the databases were imported into Mendeley, duplicates were removed, and the remaining studies were extracted into an Excel sheet for selection based on the suitability of their title and abstract according to the inclusion and exclusion criteria.

In the subsequent step, we collected full-text publications for studies that satisfied the selection criteria or could not be rejected based solely on the title and abstract. These articles were then evaluated using the selection criteria. Disagreements among reviewers were addressed through discussion and contact with a third reviewer. The selected articles were documented in a table to extract relevant data, including author(s), year of publication, country, method/study design, sample size, participant characteristics (age, gender, time since stroke, severity of stroke, diagnostic information), outcome measures of barriers to physical activity, and study results. An independent reviewer evaluated the study's findings,

while additional reviewers analyzed the extracted data to identify any problems.

This scoping review examined both qualitative and quantitative studies. Descriptive statistics was used to describe the characteristics of the studies and data. The data were then mapped into the TDF, which has 14 domains. The findings were summarised in charts and tables, with a focus on the barriers to PA among stroke survivors, the relevant TDF domains, and the outcome measures used to identify these barriers.

RESULT

A PRISMA-ScR flow diagram in Figure 1 illustrates the stages of screening and article selection. Initially, a database search yielded 793 entries, but after removing duplicates, 776 articles remained. Screening of titles and abstracts led to the exclusion of 756 studies due to irrelevant titles, unrelated objectives, or review article status. After screening full-text articles, two more articles were eliminated. Ultimately, the review included 18 articles for data extraction. Among these, 12 were quantitative[16–27], 5 were qualitative [28–32], and one mixed method[33] study design. Data from the mixed-method article were categorized based on the quantitative data and the qualitative data will be analysed separately.

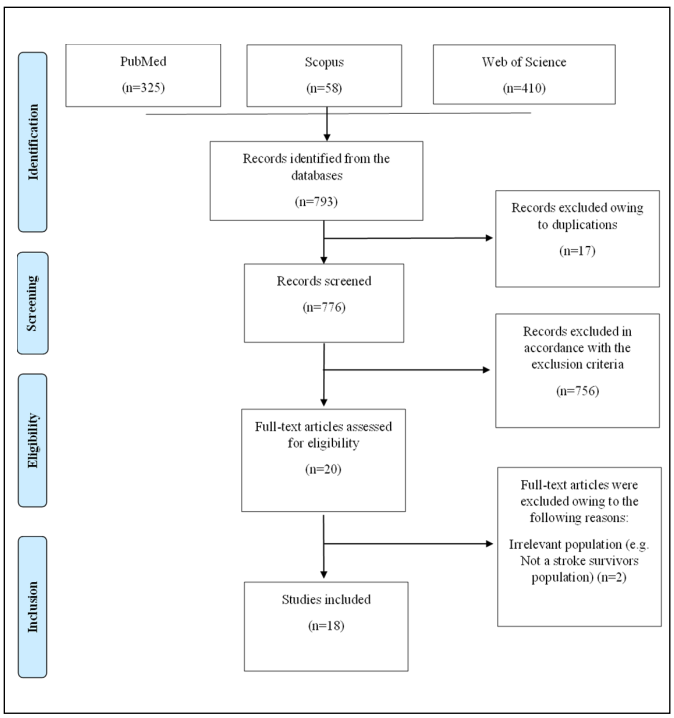

Figure 1: PRISMA-ScR flowchart of the scoping review.

Articles characteristics

Table 4 shows the characteristics of the included studies. The quantitative studies consist of a total of 1343 participants who had a stroke with 64% of them being males. Four out of 12 studies included participants who were 18 years or older[16,18,20,26] while one study included participants who were 20 years or older.[22] However, the rest of the studies did not determine the age requirement of the included sample. The duration of stroke in these studies ranged from 12 days to 7 years.

The qualitative data group of five studies included 1109 stroke survivors and the majority were also males (54.6%). Only two studies stated the age requirement of 18 years or older[32] and 20 years or older[33] while the remaining studies did not mention the age requirement. The duration of stroke for these studies was between 4 months and 8 years. Based on the regional chart in Figure 2 for all included studies, 28% of these studies were carried out in South America[18,22,24,27,29] and 28% were carried out in Europe.[16,17,28,32,33] The rest of the studies were conducted in North America (17%)[20,23,30], East Asia (11%)[19,31], Africa [21,26] and South Asia (6%).[25]

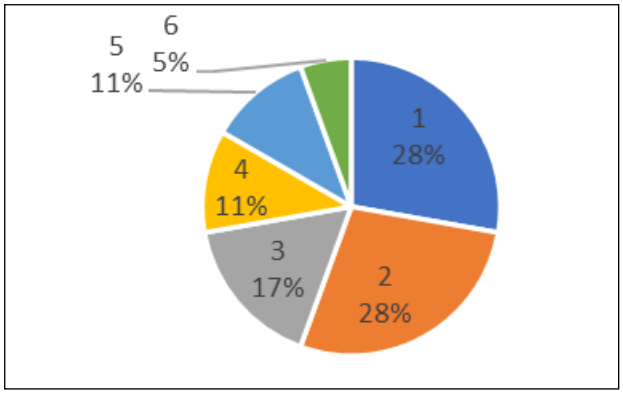

Figure 2: Distribution of studies according to geographical

From Table 4, five studies reported that the requirement to participate in the study was to be able to walk independently with or without a walking aid[16,17,24,27,28], two studies stated that the requirement to participate in the study was to have no to mild disability based on the modified Rankin Scale (mRS).[26,32] While two studies included only community walkers[22,23], and one study

included at least home walkers according to their walking speed.[18]

Barriers to physical activity

There is a total of 31 barriers were identified from the 18 studies.[17–20,22–35] These barriers are divided into internal and external barriers. Based on Table 1, the most reported group of internal barriers to PA was physical impairments such as spasticity[16–20,24,30–33] and this barrier became the most reported overall barrier. Other reported internal barriers included fatigue[17,20,22,25,32,33], fear of fall[18,20,24,25,33], cognitive and psychological issues[18,24,30,32,33], fear of injury/ damage to health[17,18,20], personal issues[18,27,28], and lacked self-confidence/ feeling embarrassed.[21,29,33] On the other hand, the least reported internal barrier was loss of independence[32,33], activity limitation[18,30], hidden disability[32], pain[18], having other medical conditions[17], communication problems[18], people with exercise clothes look funny[21], and life commitments.[18]

In addition, the most reported external barrier based on Table 2 was a lack of PA knowledge and skills[18,22–24,26,33], exercise location and facilities[18,20–22,24,30], and lack of support and motivation.[18,19,24,26,28,33] This is then followed by transportation problems[26–28,30,33], financial restrictions[16,21,27,30], unavailability of companion/lack of help[18,19,22,23], and poor weather.[18,24,33] Furthermore, the least reported external barrier was physical environment[33], delay or lack of healthcare provision[32], exercise instructors who spoke too quickly[30], negative affect[28], time restraint[18], lack of knowledge in gadgets/ internet[18], pandemic-related issues[18], policy barriers[19], and vague and complex regulations.[31]

Barrier to physical activity mapped into TDF

The identified barriers from this review were then mapped into the TDF which can be seen in Table 3. After mapping, nine domains were identified: skills, environmental context and resources, emotions, belief in capabilities, social/professional role, knowledge, social influence, memory, attention, and decision process, and behavior regulation. The most common domains mapped were environmental context and resources followed by emotion and skills. Whereas, the least common domains mapped were knowledge, social/professional role, memory, attention, and decision process, social influence, and behavioral regulation.

Table 1: Internal barriers to physical activity in stroke survivors as identified through the review

Authors / Barrier	Gagnon et al. (2022)	Débora Pacheco et al. (2021)	Sánchez-Sánchez et al. (2021)	Torriani-Pasin et al. (2021)	Nicholson et al. (2017)	Idowu et al. (2015)	Jackson et al. (2015)	Zalewski & Dvorak (2011)	Aguiar et al. (2022)	Babbar et al. (2021)	Harrison et al. (2022)	Nicholson et al. (2014)	Noukpo et al. (2023)	Simpson et al. (2011)	Zhang et al. (2018)	Blonski et al. (2014)	Jarbandhan et al. (2022)	Zhang et al. (2015)
Physical impairment (10)	√		√	√	√		√		√		√				√	√		√
Hidden disability (1)											√							
Fear of injury/ damage to health (3)	√			√	√													
Fear of fall (3)	√			√			√		√	√								
Pain (1)				√														
Other medical condition (1)					√													
Fatigue (6)	√	√			√		√			√	√							
Self-confidence/ embarrassment (3)						√	√							√				
Loss of independence (2)							√				√							
Cognitive and psychological issues (5)				√			√		√		√					√		
Personal issue (3)				√								√					√	
Communication problem (1)				√														
People with exercise clothes look funny (1)						√												
Activity limitation (2)				√												√		
Life commitment (1)				√														

Table 2: External barriers to physical activity in stroke survivors as identified through the review

Authors / Barrier	Gagu on et al. (2022)	Débora Pachec o et al. (2021)	Sánchez - Sánchez et al. (2021)	Torriani -Pasin et al. (2021)	Nichols on et al. (2017)	Idowu et al. (2015)	Jackson et al. (2015)	Zalewsk i & Dvorak (2011)	Aguiar et al. (2022)	Babbar et al. (2021)	Harriso n et al. (2022)	Nichols on et al. (2014)	Noukp o et al. (2023)	Simpso n et al. (2011)	Zhang et al. (2018)	Blouski et al. (2014)	Jarbandi han et al. (2022)	Zhang et al. (2015)
Problem with transportation (5)							√					√	√			√	√	
Lack of financial resources (4)			√			√										√	√	
Exercise location and facilities (6)	√	√		√		√			√							√		
Physical environment (1)							√											
No companion/ lack of help (4)		√		√				√										√
Lack of knowledge and skills about exercise (6)		√		√			√	√	√				√					
Delay or lack of healthcare provision (1)											√							
Lack of support and motivation (6)				√			√		√			√	√					√
Exercise instructor speak too quickly (1)																√		
Negative affect (1)												√						
Weather (3)				√			√		√									
Time restraint (1)				√														
Lack of knowledge in gadget/ internet (1)				√														
Pandemic related (1)				√														
Policy barrier (1)																		√
Vague and complex regulation (1)															√			

Table 3: Barriers to physical activity in stroke survivors according to TDF domains

No	TDF Domain	Barrier
1	Knowledge	Lack of knowledge about exercise[18,22–24,26,33]
		Lack of knowledge of gadgets/internet[18]
2	**Skills**	Physical difficulties/ impairment[16–20,24,30–33]
		Hidden disabilities[32]
		Activity limitation[18,30]
		Lack of skill and ability[33]
3	Social/Professional Role	Delay or lack of healthcare provision[32]
		Exercise instructor speaks too quickly[30]
4	Beliefs about Capabilities	Loss of independence[32,33]
		Self-confidence and embarrasment[21,29,33]
5	Optimism	No study reported
6	Belief about Consequences	No study reported
7	Reinforcement	No study reported
8	Intentions	No study reported
9	Goals	No study reported
10	Memory, Attention, and Decision Process	Cognitive and psychological issues[18,24,30,32,33]
11	**Environmental Context & Resources**	Transportation problem[26–28,30,33]
		Exercise program location and facilities[18,20–22,24,30]
		Lack of financial resources[16,21,27,30]
		Weather[18,24,33]
		Physical environment- poor maintenance of pavement[33]
		Pandemic related[18]
		Policy barrier[19]
		Communication problem[18]
		Life commitment[18]
12	Social Influence	Lack of professional support on discharge from hospital and follow-up[28]
		Exercise instructor speaks too quickly, impatience[30]
13	**Emotion**	Fatigue[17,20,22,25,32,33]
		Psychological difficulties[18,24,30,32,33]
		Lack of control[28]
		Negative affect[28]
		Fear of falling[18,20,24,25,33]
		Fear of injury/ damage health[17,18,20]
		Pain[18]
14	Behavioral Regulation	Vague and complex regulation[31]

Measurement tools

Table 4 shows that 12 studies measured barriers to PA using a questionnaire[16–27,33] while the remaining studies used an in-depth interview with an open-ended question[29,31,32] and other studies used a framework to guide the interview.[28,30,33] From that, it was found that two studies used the Exercise Benefits and Barriers Scale (EBBS)[21,22], one study used the Barrier to Being Active Quiz BBAQ)[23], one study used the Stroke Exercise Preference Inventory-13 (SEPI-13)[26] and one study used the Barrier to Physical Activity and Disability Questionnaire (BPAD).[27] Whereas, only one study used a specific questionnaire that asked about the barriers to PA specifically for stroke survivors, which is the Barrier to Physical Activity after Stroke Scale (BAPAS).[16] The remaining studies used a survey prepared based on previous studies and based on the theory-planned behavior framework to do a survey question.[18,24] Several studies used a 21-item survey[20], Mutrie scale[17], Adherence to Home Exercise Questionnaire[25], and Craig Hospital Inventory of Environmental Factors[19] ; however, those tools are not considered specific to the barriers of PA.

Table 4: Characteristics of the included study and measurement tools used

Authors	Study design	Country	Method	Participants characteristics						Outcome measure
				Total (N)	Age	Gender	Time since stroke	Ambulatory status	Diagnostic info	
Sánchez-Sánchez et al. (2021)	Quantitative Cross-sectional study	Valencia, Spain	- recruited from the Brain Injury Association, physiotherapy outpatient services, and community exercise classes. -Face-to-face assessment	57	>18 years old	37 males (64.9%)	≥6 months from stroke onset	63.2% (36)-no disability or slight 36.8% (21)-moderate or severe disability	Chronic stroke survivors (community-dwelling)	BAPAS
Nichols on et al. (2017)	Quantitative	Edinburgh & Lothians (Scotland)	- recruited from hospital acute stroke units - ready to be discharged - completed two walk tests -After that, participants were asked to rate four possible barriers based on the Mutrie Scale.	50	72.4	29 females (58%) 21 males (42%)	12.5 days	Independently ambulatory (with/without walking aid)	Combination of ischemic & and hemorrhagic	Mutrie scale

BAPAS: Barrier to physical activity after stroke scale

Table 4. Continued

Authors	Study design	Country	Methods	Participant characteristic						Outcome measures
				Total (N)	Age	Gender	Time since stroke	Ambulatory status	Diagnostic info	
Gagnon et al. (2022)	Quantitative, cross-sectional survey (online)	Quebec	-Recruit using direct email contact by researchers, stroke organizations, and healthcare professionals	29	18 years or older	15 % (4) males	At least one -year post-stroke	NA	Any type of stroke	21-item survey (5 sections): demographic information, duration, and frequency of PA, barriers, and motivators, seden-tary behavior, and walking ability
Idowu et al. (2015)	Quantitative, cross-sectional study	Nigeria (South-west)	-Recruited from neurology and physiotherapy clinic - need to answer all the questionnaires.	121	51-60 years old	70% (85) males	4.26+- 3.14 years	NA	Chronic stroke	EBBS
(Débora Pacheco et al., 2021)	A quantitative, exploratory study	Metropolitan City, Brazil	-From the stroke unit of a public hospital in a metro-politan city in Brazil	95	Above 20 years old	64.2% (61) males	4 months (0.8)	Mild disability (community walking ability status (walk at speed >0.8 m/s with or without aids measured using a 5-meter walk test)	Sub-acute stroke (between 3–6 months onset hemorrhagic or ischemic stroke)-discharged	The Brazilian version of the Exercise Benefits/ Barriers Scale (EBBS-Brazil) – only takes the barrier subscale (14 items) An open-ended question about additional barriers based on the previous study

NA: Not address; EBBS: Exercise Benefit & Barriers Scale

Table 4. Continued

Authors	Authors	Authors	Authors	Authors						Authors
				Total (N)	Age	Gender	Time since stroke	Ambulatory status	Diagnostic info	
Zalewski (2011)	Zalewski (2011)	Zalewski (2011)	Zalewski (2011)	Zalewski (2011)	Zalewski (2011)	Zalewski (2011)	Zalewski (2011)	Zalewski (2011)	Zalewski (2011)	Zalewski (2011)
Aguiar (2022)	Aguiar (2022)	Aguiar (2022)	Aguiar (2022)	Aguiar (2022)	Aguiar (2022)	Aguiar (2022)	Aguiar (2022)	Aguiar (2022)	Aguiar (2022)	Aguiar (2022)
Babbar (2021)	Babbar (2021)	Babbar (2021)	Babbar (2021)	Babbar (2021)	Babbar (2021)	Babbar (2021)	Babbar (2021)	Babbar (2021)	Babbar (2021)	Babbar (2021)

Table 4. Continued

Authors	Study design	Country	Methods	Participant characteristic						Outcome measures
				Total (N)	Age	Gender	Time since stroke	Ambulatory status	Diagnostic info	
Noukpo (2023)	Cross-sectional study (Quantitative)	Benin, a lower middle-income country	Participants were invited to the hospitals where the clinical data were collected, and the questionnaires were completed.	87	53 +- 10 years (mean) Adult >18 years old	52 men	meantime after a stroke of 11 months at least 3 months onset	(60%) were mildly disabled (score mRS ≤3)	Stroke survivors	Stroke Exercise Preference Inventory-13 (SEPI-13).
Torriani-Pasin (2021)	Longitudinal study (Quantitative)	Brazil	-Stroke patients from the community rehabilitation program in São Paulo, Brazil were invited to join the study during the COVID-19 pandemic. -Weekly phone calls assessed perceived exercise barriers using a questionnaire.	36	Above 18 years old	23 males	98 months (mean)	Walking speed >0.4 m/s (home walker)	Stroke survivors (ischemic and hemorrhagic) in the chronic phase	Two questionnaires (via weekly telephone calls) to identify attendance, barriers, safety, and overall experience related to the program. A 5-point Likert scale was applied based on the positive and negative statements
Zhang (2015)	Cross-sectional survey (quantitative)	Rural China	-Private interview -Standardized questions and response options to minimize bias.	639	69 +- 11 years Most are married (77%)	69% male (442)	>2 years	NA	Community-dwelling stroke survivors	Craig Hospital Inventory of Environmental Factors

NA: Not address

Table 4. Continued

Authors	Study design	Country	Methods	Participant characteristic						Outcome measures
				Total (N)	Age	Gender	Time since stroke	Ambulatory status	Diagnostic info	
Jarbandhan (2022)	Cross-sectional study (Quantitative)	Suriname	Recruited from the database of the Rehabilitation Centre Paramaribo and from the local community	44	Mean age: 58.2 + -10 years	21 men	The median time post-stroke was 2.5 (range 0.5-16.6) years. last stroke >6 months ago	Walk independently or with supervision (Functional Ambulation Category score ≥3)	chronic stage after stroke Stroke survivors	BPAD questionnaire
Harrison (2022)	Sequential explanatory, mixed methods study (qualitative)	England, Wales and Northern Ireland	- recruited as in-patients or at post-stroke/ TIA clinic appointments by a Stroke Research Nurse. -Baseline questionnaire completed after consent. -Follow-up questionnaires mailed by LCTU at 6 months post-stroke/TIA. -Self-completed paper questionnaires returned to LCTU	1045	74	54.5 % (569)	NA	43.6% no disability, 40.5% slight to moderate disability A pre-stroke modified Rankin Scale (mRS) score of ≤3	Those with a clinical diagnosis of new first or recurrent stroke or TIA Stroke survivors	Open-text questions were asked about barriers and facilitators when returning to, or participating in, leisure activity. Responses were thematically analyzed and explored by participant characteristics, including the type of leisure activity undertaken.

TIA: Transcient Ischemic Attack; LCTU: Lancashire Clinical Trials Unit; NA: Not address; BPAD: Barriers to Physical Activity and Disability

Table 4. Continued

Authors	Study design	Country	Methods	Participant characteristic						Outcome measures
				Total (N)	Age	Gender	Time since stroke	Ambulatory status	Diagnostic info	
Nicholson (2014)	Qualitative study (audio -recorded and tran-scribed verbatim)	Edin-burgh & Lothians (Scotland)	- conducted at the participants' homes. -Interviews were audio recorded and transcribed verbatim.	13	76 years (median age)	38.5% (5)	345 days (median time since stroke)	Able to walk independent-ly, with or without walking aids	Stroke survivor	Semi-structured interview using TDF
Simpson (2011)	Qualitative exploratory design	Columbia	- recruited from previous patients of a local rehabilitation center and through community notices. -Observer took notes and sessions were tape-recorded with participants' permission.	11	NA	8 males	Mean 8 +-3 years post-stroke At least one year post-stroke	NA	Community-dwelling stroke Living at home	Open-ended
Zhang (2018)	Qualitative content analysis	Rural China	-Stroke survivors who participated in the quantitative part of the study	18	Mean age: 69 years old All married	Male: female: 2:1 Male: 12	Since the first stroke ranged from four months to 13 years at least three months previous stroke	NA	Community-dwelling stroke survivors	In-depth interviewing in the participants' homes

NA: Not address; TDF: Theoretical Domains Framework

Table 4. Continued

Authors	Study design	Country	Methods	Participant characteristic						Outcome measures
				Total (N)	Age	Gender	Time since stroke	Ambulatory status	Diagnostic info	
Blonski (2014)	Qualitative descriptive study (Two focus groups)	Toronto, Canada	-Participants recruited from the AI in Toronto, Canada -In-depth, semi-structured face-to-face interviews conducted using SCA. -Interviews were audio recorded and transcribed verba-tim.	10	60–69 years	6 men (60%)	Median 3 years	NA	Stroke survivors (having aphasia)	In-depth, semi-structured face-to-face interviews using SCA.
Jackson (2015)	Mixed method (survey & focus group)-cohort study	South England	- identified from the database of patients admitted to the local hospital. The survey group received study packs with an invitation letter, information leaflet, questionnaire, and return envelope. -Focus group interviews conducted by principal researchers using a semi-structured format.	76 (survey) 12 (focus group)	75 years old Over 55 years of age	55.3% (49) males	42.1% - 12-23 months since stroke At least six months and not more than five years post-stroke	NA	Community-dwelling stroke survivors Living in a com-munity setting	The questionnaire was developed based on the Theory of Planned Behaviour Focus group – interview questions based on TDF

SCA: Supported Conversation for Adults with Aphasia; NA: Not address; TDF: Theoretical Domains Framework

DISCUSSION

This scoping review aimed to investigate barriers to PA among stroke survivors. The 18 reviewed studies employed different outcome measures to assess the barriers to PA, with some utilizing a qualitative approach. The barriers were then mapped into the TDF to find the main domains. Using the TDF provided this study with a strong approach to gain a comprehensive understanding of the barriers to PA among stroke survivors and identified the domains that can be targeted during the management of stroke survivors to improve their adherence to PA.

This review mapped 9 domains including skills, environmental context and resources, emotion, belief in capabilities, social/professional role, knowledge, social influence, memory, attention, and decision process and behavior regulation. Those findings underscore the importance of addressing physical impairments and providing a convenient environment and resources to increase the engagement of stroke survivors in PA.

Physical limitations are frequently mentioned as a barrier to physical activity (PA) for stroke survivors. According to prior research, these restrictions are a major source of inactivity.[16] A qualitative study revealed that even those who were physically active prior to a stroke are commonly unable to engage in physical exercise due to post-stroke physical limitations.[36] This demonstrates how physical impairments are disabling and influence adherence to PA. Approximately half of stroke survivors have motor deficiencies in their lower limbs, making it difficult to stand, walk, and climb stairs, further restricting their activity and participation.[37]

Stroke survivors also reported fatigue as a barrier to PA in this review.[17,20,22,25,32,33] A recent study confirmed that fatigue symptoms can limit PA in stroke survivors.[38] Furthermore, in a systematic review of longitudinal studies, fatigue frequency was found to range from 35% to 92% and can persist for at least 36 months after stroke.[39] This demonstrates that most stroke survivors experience fatigue, which limits their participation in PA and lowers their quality of life. Healthcare practitioners should recognize this symptom and customize exercise programs to patients' capacity and fatigue severity.

Stroke survivors have significant barriers to exercise, including location and facilities. This is consistent with a prior study, which identified environmental barriers including transportation as the most commonly reported barrier.[14] This is frequently due to insufficient public transit services and facilities for people with impairments, particularly in developing countries. Although some countries have provided special accommodations for disabled people, access remains limited.[40] Stroke survivors often have limited access to exercise facilities, particularly gyms, which are frequently on upper floors and require stair climbing—a difficult chore due to lower extremity limitations and exhaustion.[41] As a result, these barriers reduce stroke survivors' access to exercise facilities, leading to their inactivity.

Furthermore, this review also identified a lack of knowledge and skills as a barrier to PA. Many participants were unaware of the benefits of exercise for their functional abilities, as well as proper exercise techniques. Raising awareness among stroke survivors about the benefits of exercise is critical for avoiding consequences such as muscle atrophy, balance difficulties, falls, decreased cardiovascular fitness, and a deterioration in quality of life.[42] This barrier falls under the "skills" domain of the TDF, emphasizing the significance of physiotherapists having sufficient knowledge and awareness to assist stroke survivors in adhering to their exercise programs.

In addition, the lack of support and motivation was also one of the cited barriers in this review, which is consistent with the results of the systematic review conducted on stroke survivors.[14] According to AHA, one of the reasons for inactivity in stroke survivors is the lack of motivation and family and social support, which negatively affect their adherence to recommended PA.[3] Hall et al. (2020) reported that support from caregivers or family members when performing PA would increase stroke survivors' engagement.[43] Most stroke survivors also have psychological problems, such as being depressed and unmotivated to perform their regular

activities due to their impairments. Therefore, social support, especially from family members or spouse is essential in their functional recovery after stroke.[44]

Having physical impairments would lead to the psychological concern of fear of falling as one of the barriers to perform PA. Fear of falling can be a secondary complication of physical impairments experienced by stroke survivors and a previous fall which led to the risk of falls. This is shown by a study that found about one-quarter of stroke survivors suffer from balance disorders after discharge.[45] Stroke survivors might have a feeling of instability during walking, which may exacerbate their fear of falling and restrict their walking activity.[46] In addition to that, fear of falling among stroke survivors can also be induced by the perception and psychological influence resulting from previous falls.[47] Therefore, stroke survivors limit their activities and restrict their participation due to their fear avoidance beliefs.

In this review, we integrated the TDF in categorizing the barriers to identify its domains that might influence the behaviors of stroke survivors in performing their PA. The most common mapped domain using the TDF in this review was the environmental context and resources. This finding emphasizes the importance of the physical environment and available resources in shaping the behaviors of stroke survivors. Environmental context and resources were found the most important domain in one of the qualitative studies that identified barriers to PA in stroke survivors.[28] This indicates that one of the healthcare providers' aims should focus on improving the environment or allocating resources of exercise locations to stroke survivors.

Emotion was the second most common domain mapped in this review. Emotional states have a substantial impact on behavior modification, especially since many stroke survivors suffer from emotional disorders as a result of limitations in daily activities and job loss, which can reduce income and exacerbate mental distress. A 2021 study discovered a link between anxiety and mobility, with higher anxiety levels associated with larger mobility limits. The same study found that stroke survivors were at high risk of anxiety and depression.[12] Based on this review, psychological and emotional issues would influence their adherence rate to PA. As a result, recognizing and controlling emotional components is crucial for developing treatment regimens that meet these concerns and increase stroke survivors' adherence to PA.

The variability in the barriers reported in this review is related to the heterogeneity in the outcome measure used to assess barriers to PA. Some studies employed generic questionnaires, such as the Barrier Being Active Questionnaire (BBAQ) and the Exercise Benefit Barrier Scale (EBBS), while others conducted interviews, yielding a diverse set of results. The heterogeneity of selecting measuring instruments influenced the comparability of research findings. In this review, only one study employed a specific questionnaire, the Barriers to Physical Activity After Stroke Scale (BAPAS), which was recently created and validated for stroke survivors.[48] As a result, it is not yet widely used in most studies to identify barriers to PA among stroke survivors.

The strengths of the scoping review are its systematic and transparent approach, the adherence to the PRISMA-ScR guidelines, and the inclusion of studies from various geographic regions. By conducting an extensive search of electronic databases and applying stringent inclusion criteria, the review encompassed a wide range of studies, enabling a comprehensive investigation of barriers to PA in stroke survivors. Additionally, the review provides a comprehensive understanding of barriers from many perspectives by incorporating both quantitative and qualitative data.

Despite its benefits, this scoping review also has some limitations. It focused solely on barriers to PA in stroke survivors, not facilitators or strategies for overcoming these barriers. Future studies should look into ways to overcome these barriers and increase PA engagement. Furthermore, the majority of research examined were from Europe, North and South America, with fewer from Asia and Africa, limiting the generalizability of the findings. Future studies should include more varied groups to capture a broader spectrum of viewpoints. Finally, the outcome measures utilized to quantify PA barriers differed and were not specific to stroke survivors,

resulting in various findings. Standardizing these outcome measures would increase the consistency and comparability of future studies.

CONCLUSION

In summary, this scoping review provides an overview of updated barriers to PA in stroke survivors. The incorporation of the TDF into this scoping review provided a useful perspective for investigating the challenges of behavior change. The identification of barriers to PA faced by stroke survivors and the affected TDF domains may assist physiotherapists in the development of interventions and strategies that promote PA in this population. Future research should focus on evaluating the effectiveness of targeted tailored interventions to address these barriers and enhance adherence to PA in this population.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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REVIEW ARTICLE

High-Intensity Interval Training as A Game-Changer in Type 2 Diabetes Mellitus Management: A Narrative Review

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ABSTRACT

Diabetes mellitus (DM) is a chronic health condition that affects millions of people worldwide. Diabetes mellitus is characterized by high blood sugar or glucose levels due to the body's inability to produce or use insulin, a hormone that regulates blood sugar levels. Type 2 diabetes mellitus (Type 2 DM) is the most common form of diabetes, accounting for up to 90% of all cases, and is often linked to lifestyle factors such as poor diet, lack of exercise, and obesity. Physical activity is a highly effective intervention for managing and preventing Type 2 DM. Exercise helps to lower blood sugar levels, improve insulin sensitivity, and promote weight loss. High-intensity interval training (HIIT) is a specific type of exercise that involves short bursts of intense activity followed by periods of rest or low-intensity exercise. HIIT has been found to be particularly effective for patients with Type 2 DM, as it can improve glucose control and cardiovascular health in a relatively short amount of time. This review delves into the role of HIIT in managing Type 2 DM, highlighting its ability to increase insulin sensitivity through processes such as GLUT 4 translocation, mitochondrial activity, and vasodilator function, as well as improving glycaemic control by increasing aerobic capacity and the activity of mitochondria. By synthesizing recent research, we aimed to provide insights in a narrative review of the benefits and mechanisms of HIIT for managing Type 2 DM.

Keywords
exercise, high-intensity interval training, musculoskeletal physiological phenomena, noninsulin-dependent diabetes mellitus, physical conditioning

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INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic condition that causes blood sugar levels to rise above normal values. There are two types of DM: type 1 diabetes (DM), which results from damage to pancreatic cells, and Type 2 DM, caused by diminished insulin sensitivity in the peripheral system. Other types of diabetes include monogenic and gestational diabetes.[1] Type 2 DM is a significant global health issue because it can lead to microvascular and macrovascular complications, which can increase morbidity rates, reduce quality of life, and raise mortality rates. Additionally, complications due to DM also escalate the cost of managing the condition, making it a substantial health concern that requires significant financial resources.[2]

Research suggests that DM will has a significant impact on the world's adult population, with an estimated 537 million affected between the ages of 20 and 79 years in 2021. This number is predicted to rise to 643 million (11.3%) by 2030 and 783 million (12.2%) by 2045.[3] In Indonesia, the 2018 Riskesdas report found that around 2% of the population aged 15 years and above suffer from DM, an increase from the 2013 report. Type 2 DM accounts for 90-95% of all DM cases, and a leading risk factor is the lack of physical exercise.[4]

The implementation of holistic care programs and spiritual care programs, can be beneficial for diabetic patients, improving their well-being and quality of life.[5] Particularly, individuals diagnosed with Type 2 DM can greatly benefit from engaging in physical activity, as it can lead to improved glycaemic control and insulin levels.[6] However, adhering to recommended exercise routines can be challenging due to limited available time for diabetic

persons.[2]

High-intensity interval training (HIIT) is a popular exercise method that involves short bursts of intense activity followed by brief rest periods, performed multiple times.[2,6] Compared to continuous moderate-intensity exercise (MICT), HIIT requires less time and is thus a preferred option by many.[2] Research has suggested that HIIT can enhance glycaemic control (measured by glycated haemoglobin or HbA1C), insulin sensitivity, and cardiorespiratory fitness in individuals with Type 2 DM. This means that HIIT could be a practical alternative for those with Type 2 DM who have limited time for longer exercise regimens. The purpose of this review is to delve into the molecular mechanisms underlying the benefits of HIIT for individuals with Type 2 DM.

METHODOLOGY

This study employs a narrative literature review approach to examine the effects of HIIT on the management of Type 2 DM. Literature searches were conducted using scientific databases such as PubMed and Google Scholar, utilizing keywords including "High-Intensity Interval Training," "HIIT," "Type 2 Diabetes Mellitus," "exercise intervention," and "metabolic control." The articles selected for this review used specific inclusion criteria: they were published within the last 10 years, written in English, and addressed the relationship between HIIT and Type 2 DM, with a particular focus on physiological mechanisms, clinical outcomes, and metabolic benefits. Studies that utilized different methodologies were excluded from consideration. The selection process involved the screening of titles, abstracts, and full texts. Key findings were organized into themes such as glycaemic control and enhanced insulin sensitivity. A thorough critical analysis of all relevant articles was conducted to underscore the potential impact of HIIT as a viable intervention for the management of Type 2 DM.

TYPE 2 DIABETES MELLITUS

Type 2 DM, also referred to as non-insulin-dependent diabetes mellitus (NIDDM), is a condition that impacts the body's physiological processes. It arises from a combination of genetic, metabolic, and environmental factors.[7–9] Of these factors, modifiable risks such as obesity, low physical activity, and unhealthy dietary habits are believed to heighten the possibility of developing type 2 DM. Therefore, taking steps to modify these risks could potentially prevent the onset of type 2 DM.[9]

Type 2 DM stems from an interruption in the feedback loop between insulin action and secretion. This disruption is brought about by malfunctioning pancreatic β cells, which results in inadequate insulin secretion. Consequently, the body fails to regulate glucose levels in the bloodstream effectively. Moreover, this condition is correlated with insulin resistance, which diminishes insulin sensitivity in peripheral tissues like muscle, liver, and adipose tissue.[7,8]

At the onset of Type 2 DM, insulin sensitivity declines, prompting the pancreas to augment insulin production. However, over time, the produced insulin becomes insufficient to regulate glucose levels effectively, resulting in pancreatic β cell dysfunction and insulin resistance.[7] This, in turn, leads to hyperglycaemia, ultimately culminating in the development of Type 2 DM.[9]

HIGH-INTENSITY INTERVAL TRAINING (HIIT)

High-intensity interval training (HIIT) is a form of physical exercise that involves alternating between short bursts of intense exercise and periods of rest or low-intensity exercise. The intensity of the workout is based on factors such as maximal oxygen uptake (VO2max), maximal heart rate (HRmax), maximal run velocity, peak power output (PPO), or ratings of perceived exertion (RPE). High intensity is typically defined as exercising at close to maximum capacity, usually around 80-85% of HRmax. HIIT can take various forms, including running, cycling, rowing, swimming, or full-body workouts.[10]

To incorporate a HIIT workout into a routine, one should begin with a 4–5-minute warm-up at the same level of intensity as the cool-down period. Then, proceed to the main activity, consisting of 4-8 challenging physical exercises performed at a high intensity in a brief timeframe. Finally, cool down for a total of less than 30 minutes. Depending on the length of the workout, HIIT

can be classified into three types - high-volume HIIT (HV-HIIT), moderate-volume HIIT (MV-HIIT), and low-volume HIIT (LV-HIIT). HV-HIIT is utilized for HIIT protocols requiring 15 minutes of work, MV-HIIT is used for protocols with 5-15 minutes of work, and LV-HIIT is used for protocols with only 5 minutes of work.[10]

Extensive meta-analysis studies have revealed HIIT produces more positive results compared to Moderate-Intensity Continuous Training (MICT). These benefits encompass enhancements in cardiorespiratory fitness, physical performance, body composition, and lower risk factors for cardiometabolic disease.[11,12] Additionally, scientific evidence suggests that HIIT significantly amplifies insulin sensitivity and glycaemic control in both healthy individuals and those with Type 2 DM, surpassing the effects of MICT.[11]

THE ROLE OF HIIT IN IMPROVING INSULIN SENSITIVITY AMONG TYPE 2 DM PATIENTS

Insulin is a hormone that is naturally produced by the pancreas in response to an increase in glucose levels in the bloodstream after eating. Its main function is to help increase glucose uptake in peripheral tissues such as skeletal muscle, adipose tissue, and the liver while also regulating glucose production in the liver. If there is a significant disruption in insulin activity within the body, it can lead to a decrease in insulin sensitivity.[10] To determine insulin sensitivity, there are several methods available, such as measuring fasting insulin concentration, conducting oral glucose tolerance testing (OGTT), performing hyperinsulinaemic-euglycaemic clamp or hyperglycaemic clamp tests, using the homeostatic model assessment of insulin resistance (HOMA-IR) or HOMA-β, or utilizing the quantitative insulin sensitivity check index (QUICKI).[13]

Multiple research studies have indicated that HIIT can have a positive impact on individuals with Type 2 DM. Compared to MICT or a sedentary lifestyle, HIIT has been shown to increase insulin sensitivity and decrease fasting insulin concentrations. In addition, HIIT has the potential to improve HOMA-IR and HOMA-β% values, especially in individuals with Type 2 DM who also have obesity.[10] For example, a previous study discovered a significant decrease in HOMA-IR values in Type 2 DM patients who engaged in HIIT for eight weeks, as opposed to individuals who did MICT.[14] A systematic review also demonstrated a reduction in HOMA-IR values for Type 2 DM patients who participated in Low-Volume HIIT (LV-HIIT). However, there were no significant differences in fasting insulin concentrations between Type 2 DM patients who performed LV-HIIT and the control group.[15]

Research has found that Type 2 DM patients who engage HIIT experience a boost in insulin sensitivity. This improvement can be attributed to a range of molecular mechanisms that are activated in response to HIIT, such as heightened translocation of glucose transporter 4 (GLUT 4), enhanced mitochondrial activity, and increased vasodilator function and blood flow to the muscles. These discoveries are highly noteworthy and indicate that HIIT could potentially serve as a valuable means of enhancing insulin sensitivity in individuals with Type 2 DM.[10]

Increased Translocation of Glucose Transporter 4 (GLUT 4)

Glucose enters peripheral tissues through two pathways: insulin-dependent and insulin-independent. The insulin-dependent pathway involves insulin binding to its receptor, while the insulin-independent pathway uses AMP-activated protein kinase (AMPK) and calcium/calmodulin-dependent protein kinase (CaMKK). Understanding the insulin-independent pathway helps us appreciate the benefits of physical exercise in controlling glucose balance and preventing diabetes. The uptake of glucose in skeletal muscle heavily depends on the presence of GLUT-4 in the cell membrane.[13,16] Typically, during periods of rest, most of the GLUT-4 molecules remain stored within vesicles situated inside the cell. However, upon receiving a signal, these vesicles will release GLUT-4 into the cell membrane, thus enabling glucose uptake. Hence, insulin availability plays a crucial part in glucose uptake while the body is at rest.[16]

GLUT-4 presence in muscle cells depends on transport efficiency. Insulin surge stimulates membrane transport,

while muscle contraction increases and reduces transport to and from vesicles. This increases GLUT-4 availability in the membrane and T-tubules of skeletal muscle cells. During physical activity, increased blood flow to muscles causes vasodilation and expands the surface area for glucose absorption. Muscle contractions activate specific proteins that prompt GLUT-4 translocation, leading to an increase in glucose uptake and metabolism.[16]

HIIT requires a significant amount of energy, leading to an increase in the ADP/ATP and AMP/ATP ratio. This, in turn, causes the phosphorylation of liver kinase B1 (LKB1), activating AMPK.[16,17] Numerous research studies have shown that the intensity and duration of physical exercise positively correlate with AMPK phosphorylation.[17] Once activated, AMPK phosphorylates several enzymes involved in lipid regulation, protein metabolism, and glucose transport, including TBC1D1. Phosphorylation of TBC1D1 renders it inactive, allowing GTP to react with the Rab protein present in GLUT-4 vesicles, thereby increasing GLUT-4 translocation and availability in cell membranes. This process enhances glucose uptake and insulin sensitivity.[13,16–18]

Increased Mitochondrial Activity

Type 2 DM can be caused by mitochondrial dysfunction, which is linked to insulin resistance. Reactive oxygen species (ROS) accumulation triggers this dysfunction, which can interfere with the insulin signalling pathway. The body activates mitophagy to eliminate damaged mitochondria or cause cellular stress, leading to apoptosis.[9] Cells contain organelles called mitochondria that are commonly referred to as energy stores or powerhouses. This is because mitochondria facilitate the oxidative phosphorylation process that generates ATP, an essential energy source for various cellular functions. Mitochondrial biogenesis is regulated by proliferator-activated receptor gamma coactivator 1a (PGC-1a), which activates transcription factors such as mitochondrial transcription factor A (TFAM) and nuclear respiratory factors (NRFs) by binding to them.[19,20]

Previous research indicated that physical exercise is capable of activating PCG-1a. After just one HIIT session, an increase in PGC-1a mRNA expression and other proteins associated with mitochondrial biogenesis was observed in human skeletal muscle. Similar studies have also demonstrated increased PGC-1a mRNA expression in human skeletal muscle three hours after one HIIT session.[20] These findings suggest that HIIT can promote mitochondrial biogenesis by enhancing PGC-1a expression, which may contribute to improved insulin sensitivity.

During HIIT, the skeletal muscles require a significant amount of energy for contraction. This energy demand leads to an increased need for Adenosine Triphosphate (ATP), resulting in elevated levels of Adenosine Monophosphate (AMP). This increase in AMP triggers the activation of AMP-activated protein kinase (AMPK), which is associated with improved mitochondrial number and function.[17,19,20] HIIT also promotes the release of Calcium (Ca2+) from the sarcoplasmic reticulum and the formation of Reactive Oxygen Species (ROS). The rise in ROS levels due to physical activity augments the activity of mitogen-activated protein kinase 38 (p38MAPK).[17,19] This, in turn, activates Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1 (PGC-1), either directly or indirectly. PGC-1 activation occurs through phosphorylation, deacetylation, and/or regulation of PGC -1 expression, ultimately resulting in improved mitochondrial number and function.[17,19,20]

Increased Vasodilator Function of Blood Flow to Muscles

Insulin and its receptor, IRS-1, activate two signalling pathways. The phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) pathway promotes anti-atherogenic and vasodilator signalling, while the Ras/MAPK/Edothelin-1 (ET-1) pathway stimulates pro-atherogenic and vasoconstrictor signalling. When insulin resistance occurs, it diminishes the signalling along the PI3K/Protein Kinase B (Akt)/Nitric Oxide (NO). pathway and increases the signalling along the MAPK/ET-1 pathway, or maintains the signalling pathway unchanged. This sets off an atherogenic and vasoconstrictor process, which subsequently leads to decreased blood flow to the skeletal

muscles.[21]

Studies have shown that engaging in physical exercise can enhance blood flow to the muscles that are being worked.[10,21] The degree of this blood flow increase is directly linked to the intensity of the physical activity. As the physical exercise becomes more intense, the blood flow to the muscles being worked also increases. The distribution of this blood flow is determined by the specific muscles that are being contracted during the exercise. When maximum physical activity is reached, blood flow to the muscles can increase by as much as ten times compared to when the body is at rest. This is because muscle fibres that are subjected to increased activity during exercise undergo an elevation in vascular shear stress, which is the frictional force that occurs between the blood and the walls of blood vessels.[21]

The act of contracting our skeletal muscles initiates a response in the endothelial cells that line our blood vessels. This response then prompts the activation of a signalling pathway known as the PI3K/Akt/NO pathway, which is sensitive to mechanical changes. As a result of this activation, there is an increase in the vasodilator function of blood vessels, thereby facilitating an improved flow of glucose to muscle cells.[21] This increase in glucose flow is thought to enhance insulin sensitivity and improve HOMA-IR values, ultimately leading to better health outcomes.[10]

THE ROLE OF HIIT IN MARKERS OF GLYCEMIC CONTROL IN TYPE 2 DM PATIENTS

The term glycaemic control pertains to maintaining a healthy glucose level in the bloodstream of individuals with diabetes. This can be gauged using three factors: HbA1C, fasting blood glucose concentration, and postprandial glucose concentration. Among these, HbA1C is considered the most reliable indicator of glycaemic control. When glycaemic control is inadequate, it heightens the likelihood of complications associated with Type 2 DM, which can adversely affect a patient's well-being and reduce their lifespan.[22]

The values of HbA1C can be utilized to evaluate glycaemic control over a long period. For individuals with Type 2 DM, higher levels of HbA1C are associated with decreased mitochondrial and skeletal muscle activity. One effective method of decreasing HbA1C levels in Type 2 DM patients is through HIIT. Research conducted by Elsisi et al. in 2020 found that patients with Type 2 DM who participated in HIIT for 12 weeks experienced significantly lower HbA1C levels compared to those who engaged in MICT.[10] Additionally, a systematic review by Peng et al. in 2023 demonstrated a reduction in HbA1C levels among Type 2 DM patients who performed LV-HIIT when compared to the control group.

According to recent research, there exists a positive connection between a rise in aerobic capacity, like VO2 max, and shifts in HbA1C levels post-HIIT. During physical activity, an upsurge in aerobic capacity is linked to heightened oxidative capacity and the quantity of mitochondria in skeletal muscle. HIIT triggers specific proteins that aid mitochondrial biogenesis, thus stimulating PCG-1α and amplifying the process of mitochondrial biogenesis and activity.[17,19,20] As a result, individuals with Type 2 DM who participate in HIIT can experience an increase in the number, function, and activity of mitochondria, which can lead to an improvement in both aerobic capacity and HbA1C levels.[10]

METABOLIC BENEFITS OF HIIT IN T2DM

High-intensity interval training (HIIT) is recognized for its benefits in glycaemic control and positively affects various metabolic features in individuals with Type 2 DM. Previous studies demonstrated that HIIT provides more effective improvements in anthropometric measures and cardiorespiratory health in Type 2 DM patients compared to control groups, MICT, and low-intensity training (LIT) groups.[12] It also improved lipid profiles by lowering triglyceride levels and increasing high-density lipoprotein (HDL) cholesterol, crucial for cardiovascular health.[23]

Additionally, HIIT is linked to reduced blood pressure, enhancing several aspects of metabolic syndrome in Type 2 DM patients.[24] Regular HIIT not only potentially lowers blood pressure but also improves endothelial function and

vascular health, essential for reducing cardiovascular risk. Overall, these findings suggest that HIIT is an effective intervention for improving multiple dimensions of metabolic health in individuals with Type 2 DM.

CONCLUSION

In the treatment of Type 2 DM patients, regular physical exercise can be a highly effective intervention. Among the various forms of physical activity, High-Intensity Interval Training (HIIT) has emerged as a particularly beneficial option, earning its status as "the game-changer" in Type 2 DM management. This designation is warranted due to its exceptional capability to deliver substantial health benefits in a shorter time frame compared to conventional exercise regimens. Studies shown that High-Intensity Interval Training (HIIT) significantly enhances insulin sensitivity by facilitating the translocation of GLUT-4 proteins to muscle cell membranes, which allows for effective glucose uptake. Additionally, HIIT activates PGC-1α and AMPK, improving mitochondrial function and addressing insulin resistance. Moreover, HIIT enhances vascular function and boosts blood flow to active muscles, optimizing glucose delivery during exercise. Studies have shown that HIIT yields greater improvements in glycaemic markers, such as HbA1c and fasting glucose levels, compared to Moderate-Intensity Continuous Training (MICT). This emphasizes HIIT's effectiveness in regulating glucose levels and mitigating the risk of related complications. By utilizing HIIT, healthcare providers can offer an innovative and effective strategy that addresses both metabolic health and patient adherence, ultimately transforming the landscape of Type 2 DM management - being the "game changer".

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CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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ORIGINAL ARTICLE

Diagnostic Accuracy of Fine Needle Aspiration Cytology of Thyroid in Hospital Sultanah Nur Zahirah, Malaysia

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ABSTRACT

INTRODUCTION: Fine Needle Aspiration Cytology (FNAC) is widely used as an initial screening method in the preoperative examination of thyroid lesions. However, diagnostic cytology interpretation remains inconsistent among reporting pathologists worldwide. This study aimed to determine the diagnostic accuracy of FNAC of thyroid lesions at Hospital Sultanah Nur Zahirah (HSNZ), a tertiary hospital in Kuala Terengganu, Malaysia. **MATERIAL AND METHODS:** We conducted a retrospective cross -sectional study at the Department of Pathology, HSNZ, from January 2017 to December 2019. Data of patients were collected from the Laboratory Information System (LIS) and Hospital Information System (HIS). The study included patients with thyroid lesions who underwent both FNAC and subsequent histopathological examination (HPE). **RESULT:** A total of 389 cases of thyroid lesions underwent FNAC, with 162 cases proceeding to surgical resection. The median age of the patients was 43.3 years, with a male to female ratio of 1:5.3. FNAC diagnoses were categorized as follows: 85 cases (52.5%) were benign, 23 (14.2%) as atypia or follicular lesion of undetermined significance, 9 (5.6%) as follicular neoplasm, 21 (13%) as suspicious for malignancy, and 12 (7.4%) as malignant and unsatisfactory. The diagnostic accuracy of FNAC was 85.8%, with sensitivity of 66.7% and specificity of 96.2%. The positive predictive value was 90.5%, and the negative predictive value was 84.2%. **CONCLUSION:** FNAC has proven to be an accurate diagnostic method for screening thyroid lesions. However, continuous improvement in sampling and preparation techniques and cytopathologist training is necessary to enhance its reliability further.

Keywords
Thyroid, Fine Needle Aspiration cytology (FNAC), Bethesda system

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INTRODUCTION

Fine Needle Aspiration Cytology (FNAC) of the thyroid is widely recognized for its simplicity and cost-effectiveness in initial evaluation of thyroid nodules. However, the interpretation of FNAC results presents significant challenges, primarily due to its dependence on operator skill and the substantial experience of doctors required for accurate diagnosis.

The principal difficulty of FNAC of thyroid interpretation lies is differentiating between the relatively uncommon malignant lesions and the more prevalent benign thyroid conditions. Obtaining a definitive pre-operative tissue diagnosis through FNAC is crucial for several reasons. When a benign lesion is indicated, it helps avoid unnecessary surgical interventions. This allows for the implementation of conservative management approaches when appropriate. In cases of malignancy, FNAC facilitates the planning of suitable surgical procedures and enables informed patients counseling.[1]

In 2007, the National Cancer Institute (NCI) Thyroid Fine Needle Aspiration State of the Science meeting in United States of America?, which led to the development and subsequent adoption of the Bethesda System for Reporting Thyroid Cytopathology (BSRTC). This standardized reporting system aimed to improve the consistency and accuracy of FNAC of thyroid interpretation across institution.[2] Despite these

advancement, the evolution of diagnostic accuracy for FNAC of the thyroid over the recent decades remains a subject of debate. Previous studies have reported wide ranges in diagnostic accuracy; sensitivity range between 60% to 97% and specificity between 73% to 99%. The discrepancies are largely attributed to variations in study inclusion criteria and differing definitions of sensitivity and specificity.[3–7] Given the persistent uncertainties related to FNAC of thyroid, this study aims to evaluate the diagnostic performance of FNAC in classifying thyroid nodules. The approach in in this study involves a comparative analysis of BSRTC categorizations with the gold standard histopathological examination (HPE) results obtained from surgically excised nodules. This study seeks to contribute to the ongoing refinement of thyroid nodule diagnosis and management strategies.

MATERIAL AND METHODS

Cases and sample selection

This retrospective cross-sectional study was conducted at the Department of Pathology, Hospital Sultanah Nur Zahirah (HSNZ), a tertiary hospital in Kuala Terengganu, Malaysia. The study period spanned from January 1, 2017, to December 31, 2019.

Prior to the commencement of the study, ethics committee approval was obtained from our institution's ethics committee (protocol number: USM/JEPeM/19120975).

We examined a total of 162 thyroid cases for which both preoperative cytology findings and subsequent post-surgical histological diagnoses were available in HSNZ. Data of cases data were extracted from two primary sources: Laboratory Information System (LIS) and Hospital Information System (HIS).

Patients who met the inclusion criteria were those that had histopathological confirmation and accessible preoperative FNAC results within the study period. Exclusion criteria were cases with unavailable FNAC or histopathological reports, referral cases to HSNZ with incomplete documentation, and cases with missing FNAC or histopathological examination (HPE) slides. Clinicopathological data for each case was retrieved from electronic medical records. To facilitate subsequent data analysis, each case was assigned a unique pathology laboratory number, and information was recorded on separate proforma forms. The evaluation included the following variables: age, gender, ethnicity, duration and size of neck swelling, and family history of malignancy.

Statistical analysis

Data entry, calculations, and analysis were performed using IBM SPSS statistics for Windows, Version 26.0. Descriptive statistics were used to present demographic variables. Chi-Square test was employed to assess the association between FNAC and HPE reports. A value <0.05 was considered statistically significant.

The accuracy of FNAC was evaluated against the gold standard method which is the histopathological evaluation. After excluding unsatisfactory smears, cytological results were categorized as follow: Negative result based on BSRTC (2007), is case with benign interpretation. Positive results are case interpreted as one of the following categories: atypia of undetermined significance or follicular lesion of undetermined significance, follicular neoplasm/Suspicious for a follicular neoplasm, suspicious for malignancy, and malignant. False negative defined as cases with negative result by cytological examination but interpreted by histopathological examination as: follicular carcinoma, papillary thyroid carcinoma, follicular carcinoma; Hurthle cell variant, and diffuse large B-cell lymphoma (DLBCL).

False positive was defined as cases with positive cytological examination and interpreted by histopathological examination as nodular hyperplasia, follicular adenoma, Hurthle cell adenoma, Hashimoto's thyroiditis and cyst content. True negative was defined as cases reported as benign by cytological examination and confirmed by histopathological examination as one of the following categories: nodular hyperplasia, follicular adenoma, Hurthle cell adenoma, Hashimoto's thyroiditis and cyst content. True positive cases were defined as cases diagnosed by cytopathology as atypia of undetermined significance or follicular lesion of

undetermined significance, follicular neoplasm/ Suspicious for a follicular neoplasm, suspicious for malignancy, and malignancy and confirmed by histopathology as follicular carcinoma, papillary thyroid carcinoma, follicular carcinoma; Hurthle cell variant, and DLBCL.

RESULTS

Clinicopathological features

During the period of study, a total of 389 patients had undergone FNAC testing at HSNZ. Of these, 162 patients met the inclusion criteria for this study. The age of the patients ranged from 15 to 76 years, with a mean age of 43.3 years. Thyroid lesions were found to be more prevalent in females, constituting 84% (136/162) of the cases, compared to males, who accounted for 16% (26/162), resulting in a female-to-male ratio of 5.3:1. The vast majority of patients (94.4%) reported no family history of thyroid disease. Table I presents the clinicopathological characteristics of thyroid cases included in the present study.

Table I: The clinicopathological features of thyroid cases included in the present study (n=162)

Variables	N (%)
Age	
15 to 35 years old	52 (32.1)
36 to 55 years old	80 (49.4)
56 to 75 years old	29 (17.9)
76 years old and above	1 (0.6)
Gender	
Male	26 (16)
Female	136 (84)
Ethnicity	
Malay	159 (98.1)
Chinese	2 (1.2)
Others	1 (0.6)
Family history of thyroid	
Yes	9 (5.6)
No	153 (94.4)
Duration of neck swelling	
1-11 months	48 (29.6)
1 – 5 years	71 (43.9)
5 – 10 years	17 (10.5)
More than 10 years	26 (16.0)

Cytology diagnosis according to BSRTC

Based on the BSRTC, 85 cases were diagnosed as benign (52.5%), 23 cases (14.2%) as atypia or follicular lesion of undetermined significance, 9 cases (5.6%) as follicular neoplasm, 21 cases (13%) as suspicious for malignancy, and 12 cases (7.4%) as malignant. Additionally, due to inadequate sampling, 12 cases (7.4%) could not be diagnosed despite repeated aspirations in different settings and were categorized as non-diagnostic cases (Figure 1).

Histopathological Examination (HPE)

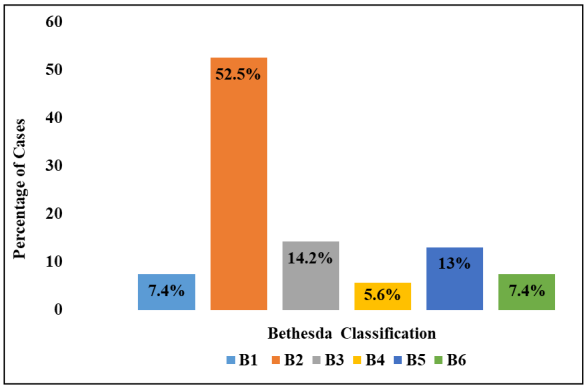

Figure 1. The diagnosis of FNAC thyroid cases based on Bethesda Classification. B1: Non-diagnostic or unsatisfactory; B2: Benign; B3: Atypia of undetermined significance or Follicular lesion of undetermined significance; B4: Follicular Neoplasm or Suspicious for a Follicular Neoplasm; B5: Suspicious for Malignant; B6: Malignant.

The distribution of cases according to HPE, revealed that the majority were benign. Specifically, 92 cases (56.8%) were diagnosed as nodular hyperplasia, 9 cases (5.6%) as follicular adenoma, 3 cases (1.9%) as Hurthle cell adenoma, and one case (0.6%) as Hashimoto's thyroiditis. Regarding malignant diagnoses, papillary thyroid cancer (PTC) was predominant, comprising 47 cases (29%) with follicular variation and one case (0.6%) of micropapillary PTC. Additionally, there were 7 cases (4.3%) diagnosed as follicular carcinoma and one case (0.6%) of DLBCL in the context of lymphocytic thyroiditis. (Table II).

Table II: The distribution of FNAC thyroid cases according to the histopathological diagnosis.

Type	Number	%
Benign Conditions		
Cyst content	1	0.6
Nodular Hyperplasia	92	56.8
Follicular Adenoma	9	5.6
Hurthle Cell Adenoma	3	1.9
Hashimoto Thyroiditis	1	0.6
Malignant Conditions		
Papillary Thyroid Carcinoma	47	29
Follicular Carcinoma	7	4.3
Follicular Carcinoma, Hurthle Cell	1	0.6
DLBCL in background lymphocytic thyroiditis	1	0.6
Total	162	100

Cytology and Histopathology results correlation

The correlation between FNAC and HPE results revealed interesting findings. Out of the 85 cases cytologically classified as benign (non-neoplastic), HPE confirmed 70.8% (75 cases) as non-neoplastic. However, 16.1% (9 cases) were histologically diagnosed as malignant, consisting of follicular and papillary carcinoma. Among the cases initially diagnosed as follicular neoplasm, HPE revealed that 5.6% (5 cases) were malignant, while 4.4% (4 cases) were benign.

The FNAC-HPE correlation showed that in Bethesda II (benign) category, 88.2% of cases were confirmed as benign, while 11.8% were found to be malignant. In Bethesda III (AUS/FLUS), 65.2% were benign and 34.8% were malignant. For Bethesda IV (follicular neoplasm), 44.4% were benign and 55.6% were malignant. In both Bethesda V (suspicious for malignancy) and VI (malignancy), 100% of cases were confirmed as malignant by HPE (Table III).

Table III: Correlation between the cytology and histopathology results

Bethesda Classification	Histopathology n (%)		Total (%)
	Benign	Malignant	
B1	11 (6.8)	1 (0.6)	12 (7.4)
B2	75 (46.3)	10 (6.2)	85 (52.5)
B3	15 (9.3)	8 (4.9)	23 (14.2)
B4	4 (2.5)	5 (3.1)	9 (5.6)
B5	0 (0.0)	21 (13.0)	21 (13.0)
B6	0 (0.0)	12 (7.4)	12 (7.4)
Total	105 (64.8)	57 (35.2)	162 (100%)

The sensitivity and specificity of FNAC of the thyroid

In Table IV, the sensitivity and specificity of FNAC of the thyroid compared to the gold standard method (HPE) was presented. Out of a total of 101 cases, representing 62.3%, benign cytological findings were confirmed as benign by HPE, indicating true negative cases. Conversely, there were 19 cases (11.7%) initially diagnosed as benign by FNAC but were found to be carcinomas upon HPE, indicating false negative cases. In all 38 cases (23.5%) were diagnosed as malignant both on FNAC cytology and histopathological examination, indicating true positive cases. However, four cases (2.5%) initially diagnosed as carcinoma by FNAC were revealed to be goitre upon HPE, representing false positive cases. Overall, FNAC achieved a total diagnostic accuracy of 85.8%, with a sensitivity rate of 66.7% and specificity of 96.2%. The positive predictive value (PPV) was 90.5%, and the negative predictive value (NPV) was 84.2%.

Table IV: The sensitivity and specificity of FNAC of thyroid lesions

Variables	Histological, n (%)		Combo value
	Benign	Malignant	
FNAC			
Benign	101	19	Sensitivity (39/ 38+19) = 66.7%
Malignant	4	38	Specificity (101/ 101+4) = 96.2%
			PPV (38 / 38+4) = 90.5%
			NPV (101 / 101+19) = 84.2%
			Accuracy (101+38)/(162) = 85.8%

*Chi Square significant at p value < 0.05
*Sensitivity = ability of the test to detect true malignant case
*Specificity = ability of the test to detect true benign case
*PPV = Positive Predictive Value
*NPV = Negative Predictive Value

DISCUSSION

Thyroid cancer has been reported to rank seventeenth among the most prevalent cancers in men and ninth among women, according to earlier findings by Azizah et al.[8] FNAC has emerged as the most cost-effective approach for assessing thyroid nodules. Many healthcare facilities offering this procedure have significantly reduced the number of patients requiring surgical intervention.[9,10]

In our study, we aimed to assess the diagnostic accuracy of the FNAC of thyroid by comparing the FNAC diagnoses with HPE. We observed a predominance of female cases. With female-to-male ratio of approximately 5.3:1 which aligns with previous literature.[10,11]

This gender disparity reflects a higher prevalence of thyroid disorders in women. Interestingly, the majority of included patients had no family history of thyroid disease, suggesting that environmental or other non-genetic factors may contribute significantly to the development of thyroid lesions. It is well established that the primary environmental determinant affecting the prevalence of goitre is iodine levels. However, other environmental factors impacting entire populations have also been recognized, including goitrogens present in food and

drinking water.[12]

Consistent with findings in previous studies,[10,13] the majority of cases in our study were benign conditions (65.4%). Among these, nodular hyperplasia was the most commonly diagnosed condition, comprising approximately 86.7% of all benign cases, followed by follicular adenoma, which accounted for 8.4% of benign cases. Regarding malignancies, papillary thyroid carcinoma was the most frequently diagnosed, representing approximately 83.9% of all malignant cases, followed by follicular carcinoma at 12.5%.

Inadequate smears in cytology lab are an unavoidable aspect of the procedure. In our study, approximately 7.4% (12 cases) of included patients had smears deemed inadequate for evaluation. The adequacy of thyroid FNA depends on the number of cells observed under the microscope. To deem a thyroid FNA adequate for evaluation, we need to observe six clusters of follicular cells, each cluster containing no fewer than ten cells. The normal or suggested range for inadequate samples typically falls between 2% and 20%,[14] thus our findings fall within this acceptable range.

To assess the diagnostic accuracy of FNA of thyroid, we correlated cytopathological diagnoses with histopathological results. Sensitivity, defined as "the ability of the test to correctly identify patients with a disease"[15] is a crucial measure of FNAC effectiveness. In our study, FNAC demonstrated a sensitivity of 66.7%, indicating that it correctly identified approximately two-thirds of malignant thyroid cases while missing about one -third. This sensitivity result falls within the range reported in recent literature, higher than study reporting (42.8%) [16] but lower than others reporting (82.3%),[14] (94%).[17] The significant variation in sensitivity across studies suggests that the success of thyroid FNAC may largely depend on the operators expertise.

Regarding specificity, which is defined as "the ability of a test to correctly identify people without the disease",[15] our study observed a high value of 96.2%. This high percentage indicates FNAC's strong ability to rule out benign conditions in the majority of cases diagnosed as benign histopathological examination. Similar to sensitivity, previous studies have shown variations in FNAC specificity for thyroid lesions, with percentages ranging from 64.3% to 98.5%. [14,16,17]

In our study, the correlation between cytopathology and histopathological examination revealed a false negative rate of 11.7%. This rate is higher than ideal, as previous studies investigating the accuracy of FNAC of thyroid have shown a wide variation in false negative results, ranging from 5% to 21%, with most studies reporting 5% or less.[18,19] Moreover, the American Thyroid Association guidelines recommend that the false negative rate should be within 0-5%.[20] These findings highlight the need for continued improvement in FNAC techniques and interpretation to reduce false negative rates and enhance overall diagnostic accuracy in thyroid lesions assessment in our hospitals.

The discrepancies between cytology and histopathology examinations in thyroid nodule diagnosis can be attributed to various factors, depending on the condition under investigation. Generally, false positive and false negative results, as well as the non-diagnostic aspirates, are related to both the nature of the lesion and the experience of the cytopathologist.[21] For example, a previous study emphasized that up to 50% of FNAs performed on thyroid nodules measuring ≥4 cm were inaccurately classified as benign.[22] Moreover, multiple nodules present a challenge for cytopathologist, as they need to assess the entire lesion by taking several aspirates from different sites.

Earlier reports have highlighted that atypical nuclear features in cases of papillary carcinoma may result in missed diagnoses and false negative results. Additionally, papillary carcinoma cases with a diameter less than 0.5 cm and adjacent to benign follicular neoplasm; often yield false negative results.[21]

Our study found a 2.5% false positive rate. It's important to note that certain morphological features such as nuclear grooves, papillary architecture, absence of colloid

material, and intranuclear inclusions are consistent with papillary carcinoma diagnosis. However, these features may also be present in benign conditions such as Hashimoto thyroiditis, nodular hyperplasia, Hurthle cell adenoma, and follicular adenoma, leading to false positive interpretations. Another source of false positives in papillary carcinoma; is the follicular variant cases, which may lack typical nuclear features and exhibit cytomorphological features shared with follicular neoplasms[21]. In these instances, a preoperative diagnosis of "follicular lesion suggestive of papillary carcinoma" often leads to a cautious surgical evaluation until a conclusive diagnosis can ascertain the suitable course of treatment.[23]

The implications of false negative and false positive diagnoses are significant. False negatives may lead to delayed diagnosis and treatment of thyroid carcinomas, potentially impacting patient clinical outcomes. Conversely, false positives may result in unnecessary surgeries or treatments, emphasizing the importance of minimizing such scenarios.

Many cytopathologists concur that several factors play crucial roles in determining the accuracy of FNAC. These factors encompass clinical and imaging observations, lesion size, aspiration characteristics, the expertise of the individual performing the aspiration,[24] and the incapacity of FNAC of thyroid to differentiate between benign and malignant follicular lesions without the presence of nuclear characteristics typical of papillary carcinoma, FNAC faces challenges in accurately diagnosing follicular neoplasms. The indeterminate diagnosis of follicular neoplasm encompasses various thyroid lesions, such as cellular adenomatoid nodules, follicular adenomas, and follicular carcinomas, which exhibit heterogeneity.[25]

The present study provides a critical evaluation of FNAC diagnostic accuracy within the setting of hospitals in Malaysia, thus providing an essential benchmark for cytopathology practice in Malaysian. By sharing our current diagnostic performance, the data serves as a crucial reference point for understanding the strengths and limitations of thyroid FNAC Malaysia. The findings emphasized the need for continuous quality improvement initiatives. With a sensitivity of 66.7% and specificity of 96.2%, our results donate that while the overall diagnostic accuracy is robust, there remains room for improvement, mainly in reducing false negative cases. When we compared our results with international standards both alignments and disparities were observed, providing stakeholders with clear insights into our current diagnostic capabilities. The current research is useful for focused training, method refining, and creating benchmarks to guide future quality improvement efforts in thyroid cytopathology in Malaysian institutions.

The observed false negative rate of 11.7%, which exceeds the American Thyroid Association's recommended benchmark of 0-5%. This significant false negative rate emphasises the crucial need for a thorough review of FNAC thyroid practice in our environment. The clinical consequences are important, since false negative findings may result in delayed detection and treatment of thyroid carcinomas. Our findings indicate an urgent need for targeted interventions, including improvement operator training, enhancing sampling techniques, and more stringent cytopathological interpretation standards. The false negative rate highlights possible issues such as poor sampling, limits in detecting minor morphological alterations, especially in instances with unusual or overlapping morphological characteristics. This data is a significant call to action for local healthcare facilities to engage in ongoing medical education, adopt stricter quality control methods, and maybe introduce new diagnostic protections to reduce missed cases.

This study on FNAC of thyroid nodules has several limitations. The study was carried at a single tertiary hospital in Malaysia with a sample size of 162 cases, in addition the retrospective cross-sectional nature limits generalizability. Moreover, the research was confined to a specific three-year period (2017-2019), potentially not reflecting more recent practices. These limitations underscore the need for further research to improve thyroid nodule diagnostic practices.

CONCLUSION

In conclusion, FNAC emerges as a valuable diagnostic tool for evaluating thyroid nodules, offering high specificity and moderate sensitivity in distinguishing between benign and malignant lesions. While FNAC represents a cornerstone in thyroid nodule assessment, ongoing efforts to refine sampling techniques and enhance interpretation accuracy are essential for optimizing diagnostic outcomes in clinical practice.

INSTITUTIONAL REVIEW BOARD (ETHICS COMMITTEE)

This study was approved by the National Medical Research Register and Medical Research & Ethics Committee (MREC) with (NMRR-ID19-3559-51702 S4 R1). It was also approved by the Human Research Ethical Committee, Universiti Sains Malaysia, protocol number (USM/JEPeM/19120975).

AVAILABILITY OF DATA AND MATERIALS

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

COMPETING INTEREST

The authors declare that they have no competing interests.

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AUTHORS'S CONTRIBUTIONS

Conception and design: N.N.A & W.F.W.A.R, Data analysis and article drafting: A.S., N.H.I, NNA, Critical revision and Editing: WFWA.R, A.A.M.Z, Project supervision: W.F.W.A.R

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ORIGINAL ARTICLE

Optimizing Antibiotic Dosing: A Prospective Observational Study of Piperacillin/Tazobactam Plasma Levels in Critically Ill Patients with Augmented Renal Clearance

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ABSTRACT

INTRODUCTION: Managing antibiotic dosing in critically ill patients presents challenges especially in achieving optimal therapeutic levels. Thus, we conducted a study to evaluate how augmented renal clearance (ARC) affects the attainment of pharmacokinetic/pharmacodynamic (PK/PD) targets in patients receiving piperacillin/tazobactam (PTZ) via continuous infusion. **MATERIALS AND METHODS:** A single-centred, prospective, observational study was conducted in intensive care unit at Sultan Ahmad Shah Medical Center @IIUM, Kuantan Pahang. A total of 43 adult patients with normal renal function treated as sepsis with standard PTZ doses via continuous infusion were included for the study and their blood were sampled for assessment of drug concentrations and PK/PD target attainment. **RESULTS:** There was substantial PK variability with 60% diagnosed with ARC and 37.2% of experienced piperacillin underexposure in which patients with ARC had significantly higher rates of underexposure at both distribution and steady-state phases. **CONCLUSION:** The high prevalence of ARC in these patients impacted the therapeutic PTZ levels and as many patients did not reach desired drug concentrations, there is increased risk of treatment failure without dose adjustment. These findings underscore the importance of individualized dosing strategies, particularly in critically ill patients with ARC, to optimize antibiotic therapy efficacy and mitigate the risk of inadequate treatment.

Keywords
augmented renal clearance, critically ill, piperacillin-tazobactam, subtherapeutic

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INTRODUCTION

Critically ill patients with augmented renal clearance often pose a formidable challenge in determining appropriate drug dosages to achieve optimal therapeutic efficacy. Augmented renal clearance (ARC) which is characterized by enhanced renal function and increased clearance of renally eliminated drugs is a common phenomenon observed in critically ill patients.[1-3] The dynamic nature of ARC complicates the attainment of target drug concentrations particularly for antibiotics like Piperacillin/Tazobactam (PTZ) which are predominantly excreted renally.

In recent years, pharmacokinetic studies have emerged as invaluable tools in understanding the disposition of drugs in critically ill patients especially those with altered renal function. Many studies have provided critical insights into the pharmacokinetic parameters governing drug disposition, absorption, distribution, metabolism, and elimination in this patient population.[4-7] By quantifying plasma concentrations of drugs like PTZ, pharmacokinetic studies have facilitated the optimization of dosing regimens, thereby improving therapeutic outcomes, and minimizing the risk of treatment failure or adverse events.

Piperacillin/Tazobactam is a broad-spectrum β-lactam antibiotic combination that is commonly used in the management of severe infections including pneumonia,

sepsis, intra-abdominal infections, and in critically ill patients. However, the pharmacokinetics of PTZ can be significantly altered in the presence of ARC/ leading to suboptimal drug exposure and potentially compromising treatment efficacy.[8-10] Consequently, understanding the impact of ARC on PTZ pharmacokinetics is crucial for tailoring dosing strategies and ensuring therapeutic success in this vulnerable patient population.

Pharmacokinetic studies evaluating PTZ plasma concentrations in critically ill patients with ARC have provided valuable insights into the factors influencing drug disposition and the challenges associated with achieving target drug levels.[10-14] Studies have highlighted the importance of considering patient-specific factors such as renal function, body weight, and severity of illness, in dose individualization and therapeutic drug monitoring.[12-14]

Pharmacokinetic modelling and simulation techniques have been instrumental in predicting drug exposure and guiding dose adjustments in patients with ARC. By integrating pharmacokinetic data with clinical parameters, these modelling approaches enable clinicians to optimize dosing regimens and achieve target drug concentrations while minimizing the risk of toxicity or treatment failure.[12]

Despite the advancements in pharmacokinetic research, several knowledge gaps persist regarding the optimal management of PTZ therapy in critically ill patients with ARC. Limited data are available on the impact of ARC on PTZ pharmacokinetics in specific patient populations such as those with varying degrees of renal dysfunction or concomitant organ dysfunction. Additionally, the clinical implications of subtherapeutic drug concentrations and the potential strategies for dose optimization remain areas of active investigation.

In view of all these considerations, our study was conducted to explore the assessment of PTZ plasma concentration in critically ill patients with ARC, emphasizing the importance of pharmacokinetic parameters in guiding precise dosing strategies. By synthesizing existing evidence and highlighting key research findings, our study aimed to underscore the significance of pharmacokinetic studies in optimizing PTZ therapy and improving clinical outcomes in critically ill patients with ARC.

MATERIALS AND METHODS

This study which was a single-centre, prospective observational study design had been approved by the medical ethical committee of the the International Islamic University Malaysia (IREC 2020-110, 29 March 2021).

SUBJECT

All patients who were admitted to the intensive care unit (ICU) at Sultan Ahmad Shah Medical Centre (SASMEC) @ IIUM during the study period were screened for the study. Patients who fulfilled the inclusion and exclusion criteria were recruited after informed consents were obtained. The inclusion criteria were patient age 18 years old or more with serum creatinine <120μmol/L, ICU stay >24hours and received continuous infusion of PTZ for a sepsis. The exclusion criteria were pregnant and lactating mother, history of allergy to β-Lactam antibiotics, was having an acute kidney injury (AKI) according to KDIGO criteria, underlying chronic kidney disease (CKD), and receiving diuretics during the screening period.

ANTIBIOTIC ADMINISTRATION

Selected patients were administered a loading dose of 4.5g PTZ over 30min, followed by continuous infusion 4.5g Q6hr (16g/2g in 24 hours). The syringe was changed every 8 h using a syringe pump through a central venous catheter.

BLOOD COLLECTION

A serial blood sampling was performed at the following time: T1 and T2 (with an hour apart) at two separate occasions; occasion 1 (distribution phase from day 1 or 2) and occasion 2 (steady phase from day 3 or 4). Each time the sampling was performed, a total of 3 ml of blood was withdrawn from a central line and transferred into heparinized tubes All samples were immediately kept in a

-4°C freezer and later were centrifuged at 3600 rpm for 10 minutes to separate plasma before stored in -80°C freezer prior to analysis. The antibiotic concentrations in plasma were measured using Liquid Chromatography Mass Spectrometry (LCMS) method with Ultraviolet (UV) detection.

CREATININE CLEARANCE MEASUREMENT

For measurement of creatinine clearance, 8-hours of urine output were collected on day-1. The creatinine clearance (CrCL) was calculated using the rate blanked, compensated, and uncompensated Jaffe technique, respectively. (Modular P and Cobas 6000, Roche Diagnostics GmbH, Mannheim, Germany).

$$\text{Creatine clearance (CrCL)} = \frac{\text{Urine Volume (ml) x urine creatinine (µmol/L) x 1.73}}{\text{Serum creatinine (µmol/L) x 480 x BSA}}$$

CrCL>>130 mL/min/1.73 m2 by an 8-hour urine creatinine collection is referred as Augmented Renal Clearance (ARC).

STATISTICAL ANALYSIS

A statistical analysis was performed using the statistical software package IBM-SPSS statistics version 20.0 (IBM Corp., New York, NY, USA). The sociodemographic data are expressed as mean ± SD, n (%), or median (lower quartile-upper quartile), and the association between ARC and sub-optimal PTZ concentration was analyzed by Chi-square test.

The variables or factors predicting sub-optimal PTZ concentrations and patient outcomes was assessed by multivariate logistic regression model with target attainment 100% for f T>MIC and target attainment 50% f T>MIC as dependent variable using the variables which gave a p value of <0.10 in the univariate analysis. The goodness of fit was assessed by the Hosmer-Lemeshow statistic. All tests were two-tailed, and P<0.05 was considered statistically significant.

RESULTS

A total of 43 patients were recruited in the study. Majority of them were female (60.5%) and Malay ethnicity (86%). The prevalence of ARC was 60.5% (Table I) and there was no significant difference in term of length of ICU/hospital stay and mortality (p>0.05).

Table I: Patients Demographics, Clinical Characteristics, and Outcomes

Variables	ARC (n= 26)	No ARC (n= 17)	p value
Age (years)	53.1 ± 18.4	57.53 ± 16.3	0.656
ETHNICITY			
Malay	22 (84.6)	15 (88.2)	0.310
Chinese	4 (15.4)	1 (5.9)	
Indian	0 (0.0)	1 (5.9)	
GENDER			
Male	12 (46.2)	5 (29.4)	0.272
Female	14 (53.8)	12 (70.6)	
Weight (kg)	63.8 ± 14.5	70.3 ± 19.4	0.739
Height (cm)	157.5 ± 8.0	157.9 ± 8.6	0.758
Baseline APACHE II Score	11.3 ± 2.5	10.9 ± 3.4	0.302
Baseline SOFA Score	3.4 ± 2.3	3.7 ± 2.3	0.852
Delta SOFA score D1-D4	0.85 ± 1.8	-1.1 ± 2.2	0.743
Charlson Index	3.7 ± 1.9	3.6 ± 1.7	0.521
Se Albumin (g/L)	27.5 ± 6.3	27.2 ± 7.8	0.393
Se Creatinine (µmol/L)	55.6 ± 15.3	68.2 ± 23.7	0.048
Cr Cl (ml/ min/1.73m²)	296.6 ± 145.6	73.3 ± 34.7	<0.001
ADMISSION			
Medical	17 (65.4)	14 (82.4)	0.225
Surgical	9 (34.6)	3 (17.6)	
OUTCOME			
Length of ICU stay (days)	7.2 ± 4.4	9.4 ± 6.7	0.171
Length of Hospital stay (days)	28.3 ± 49.3	26.6 ± 35.8	0.900
ICU mortality	7 (26.9)	4 (23.5)	0.802
Hospital Mortality	8 (30.8)	5 (29.4)	0.925

Data expressed as mean ± SD, n (%), or median (lower quartile – upper quartile).

ARC: Augmented Renal Clearance with CrCL > 130ml/min/1.73m2

APACHE II Score: Acute Physiology and Chronic Health Evaluation II

SOFA score: Sequential Organ Failure Assessment Score

There was no significant difference in number of patients with ARC who achieved target MIC ≥16mg/l PTZ at 50% interval between occasion 1 and 2 (p>0.05) (*Table II*). However, the number of patients with ARC reduced from occasion 1 (57.7%) to occasion 2 (42.3%) at 100% interval. For patients without ARC, the number of patients who achieved target MIC slightly reduced from occasion 1 to 2 at both 50% and 100% interval.

Table II: Association between patients with and without ARC and suboptimal therapeutic range at 4 different time point

Achieved target MIC (EUCAST ≥16 mg/L)	ARC N=26	No ARC N= 17	p value
Occasion 1 Time1 (50%fT>MIC)	22 (84.6)	17 (100)	
Time2 (100%fT>MIC)	15 (57.7)	17 (100)	0.091
Occasion2 Time3 (50%fT>MIC)	22 (84.6)	16 (94.1)	
Time4 (100%fT>MIC)	11 (42.3)	16 (94.1)	

Data expressed as mean ± SD, n (%) or median (lower quartile-upper quartile).

ARC: Augmented Renal Clearance with CrCL> 130ml/min/1.73m2

The concentration of PTZ was lower in ARC group compared to non-ARC group at 50% interval (Table III). Similar pattern was also observed at 100% interval where the PTZ concentration was significantly reduced from time 2 to time 4 (p<0.01) and PTZ concentration at time-4 was the lowest among all (23.2 ±23.1 mg/l).

Table III: Free Plasma concentration of Piperacillin-Tazobactam (PTZ) at 4 different time points in patients with ARC and without ARC.

Free Plasma Concentration of PTZ (mg/L)	ARC N=26	No ARC N= 17	p value
Occasion 1			
Time 1 (50%fT>MIC)	32.8 ±20.9	56.3 ± 26.2	<0.001
Time 2 (100%fT>MIC)	25.3 ±23.8	48.4 ± 17.2	
Occasion 2			
Time 3 (50%fT>MIC)	31.5 ±20.5	48.4 ± 17.2	
Time 4 (100%fT>MIC)	23.2 ±23.1	46.5 ± 29.6	

Data expressed as mean ± SD.

ARC: Augmented Renal Clearance with CrCL>130ml/min/1.73m

In addition, the ICU patients with ARC had a much higher rate of therapeutic failure than those without ARC, 57.7% and 5.9%, respectively (Table IV).

Table IV: Association between ARC and Therapeutic failure

	ARC N=26	No ARC N= 17	p value
Therapeutic Failure			
Yes	15 (57.7)	1 (5.9)	<0.001
No	11 (42.3)	16(94.1)	

Data expressed as median (%)

ARC: Augmented Renal Clearance with measured CrCL >130ml/ min/1.73m2

Therapeutic Failure: Free plasma concentration of PTZ > 16mg/L at any one of the time points

The multivariable regression analysis demonstrated a statistically significant association between patients' weight and their CrCL levels with suboptimal PTZ free plasma concentrations. This association was significant at the 0.05 and 0.002 levels. However, there was no significant differences were observed with respect to age, height, or baseline APACHE II score (Table V).

Table V: Multivariable Logistic Regression for suboptimal Piperacillin/ Tazobactam (PTZ) plasma concentration in ARC

Variables	Odds Ratio (95% CI)	p value
Age	1.00	0.80
Height (cm)	0.99	0.97
Weight (kg)	1.02	0.05
Baseline APACHE II Score	1.12	0.48
CrCl	1.01	0.002

Data expressed as Odds Ratio with 95% confidence interval

APACHE II Score: Acute Physiology and Chronic Health Evaluation II'

CrCL: Creatinine clearance

DISCUSSION

Our study represents a pioneering investigation in Malaysia, examining the interplay between augmented renal clearance (ARC) and the pharmacokinetics of β-lactam antibiotics such as Piperacillin-Tazobactam (PTZ) in critically ill patients. Through the development of a population pharmacokinetic model, we aimed to elucidate the impact of ARC on plasma concentrations of PTZ. A critically ill patients often experience altered pharmacokinetics due to the severity of their condition, leading to suboptimal medication levels. ARC, identified in 60% of our study cohort and reported in 20-65% of

critically ill patients elsewhere,[2,8] poses a significant challenge in achieving therapeutic drug concentrations particularly for renally eliminated antibiotics such as PTZ .[4]

Studies has extensively documented the implications of ARC on drug clearance, particularly related to antibiotics that primarily excreted by the kidneys.[12,14] Our findings corroborate existing literature demonstrating a high prevalence of ARC and its association with subtherapeutic antibiotic concentrations. Despite the administration of PTZ via continuous infusion, a significant proportion of patients with ARC had failed to reach the pharmacokinetic/pharmacodynamic (PK/PD) targets, raising concerns regarding treatment efficacy.

Continuous infusion of PTZ aimed at optimizing antibiotic exposure is a common practice in the ICU setting.[12,14] However, our study suggested that even this common practice may not guarantee the target attainment in patients with ARC. This highlights the critical need for personalized dosing strategies and vigilant monitoring of renal function to ensure adequate drug exposure and therapeutic efficacy.

Based on our study results, we believe that our study had made a significant contribution to the expanding body of literature on ARC and antibiotic pharmacokinetics in critically ill patients, particularly within the Malaysian context. By employing robust methodology, including liquid chromatography-mass spectrometry (LC-MS) with ultraviolet (UV) detection for plasma antibiotic measurements, we are offering a valuable insight into the pharmacokinetics of PTZ in patients with ARC.

Nevertheless, there were several limitations of our study that we should acknowledged. Firstly, the small sample size and single-centred design of our study may restrict the generalizability of our findings. Secondly, lack of the external validation for the population pharmacokinetic model and the absence of clinical outcome data underscores the need for further investigation. Thus, we would suggest that further studies should be conducted in the future aim to recruit a larger sample size and involve a multicentre cohorts encompassing diverse patient populations to validate our results and assess clinical outcomes comprehensively.

Our study findings underscore the necessity for more tailored antimicrobial therapy especially in critically ill patients with augmented renal clearance (ARC) and the initial dosing should be guided by CrCL to avoid falling below therapeutic thresholds. Additionally, determining pathogen minimum inhibitory concentrations (MICs) and applying therapeutic drug monitoring (TMD) can further optimize antibiotic exposure, considering the variability in local susceptibility patterns.

Although optimizing dosing regimens can be achieved through dosage adjustments or medication changes, clinicians should be vigilant regarding the adequacy of standard doses in patients exhibiting ARC. Further research looking into innovative administration strategies for this patient population should be prompted. Thus, exploring alternative dosing strategies that may have a potential to improve the outcomes and reduce risks of treatment failure is imperative.

Moving forward, clinical practice guidelines may need to incorporate considerations for ARC, emphasizing personalized dosing approaches based on individual patient characteristics. Furthermore, ongoing research should focus more on developing and validating novel dosing algorithms specifically tailored for critically ill patients with ARC, ultimately enhancing therapeutic efficacy and minimizing the emergence of antimicrobial resistance.

In summary, addressing the impact of ARC on antibiotic dosing represents a critical step towards optimizing treatment outcomes in critically ill patients. By adopting individualized dosing strategies and leveraging innovative approaches, clinicians can navigate better the complexities of antimicrobial therapy in this vulnerable patient population, ultimately improving patient care and reducing the burden of infectious diseases in intensive care settings.

CONCLUSION

In conclusion, while continuous administration of PTZ 16g/2g/day is believed to be the best practice for critically ill patients, those with a high creatinine clearance (CrCL) above 130 mL/min remain at risk of receiving suboptimal doses. These patients may require higher doses of Piperacillin/Tazobactam than currently licensed, without increasing the risk of overdose or neurotoxicity.

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ORIGINAL ARTICLE

Consensus Development of Resilience Components in Malaysian Breast Cancer Survivors: Findings from a Delphi Study

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ABSTRACT

INTRODUCTION: Resilience significantly influences the mental health and treatment outcomes of cancer patients. This study aimed to establish expert consensus on key resilience components specific to Malaysian breast cancer survivors using a Delphi method. **MATERIALS AND METHODS:** A Three-Round Modified Delphi Technique was conducted on 10 expert panelists involving psychiatrists, psychologists, and breast cancer survivors. In Round 1, open-ended questions identified initial resilience components. In Rounds 2 and 3, panelists rated the importance of each component using a 5-point Likert scale. Consensus was defined as a mean score ≥4.0 with at least 75% agreement. Both median scores and percentage agreement were used to ensure reliability. **RESULTS:** The final framework consisted of 10 main components and 25 subcomponents, with two subcomponents excluded due to low consensus. Main components included emotional, cognitive, knowledge, physical, religious and spirituality, social support, family support, mental health, financial, and other relevant domains. Endorsed subcomponents included emotional flexibility, self-regulation, optimism, gratitude, knowledge of cancer, physical health, religious coping, spiritual practices, social and family support, mental health self-efficacy, and financial status. **CONCLUSION**: This expert-endorsed framework offers a culturally relevant foundation for developing resilience-building strategies among Malaysian breast cancer survivors. These identified components may guide future psychosocial interventions aimed at improving emotional well-being and treatment outcomes among breast cancer survivors.

Keywords
Resilience, breast cancer survivors, expert consensus, Delphi technique

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INTRODUCTION

Breast cancer remains a major public health issue in Malaysia, affecting not only the physical health of women but also their emotional and social well-being. Although advancements in treatment have led to improved survival rates, the journey from diagnosis through treatment can pose significant challenges, leading to considerable physical and psychological distress. A breast cancer survivors refer to individuals who have completed active treatment following a breast cancer diagnosis. Survivorship begins at the end of treatment end and encompasses ongoing care and long-term health and wellness across multiple aspects of life.

The Delphi method is a widely recognized qualitative research approach study, commonly used across various fields such as business, education, and social sciences.[1-3,5-6] The key factor in the successful implementation of a Delphi study is the active cooperation of participants. Therefore, researchers must play a proactive role in maintaining engagement and ensuring a high response rate.[8] Delphi techniques is considered as one the most popular consensus methods, utilizing a structured process involving multiple rounds of questionnaires to systematically gather and refine input from a panel of selected experts.[3,7] It is particularly valued for its ability to obtain expert consensus on complex issues.

The Delphi method is a powerful tool, particularly well-suited for achieving expert consensus. The justification for using this method becomes stronger when explicitly

compared to alternative methods such as focus groups or systematic reviews. Unlike a focus group, the Delphi method is inherently designed for consensus-building. The focus group often is at risk of being influenced by the dominant participants, which then can lead to potential bias and skewed results. The Delphi method maintains participant anonymity, uses a structured feedback process, minimizes the risk of groupthink, and encourage for a more thoughtful and independent input over multiple iterative rounds.[8]

In Delphi, the controlled feedback ensures comprehensive and balance contributions, while preventing any single expert from dominating the discussion.[9] On the other hand, the focus group inhibits the honest expression of opinion due to social pressure or power dynamics among participants.

Resilience is vital for cancer patients, as it significantly enhances mental health and treatment outcomes.[10] It involves overcoming mental and emotional difficulties during a crisis or rapidly returning to a pre-crisis state. Resilience is often regarded as a form of "positive adaptation" following a stressful or adverse situation.[11] It encompasses both the process and outcome experiences, primarily through mental, emotional, and behavioural flexibility in response to both internal and external demands.[11]

Breast cancer survivors face unique challenges and require specialized care to address their long-term medical issues and lifestyle recommendations.[11] According to Seiler and Jenewein, there are numerous factors that contribute to resilience in cancer patients.[12] These include demographic characteristics, cancer-related variables, personality traits, social context, coping strategies, optimism, hope, spirituality, and a sense of coherence. Collectively, these factors serve as the protective elements that help individuals navigate the cancer experience.

In a similar study, three protective factors were identified:- biological (gene-environment), personal (sense of coherence, optimism, and hope), and social (social support). These three factors are associated with positive life changes and plays a significant role in fostering resilience among cancer patients. The enhanced resilience, in turn, contributes to improved psychological well-being and better treatment-related outcomes.

The study highlighted the biological domain as particularly critical when individuals are confronted with serious stressors, such as a cancer diagnosis. Within this domain, the researchers identified factors including a coherent self-concept, self-esteem, optimism, and positive emotions as key contributors to resilience. In terms of personal factors, a sense of personal control was noted as an important personality-related trait that promote resilience in cancer patients. As for the social domain, social support derived from social engagement initiatives was found to enhance coping mechanisms, strengthen resilience, and foster the social connectedness, and contribute positively to both physical and mental health.[10]

In addition, a previous study identified three protective factors of resilience for breast cancer patients: social support, the ability to cope with diagnosis and treatment, and optimism.[13] These factors were associated with positive psychological outcome and improved overall well-being. Furthermore, a global survey reported that 59% of people worldwide consider themselves as religious.[12] Many cancer patients turn to religion as a coping mechanism during their illness and treatment journey. A recent study conducted in year 2020 found that religion can foster resilience and play a significant role in helping patients manage the stress associated with breast cancer.[14]

In promoting resilience, it is essential to enhance patients' religiosity and psychological resilience skills through counseling interventions. Such efforts can help alleviate the adverse effects of cancer treatment. Additionally, breast cancer patients who possess strong biological and psychological resources are more likely to respond positively to their illness. One study identified five key resilience factors focused on biological and psychological aspects: hardiness, optimism, confidence, gratitude, and mastery.[15] In Malaysian, a study on local cancer survivors highlighted the significance of three core components that contribute to enhanced resilience,

namely community support, personal coping mechanisms, and spiritual well-being.[16] Further evidence suggests that five protective factors, such as self-efficacy, perceived social support, optimism, and mastery, can significantly improve resilience among breast cancer patients.[17]

Despite the extensive discussion of protective factors that optimize resilience, current clinical practice still lacks the integration of psychosocial interventions that specifically leverage these factors specifically to support resilience breast cancer patients. Psychosocial interventions grounded in the protective elements identified above have the potential to enhance recovery and strengthen resilience in this population, particularly within the Malaysian context.

Similarly, previous research has highlighted the importance of resilience across various populations, including cancer survivors. However, a comprehensive understanding of resilience components specific to Malaysian breast cancer survivors remains limited. This study aims to address this gap by establishing a consensus on the key components and subcomponents of a resilience framework tailored for Malaysian breast cancer survivors.

Given the scarcity of local evidence on resilience in breast cancer survivors in Malaysia, developing a culturally sensitive and contextually relevant framework is critical. By seeking the expert consensus on the essential elements of resilience, this study aspires to provide invaluable insights for developing targeted psychosocial interventions that can improve the resilience and enhance the overall quality of life for Malaysian breast cancer survivors. Utilizing a Three-Round Modified Delphi Technique, this research will produce a comprehensive and expert-endorsed consensual understanding of resilience components that are directly aligned with the lived experiences and cultural context of Malaysian breast cancer survivors.

MATERIAL AND METHODS

A Delphi study was conducted in three stages to propose components and subcomponents of resilience for cancer survivors in Malaysia.

Stage I: Generation of Initial Domains

Data were obtained through three methods: face-to-face interviews with the patients, individuals, and specialists at the Breast Cancer Awareness and Research Unit (BestARi) in Specialist Universiti Sains Malaysia Hospital (HPUSM), an intensive reviews of previous studies in the examined area; and exploration of models and theoretical framework on resilience among cancer survivors. A total of 10 expert panel members participated in the study. A purposive sampling was used to identify eligible participants.

According to existing literature, the number of panel participants in Delphi studies ranges from a few to several hundred.[18-21] For homogenous groups, the ideal panel size may range between 10 to 15 participants.[22] Another study also supported the use of small panels, suggesting that a group of 10 to 15 experts is sufficient to achieve a quality outcomes.[23] Thus, this study included 10 expert panelists in the Delphi process.

The inclusion criteria required experts to have a minimum three years of professional experience in relevant fields, along with direct clinical experience in managing breast cancer cases in Malaysia. The research team carefully evaluated examined each candidate's expertise, and two independent researchers reviewed and selected the final panel members.

Data collection was conducted over a three month period in 2023. Participation is voluntary, and could withdraw from the interview sessions without penalty. Informed consent was obtained from all participants. Each interview was audio-recorded with participants' permission to prevent data recorded to avoid missing data and only started after getting permission from the participants. Data collection commenced following an approval from the relevant ethics committee.

Thematic analysis method was used to analyze the qualitative data. Interview transcripts were transcribed verbatim and thoroughly reviewed to ensure familiarity

with the content. Open coding was conducted whereby meaningful data segments were assigned descriptive codes. Initial codes were generated and assessed independently by two researchers. These codes were then grouped into categories based on similarities and emerging patterns which were refined iteratively into overarching themes. For example, in analyzing participants' coping strategies, initial codes such as "nuclear family" and "extended family" were categorized under the theme "family support.".

Any disagreements between coders were resolved through discussion and mutual agreement. The research team discussed and refined the identified themes, reaching consensus through collaborative dialogue. As a result, a preliminary framework of 10 components and 27 subcomponents was developed. This draft was s ubmitted to the expert panel for review and consensus through three iterative rounds of the Delphi process.

In the context of Delphi studies, selecting an appropriate threshold is essential to guide decision-making and establish the validity of findings. A widely accepted threshold is a mean score of 4.0 or higher on a likert-type scale, along with a minimum of 75% agreement among experts. The rationale for this criterion is to ensure a strong level of expert agreement in qualitative assessments.

Previous studies have suggested that consensus thresholds in Delphi studies may vary, with many recommending at least a 60% to 75% agreement to validate results effectively.[24] Moreover, Delphi panels typically predefine a percentage threshold for consensus, often ranging from 51% to 100%, with 75% representing a decisive majority and reflecting a robust consensus.[25] Therefore, using a mean score threshold of 4.0 or higher and a 75% agreement rate in this study aligns with established best practices, helping to ensure clarity, reduce bias, and validate the credibility of expert consensus outcomes.

Stage II: Initial survey

Before being submitted to the expert panels for the Delphi process, the proposed components and subcomponents were reviewed by four academicians to assess the readability and feasibility of the module. Based on their feedback, the initial components and subcomponents module were refined and finalized for use in the Delphi technique (Table I). Expert panel members of the Delphi technique must meet specific criteria: (i) they must be knowledgeable and experienced in the area of study, (ii) capable of active participation, (iii) able to communicate effectively, and (iv) available during the study period.[26] In Delphi methodology, a small number of expert panelists can be sufficient to yield meaningful results.[19,27] For this study, 10 expert panels were selected to participate in the Delphi process. They were the breast cancer patients, counselors, religious leaders, a medical specialist, and a matron.

Table I: Initial components and sub-components of Resilience module for breast cancer survivors

No	Component	Subcomponents	
1	Emotional	1	Emotional flexibility - Positive feeling
		2	Emotional self-regulation/self-control skills
2	Cognitive	3	Mental flexibility
		4	Positive thought
		5	Optimistic view
		6	Gratitude
3	Knowledge	7	Knowledge of cancer diagnosis
		8	Intelligent
4	Physical	9	Physical fitness - Exercise status
		10	Physical health - Good nutrition intake
		11	Physical Activities
5	Religion and spirituality	12	Religious coping - religious belief
		13	Spiritual relaxation activities
		14	Regular religious attendance
		15	Commitment of core values
		16	Flexibility and tolerance of other's belief
6	Social support	17	Social networking - friend/neighbour
		18	Medical professional
		19	Cancer group
		20	Resilient role model
7	Family support	21	Nucleus family
		22	Extended family
8	Mental health	23	Mental health
9	Financial	24	Financial status
10	Others	25	Self-efficacy
		26	Cancer stages
		27	Gender

Stage III: Seeking a consensus via the Delphi study

Delphi Round 1

In the first round, expert panelists were emailed an invitation letter, the module, and informed consent form. The module consisted of 10 components and 27 subdomains. The participants were asked to review and rate each domain and items using a 5-point likert scale ranging from I (extremely not important) to 5 (strongly very important). They were also encouraged to suggest addition, modification, or removal of components or

subcomponents as appropriate. The mean scores and percentage agreement (ratings of "important" or "very important") were calculated to determine the level of consensus for each item. These results were then used to revise the questionnaire and prepare it for the second round of the Delphi process.

Delphi Round 2

In the second round, the expert panelists were once again asked to review the responses obtained from the previous round and rate each item using the same 5-point likert scale. The objective of this round was to seek consensus among the participants. The collected data were them analyzed to determine the level of agreement and refine the proposed components accordingly.

Delphi Round 3

In the third round, each Delphi panelist received a questionnaire that included the components, subcomponents, and aggregated ratings from the previous round, as summarized by the researchers. The panelists were invited to reconsider their judgments to help achieve consensus. They were asked to review their prior responses, re-rate the items using the same scale, and provide any additional comments. Selected comments are cited in the text, while others are presented in the results of Delphi Round 3.

This round successfully established consensus on the components and subcomponents of the proposed resilience module for breast cancer survivors. The mean score represented the importance of each items of components and subcomponents, while the percentage agreement represented the proportion of panelists rating an item as "important" or "very important. A mean score of 4.0 or higher, along with a percentage agreement of 75% or more, was considered indicative of consensus.[20,21]"

RESULTS

Profile of Delphi expert panels

A total of 10 expert panelists participated in all three rounds of the modified Three-Round Modified Delphi study. The majority of participants were female (70%), while the remaining 30% were male. In terms of professional experience, nine experts possessed more than five years of relevant service, while one participant was a cancer survivor provided valuable insights based on lived experience with a breast cancer diagnosis. Among the panelists, three experts (30%) were medical specialists including two psychiatrists and one pathologist. Another three experts (30%) comprised of matron (head nurse), a clinical psychologist and a counselor. The remaining four experts (40%) included two religious leaders, an educator, and the breast cancer survivor (Table II).

Table II: Profile of the Delphi expert panels.

Item	Round 1	Round 2	Round 3
Gender, n(%)			
Male	3 (30%)	3 (30%)	3 (30%)
Female	7 (70%)	7 (70%)	7 (70%)
Work experience (years) n (%)			
< 5	1 (10%)	1 (10%)	1 (10%)
> 5	9 (90%)	9 (90%)	9 (90%)
Background, n (%)			
(Medical doctor)	3 (30%)	3 (30%)	3 (30%)
Psychiatrists	2		
Pathologist	1		
(Non-medical doctor)	7 (70%)	7 (70%)	7 (70%)
Matron	1		
Clinical psychologist	1		
Counsellor	1		
Religious counsel	2		
Educator	1		

Delphi Round 1

Following the expert panels' evaluation of the questionnaire, all ten components and 27 subcomponents were retained. The median (M), interquartile range, and quartile deviation (QD) were calculated for Delphi Rounds 1, 2, and 3. In the first round, the QD values for all subcomponents ranged from 0.38 to 1.38. Subcomponents 8 and 27 recorded QD values greater than 1.0 specifically, 1.38 and 1.25 indicating a low level of consensus was low and, therefore no consensus. Although these two subcomponents did not meet the consensus threshold (QD>1.0), they were still rated as "important" or "very important" with a median of 4 or higher. In contrast, the remaining subcomponents had QD Values less than or equal to 0.5 (QD<0.5), reflecting a high level of consensus and importance. Furthermore, the median (M) scores were used to assess overall expert agreement. All subcomponents recorded median scores of 4.0 or above (M>4), indicating a generally high level of consensus across the panel.

Delphi Round 2

In the second round of the Delphi process, modifications were made to the subcomponents based on expert feedback from Round 1. However, subcomponent 8 continued to show a low and no consensus, while a quartile deviation (QD) value remaining above 1.0 (QD>1.0), indicating a persistent disagreement among experts. The median (M) scores were used to further analyse the level of expert consensus. For subcomponent 27, the median score was less than 3.5 (M=3), indicating limited perceived importance. Nevertheless, subcomponent 27 showed some improvement in agreement with a QD value of 1.0, suggesting a moderate level of consensus. This outcome may indicate that some experts continued to rate the subcomponent as "not relevant" (scale rating of 2), despite the modifications made in response to their previous comments. In contrast, all remaining subcomponents demonstrated high level of consensus, with QD value less than or equal to 0.5 (QD≤0.5) and median scores of 4.0 or above. These results reflect strong agreement among the expert panel regarding the importance of those subcomponents.

Delphi Round 3

In the third round of Delphi process, further modifications were made based on expert feedback. Despite these efforts, subcomponents 8 and 27 still failed to reach acceptable level of consensus and were therefore removed from consideration. Both subcomponents showed low consensus and importance, with QD values of 1.375 and 1.0, respectively. Additionally, the median scores for these subcomponents were below 3.5, with an average of 3 (M=3), indicating low perceived relevance among panelists. Subcomponents 7 and 22 showed differing results. Although both had QD values of 0.875 (QD>0.5), indicating moderate consensus, they were still regarded as "important" and "very important", with median scores above 4 (M>4). All remaining subcomponents, excluding subcomponents 7, 8, 22, and 27, achieved high levels of consensus, with QD values less than or equal to 0.5 (QD≤0.5), and were considered "important" and "very important" with median scores of 4.0 or higher. The final results of all three Delphi rounds are summarized in Table III,

Table III: Consensus in resilience module component and subcomponent for breast cancer through Three-Round Modified Delphi Technique

Bil	Component	Sub components	Round of Delphi								
			Round 1			Round 2			Round 3		
			Median	Mean	QD*	Median	Mean	QD*	Median	Mean	QD*
1	Emotional	1	5	4	0	5	4	0	5	4	0.375
		2	5	4	0.38	5	4	0.375	5	4	0
		3	5	4	0	5	4	0	5	4	0
2	Cognitive	4	5	4	0	5	3	0.5	4.5	3	0.5
		5	5	2	0	4.5	3	0.5	4	3	0.5
		6	5	4	0.38	5	4	0	5	4	0.375
3	Knowledge	7	5	3	0.5	5	3	0.375	5	3	0.875
		8	4	1	1.38	3.5	1	1.375	3	1	1.375
		9	4	1	1	5	4	0	5	3	0.5
4	Physical	10	5	4	0	5	5	0	5	4	0
		11	5	3	0.38	5	4	0	5	4	0.375
		12	5	5	0	5	5	0	5	5	0
5	Religion and spirituality	13	5	1	0	5	4	0.38	5	5	0
		14	4	1	0.5	5	3	0.375	5	3	0.375
		15	5	2	0	5	4	0	5	2	0.375
		16	4	3	0.38	4	3	0.5	4	3	0
6	Social support	17	5	4	0	5	5	0	5	5	0
		18	5	3	0	5	3	0.5	5	4	0
		19	5	4	0.5	5	4	0	5	3	0
		20	4	1	0.38	4.5	4	0.5	4	4	0.5
7	Family support	21	5	3	0.88	5	3	0	5	3	0
		22	5	2	0	4	2	1	4.5	2	0.875
8	Mental health	23	5	2	0	5	4	0	5	4	0
9	Financial	24	5	2	0	5	4	0.375	5	4	0
		25	5	3	0	5	4	0	5	3	0
10	Others	26	5	3	0.38	4.5	1	1	5	3	0.5
		27	5	1	1.25	3	1	1	3	2	1

Finally, the researchers achieved a high level of consensus from the Delphi expert panel on ten components and twenty-five subcomponents of the resilience module (Table IV).

Table IV: The final components and subcomponents of the resilience module for breast cancer

No	Component	Subcomponents	
1	Emotional	1	Emotional flexibility - Positive feeling
		2	Emotional self-regulation/self-control
2	Cognitive	3	Mental flexibility
		4	Positive thought
		5	Optimistic view
		6	Gratitude
3	Knowledge	7	Knowledge of cancer diagnosis
4	Physical	9	Physical fitness - Exercise status
		10	Physical health - Good nutrition intake
		11	Physical Activities
5	Religion and spirituality	12	Religious coping - religious belief
		13	Spiritual relaxation activities
		14	Regular religious attendance
		15	Commitment of core values
		16	Flexibility and tolerance of other's belief
6	Social support	17	Social networking - friend/neighbour
		18	Medical professional
		19	Cancer group
		20	Resilient role model
7	Family support	21	Nucleus family
		22	Extended family
8	Mental	23	Mental health
9	Financial	24	Financial status
10	Others	25	Self-efficacy
		26	Cancer stages

DISCUSSION

The aim of the study was to achieve expert consensus on the components and subcomponents of a resilience module tailored for breast cancer survivors. Initially, ten components and 27 subcomponents were proposed to the panel of experts. After three Delphi rounds, a high level of consensus was achieved on ten components and 25 subcomponents of the resilience module. However, the subcomponents 8 (intelligence) and 27 (gender) were removed due to low consensus. Previous research supports this exclusion, suggesting that psychological constructs are more influential for resilience than inherent traits such as gender or intelligence.[28] For example, one study found that while the clinical stage of cancer correlated with resilience, variables including age, marital status, and socio-economic status did not show a significant relationship with resilience.[29] In fact, by emphasizing the adaptive skills and coping strategies, patients can enhance their resilience and quality of life, not through cognitive intelligence or gender, but by fostering effective emotional responses when dealing with cancer.[30] This finding suggests that resilience is influenced more by environment and relational factors than by inherent traits such as gender or intelligence.

Almost all the components and subcomponents were rated as highly important, with only a few receiving lower levels of consensus. These findings are consistent with previous studies which identified emotion, knowledge, physical, religious and spiritual, social support, family support, and mental health as key domains from the perspective of cancer survivors.[15,17,31-33] The following discussion will justify why these subcomponents received strong consensus from the expert panels. Breast cancer is often a traumatic experience, and many survivors face emotional challenges such as anxiety, depression, fear, and others. Therefore, strong emotional support from family, friends, and healthcare providers is essential. Emotional abilities, such as emotional intelligence, emotion management, mood repair, and coping, play a crucial role in the quality of life of breast cancer survivors.[34] The high level of consensus on the emotional subcomponent reflects its central and unique role in survivorship care.

The cognitive component is essential for breast cancer survivors, as many experience changes in cognitive functioning, including difficulties with memory, attention, and concentration. As a result, cognitive rehabilitation programs are important to help survivors manage these challenges effectively. In addition, breast cancer survivors need accurate and up-to-date information about their diagnosis, treatment options, and potential long-term effects to make informed decisions about their health and well-being. These considerations support the strong consensus on cognitive subcomponents, highlighting the critical role of cognition in overcoming the challenges faced by breast cancer survivors. Similarly, the physical component is equally important and was appropriately prioritized by the expert panels. Breast cancer survivors often endure a range of physical side effects from treatment, such as fatigue, pain, and lymphedema. Interventions like exercise and physical therapy have been shown to alleviate these symptoms and enhance overall physical functioning.[35] The high consensus on the physical subcomponents reflects their practical relevance in supporting recovery and improving quality of life.

A previous study found that religion and spirituality can serve as an important sources of comfort and support for many breast cancer survivors.[27] The strong agreement among expert panelists on the significance of religion and spirituality as tools for resilience reinforces the findings. For example, Malaysian participants frequently emphasized the role of "tawakkal" (trust in God) and "solat" (prayer) as powerful sources of emotional strength. This cultural dimension highlights the need for tailored psychosocial interventions that respect and incorporate diverse spiritual practices, thereby promoting a more inclusive and culturally relevant approach to building resilience among breast cancer survivors in Malaysia. Similarly, social support from family, friends, and support groups plays a critical role in helping survivors cope with the emotional and physical challenges of diagnosis and treatment.[36] Moreover, family members of breast cancer patients often face their own emotional and practical burdens. Family support programs are therefore essential not only for patients but also for their loved ones, helping to create a more supportive and resilient care environment.[36]

The breast cancer survivors may experience anxiety, depression, and other mental health challenges. These challenges can arise from physical issues such as illness or disability, psychological stress, family-related concerns, and social factors, including challenges related to employment, insurance, and supportive care access Mental health services such as counseling and psychotherapy are essential in addressing these concerns.[37] Additionally, financial burdens can significantly affect the well-being of breast cancer survivors. The high cost of treatment, coupled with potential loss of income and other related expenses, can lead to financial distress. Financial counseling and support programs play a vital role in helping survivors manage these economic challenges.[38] The expert panel's strong consensus on the importance of mental health and financial status subcomponents highlights their critical relevance. This is supported by various sources, including the report Supporting Child and Student Social, Emotional, Behavioral, and Mental Health Needs by the U.S. Department of Education, which underscores the importance of mental health across all life stages.[39]

The findings of this study underscore the need for a resilience framework specifically tailored the to breast cancer survivors in Malaysia. This has important implications for both future research and clinical practice. In terms of clinical applications, interventions such as resilience training programs designed explicitly for breast cancer survivors could be developed and implemented. These programs may include modules focused on enhancing social support, strengthening coping mechanisms, fostering optimism, and integrating spirituality elements that are culturally relevant and aligned with the survivors' needs.

Group therapy sessions can foster peer support and shared experiences, providing a sense of community and mutual understanding among breast cancer survivors. Individual counseling, on the other hand, may enhance personal coping strategies and foster greater optimism. Additionally, incorporating religious and spiritual counseling into oncology care is essential for addressing the unique cultural and spiritual needs of Malaysian patients. Future research should evaluate the effectiveness of these interventions in improving psychological well-being and treatment outcomes. Ultimately, such efforts would support a more comprehensive, patient-centered approach to cancer care that prioritizes resilience as a core component of recovery and survivorship.

The findings of this study highlight the critical importance of developing a resilience framework specifically tailored for breast cancer survivors in Malaysia. This has significant implications for both future research and clinical practice. Clinically, targeted interventions such as resilience training programs can be implemented to support survivors throughout their recovery journey. These programs may include structured modules focusing on social support, effective coping strategies, optimism, and spirituality in which these components identified as particularly relevant within the Malaysian cultural and healthcare context. For instance, a study conducted in South Korea identified resilience as a key coping resource, with its effectiveness significantly enhanced by the presence of social support. This mirrors the Malaysian context, where family and community

support play a vital role in stress adaptation.[40] Similarly, previous research has shown that resilience is closely tied to socio-cultural dynamics, with individuals from collectivist societies often exhibiting higher resilience due to strong interpersonal relationships.[29]

In European populations, resilience outcomes have been found to vary based on cultural attitudes toward illness and coping mechanisms.[13] Studies from various countries including China also suggested that resilience mediates the relationship between psychological well-being and quality of life in cancer survivors.[41-42] This body of research underscores the universal value of resilience in mitigating distress and improving overall health outcomes. Nevertheless, while the experience of breast cancer is a shared global challenge, the frameworks through which resilience is developed and expressed are shaped by cultural context. In Malaysia, resilience is deeply influenced by local beliefs and support systems, highlighting the need for culturally sensitive approaches to supportive care.[43] These findings reinforce the importance of tailoring resilience frameworks to reflect the unique social responses and collective coping strategies found across different societies.

In developing a resilience module for breast cancer patients, it is essential to draw upon elements from existing psycho-oncology interventions that support psychological well-being during treatment and recovery. Research indicates that interventions aimed at enhancing resilience can lead to improved coping mechanisms, reduced psychological distress, and better overall quality of life for breast cancer patients.

Multiple practical approaches have been recommended in the literature to incorporate resilience components into psycho-oncology care. First, resilience training should integrate evidence-based therapeutic modalities such as Cognitive Behavioral Therapy (CBT), Acceptance and Commitment Therapy (ACT), and mindfulness techniques.These methods enhance psychological flexibility and can be tailored to meet individual patient needs.[10,44,45] Second, continuous assessment of resilience and mental health should be standardized within oncology settings. This enables clinicians to personalize care based on ongoing patient feedback and adjust coping strategies accordingly.[46] Third, digital health tools such as mobile applications can play a critical role in facilitating resilience training by providing accessible, ongoing support and enabling patients to engage with resilience-building exercises at their own convenience.[47] In addition, training healthcare professionals through educational programs focused on resilience promotion skills can further enhance the effectiveness of psycho-oncology interventions.[45,48] By embedding these multifaceted components into existing psycho-oncology interventions, healthcare providers can strengthen patient resilience, ultimately contributing to improved psychological outcomes and quality of life for breast cancer survivors.

In summary, breast cancer survivors face a wide range of challenges that affect their emotional, cognitive, physical, and mental health, as well as their social and financial well-being. The findings of this study indicate that the expert panels reached a high level of consensus on these key subcomponents, reinforcing their relevance and importance. Based on this consensus, the present study proposes a set of initial components and subcomponents for a resilience module specifically designed for breast cancer survivors.

Study Limitation

Several limitations may affect the generalizability and robustness of the study's findings. One significant limitation is the relatively small sample size of experts involved in this study. A limited number of participants may not fully capture the diversity of perspectives, opinions, and experiences within the field of breast cancer resilience including a broader panel of representatives such as cancer survivors, multidisciplinary healthcare professionals, and community advocates would enhance the comprehensiveness and applicability of the identified resilience components.[44]

Another important limitation is the potential bias in the expert selection process. In particular, the underrepresentation of breast cancer survivors among the expert panel may have limited the depth of insights from

the lived experience perspective. Given that survivor input is essential for ensuring the relevance and effectiveness of any resilience intervention, future studies should prioritize balanced representation to better reflect the real-world needs of breast cancer survivors. The absence of survivor voices may skew the recommendations towards the perspectives of healthcare professionals or researchers, thereby limiting the holistic understanding essential for the development of an effective resilience training program.[46]

While the Delphi method is valuable for gathering expert opinions and building consensus, it also has inherent limitations. The Delphi technique relies primarily on the subjective judgments of selected experts. As a result, the depth and quality of the data can vary, since it is shaped by individual experiences, interpretations, and expertise rather than empirical evidence. Consequently, the consensus achieved may not represent an entirely objective or comprehensive viewpoint but may instead reflect the specific biases, perspectives, or knowledge gaps of the expert panel.[49,49]

CONCLUSION

The present study has developed a resilience module for cancer survivors, incorporating credible and evidence-based subcomponents. This tool is particularly valuable, as the breast cancer survivors often lack access to structured resources that address their psychosocial and emotional needs. By proposing this module, the study aims to bridge this critical gap in survivorship care. Furthermore, the resilience module holds relevance not only for individual patients but also for cancer care units, where it can serve as a resource for staff training and development to enhance supportive care practices.

CONFLICT OF INTEREST

The authors disclose that they have no conflicting interests.

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ORIGINAL ARTICLE

Improving Exercise Interventions for Older Adults with Dementia: A Qualitative Exploration of Physiotherapists' Knowledge, Attitudes, and Practices

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ABSTRACT

INTRODUCTION: Dementia creates significant challenges to physical activity management in older adults due to progressive cognitive and behavioural impairments. Physiotherapists serve a critical role in designing exercise interventions. However, the lack of standardized dementia-specific training compromises the efficacy of care. Despite evidence on the benefits of physical activity for older adults with dementia (OAwD), the physiotherapists' knowledge, attitude, and practices (KAP) to meet these specific needs remains unclear. This qualitative study explores the physiotherapists' KAP in exercise prescription, aiming to identify unmet training needs and inform targeted strategies to optimize therapeutic outcomes for OAwD. **MATERIALS AND METHODS:** A qualitative approach was used, employing semi structured interviews with 9 physiotherapists experienced in dementia care. Participants were selected through purposive sampling to capture diverse expertise. Data was analysed through thematic analysis uncovering patterns and insights related to KAP and its impact on care delivery. **RESULTS:** Four central themes emerged: Knowledge (theme 1), attitudes (theme 2), and practices (theme 3 and theme 4). Firstly, physiotherapists emphasized the importance of comprehensive assessments, utilizing tools such as the 'Timed Up and Go test' and 'Montreal Cognitive Assessment'. Secondly, patience and adaptability were highlighted as essential due to cognitive decline associated with dementia. Thirdly, caregiver involvement and education were essential. Fourthly, goal oriented and functional exercises were prioritized. **CONCLUSION:** Physiotherapists showed a strong understanding of dementia care but highlighted the need for enhanced, specialized training. Addressing these gaps could improve exercise interventions and foster better health outcomes for OAwD.

Keywords
Attitude, dementia, exercise, knowledge, practice

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INTRODUCTION

Dementia, a group of disorders characterized by cognitive decline, increasingly impacts the health and daily functioning of older adults.[1] Cognitive impairment in dementia increases fall risk due to postural instability, reduces individual's attention to balance and gait, reduces ability to adapt towards environment obstacles, muscle weakness, and functional limitations, compounding the challenges of physical activity engagement.[2,3] These physical deficits, combined with behavioural changes and emotional challenges, often interfere with the ability to participate in structured exercise, further exacerbating health decline in individuals with dementia.[3,4] Falls and their associated consequences lead to substantial healthcare costs, impacting families and national economies alike.[5] Current projections estimate the global number of older adults with dementia (OAwD) to surge from 57.4 million in 2019 to 152.8 million by 2050, signalling a pressing need for effective healthcare interventions.[6] In Malaysia, the prevalence of dementia among those aged 60 years old and above is estimated between 8.5%-14.3%, with expectations of continued growth.[7,8] Given this rising prevalence, enhancing healthcare services to address dementia-specific needs has become an urgent priority.

Physical exercise, an intervention with established benefits for muscle strength, balance, mobility, and endurance, is essential in promoting health and functional independence among OAwD.[9,10] Systematic reviews affirm that exercise can mitigate fall risk when tailored to individual's capabilities and interests, promoting engagement and adherence.[11] According to WHO guidelines, older adults should engage in at least 150 minutes of physical activity per week to achieve optimal health outcomes.[12] However, adherence to these recommendations can be challenging for OAwD, due to limited awareness of the benefits of physical activity, cognitive and behavioural barriers, and the difficulty of sustaining engagement in structured programs.[13]

Physiotherapists, as frontline healthcare providers, play a critical role in designing and implementing exercise programs for OAwD, yet there are notable gaps in dementia-specific training and confidence in handling behavioural and cognitive symptoms.[14,15] Previous studies highlight a need for physiotherapists to receive training tailored to the unique challenges of dementia care, as limited knowledge and skills can compromise the quality of care.[14,16] While some research has explored the general management of OAwD, there is limited focus on the specific knowledge, attitudes, and practices (KAP) of physiotherapists regarding exercise prescription for this population. This gap in the literature underscores the need for further investigation into how physiotherapists approach exercise prescription for OAwD, and how these approaches might be refined to enhance patient outcomes.

The current study aimed to address this knowledge gap by using a qualitative approach to explore the knowledge, attitudes, and practices of physiotherapists in exercise prescription for OAwD. Through in-depth interviews and thematic analysis, this study sought to identify key areas where physiotherapists excel and areas where additional support or training may be beneficial. Findings from this research are expected to contribute valuable insights into enhancing the quality of physiotherapy care for OAwD, ultimately informing more effective interventions that can improve patient engagement, safety, and functional outcomes.

MATERIALS AND METHODS

Study design

This study employed a qualitative research design, specifically a descriptive approach, to explore KAP of physiotherapists in prescribing exercise for OAwD. Qualitative methods were chosen to gain an in-depth understanding of the nuanced perspectives and practices of physiotherapists in dementia care. The study was conducted as part of a broader mixed-methods project focusing on exercise interventions for OAwD, with ethical approval granted by the Universiti Kebangsaan Malaysia Research Ethics Committee (JEP-2021-899).

Theoretical framework

The study applied the KAP model as a guiding framework.[17] This model posits that knowledge informs attitudes, which subsequently shape practices, making it well-suited for exploring how physiotherapists approach exercise prescription for OAwD. To capture the complexity of their behaviours, a qualitative approach was adopted to move beyond the limitations of traditional KAP surveys and allow for a more detailed exploration of the emotional and contextual factors influencing exercise prescription.

Participant selection

Purposive sampling was used to recruit physiotherapists with relevant experience in dementia care, aiming for diverse perspectives within the sample. Inclusion criteria required participants to hold a Bachelor's Degree in Physiotherapy which is verified by their workplace Human Resources Department, possess a minimum of two years of clinical experience in geriatric care and other clinical areas, as well as have direct experience in exercise interventions for OAwD. Physiotherapists were recruited through the alumni network of the Universiti Kebangsaan Malaysia, ensuring a selection of individuals with specialized expertise. Of the 20 individuals contacted, 12 expressed interests, and 9 were ultimately interviewed to achieve data saturation, indicated by a less than 5% threshold for new information in the final interviews.[18]

Data collection

Prior to data collection, written informed consent was obtained, with participants retaining a copy. For virtual interviews, e-consent forms were signed electronically. Data was collected through semi-structured, in-depth interviews conducted between January-March 2024. A semi-structured interview guide was designed to align with the study objectives, focusing on key areas of knowledge, attitudes, and practices in exercise prescription for OAwD. The guide included open-ended questions and follow-up prompts were used (such as *'Can you elaborate on that? Can you explain further? How did you feel about that? Can you give an example?*') that encouraged participants to elaborate on their perspectives in greater depth. Key questions asked were: (i) *What is your opinion on the knowledge of physiotherapists in prescribing exercise for OAwD?,* (ii) *What is your opinion on the attitudes of physiotherapists in prescribing exercise for OAwD?,* and (iii) *What is your opinion on the practices of physiotherapists in prescribing exercise for OAwD?*. The interview guide was piloted with two physiotherapists, who were excluded from this study, and refined for clarity. The questionnaires were confirmed through discussion among three research members which were guided by previous studies.

Two trained researchers (N.I. and N.M.) jointly conducted the interviews in either Malay or English, based on the participants' language preference to ensure their comfort and facilitate the accurate expression of nuanced perspectives. Both researchers received joint training using a standardized interview guide. Initially, N.M. led the interviews while N.I. observed, until N.I. gained sufficient confidence and competence to conduct the interviews independently. For participants practicing outside the Hospital Canselor Tuanku Muhriz (HCTM), virtual interviews were held via online platform namely Google Meet or Zoom. In-person interviews were conducted at HCTM for available participants. Each session, lasted 30-45 minutes, was audio-recorded with the consent of the participants to ensure accurate data capture.

Data analysis

A deductive thematic analysis approach was employed to analyse the qualitative data, following Braun and Clarke's six-phase framework.[19] Recorded interviews, conducted in both Malay and English were transcribed verbatim to preserve the richness of narratives of the participants. Thematic analysis was performed using the original transcripts in their respective languages. Researchers (N.I. and N.M.) began by familiarizing themselves with the transcripts in their original languages, conducting multiple readings to identify initial patterns and themes. Coding was performed iteratively, with codes grouped into categories that captured core insights into physiotherapists' KAP in exercise prescription. Through a reflexive and iterative process, broader themes were generated, representing commonalities and nuanced perspectives. Regular team discussions were held to compare and refine emerging themes, ensuring conceptual alignment regardless of language structure. This process helped to minimize the risk of language-based discrepancies and ensured that the themes reflected equivalent meanings and interpretations in both Malay and English. To enhance rigor, bilingual researchers (N.M., N.A.A., and M.A.A.) independently reviewed coded data and emergent themes, refining the findings to ensure validity and credibility. All relevant quotes originally in Malay were translated into English by bilingual researchers (N.M., N.A.A., and M.A.A.), and then back-translated to ensure accuracy and preserved both linguistic and contextual consistency. In addition, to establish trustworthiness, several methodological strategies were employed. Member checking was conducted, allowing participants to validate and clarify key interpretations, thus enhancing the credibility of the findings. Participants were provided with summaries of their interview transcripts and preliminary themes for feedback. No changes were made to the interpretation of the data. Additionally, the use of peer debriefing among researchers contributed to consistency and reduced researcher bias. Through ATLAS.ti software is often recommended for managing qualitative data, manual

analysis was preferred due to the manageable size of transcripts, enabling a more immersive engagement with the data. Analysis occurred iteratively, preliminary coding after each interview, with full thematic development after all 9 interviews were completed.

RESULTS

The study included 9 physiotherapists (5 females, 4 males) with experience working with OAwD. Of the 20 alumni contacted, 12 responded, and data saturation was achieved after 9 interviews. Participants were primarily Malay (6 Malays, 3 Chinese), aged between 27-39 years old. All held Bachelor's Degrees in Physiotherapy, areas of practice include: musculoskeletal (n=6), neurology (n=5), geriatric (n=4), and cardiorespiratory (n=2). They were employed in hospitals across Kuala Lumpur (n=5), Selangor (n=1), Kedah (n=1), Kelantan (n=1), and Melaka (n=1), with experience ranging from 3-14 years (Table I).

Four main themes emerged from the analysis of the physiotherapists' perspectives on exercise prescription for OAwD: (1) comprehensive assessment and safety considerations, (2) patience, adaptability, and communication, (3) caregiver involvement and support, and (4) goal-oriented and functional exercises. These themes reflect the knowledge (theme 1), attitudes (theme 2), and (theme 3 and theme 4) practices of physiotherapists in dementia care, highlighting both strengths and challenges in their approaches.

Knowledge

Theme 1: Comprehensive assessment and safety considerations

Physiotherapists emphasized the need for dementia-specific assessments to ensure safety and effectiveness in exercise interventions for OAwD. Recognizing that cognitive impairments and psychological challenges, including memory loss, depression, and aggression significantly impact physical abilities, physiotherapists reported the importance of conducting thorough evaluations to inform exercise plans. Several physiotherapists expressed the need for *"evaluating cognitive function using tools like the Montreal Cognitive Assessment (MoCA)"* to understand the cognitive level and tailor interventions accordingly (P3). The 'Timed Up and Go' (TUG) test was frequently used to assess balance, functional status, and fall risk, with physiotherapists noting its usefulness in guiding safe exercise intensity and progression.

Patient safety was a consistent focus, with participants reporting high vigilance in monitoring patients' medical histories, including hypertension, diabetes, and mobility limitations, as these could increase the risk of falls. Physiotherapists stressed the importance of assessing vital signs and preparing necessary support measures, such as mobility aids and seating arrangements, to reduce risks. One participant highlighted, *"We prepare chairs for resting, have walking aids available, and ensure that at least two physiotherapists are on standby in case of a fall,"* showing the collaborative safety protocols involved in managing OAwD (P6).

Attitudes

Theme 2: Patience, adaptability, and communication

Effective exercise prescription for OAwD required physiotherapists to be patient, adaptable, and skilled in varied communication techniques. Cognitive challenges among patients often necessitated repeated instructions, with some physiotherapists noting that *"repeating exercises multiple times was essential for memory retention and engagement"* (P1). The need for adaptive strategies was evident, as participants described frequently adjusting their communication styles, using a combination of verbal cues, demonstrations, and non-verbal methods such as touch, to enhance understanding and cooperation.

Physiotherapists also relied on flexibility in exercise routines, adapting methods based on patients' responses and levels of engagement. If a patient was resistant or unresponsive, physiotherapists would *"let go of rigid expectations and find alternative ways to facilitate participation"* (P7). This flexible approach allowed physiotherapists to maintain a supportive environment while reducing frustration for both patients and themselves. Participants indicated that collaboration with caregivers was valuable in extending this adaptability, as caregivers could reinforce exercises at home, promoting long-term engagement and continuity.

Table I: Demographic profile of the participants

Participant	Age	Gender	Ethnicity	Education	Areas of practice	Workplace	Years in service
P1	39	Male	Malay	Bachelor's Degree	Musculoskeletal	Kuala Lumpur	14 years
P2	35	Female	Malay	Bachelor's Degree	Cardiorespiratory	Kuala Lumpur	10 years
P3	29	Male	Malay	Bachelor's Degree	Neurology	Kuala Lumpur	4 years
P4	27	Male	Malay	Bachelor's Degree	Musculoskeletal	Kuala Lumpur	3 years
P5	32	Male	Chinese	Bachelor's Degree	Musculoskeletal; Neurology; Geriatric	Kuala Lumpur	7 years
P6	29	Female	Malay	Bachelor's Degree	Musculoskeletal; Neurology; Geriatric	Kedah	4 years
P7	30	Female	Malay	Bachelor's Degree	Musculoskeletal	Kelantan	5 years
P8	27	Female	Chinese	Bachelor's Degree	Musculoskeletal; Neurology; Cardiorespiratory; Geriatric	Selangor	3 years
P9	32	Female	Chinese	Bachelor's Degree	Neurology; Geriatric	Melaka	7 years

Practices

Theme 3: Caregiver involvement and support

Caregiver involvement emerged as essential in supporting exercise adherence and continuity for OAwD. Physiotherapists consistently involved caregivers during sessions, educating them on exercises to reinforce routines at home and ensure safety. This involvement was viewed as crucial for the patient's progress and well-being, with caregivers providing motivation and support beyond the clinical setting. One physiotherapist explained, *"Caregivers should be involved so they can understand how to assist with exercises at home,"* illustrating the collaborative approach needed in dementia care (P4).

In addition, physiotherapists emphasized educating caregivers not only on the exercises themselves but also on strategies to motivate and support the patient regularly. Frequent reminders and encouragement were necessary to counter patients' memory impairments, which often made it difficult for them to maintain exercise routines independently. Equipping caregivers with these tools ensured that patients could benefit from consistency in care and engagement even outside of therapy sessions.

Theme 4: Goal-oriented and functional exercises

Physiotherapists stressed the importance of goal-oriented and functional exercises to enhance both physical and cognitive engagement in OAwD. Rather than focusing on isolated strength training, exercises were integrated into daily routines, emphasizing practical, functional movements such as standing up from a chair or reaching for familiar objects. This alignment with real-life activities was found to increase patient engagement, as it provided relevance and familiarity, helping patients connect exercises to their daily needs. One participant shared, *"For dementia, we focus on functional exercises instead, as these are more relevant and easier for patients to engage with"* (P9). Setting specific, goal-oriented tasks also supported patient motivation by giving them a clear purpose for each exercise. For example, physiotherapists structured exercises around meaningful objectives, such as *"walking toward a target"* or *"reaching for an object,"* which helped patients grasp the purpose of their movements (P8). This approach fostered a sense of achievement and encouraged compliance with the exercise regimen, as patients could better understand and relate to the goals.

Participants also recognized the role of familiar environments and routines in overcoming cognitive challenges. Engaging in exercises within well-known settings helped reduce the cognitive load for patients, making it easier for them to participate effectively. One physiotherapist noted, *"If we bring the patient near a familiar area, it prompts recognition, and they can engage more easily"* (P9). By embedding exercises in familiar contexts, physiotherapists created a patient-centred approach that supported sustained engagement and functional improvement for OAwD. Common exercise prescription practices among participants for OAwD are summarized in Table II.

Table II: Physiotherapist exercise prescription practices for older adults with dementia (extracted from the interview)

	Type of exercise	Duration	Frequency	Intensity	Diversity of exercises
P1	Balance, strength, cardiovascular, functional activities of daily living	45min or 20-30min	1x/day or 2x/day	Low - moderate	Image illustration
P2	Cardiovascular	5-15min/exercise, 30min cardio,	150min/week,	Moderate	Home exercise, group exercise, community programs
P3	Balance, strength, cardiovascular, flexibility, mobility	30min	1x/day or 150min/week	Low	Based on interests, dyadic exercise, play exercise, gardening
P4	Balance and coordination, strength	40-45min	2x/week	Moderate	Visual cues, cognitive exercises
P5	Balance, strength, flexibility, mobility, functional activities based on daily	60min (10min/exercise)	1x/day or 3x/week	Low – moderate (Dependent on frequency)	Video exercises, fall prevention education
P6	Balance, strength, mobility, functional activities of daily living	30min,	3-5x/week	Moderate	Cognitive exercises
P7	Balance, strength	30-50min (10min rest)	3-5x/week	Low - moderate	Simple exercise
P8	Functional activities of daily living	30-45min	3-4x/week (with physio) or 1x/day (with caregiver)	Depending on the ability	Group play exercises (according to creativity)
P9	Balance, strength, mobility, and functional activities of daily living	60min (15min/exercise)	Depending on the caregiver's readiness	Low – moderate	Short and enjoyable exercises

DISCUSSION

This study aimed to explore physiotherapists' KAP regarding exercise prescription for OAwD. Through thematic analysis of in-depth interviews, 4 primary themes were identified: Knowledge theme was (1) comprehensive assessment and safety considerations, Attitude theme was (2) patience, adaptability, and communication, and Practices theme was (3) caregiver involvement and support, and (4) goal-oriented and functional exercises. These findings provided insights into the roles and challenges faced by physiotherapists in managing exercise interventions for OAwD.

The results underscore that while physiotherapists possess a foundational understanding of dementia, there is a clear need for additional dementia-specific training to enhance the quality of care. The physiotherapists in this study recognized the cognitive and physical challenges associated with dementia, yet frequently highlighted limitations in specialized knowledge and skills for effectively managing these challenges. For instance, P2 stated *"Not all physiotherapists can handle this population. So, if you really want to do it properly, you need to specialize in geriatrics and you [must] have in-depth knowledge of the psychology of geriatric and dementia patients"*. This aligns with previous research indicating that healthcare providers often lack sufficient dementia-specific education, which can hinder effective treatment.[14,15] The findings here emphasize that comprehensive training programs focused on dementia could empower physiotherapists to deliver safer, more effective, and individualized care to OAwD.

The emphasis on comprehensive assessment and safety considerations in this study supported existing literature on the importance of multi-faceted evaluations in dementia care. Participants frequently highlighted the importance of cognitive assessments, such as the MoCA, alongside physical evaluations like the TUG test to assess balance and mobility.[11] These tools provide critical insights that allow physiotherapists to tailor exercise programs according to patients' specific cognitive and physical abilities. Furthermore, physiotherapists demonstrated awareness of potential health risks, including fall risks, that may arise from the interaction of cognitive decline and physical impairment. Safety-focused strategies, such as preparing adaptive equipment and monitoring vital signs, are essential to minimize risks, a need consistently highlighted across dementia care research.[20,21] Physiotherapists' attentiveness to these considerations reflects a patient-centred approach that prioritizes both safety and therapeutic effectiveness.

The findings related to patience, adaptability, and communication revealed the complexity of engaging OAwD in exercise routines. Physiotherapists described the need for patience and flexible approaches, especially given the cognitive limitations that will make it difficult

for patients to retain instructions and follow routines independently. Participants in the current study noted that repeated instructions and creative adaptations were essential to sustaining patient engagement. Flexibility in exercise methods helped alleviate frustration for both physiotherapists and patients, fostering a supportive atmosphere that encourages participation. The need for collaborative, adaptive approaches in dementia care is well-documented, as healthcare providers often benefit from adjusting interventions based on patient responses.[22]

Caregiver involvement was also a prominent theme, underscoring its significance in facilitating effective exercise interventions. Involving caregivers not only enhances adherence but also supports the continuity of care beyond the clinical setting. Physiotherapists in this study emphasized the necessity of caregiver education, highlighting the importance of teaching the caregivers practical strategies to motivate and guide patients in maintaining their exercise routines. This aligns with findings from Marulappa[23] and Kuluski[24], who stressed that caregivers play an integral role in reinforcing exercise adherence and supporting patients with dementia in managing their daily activities.[23,24] By integrating caregivers into the exercise regimen, physiotherapists foster an environment conducive to sustained engagement, helping to ensure that exercise remains a consistent aspect of OAwD care.

The theme of goal-oriented and functional exercises underscores the value of meaningful, daily-life-based activities in dementia care. Physiotherapists in this study frequently tailored exercises to mirror routine tasks, such as standing from a chair or reaching for familiar objects, to provide patients with a sense of purpose and relevance. This finding resonates with existing literature, which suggests that exercises connected to real-life activities enhance engagement and compliance among patients with cognitive impairments.[10,11] Participants noted that goal-oriented exercises not only motivate patients but also foster a sense of accomplishment, supporting both physical and cognitive well-being. By structuring exercises around familiar tasks, physiotherapists enable patients to draw connections between therapy and their everyday experiences, making interventions more accessible and meaningful.

However, this study has several limitations that may impact the generalizability of the findings. First, the sample size was limited, and participants were selected from specific geographic locations, which may not fully represent the diversity of practices across broader regions or healthcare settings. Additionally, the qualitative design of the study limits the ability to establish causal relationships between physiotherapists' knowledge, attitudes, and practices and the effectiveness of their exercise interventions for OAwD. The reliance on self-reported data may also introduce social desirability bias, as participants may have presented idealized versions of their knowledge and practices. Future studies with larger, more diverse samples and the inclusion of quantitative measures could provide a more comprehensive understanding of physiotherapists' approaches to dementia care.

CONCLUSION

In conclusion, this study sheds light on the critical role of physiotherapists in promoting exercise for OAwD. Physiotherapists demonstrated robust knowledge in safety assessments but expressed gaps in dementia-specific skills (Knowledge). The findings suggested that physiotherapists bring valuable knowledge and adaptive strategies to dementia care, but there remains a need for specialized training to further enhance their effectiveness. By addressing these training gaps, healthcare providers and policymakers could improve the quality of exercise interventions for OAwD, fostering patient engagement, safety, and overall well-being. Physiotherapy attitudes emphasized the critical role of patience, adaptability, and effective communication in facilitating exercise engagement among older adults with dementia, emphasizing the importance of flexible, collaborative approaches tailored to individual needs within physiotherapy practice. Whereas the practices on patient-centred, functional exercises and caregiver involvement highlights the potential for more targeted, supportive interventions in dementia care, contributing to improved health outcomes and quality of life for this growing population.

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

INSTITUTIONAL REVIEW BOARD (ETHIC COMMITTEE)

Ethical approval granted by the Universiti Kebangsaan Malaysia Research Ethics Committee (JEP-2021-899).

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ORIGINAL ARTICLE

The Relationship between Psychological Well-Being and Self-Directed Learning in Medical Students

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ABSTRACT

INTRODUCTION: Student well-being plays a crucial role in influencing self-directed learning (SDL), particularly among medical students who face intense academic demands. This study aimed to assess the levels of psychological well-being and SDL among undergraduate students at the Faculty of Medicine, Universitas Islam Indonesia (FM UII), and to examine the relationship between the two variables. **MATERIALS AND METHODS:** An observational, cross-sectional study design was employed, involving 317 undergraduate medical students from FM UII. Data collection utilized the Indonesian versions of Ryff's Psychological Well-Being Scale and the Self-Directed Learning Readiness Scale. Univariate and bivariate analyses were conducted to evaluate the data and determine correlations. **RESULTS:** Findings revealed that most students demonstrated moderate to high psychological well-being. SDL levels were predominantly high, with 74.8% of respondents reporting a high level of SDL, 25.2% reporting a moderate level, and none reporting low SDL. A statistically significant positive correlation was identified between psychological well-being and SDL ($p=0.000$; $r=0.352$), indicating a moderate relationship. **CONCLUSION:** The results suggest that most medical students at FM UII possess good psychological well-being and strong SDL readiness. A positive correlation between psychological well-being and SDL indicates that students with higher well-being are more likely to be confident and proactive in managing their own learning. These findings highlight the importance of fostering a supportive academic environment that prioritizes student mental health to enhance SDL capabilities. Faculty and educators should therefore integrate strategies that promote psychological well-being to improve learning outcomes.

Keywords
psychological well-being, self-directed learning, medical students

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INTRODUCTION

One of the main objectives of learning in higher education is the achievement of student competencies. The achievement of learning competencies is influenced by many factors, one of which is self-directed learning. Students need self-directed learning (SDL) to support their learning success, especially medical students who study in a student-centred learning system. Student-centred learning is a learning system that requires students to take an active role in the learning process instead of only receiving material from the lecturers as their facilitators. Medical students also need self-directed learning due to the significant amount of learning load and complexity of the learning material.[1]

The high learning load and demand for mastering the competencies in the medical faculty become a stressor for students. Previous studies have shown that the prevalence of stress among medical students is quite high, reaching more than 30%. In addition, many medical students experience anxiety or other psychological disorders, which can lead to mental health disorders.[2,3] This psychological condition can affect students' well-being, especially their psychological well-being.

Psychological well-being is the integration of six dimensions which include the ability of individuals to accept themselves as they are (self-acceptance), establish

a positive relationship with other individuals (positive relation with others), have independence in dealing with social pressure (autonomy), control the external environment (environmental mastery), have a life purpose (purpose in life), and have the ability to materialize and continuously develop their potential (personal growth).[4]

Achieving psychological well-being will have a positive impact on the corresponding dimensions. In the self-acceptance dimension, individuals will feel satisfied with themselves and accept any past events in their lives. In the positive relationship with others and environmental mastery dimensions, individuals will feel the freedom in socializing and be able to create an environment that suits their needs. In addition, in the autonomy and personal growth dimensions, individuals will be able to develop their attitudes and actions without depending on others. In the purpose in life dimension, individuals will focus not only on the past but also on the directed goals which have been set for the future life.[5] A failure to achieve psychological well-being will have an impact on the inability to control situations. This will negatively affect the cognitive, emotional, physiological, and behavioural aspects of individuals.[6] Furthermore, decreased psychological well-being in students is likely to influence their self-directed learning, which will further play a role in reducing student achievement.[7]

Self-directed learning is the attitude of an individual towards being independent of others while going through a learning process, having the freedom to make decisions, and showing great initiative and effectiveness in taking action, which is spurred by self-encouragement or intrinsic motivation to master specific competencies although there is still the possibility of involving others. One of the characteristics of individuals with self-directed learning is that they have the willingness to progress and develop, along with the ability to think critically, creatively, and innovatively.[8] In addition, such individuals can work independently with perseverance and discipline, as well as being able to master the skills in their field.[9]

Both characteristics can be influenced by psychological well-being since they reflect the impact of achieving psychological well-being from the autonomy and personal growth dimensions. Individuals who can take on the autonomy and personal growth dimensions of psychological well-being will be eager to improve their attitudes and actions without relying on others.[5] Several previous studies have examined the correlation between student psychological well-being and students' ability to manage their learning (self-regulated learning). Some findings show that psychological well-being is associated with self-regulated learning.[10] Furthermore, another study specifically assessing self-directed learning and well-being also found that there is a correlation between both aspects.[11,12] However, as far as the researchers are concerned, there have been no studies examining the correlation between psychological well-being and the self-directed learning of medical students who have more specific characteristics compared to students majoring in other subjects. Therefore, this research aims to identify the levels of self-directed learning and psychological well-being of medical students and their correlation.

MATERIALS AND METHODS

This study is an analytical observational study with a cross-sectional design. The population of this study was undergraduate students of the Faculty of Medicine of Universitas Islam Indonesia. The samples were determined by using a proportionate stratified random sampling technique. The inclusion criteria for the research samples were active undergraduate students of the Faculty of Medicine of Universitas Islam Indonesia for the 2021/2022 academic year who had never taken academic leave. Meanwhile, the exclusion criteria were for students who were receiving scholarships, students who were being diagnosed with severe medical disorders in the last month, students who had been or were being diagnosed with psychiatric disorders, and students who were taking psychiatric drugs.

To determine the level of psychological well-being of the respondents, the questionnaire instrument Ryff's Psychological Well-Being Scale (RPWBS) was used. This questionnaire was developed based on the

psychological well-being dimensions invented by Ryff.[4] The psychological well-being instrument used in this study was a form of adaptation by Revelia (2018) with its 43 statement items and 4 answer choices, including "absolutely appropriate", "appropriate", "inappropriate", and "absolutely inappropriate", which were then converted into numbers 1-4 with a Likert scale according to the favourable and unfavourable items.[13] The questionnaire was tested for construct validity with a t value of >1.96 and for reliability with a Cronbach alpha score of 0.810.

Furthermore, the level of students' self-directed learning was measured by using the Self-Directed Learning Readiness Scale questionnaire. The instrument was developed by Guglielmino, containing several questions related to the characteristics, independence, desire, and learning motivation of the respondents.[14,15] This study used the adapted version in the Indonesian language.[16] The questionnaire had been validated with a validity score of r>0.268 and a Cronbach alpha reliability score of 0.90.[17] There were 36 statements to answer with the choices in a Likert scale consisting of "strongly agree", "agree", "neither agree nor disagree", "disagree", and "strongly disagree".

Following the distribution, a total of 355 students from year 1 to year 4 filled out the questionnaire; of this total, 38 responses were excluded from this study since they did not meet the inclusion criteria. The data from 317 respondents was analyzed by using both descriptive analysis and correlational analysis. The descriptive analysis was carried out to identify the distribution of characteristics among the research samples, especially those related to the level of psychological well-being and self-directed learning. Meanwhile, the correlational analysis was performed to examine the correlation between the two ordinal-scale variables.

This research received ethical approval with No. 7/ Ka.Kom.Et/70/KE/VIII/2021 from the Medical and Health Research Ethics Committee of the Faculty of Medicine of Universitas Islam Indonesia. All the respondents had been informed about the study and had signed an informed consent form.

RESULTS

A total of 317 students participated in this study, with an average age of 19.63 years, comprising 85 male respondents (26.8%) and 232 female participants (73.2%).

Table I: Sociodemographic characteristics of participants (n=317)

Variables		Frequency	%
Age			
	16-20	228	71.9 %
	21-24	89	28.1 %
Gender			
	Male	85	26.8 %
	Female	232	73.2 %
Grade/Year			
	4th	69	21.8 %
	3rd	92	29.0 %
	2nd	77	24.3 %
	1st	79	24.9 %

Most of the respondents self-reported having a high level of self-directed learning (237 respondents or 74.8%). Meanwhile, 80 respondents with a percentage of 25.2% self-reported having a moderate level of self-directed learning, and none of them self-reported having low self-directed learning (Table 2).

Table II: Distribution of the levels of self-directed learning

Indicator	Mean ± SD	N	%
Low		0	0 %
Moderate	122.1 ± 8.6	80	25.2 %
High	145.2 ± 10.5	237	74.8 %
Total		317	100 %

Low: (X<84); Moderate (84 ≤X<132); High: (X≥132)

In addition, Table 3 shows that psychological well-being is at a moderate level, with a percentage of 69.4% and a frequency of 220 respondents. The remaining 94 respondents (29.7%) self-reported having a high level of psychological well-being, whereas 3 or 0.9% of respondents self-reported having a low level of psychological well-being.

Table III: Distribution of the levels of psychological well-being

Indicator	Mean ± SD	N	%
Low	74.7 ± 7.6	3	0.9 %
Moderate	116.8 ± 8.3	220	69.4 %
High	137.3 ± 8.3	94	29.7 %
Total		317	100 %

Low: (X<86); Moderate (86 ≤ X < 129); High: (X ≥ 129)

In terms of the other variables (confounding variables) that might influence students' self-directed learning and psychological well-being, which are gender, age, and year of study, the results are described in Figures 1, 2, and 3. The results in Figure 1 show that most male and female

students self-reported having high self-directed learning skills, and only about 25% of students in both groups reported having moderate levels of self-directed learning skills. No students reported having low self-directed learning skills. On the other hand, the level of psychological well-being in both male and female students, as self-reported, was moderate (more than 65%) and followed by a high level. Only less than 1% of male and female students self-reported low psychological well-being.

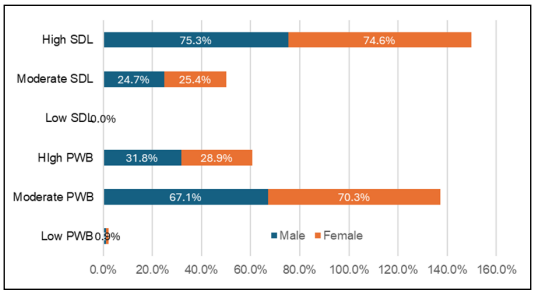

Figure 1: Distribution of self-directed learning (SDL) and psychological well-being (PWB) based on gender.

Figure 2 shows that older students self-reported having better psychological well-being than younger students (40.4%). Most younger students self-reported having moderate psychological well-being. Figure 2 also indicates that most students in the younger and older groups reported having high self-directed learning.

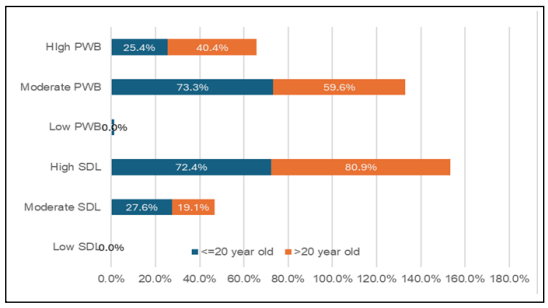

Figure 2: Distribution of self-directed learning (SDL) and psychological well-being (PWB) based on age

Figure 3 indicates that most students in each year self-reported having high self-directed learning skills, and there was an increasing trend from year 1 to year 4. No students each year self-reported having low self-directed learning skills. On the other hand, most students each year self-reported having moderate psychological well-being. The highest percentage was in year 2 (more than 80%). Students with high levels of psychological well-being were around 18%-35%. Only a few students self-reported having low psychological well-being each year (< 1%).

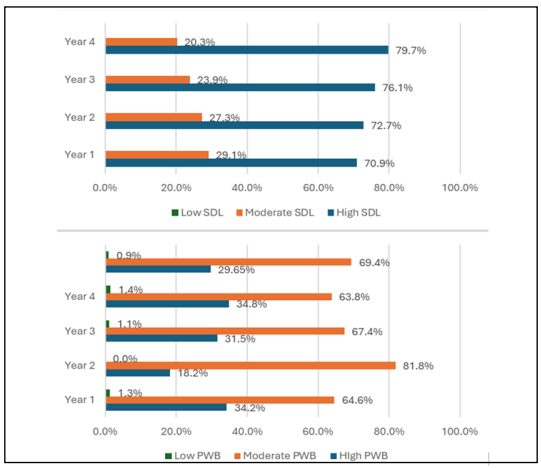

Figure 3: Distribution of self-directed learning (SDL) and psychological well-being (PWB) based on year of study

The chi-square test resulted in a p-value of 0.000 (<0.05), indicating that there was a statistically significant correlation between psychological well-being and self-directed learning of the students of FM UII (Table 4). From Spearman's correlation test, the obtained correlation coefficient was 0.352, which indicated that the strength of the correlation between the two variables was moderate. The positive correlation coefficient resulted in this study showed that the higher the level of psychological well-being of the respondents, the higher the level of self-directed learning, whereas the lower the level of psychological well-being, the lower the level of self-directed learning.

Table IV: Correlation between psychological well-being and self-directed learning

		Self-directed Learning				Total		p value *	Correlation Coefficient
		Moderate		High					
		n	(%)	n	(%)	n	(%)		
Psycho-logical well-being	Low	2	0.6	1	0.3	3	0.9	0.000	0.352
	Moderate	76	24	144	45.4	220	69.4		
	High	2	0.6	92	29.1	94	29.7		
Total		80	25.2	237	74.8	317	100		

The Chi-square analysis was also conducted to analyze the correlation between students' self-directed learning, psychological well-being, and confounding variables (gender, year of study, and age). There was no correlation between the confounding variables (gender, year of study, and age) and students' self-directed learning skills (p>0.05). The results also show no correlation between the variables of gender, year of study, and psychological well-being. However, a significant correlation was found between age and psychological well-being (p<0.05).

DISCUSSION

In this study, most of the respondents self-reported having high and moderate levels of self-directed learning, and no students reported having a low level of self-directed learning. The results also show that the level of self-directed learning increased from year to year (year 1 to year 4). One of the likely causes of this finding is the active, self-directed learning system applied in the Problem-Based Learning (PBL) method. FM UII has been implementing PBL as the main learning method for approximately 21 years. The PBL method is a learning approach that presents problems in life as a learning context for students. This allows students to think more critically and to hone their skills in solving existing problems. The PBL method can encourage students to be more independent since they are required to be able to determine their learning goals and essential concepts based on the lectures or learning material given. In addition, the high level of self-directed learning among these medical students can result from the learning methods and activities used in the medical faculty, which can significantly improve their self-directed learning, such as the individual and group assignments, research programs, and Focus Group Discussions (FGDs).[8]

The result also shows that the older students tend to have higher self-directed learning levels than the younger ones. Even though the level of self-directed learning between younger and older students was not significantly different, the results indicate that self-directed learning is a skill that develops over the life span until someone is 50. The development of self-directed learning is consistent in both females and males. This condition is the underlying reason why there were no significant differences in the level of self-directed learning across genders in this study.[18]

In this study, the respondents' psychological well-being was reported to be at moderate and high levels. One of the factors that has been found to affect the level of psychological well-being is educational attainment and socioeconomic status; the better the education that an individual attains, as well as the social status and income, the better the psychological well-being.[16,19,20] According to a study involving FM UII students as the respondents, it was found that 46% of the respondents had an allowance of >1 million IDR per month.[21] This indicates that FM UII students are likely to have a high economic status. In addition, education is one of the factors that is directly proportional to social status.[22] The respondents involved in this study were undergraduate students, thus showing that they pursue higher education, which correspondingly indicates their likely high social status.

The results of this study also show that the level of psychological well-being did not correlate with gender. It means that the levels of psychological well-being in males and females were not significantly different. This finding aligns with previous research showing that psychological well-being was not influenced by gender.[23] Other previous research showed various results regarding the correlation between gender and psychological well-being. These results depended on the context of the research, culture, and other factors, such as the characteristics of the research subject.[24]

The result of this study also reveals that the age of the subjects is related to the level of psychological well-being; the results indicate that older students had a higher level of psychological well-being. This research aligns with previous research conducted in three age groups (young, adult, and elderly). The result of previous research showed that each age group had different psychological well-being levels. This condition might happen because age or maturity could influence someone's ability to make meaning in life and psychological well-being.[25]

In addition, the research revealed that there was a correlation between psychological well-being and students' self-directed learning ($p<0.05$), with a positive correlation strength. This indicates that the higher the level of psychological well-being of the respondents, the higher the level of their self-directed learning. A high level of psychological well-being indicates optimal positive psychological functioning. One of the impacts of

achieving psychological well-being is the ability to develop without depending on others.[26] Students with high psychological well-being will have confidence in their abilities and efforts to develop, thus leading to a higher level of self-directed learning. On the other hand, students with a low level of psychological well-being will tend to be insecure, depend on others, have difficulty establishing good relationships with others, have no purpose in life, and have problems in opening up to new experiences, making their self-directed learning level tend to be low.[27]

The results of this study are in line with research that investigates the relationship between psychological well-being and self-adjustment, the findings of which indicate that good psychological well-being can also improve the adaptability of an individual. One aspect of adaptability is independence, self-evaluation, and determination of purpose in life. Therefore, individuals with high adaptability will also become highly independent. This is in accordance with a study that found that there is a fairly strong positive correlation between self-adjustment and self-directed learning.[28]

The results of this study are also in line with the findings of a study that shows a correlation between psychological well-being and self-directed learning. The study found that the higher the psychological well-being, the higher the respondents' intention and perseverance in learning, thus resulting in optimal self-directed learning.[29]

Since the research hypothesis is accepted, this study shows that the level of psychological well-being is considered to be one of the determining factors in the high or low level of students' self-directed learning. In addition, the problem-based learning system implemented at FM UII can also stimulate students' self-directed learning. This is in accordance with the results of a study in which there is a positive correlation between the problem-based learning system and self-directed learning.[8] The problem-based learning system and efforts to stimulate self-directed learning carried out at FM UII during the tutorial process, concomitantly with high psychological well-being, will increase the level of self-directed learning among FM UII students. Self-directed learning is defined as a concept of independency in learning, which includes the concept of active learning to achieve a competency that will subsequently become useful in problem-solving processes with the support of independently acquired knowledge and competencies that include learning goals and how to achieve them as well as the learning time, place, rhythm, pace, method, and evaluation.[9,30]

The strength of this research lies in its role in enriching references related to the correlation between psychological well-being and self-directed learning in medical students, which, to our knowledge, has never been studied in Indonesia. Medical students have a heavy learning load with different learning characteristics from other study programs; thus, the findings of this study provide benefits for optimizing the existing learning processes. This research has a limitation in that it was only carried out in one institution, thus requiring further studies to obtain generalizations in other contexts.

CONCLUSIONS

The self-directed learning of medical students was at moderate and high levels. The students' psychological well-being was also at medium and high levels. In addition, there was a significant correlation between the psychological well-being and self-directed learning of FM UII students, with a moderate level of correlation. Regarding the correlation between self-directed learning, psychological well-being, and confounding factors, such as gender and year of study, the results show no significant correlation. Only age had a significant relationship with psychological well-being. This study recommends that future research should use more comprehensive methods, such as mixed methods, to identify deeper insights into the other factors that can influence the levels of self-directed learning and psychological well-being among students. Further studies should also consider the confounding factors influencing students' psychological well-being and self-directed learning. As practical implications of this study, faculty and teachers should provide learning environments that support students' psychological

well-being and self-directed learning. For instance, in the PBL tutorial context, the teachers/ tutors could provide constructive feedback that stimulates students' psychological well-being, so students' self-directed learning would improve.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

INSTITUTIONAL REVIEW BOARD (ETHIC COMMITTEE)

This study has been approved by the Ethics Committee of FM UII with number 7/Ka.Kom.Et/70/KE/VIII/2021. Written informed consent was obtained from the students who participated in this study.

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ORIGINAL ARTICLE

Effect of Quercetin and Glibenclamide Combination on PPAR-γ and Oxidative Stress: A Study on Cardiac Tissue of Diabetic Animal Model

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ABSTRACT

INTRODUCTION: Type 2 diabetes mellitus (DM) contributes to cardiac failure through oxidative stress and reduced expression of peroxisome proliferator-activated receptor-γ (PPAR-γ). PPAR-γ plays a protective role by enhancing metabolism and mitigating oxidative stress. Quercetin has been shown to activate PPAR-γ and reduce lipid peroxidation. This study aims to evaluate the effects of combining quercetin with glibenclamide on cardiac PPAR-γ expression and lipid peroxidation in diabetic rats. **MATERIALS AND METHODS:** This experimental study involved 25 paraffin-embedded cardiac tissue samples from three-month-old Wistar rats, divided into five groups: healthy control, diabetic control (placebo), diabetic with glibenclamide (5 mg/kg/day), diabetic with quercetin (20 mg/kg/day), and diabetic with both glibenclamide and quercetin. Treatments were administered orally for 4 weeks. Cardiac PPAR-γ expression was assessed via immunohistochemistry, and malondialdehyde levels were measured using the thiobarbituric acid reactive substances (TBARS) assay. **RESULTS:** Both quercetin and glibenclamide monotherapies significantly increased cardiac PPAR-γ expression. However, the combination therapy further enhanced PPAR-γ expression compared to either treatment alone ($p<0.05$). Malondialdehyde levels significantly decreased in all treated diabetic groups compared to the diabetic control, with no significant difference between monotherapy and combination groups. **CONCLUSION:** The combination of quercetin and glibenclamide enhances cardiac PPAR-γ expression more effectively than monotherapy, while reducing lipid peroxidation to a similar extent. This suggests potential synergistic benefits in managing oxidative stress-related cardiac complications in type 2 DM.

Keywords
quercetin, glibenclamide, type 2 diabetes mellitus, cardiac PPAR-γ, cardiac malondialdehyde

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INTRODUCTION

The global prevalence of diabetes mellitus (DM) among adults in 2021 reached 537 million.[1] This current prevalence of DM may not reflect the actual phenomenon in the population due to data variation among nations.[1] The prevalence of DM is predicted to reach 783 million in 2045, which may be caused by a higher prevalence of obesity, higher popularity of high-calorie food and beverages, and a higher prevalence of a sedentary lifestyle.[2–4] There are four types of DM, with the vast majority of patients suffering from type 2 DM, which reaches 95% of the total.[1]

Diabetes mellitus causes multiple organ damage, dysfunction, and failure, such as eyes, kidneys, heart, and blood vessel.[5] Type 2 diabetes mellitus is indicated by hyperglycemia, peripheral resistance to insulin, and damage on β pancreas cells.[6] Long-term hyperglycaemia in diabetes condition is the main cause of diabetes complications.[7] Various complications occurring in diabetes mellitus also may be caused by the dyslipidaemia condition related to diabetic milieu. Diabetes mellitus causes lipid metabolism disorders, which increase lipid peroxidation and increase malondialdehyde (MDA).

Increased MDA further increases the occurrence of insulin resistance and oxidative stress.[8] The increasing amount of glucose in the cell causes reactive oxygen species (ROS) formation, which activates the polyol pathway, advanced glycation end products (AGEs), protein kinase C (PKC), and hexosamine pathway. The increase in ROS is the result of imbalanced conditions of production and scavenging performed by antioxidant endogens, which directly or indirectly cause physiology function disorders on cellular macromolecules, such as DNA, protein, and lipids. Reactive oxygen species also activate sensitive signal pathways toward stress.[9] Moreover, excessive ROS production such as MDA causes diabetes complication such as neuropathy and cardiomyopathy.[10] Diabetes complication prevention can be done by decreasing ROS production. An example of ROS production alleviation through a scavenging mechanism performed by endogenous antioxidants is the superoxide dismutase enzyme (SOD) which alters the super-oxidant to be an unhazardous substance for cells.[11]

The important gene related to glucose and lipid metabolism is peroxisome proliferator-activated receptor-γ (PPAR-γ). This gene is primarily expressed in adipose cells, the liver, and muscles. In glucose metabolism, PPAR-γ increases the activity of insulin receptor substrate (IRS-1) and glucose transporter (GLUT)-4, and thus, insulin sensitivity improves.[12] PPAR-γ increases lipid metabolism through inducing lipoprotein lipase, decreasing leptin, and increasing adipose cell differentiation.[13]

Nowadays, the administration of oral hypoglycemic agents is less effective in reducing oxidative stress in a diabetic patient. Therefore, giving antioxidants such as flavonoids plays an important role in DM therapy to protect cells from damage induced by free radicals. Quercetin is one of the flavonoid antioxidants. This compound is found in some plants, such as garlic, onion, green cabbage, apple, green tea leaf, and red grape. Quercetin and other antioxidants have the potential to prevent oxidative stress and thus prevent complications.[14,15]

Quercetin can increase the activity of antioxidant enzymes such as SOD, glutathione peroxidase, and catalase because they can increase the expression of nuclear factor erythroid 2-related factor 2 (Nrf2) and have a protection effect on the cardiac muscle and from damage caused by oxidative stress.[16,17] Hypoglycemic effect of quercetin can be done through increasing phosphorylation of tyrosine kinase, and thus, insulin activity increases.[18] Quercetin affects PPAR-γ expression. Activated PPAR-γ will bind to Liver X receptors (LXRs) and prevent lipogenic activity. Liver X receptors is a gene that triggers lipid metabolism, including decreased lipid peroxidation and MDA production, and the expression of lipogenic gene through the gene transcription of sterol regulatory element binding protein (SREBP)-1c.[19,20] PPAR-γ increases insulin sensitivity and glucose removal by cells. Quercetin increases PPAR-γ expression, thus increasing insulin sensitivity and glucose removal by cells. This mechanism decreases the blood sugar level of a diabetic patient.[21,22] Quercetin reduces malondialdehyde in various tissues such as the cardiac, kidneys, and liver.[23] Sulphonylureas such as glibenclamide and glimepiride have been studied to increase the hormone adiponectin. It is suspected that this effect is because sulphonylureas directly or indirectly affect the PPAR-γ expression pathway.[24] Glibenclamide also reduces oxidative stress by reducing malondialdehyde and increasing reduced glutathione (GSH) in various tissues.[25] Quercetin is often compared with diabetes mellitus drugs of choice, such as glibenclamide and metformin, in terms of its effect on reducing oxidative stress and improving condition in diabetes mellitus. According to previous research, quercetin can be combined with standard medicine for DM therapy and is thought to have better effects.[26] There has been no research combining quercetin and glibenclamide on the expression of PPAR-γ and malondialdehyde, including in cardiac tissue.

It is important to investigate the effects of the combination of quercetin and glibenclamide for DM treatment by reducing oxidative stress and increasing the expression of PPAR-γ. It is necessary to investigate whether combining quercetin with glibenclamide has a synergistic or antagonistic effect. This research aims

to investigate the effect of quercetin and glibenclamide combination on PPAR-γ and MDA in cardiac diabetic rats. The result of this research gives a crucial contribution to an elaborate comprehensive understanding of the usage of antioxidants in the treatment of diabetes mellitus.

MATERIALS AND METHODS

Research Design

This study used the post-test only with a control design. It was conducted at the Integrated Research Laboratory, Universitas Islam Indonesia, from May to August 2020.

Population and Sample

The protocol of this study was approved by the Ethical Comittee of Medical and Health Research Faculty of Medicine Universitas Islam Indonesia, number 04/Ka.Kom.Et/70/KE/XII/2015. This research used paraffin blocks of cardiac tissue of three-month-old male Wistar rats weighing 150-250 grams.

The number of samples was calculated based on the formula Federer:[27]

(n-1) (t-1) ≥15
n= the number of subjects in each group.
t= number of groups
(n-1) (5-1) ≥15 ➡ (n-1)X4≥15
(n - 1) ≥ 1 5 / 4 ➡ n≥3,75+1
n≥4,75 ~ 5

Thus, the number of rats per group was five rats in each group. This study used 25 rats randomly divided into 5 groups, each of which consisted of 5 rats (see Table I). Diabetic conditions were induced using intra-peritoneally streptozotocin (Sigma®) dosage 60 mg/kg, dissolved in citrate buffer with pH 4.5, and nicotinamide (Sigma®) dosage 120 mg/kg, dissolved in citrate buffer with pH 4.5. One week after the induction, the rat's fasting blood sugar was examined using spectrophotometry. Rats with fasting blood sugar of more than 126 mg/dL were considered diabetic rats and were involved in the study. Treatment was given orally for 4 weeks.[28,29]

Table I: The group description

Groups	Description
K1	Group of healthy rats without treatment
K2	Group of diabetic rats given placebo/day
K3	Group of diabetic rats given glibenclamide 5 mg/kg/day[29]
K4	Group of diabetic rats given quercetin 20 mg/kg/day
K5	Group of diabetic rats given quercetin 20 mg/kg/day and glibenclamide 5 mg/kg/day

Histological analysis

After treatment, the rats were anesthetized using ketamine 1 mg/kg intramuscular and underwent euthanasia. A surgical incision was performed at the thoracal area and cardiac tissue was taken and then fixed in formalin 10% for 3x 24 h. The tissue specimen was then dehydrated with a serial alcohol solution, and then the tissue was embedded in a paraffin block. The paraffin block was sectioned off 5 mm thick and then processed in 3% hydrogen peroxide for 20 minutes at 24-25°C. The slides were then treated with 0.01 M citrate buffer with a pH of 6.0 in boiling water. The slides were then incubated with primary antibody anti-PPAR-ϒ (Sigma®, catalog No. SAB4502262) and then left overnight at room temperature. After that, the slides were washed in PBS (phosphate-buffered saline) and treated with streptavidin complex and chromogen (diaminobenzidine). After the slides were counterstained with hematoxylin, the slides were ready to be measured for the expression level of PPAR-ɣ. Cells that positively expressed PPAR-ɣ showed brown nuclei while cells with negative expression showed blue nuclei. The PPAR-ɣ expression level was measured as percentage of positive cells divided by all cells. PPAR-ɣ percentage was examined from 5 fields of view on each slide.[28] The calculations were performed independently by two individuals using a blinded method, and the results were subsequently averaged.

MDA analysis

The cardiac wall was dissected and then rinsed with cold saline. The tissue was then weighed and pushed between filter papers. The tissue was homogenized in a cold solution made from PBS and potassium phosphate 50 mM at pH 7.4. The homogenate was then centrifugated at 3,000 rpm at 4°C for 20 minutes, and then the supernatant was taken to analysis. A 200 µl of 20% TCA

(trichloroacetic acid) and 400µl 0.67% thiobarbituric acid were added into 400µL supernatant. The mixture was then mixed with a vortex, heated for 50 minutes, and cooled at room temperature. The absorbance of the sample was measured at 532 nm, as a result was expressed in nmol/g.[30]

Statistics

We ran statistical analyses using IBM SPSS Statistics version 20.0 (SPSS Inc., Chicago, IL, USA). The normality of the data was tested with Shapiro-Wilk. Normally distributed data were presented as mean ± standard deviation. The differences in PPAR-ɣ expression levels were analyzed using one-way ANOVA and post hoc LSD. The differences in MDA levels were analyzed using one-way ANOVA and post hoc LSD.

RESULTS

The weight and fasting blood glucose in this study were eligible, so all rats were given complete treatment. The MDA levels and PPAR-ɣ expression level data were normally distributed and had same variance, so the data was tested using One-Way ANOVA. Figure 1 shows the cardiac muscles that express PPAR-γ in the nucleus of each group. Figure 2 shows the comparison of PPAR-ɣ expression percentage each group.

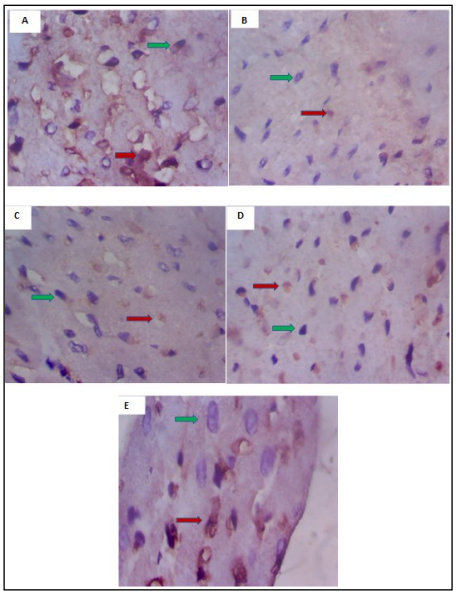

Figure 1. Representative photomicrograph of cardiac muscles each group. Cardiac muscle cells' nuclei that express PPAR-ɣ were stained brown (red arrow) while cardiac muscle cells' nuclei that did not express PPAR-ɣ were stained blue (green arrow). K1 (A): healthy rats, K2 (B): diabetic rats, K3 (C): diabetic rats given glibenclamide 5 mg/kg/day, K4 (D): diabetic rats given quercetin 20 mg/kg/day (D), and K5 (E): diabetic rats given quercetin 20 mg/kg/day and glibenclamide 5 mg/kg/day, 400X magnification.

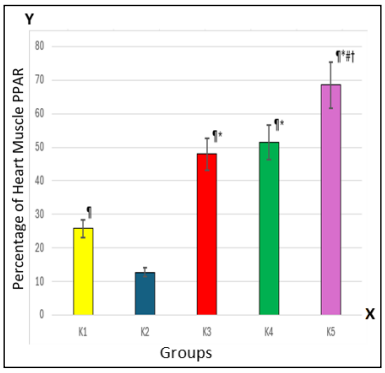

Figure 2: Comparison of PPAR-ɣ expression percentage among groups. The X-axis represents the groups, and the Y-axis represents the percentage of PPAR-ɣ in heart muscle. K5 expresses the highest PPAR-ɣ, and K2 expresses the lowest PPAR-ɣ. K3 and K4 express PPAR-ɣ higher than K1. ¶p < 0.05 compared with K2, *p<0.05 compared with K1, # p<0.05 compared with K3, †# p<0.05 compared with K4, ANOVA followed with LSD analyses. K1: healthy rats, K2: diabetic rats, K3: diabetic rats given glibenclamide 5 mg/kg/day, K4: diabetic rats given quercetin 20 mg/kg/day, and K5: diabetic rats given quercetin 20 mg/kg/day and glibenclamide 5 mg/kg/day.

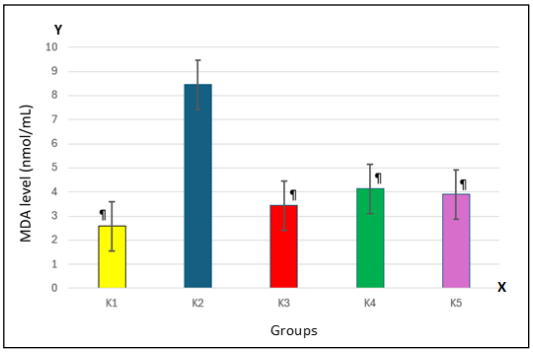

Figure 3: Comparison of MDA level among groups. The X-axis represents the groups, and the Y-axis represents the MDA level (nmol/ml). ¶p < 0.05 compared with K2, ANOVA followed with LSD analyses. K1: healthy rats, K2: diabetic rats, K3: diabetic rats given glibenclamide 5 mg/kg/day, K4: diabetic rats given quercetin 20 mg/kg/day, and K5: diabetic rats given quercetin 20 mg/kg/day and glibenclamide 5 mg/kg/day.

Based on Figure 2, group K5 expresses the highest PPAR-ɣ, and group K2 expresses the lowest PPAR-ɣ. Group K3 and K4 express PPAR-ɣ higher than K1.

Figure 3 shows a comparison of MDA levels among groups, where group K2 shows the highest MDA level and groups K3, K4, and K5 show higher MDA levels than K1. Post hoc test reveals significant difference between K2 and all other groups.

DISCUSSION

From the results, the untreated diabetic group showed the highest cardiac tissue MDA level, representing a high status of oxidative stress. This result is concomitant with other research that reported elevated cardiac myocytes' MDA levels.[31,32] Previous research reported that diabetes mellitus induces lipid metabolism dysfunction, and increases lipid peroxidation and malondialdehyde.[33] Oxidative stress plays a substantial role

in the organ-targeted complications of diabetes. The imbalance of redox status may be caused by the robust production of free radicals and reduction of the antioxidant system, which is detrimental to the cells and may lead to cellular dysfunction and further cellular injury.[34,35]

From this perspective, oxidative stress, chronic inflammatory reaction, defects in glucolipid metabolism, and reactive oxygen species (ROS) generation are considered as the potential pathophysiological condition underlying diabetic cardiomyopathy.[36] Therefore, the administration of antioxidants, which bring back the balance between reactive oxygen species (ROS) accumulation and scavenging, can be a promising candidate for cardiac myopathy treatment.[37]

Our current research also reported that the administration of glibenclamide reduces cardiac muscle cells MDA level. This result is consistent with a previous study, which reported that sulfonylurea, such as glibenclamide, were shown to have antioxidant effects and reduce MDA levels.[38] Conversely, a previous study reported that glibenclamide produced no significant effects on TBARS and antioxidant enzymes except GPx in diabetic rats.[39] Another study reported that despite glibenclamide reducing oxidative stress biomarkers in diabetic patients, the level of antioxidant properties is still less than metformin.[25]

We reported that administering quercetin reduces cardiac muscle cells MDA level. In previous studies, quercetin was able to reduce oxidative stress, including reducing MDA levels.[17] We previously also reported that quercetin improves cardiac cell damage and attenuates diabetes-induced cardiac muscle cell fibrosis via promoting the nuclear translocation of Nrf2 in cardiac cells of diabetic rats.[40,41]

In this study, the combination of quercetin and glibenclamide showed no difference in reduced MDA levels capability as with each administration. However, the authors have not found any research that measures the effect of quercetin and glibenclamide combinations on the MDA level. A previous study showed that combining quercetin and gliclazide (another sulphonylurea agent) reduces oxidative stress by increasing superoxide dismutase enzymes and GSH better than without a combination, but no difference in MDA levels. Both probably do not have agonistic or antagonistic properties on MDA levels.[42]

On PPAR-*γ* expression level percentage measurement of cardiac muscle cells, the lowest percentage of PPAR-*γ* is found in a group of diabetic rats given a placebo (K2), and the highest percentage of PPAR-*γ* is found in a group of diabetic rats given quercetin 20 mg/kg/day (K4) and glibenclamide dose 5 mg/kg/day combination. In the diabetic rats group given a glibenclamide dose of 5 mg/kg/day, the PPAR-*γ* percentage was significantly increased. Gene PPAR-*γ* bound to its ligands will translocate from the cytoplasm to the nucleus and become active. Those transcription factors have a role in adipose cell differentiation and can trigger gene expression, which involves fat metabolism. Previous research showed that diabetes mellitus agents are ligands for PPAR-*γ* and can increase expression and activity of PPAR-*γ,* thus being profitable for patients of type 2 DM because PPAR-*γ* will improve fatty acid storage in adipose tissues, thus improving muscle sensitivity toward insulin.[43] This condition is in line with the previous research that sulphonylureas, such as glimepiride and glibenclamide, can increase the transcription activity of PPAR-*γ* because they become the ligands.[44] Another research also reports that sulphonylureas are an agonist for PPAR-*γ* and increase the transcriptional activity of PPARγ.[45]

In the group of diabetic rats given quercetin 20 mg/kg/day, the PPAR-*γ* percentage significantly increased. This finding aligns with the previous research that quercetin can increase PPAR-*γ* gene expression because quercetin is a ligand for the PPAR-*γ* receptor. Therefore, quercetin can activate PPAR-*γ*. Liu et al. reported that quercetin improved cardiac damage induced by ischemia and reperfusion injury by activating PPARγ and probably inhibiting the NF-κB (Nuclear factor kappa B) pathway.[46] Another study showed that quercetin can increase the activity of Nrf2, which can form a complex heterodimer and DNA along with PPAR-γ. Therefore, quercetin can

indirectly activate PPAR-γ.[19] Previous research reported that quercetin influences signal transduction and intensifies the utilization of glucose by intervening in the transportation of glucose and insulin-receptor signaling. This function is similar to the effect of a PPAR-γ agonist.[47]

In the group of diabetic rats given a combination of quercetin 20 mg/kg/day and glibenclamide 5 mg/kg/day, PPAR-*γ* percentage in the nucleus of cardiac muscle cells significantly increased higher than both single administrations of quercetin and glibenclamide. The authors have not found any research that measures the effect of quercetin and glibenclamide combinations on PPAR-γ expression. However, a previous study reported that a combination of quercetin and pioglitazone (thiazolidinedione, also known as PPAR-ϒ agonist) had shown beneficial in inhibiting aortic tissue contraction modulated by angiotensin-II in type-2 diabetic animals induced by fructose and streptozotocin.[48] Previous research also showed that giving a combination of two agonists of PPAR-γ, such as fenofibrate combined with pioglitazone, tends to give effects to three types of PPAR-α,γ,δ.[49] The limitation of this study is that no dose variation was used.

CONCLUSION

Combining quercetin 20 mg/kg/day and glibenclamide 5 mg/kg/day increases cardiac muscle PPAR-γ expression better than no combination. The combination also decreases cardiac tissue MDA levels compared to no combination. From the conclusion, combining quercetin and glibenclamide can be considered as DM therapy to prevent cardiac damage. Further research involving a longer duration and dose variation of treatment is needed to establish the effect of quercetin and glibenclamide combination therapy in preventing myocardial complications from DM.

CONFLICT OF INTEREST

The authors do not have any conflicts of interest.

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AUTHORS CONTRIBUTION

AH: Concept and designed the experiments, wrote and revised the manuscript; ES: Wrote and revised the manuscript

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ORIGINAL ARTICLE

Knowledge, Attitudes, and Implementation Challenges of Preventive Rehabilitation Programs among Malaysian Collegiate Football Players: A Cross-Sectional Analysis

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ABSTRACT

INTRODUCTION: Football is a high-risk sport for lower limb injuries, prompting the use of Football Injury Prevention Programs (FIPP). Despite evidence of effectiveness, implementation remains inconsistent. This study aimed to (i) explore Malaysian collegiate football players' knowledge, attitudes, and challenges regarding FIPP and (ii) examine the influence of demographic and institutional contexts, particularly between public and private institutions. **MATERIALS AND METHODS:** A cross-sectional survey using an online structured interview was conducted among Malaysian collegiate football players aged 18 and above who were actively participating at the college or university level. The survey comprised seven sections: demographics, football background, FIPP implementation, injury rates, knowledge of FIPP, attitudes, and barriers to implementation. Data were analysed using descriptive, cross-tabulations, and correlation statistics. **RESULTS:** Out of 103 responses, 80 met the inclusion criteria. The respondents were predominantly Malay (51.2%) and Chinese (36.3%), with a mean age of 23.4±4.55 years. Notably, 82.5% reported previous football-related injuries, while 81.3% utilized some form of injury prevention, primarily running (56.3%) and strength training (52.5%). Despite 67.5% acknowledging the benefits of FIPP, 46.3% perceived their knowledge as insufficient, and only 36.3% had received any formal training. Furthermore, a significant positive correlation was found between knowledge and attitudes toward FIPP ($r = 0.438$, $p < 0.001$). Key barriers included insufficient knowledge (41.3%) and limited access to qualified instructors (40.1%). **CONCLUSION:** Despite positive attitudes toward preventive rehabilitation, knowledge deficits and implementation barriers persist, underscoring the need for targeted education to improve FIPP adoption and reduce injury rates.

Keywords
football, injury prevention, knowledge, attitudes, FIFA 11+

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INTRODUCTION

Football is widely played globally, with over 275 million players across 211 FIFA member associations.[1] Despite its appeal, football has a high injury risk, especially to the lower limbs, making injury prevention essential for player safety.[2,3] In Malaysia, football-related injuries were notably high during the 2018 Malaysian Games, with 64.6 injuries per 1000 match hours reported.[3] Data from the 2018-2019 season indicated an injury rate of 0.58 injuries per player among youth players (U19 and U22), primarily affecting the knee and ankle joints.[4] Similar trends were observed in the 2010 Football Association of Malaysia league, with a rate of 61 injuries per 1000 match hours.[5] These statistics underscore the need for targeted injury prevention programs, especially for youth and collegiate football athletes in Malaysia.

Youth and collegiate players face a significantly higher injury risk than professionals.[6] This risk arises from factors like developmental differences (e.g., growing bones and muscles), less refined motor skills (e.g., coordination challenges during quick movements), and a higher likelihood of overuse injuries due to ongoing physical development and limited injury prevention knowledge (e.g., improper warm-ups or inadequate

recovery).[6,7] Injuries in youth players can lead to extended absences, long-term effects on physical development, and psychological impacts like reduced motivation or confidence.[6,8] Studies show that lower limb injuries are common among players, with males more prone to thigh muscle injuries, while females more frequently experience joint or ligament injuries in the knee and ankle.[8] Injury risk is also higher during matches than in training for both youth and professional players.[2,6]

In response, FIFA, in collaboration with the Santa Monica Sports Medicine Foundation and the Oslo Sports Trauma Research Center, launched the FIFA 11+ program in 2006.[9] This preventive warm-up program addresses strength, stability, and biomechanical deficiencies to mitigate injury risks.[9] The program includes three core components: running drills, strength and balance exercises, and plyometric exercises, each targeting key aspects of injury prevention.[9] Running drills focus on warm-up and neuromuscular activation, incorporating progressive intensity and direction changes to enhance cardiovascular fitness, agility, and motor control.[9] Strength and balance exercises target muscle groups such as the hamstrings, quadriceps, and core muscles to improve muscular strength, balance, and coordination, reducing injury risks associated with muscle imbalances and instability.[9] Plyometric exercises emphasize explosive movements, such as jumps and bounds, to enhance power, agility, and dynamic stability while improving proprioception and landing mechanics, which are critical for reducing lower limb injuries, particularly ACL tears.[9] Research shows that the FIFA 11+ program effectively reduces injuries, including ACL tears, hamstring injuries, and ankle sprains,[10] while enhancing dynamic balance, agility, proprioception, and hamstring strength.[11-13]

Although the FIFA 11+ program has proven effective, its adoption remains relatively low.[14,15] Its successful implementation depends on factors like players' and coaches' knowledge, attitudes, and perceived barriers.[16-18] Research highlights several barriers to effective FIFA 11+ implementation, including time constraints, insufficient skills and knowledge, and lack of program progression.[19] Coaches often cite challenges like limited staff and player cooperation, while players report issues such as decreased motivation and perceived exercise difficulty.[20] However, comprehensive data on how knowledge, attitudes, and barriers influence the adoption of injury prevention programs among Malaysian collegiate football players remain scarce.[3,18] Additionally, there is limited information on how institutional factors, such as the differences between public and private institutions, affect the adoption and implementation of FIPP. Exploring these differences provides valuable insights into how institutional settings shape players' knowledge, attitudes, and barriers, particularly in the Malaysian collegiate football context. Public and private institutions in Malaysia are known to attract distinct student demographics, with variations in access to resources, cultural diversity, and institutional priorities, which may influence the implementation of injury prevention programs. Identifying such differences can help tailor interventions to improve the adoption and effectiveness of FIPP.

This study aims to examine the knowledge, attitudes, and challenges faced by Malaysian collegiate football players regarding the implementation of FIPP. Additionally, it investigates whether differences in demographic and institutional contexts, particularly between public and private institutions, influence these factors. By addressing these objectives, this study aims to contribute to reducing injury rates and enhancing the adoption of effective injury prevention strategies in Malaysian collegiate football.

MATERIALS AND METHODS

Study design

This cross-sectional study used an online survey method. Data were collected via an online structured interview which was distributed from February to August 2024.

Target population

The target population for this study comprised collegiate football players from public and private colleges and universities in Malaysia. Inclusion criteria were: (i) Malaysian collegiate football players aged 18 years or older; (ii) targeting both male and female players; (iii) actively engaged in football training sessions or

matches at the college or university level within the preceding six months; and (iv) the ability to read and comprehend texts fluently in either English or Malay language. Exclusion criteria were: (i) non-players (e.g., coaches or support staff); (ii) individuals not actively engaged in football during the study period; and (iii) players who participated in football only for leisure purposes and not at a collegiate competitive level.

Sample size

The estimated population of collegiate football players in Malaysia comprises approximately 0.1% to 0.05% of the student body. The sample size was calculated using formula, $n=(Z^2P(1-P))/d^2$.[21] For this calculation, the margin of error was set at 0.05, the estimated proportion of the population (P) was 0.05, and a confidence level of 95% was chosen, corresponding to a Z-score of 1.96. Based on these parameters, the calculation yielded a sample size of approximately 73 football players.[22] Additionally, an online calculator was employed to verify the sample size, using an acceptable error level of 5% (d=0.05), an expected proportion in the population of 0.05 (p=0.05), and a Type I error rate of 5% (α=0.05). This also resulted in a required sample size of 73 players. To account for non-responses, the sample was rounded up to 75 players.

Sampling method

A convenience sampling method was employed for respondents' selection based on predefined inclusion and exclusion criteria. Initial contact with university representatives was made through email and social media channels, where the study's objectives were explained. Upon obtaining consent and support from these representatives, a link to the online structured interview was disseminated to the football players via email and social media platforms. Clear instructions on completing the survey were provided, and response rates were actively monitored, and periodic reminders were sent to enhance participation. To reduce selection bias, multiple outreach methods were used to recruit a diverse range of participants, including different types of universities (public and private) and ensuring representation of both male and female players. This approach aimed to maximize participation while ensuring that the sample represented the target population effectively.

Online structured interview

Data were collected through a structured online interview survey via Google Forms, available in English and Malay to suit participants' language preferences. The questions included multiple-choice, Likert scale, and open-and closed-ended questions, adapted from established studies to ensure relevance and validity.[19,20,23,24] Measures to minimize bias included randomized question order, anonymity to reduce social desirability bias, and neutral language. The survey was organized into seven sections; (i) demographics: basic details (e.g., age, gender, race, height, institution), (ii) football background: playing position, experience, level, and participation regularity, (iii) FIPP implementation and injury rates: injury prevention practices (e.g., running, strength exercises), injury occurrence, and frequency, (iv) knowledge of FIPP: awareness of FIPP, understanding of its goals, training received, and knowledge of the FIFA 11+ program, (v) attitudes and perceptions toward FIPP: views on FIPP's effectiveness, value, feasibility, and integration into training, (vi) barriers to FIPP implementation: identified obstacles like limited awareness, knowledge gaps, time constraints, and lack of support or motivation, and (vii) additional comments: open-ended section for further input.

Data analysis

Data were analyzed using SPSS version 26. To ensure data quality, responses were screened based on the inclusion and exclusion criteria, with incomplete or ineligible responses removed before analysis. Data entry and analysis were conducted collaboratively by two authors to enhance the reliability of the findings and to minimize data entry errors or bias. Normality tests were conducted, and duplicate entries were eliminated. Descriptive statistics, including means and standard deviations for continuous variables (e.g., age, BMI), and frequencies and percentages for categorical variables (e.g., playing position, playing level, FIPP implementation, and injury information), were calculated. Inferential statistics,

such as chi-square tests and one-way ANOVA, were performed to identify significant associations or differences between variables.

In addition, subgroup analyses were conducted to compare responses between players from public and private institutions, focusing on differences in FIPP implementation, knowledge, and injury rates. Sensitivity analyses were performed to assess the robustness of the findings by excluding participants with incomplete data or those who reported inconsistent responses. Frequency analysis was utilized to assess the distribution and percentage of responses for each item, revealing the most and least common answers. Spearman's correlation coefficient was used to examine the relationships between knowledge levels, attitudes, playing levels, playing experience, and FIPP implementation. The significance level was set at $p < 0.05$.

RESULTS

Characteristics of the respondents

A total of 103 responses were collected from the online questionnaire distributed over a six-month period (February to August 2024). After applying exclusion criteria, 23 respondents were excluded for the following reasons: 7 were not collegiate football players, and 16 had not actively participated in training or matches in the past six months. This resulted in a final sample size of 80 respondents, surpassing the target minimum sample size of 75. All respondents were male, with a mean ± SD age of 23.44 ± 4.55 years and a mean ± SD body mass index of 22.65 ± 3.31 kg/m². The ethnic distribution was 51.2% Malay (n=41), 36.3% Chinese (n=29), 8.8% Indian (n=7), and 3.8% from other ethnicities (n=3). The respondents were distributed across various playing positions: goalkeeper (12.5%), defender (36.3%), midfielder (20.0%), and forward (31.3%). The majority were amateur players (85.0%), xwith a smaller proportion being semi-professional (12.5%) and professional (2.5%). Playing experience varied among the respondents: 38.8% had over 10 years of experience, 20% had 7-9 years, and the remainder had shorter durations.

The analysis was further stratified by institution type: 55% of the respondents (n=44) were enrolled in public institutions, and 45% (n=36) were from private institutions. Respondents from private institutions were significantly older on average (F=4.55, p=0.036), and there was a notable difference in ethnic composition between the two groups: Malay participants were predominantly from public institutions, while Chinese participants were the majority in private institutions (X^2=31.61, p<0.001). No significant differences were observed between the institutions concerning playing position, playing level, or years of experience. A detailed breakdown of the respondents' characteristics, stratified by institution type, is provided in Table I.

Table I: Demographic characteristics and the implementation of football injury prevention programs among collegiate football players

Variables		Overall (n=80)	Public institution (n = 44)	Private institution (n = 36)	X^2 or F-value	p-value
		n (%) or mean ± SD				
Age	Years	23.44 ±	22.48 ±	24.61 ±	F=4.55	0.036*
BMI	kg/m²	22.65 ±	22.21 ±	23.18 ±	F=1.74	0.191
Ethnicity	Malay	41	35 (79.5)	6 (16.7)	X^2=31.61	0.000*
	Chinese	29	6 (13.6)	23 (63.9)		
	Indian	7 (8.8)	2 (4.5)	5 (13.9)		
	Others	3 (3.8)	1 (2.3)	2 (5.6)		
Position	Goalkeeper	10	7 (15.9)	3 (8.3)	X^2=1.41	0.702
	Defender	29	16 (36.4)	13 (36.1)		
	Midfielder	16	9 (20.5)	7 (19.4)		
	Forward	25	12 (27.3)	13 (36.1)		
Playing level	Amateur	68	39 (88.6)	29 (80.6)	X^2= 2.70	0.260
	Semi-pro	10	5 (11.4)	5 (13.9)		
	Professional	2 (2.5)	0 (0)	2 (5.6)		
Playing experience	<1 year	10	8 (18.2)	2 (5.6)	X^2=7.08	0.135
	1-3 years	12	9 (20.5)	3 (8.3)		
	4-6 years	11	5 (11.4)	6 (16.7)		
	7-9 years	16	9 (20.5)	7 (19.4)		
	>10 years	31	13 (29.5)	18 (50.0)		
Implementation of FIPP	Yes	65	35 (79.5)	30 (83.8)	X^2=1.19	0.666
	No	15	9 (20.5)	6 (16.7)		
Running exercise	Yes	45	25 (56.8%)	20 (55.6)	X^2=0.01	0.910
	No	35	19 (43.2)	16 (44.4)		
Strength exercise	Yes	42	23 (52.3)	19 (52.8)	X^2=0.002	0.964
	No	38	21 (47.7)	17 (47.2)		
Plyometric exercise	Yes	27	15 (34.1)	12 (33.3)	X^2=0.005	0.943
	No	53	29 (65.9)	24 (66.7)		
Sports injury	Yes	66	37 (84.1)	29 (80.6)	X^2=0.17	0.679
	No	14	7 (15.9)	7 (19.4)		
Number of injuries	0	14	7 (15.9)	7 (19.4)	X^2=4.47	0.215
	At least 1	24	13 (29.5)	11 (30.6)		
	2 to 3	24	17 (38.6)	7 (19.4)		
	4 or more	18	7 (15.9)	11 (30.6)		

Note: Values are presented as frequency (n) and percentage (%) within each institution, except for age and BMI, which are presented as mean ± standard deviation. All variables were analyzed using cross-tabulations with the Chi-square test, except for age and BMI, which were analyzed using one-way ANOVA.

Rates of football-related injuries and implementation of FIPP

A majority of respondents (82.5%, n=66) reported experiencing at least one football-related sports injury.

Among these, 30% experienced a single injury, 30% reported 2-3 injuries, and 22.5% reported four or more injuries. No significant differences in the injury rates or number of injuries were observed between the institutions (Table I). Regarding the implementation of FIPP, 81.3% of respondents (n=65) reported incorporating at least one component. Running exercises were the most commonly performed (56.3%, n=45), followed by strength exercises (52.5%, n=42), and plyometric exercises (33.8%, n=27). There were no significant differences in the implementation of these exercises between the institutions.

Knowledge, attitude and perceptions on FIPP

The analysis of respondents' knowledge revealed that approximately 67.5% (n=54) demonstrated an understanding of the purpose and benefits of the FIPP (p=0.000) (Table II). However, 46.3% (n=37) lacked knowledge about the FIPP, particularly the FIFA 11+ (p=0.026). Regarding general awareness, 40% (n=32) of football players were aware of the FIPP, though this difference was not statistically significant (p=0.387). The primary sources of information about the FIPP, particularly the FIFA 11+, were online exposure (44%; n=35), coaches (29%; n=23), teammates (24%; n=19), and only 18% (n=14) had received formal training or education on the FIPP (Figure 1).

Table II: Summary of knowledge, attitudes, and perceptions towards the football injury prevention program among respondents

Variables	No n (%)	Neutral n (%)	Yes n (%)	p-value
Domain: Knowledge				
Awareness of FIPP	22 (27.5)	26 (32.5)	32 (40)	0.387
Understanding of the purpose and benefits of FIPP	11 (13.8)	15 (18.8)	54 (67.5)	0.000*
Self-perceived knowledge level of the FIFA 11+ Injury Prevention Program	37 (46.3)	23 (28.7)	20 (15.0)	0.026*
Domain: Attitude and Perceptions				
Effectiveness of FIPP in reducing risk of injuries	2 (2.6)	7 (8.8)	71 (88.8)	0.000*
Worthwhile of FIPP implementation	2 (2.5)	9 (11.3)	69 (86.3)	0.000*
Willingness to incorporate FIPP into training routine	4 (5.0)	9 (11.3)	67 (83.8)	0.000*
Adequacy of variation and progression of FIFA 11+	4 (5.0)	15 (18.8)	61 (76.3)	0.000*
Feasibility of FIFA11+	3 (3.8)	18 (22.5)	59 (73.8)	0.000*

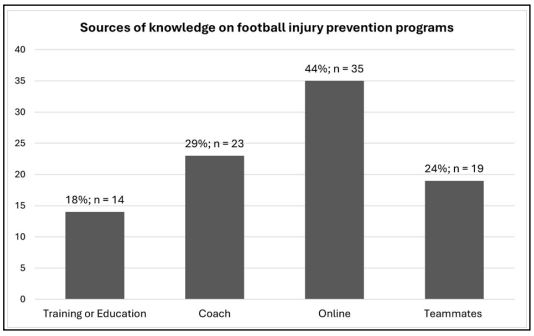

Figure 1: Sources of knowledge on football injury prevention programs

The majority of respondents demonstrated a positive attitude towards the FIPP (Table II). Specifically, 88.8% (n=71) of participants believed that the program effectively reduces the risk of injuries in football (p<0.001). Additionally, 86.3% (n=69) considered the implementation of the FIPP to be worthwhile (p=0.000). A significant 83.8% (n=67) expressed a willingness to incorporate the FIPP into their regular training routines (p<0.001). Furthermore, 76.3% (n=61) agreed that the FIFA 11+ provides adequate variation and progression for their teams (p<0.001), while 73.8% (n=59) found the program feasible for their football training (p<0.001).

Table III: Barriers to implementing football injury prevention programs.

Barriers	Barrier n (%)	Neutral n (%)	Not a barrier n (%)	p-value
Lack of awareness about the FIPP	26 (32.5)	26 (32.5)	28 (35.0)	0.951
Insufficient knowledge or understanding of proper exercise execution	33 (41.3)	23 (28.7)	24 (30.1)	0.321
Limited time availability for additional training or warm-up exercises	21 (26.3)	34 (42.5)	25 (31.3)	0.112
Lack of support or encouragement from coaches or team management	22 (27.5)	35 (43.8)	23 (28.8)	0.141
Difficulty in finding qualified instructors or trainers for implementation	32 (40.1)	29 (36.3)	19 (23.8)	0.176
Lack of player motivation due to perceived monotony or boredom of exercises	27 (33.8)	33 (41.3)	20 (25.0)	0.204

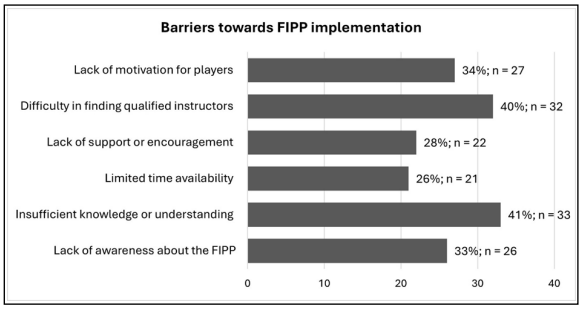

Figure 2: Barriers to the implementation of football injury prevention programs

Analysis of relationships between knowledge, attitudes, and implementation of FIPP

Spearman's rho correlation coefficient indicated a significant positive correlation (r=0.438, p<0.001) between participants' knowledge and attitudes towards FIPP implementation, suggesting that increased knowledge is associated with more positive attitudes towards the injury prevention program. However, the correlations between knowledge level, playing level, playing experience, and FIPP implementation showed no statistically significant relationships. The correlation between attitude level and playing level revealed a negligible negative association (r=-0.028, p=0.808), indicating no significant relationship. Additionally, the correlations between attitude level and playing experience (r=0.159, p=0.159) and FIPP implementation (r=0.165, p=0.144) were also not significant.

DISCUSSION

This study underscores the persistent gap between knowledge and implementation of FIPP among collegiate football players in Malaysia. Despite the high rate of self-reported injuries (82.5%), only 36.3% of participants received formal training in FIPP, with a substantial portion (46.3%) perceiving insufficient knowledge. This finding is consistent with literature, which indicates that awareness of injury prevention strategies, such as FIFA 11+, is insufficient for effective implementation.[15,17] The discrepancy between positive attitudes toward FIPP and low implementation rates points to a need for structural and educational improvements. Enhancing player education and addressing barriers is crucial for reducing injuries and improving safety in collegiate football.

Our subgroup analysis identified significant demographic differences between private and public institution respondents. Students from private institutions were notably older, likely due to flexible scheduling appealing to working professionals seeking career changes or advancement.[25] Conversely, public universities primarily attracted younger students, likely due to competitive admission criteria or limited quotas.[25] Additionally, public universities had a majority of Malay participants, while private institutions had a majority of Chinese participants. This reflects broader socioeconomic and cultural factors influencing educational choices, with Malay families potentially prioritizing public institutions for cultural reasons, while Chinese families may prefer private institutions for perceived academic quality or language preferences.[26]

The significant knowledge gap identified in this study is concerning, given the proven efficacy of programs like FIFA 11+ in reducing lower limb injuries.[9,10] Limited formal education on these programs, with only 18% of respondents having received formal instruction, aligns with findings in both local and global contexts. Studies indicate a lack of structured training as a barrier to widespread adoption.[19,23] The correlation between knowledge and positive attitudes toward FIPP suggests that increasing educational outreach could enhance adoption and effectiveness of these programs.[15] However, our data also show knowledge alone may be insufficient, as there was no significant relationship between knowledge levels and actual implementation. This highlights logistical and structural barriers as critical factors beyond just knowledge.[13]

One of the most notable challenges identified is the limited access to qualified instructors (40.1%) and the perceived lack of motivation among players (33.8%), which aligns with barriers highlighted in prior research.[19,20] While a significant number of players engaged in components of FIPP, like running (56.3%) and strength exercises (52.5%), the absence of qualified guidance likely reduces efficacy. This indicates a systemic issue: the interest to engage with FIPP exists, yet supporting infrastructure is lacking. Coaches and physiotherapists play a pivotal role in disseminating and facilitating these programs.[16,17] Investment in coach and trainer certification specifically for FIPP could be an essential step toward overcoming barriers.[12]

Despite generally favorable attitudes toward FIPP, the study revealed a concern regarding motivation. Player perception of the monotony of injury prevention exercises, reported by 33.8% of participants, aligns with

findings where complexity or time-consuming nature often leads to lower adherence.[17,23] This issue is particularly concerning for collegiate players, who face a higher injury risk compared to professional athletes.[6] Unlike professionals, collegiate players often lack structured training and may not have ongoing monitoring or motivation from coaches, increasing their injury risk due to inconsistent adherence to prevention programs.[7]

Strengths and limitations

This study used an extensive online survey to assess key factors in FIPP implementation among Malaysian collegiate football players, examining demographics, football background, injury history, IPP knowledge, attitudes, and perceived barriers. Potential confounders like age, playing level, experience, and injury history were accounted for, enhancing insights over previous studies.[14,27] While this study offers valuable insights, several limitations should be noted. Despite a six-month data collection period and follow-up efforts, recruiting a larger and more diverse sample proved challenging. Additionally, the cross-sectional design only captures a single point in time, leaving questions about how these factors may evolve. Future research should employ longitudinal designs to examine changes in knowledge and attitudes with targeted interventions, such as coach-led workshops or athlete-focused educational campaigns.[2]

CONCLUSION

Malaysian collegiate football players exhibit positive attitudes towards FIPP, yet face barriers in knowledge, access to qualified instructors, and motivation. Addressing these gaps through targeted education, certification, and tailored programs is essential for reducing injuries and enhancing player safety. Cultivating a deeper FIPP understanding, alongside structural improvements, could foster a preventive rehabilitation culture in Malaysian collegiate football. Future initiatives should prioritize accessible and engaging injury prevention strategies that integrate well into collegiate sports.

INSTITUTIONAL REVIEW BOARD (ETHIC COMMITTEE)

Ethical approval was obtained from the Universiti Kebangsaan Malaysia Research Ethics Committee (RECUKM JEP-2023-983) on 14 February 2024, following the Declaration of Helsinki principles. Informed consent was acquired from all respondents, ensuring confidentiality and voluntary participation.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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None

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ORIGINAL ARTICLE

Knowledge, Attitude, and Practice towards Disaster Preparedness among Medical Personnel in Emergency Departments in Malaysia

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ABSTRACT

INTRODUCTION: Disasters are incidents that can cause damage to properties and loss of lives. Disaster preparedness is a set of measures undertaken in planning for disaster situations. The objectives of this study were to determine the level of knowledge, attitude, and practice (KAP) towards disaster preparedness and its associated factors among emergency department (ED) medical personnel. **MATERIALS AND METHODS:** This study was conducted in 12 hospitals in Malaysia. A validated questionnaire was used and 427 participants were involved. This study was carried out from March 2019 to March 2020. **RESULTS:** This study showed that ED medical personnel in Malaysia had adequate KAP towards disaster preparedness, which scored 91.6%, 78.2%, and 61.1%, respectively. An increased level of knowledge was related to experience and training in disaster response, whereby the increased level of practice was associated with duration of working experience. However, there was no association between the level of attitude and disaster preparedness. **CONCLUSION:** Continuous education and training on disaster preparedness for ED medical personnel are necessary to prepare staff in the event of disaster and to improve the healthcare system.

Keywords
Disaster, Knowledge, Attitude, Practice, Questionnaire

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INTRODUCTION

Disasters are defined as sudden accidents or natural catastrophes that cause great damage to properties or loss of lives, exceeding the affected community's capacity to cope using their available resources. Natural disasters such as landslides, tsunamis, floods, and typhoons occur almost every year around the world. Based on the statistics from the Red Cross Society, Asia is the most disaster-prone area of the world and this is due to its geographic location.[1]

Disaster preparedness in a country is a set of measures undertaken in planning for disaster situations. The four phases of disaster preparedness are mitigation, preparedness, response, and recovery. Mitigation is a phase before or after the disaster has occurred and it involves planning to either prevent such future disasters or minimise their impact on the community. The preparedness phase is the most important, as it involves preparing to handle a disaster before it occurs. Preparation includes stockpiling of food and water, creating evacuation plans, and organizing response and rescue operations. The next is the response phase that takes place when the disaster is occurring, and execution of the preparedness plan. Finally, the recovery phase is focused on the actions taken after the disaster so as to return to its normal conditions.[2]

In Malaysia, the role of Emergency Medical and Trauma Services (EMTS) is crucial in disaster and major incident management, as outlined by the Malaysian National Security Council (MKN) and the National Disaster Management Agency (NADMA). The EMTS works in close collaboration with MKN and NADMA to ensure a coordinated response during disasters. The EMTS is responsible for providing immediate medical care at the disaster sites by conducting triage to prioritise victims and providing initial stabilisation of the injured persons. Additionally, the EMTS is responsible for ensuring rapid

and safe transport of patients to the appropriate medical facilities. Besides the response phase, EMTS also participates in all other phases of disaster preparedness, which are mitigation, preparedness, and recovery.[3] Although the EMTS may not be the leading agency for all types of disasters, it plays a crucial role in responding to medical emergencies and providing trauma care during various types of disasters, including natural disasters, man-made disasters, mass casualty incidents, and public health emergencies such as disease outbreaks or pandemics. Other rescue agencies besides the EMTS are the Fire and Rescue Department of Malaysia (JBPM), the Royal Malaysian Police (PDRM), the Malaysian Civil Defence Force (APM), and the Malaysian Armed Forces (ATM).

Climate change and deforestation in Malaysia are causing increasing in the number of disasters such as floods and landslides. This study was conducted to examine the disaster preparedness among medical personnel in Emergency Departments (EDs) in various hospitals in Malaysia. Previous studies done in other countries have shown gaps in the knowledge, skills, and abilities of emergency medical personnel regarding emergency preparedness and disaster response.[4] Currently, there are few studies conducted in Malaysia on the disaster preparedness among ED medical personnel. One study covered emergency nursing and medical personnel's knowledge, attitude, and practice (KAP) in hospitals in the East Coast region of Malaysia and the outcome showed that the level of KAP was below average, although the level of attitude was acceptable.[5] The current study explored all regions in Peninsular Malaysia and it involved more medical personnel. Since emergency medical (ED) personnel play a major role as front-line workers, it is important that all emergency hospital staff are updated and equipped in knowledge, and well-prepared to minimise the impacts of disasters. The findings of this study will benefit the EDs in identifying specific strategies to improve KAP among hospital staff.

MATERIALS AND METHODS

This is a cross-sectional study, which targeted all ED medical personnel in 12 hospitals in Kedah, Penang, Kelantan, Pahang, Johor and Klang Valley. This study was carried out from March 2019 to March 2020. The inclusion criteria encompassed all ED medical personnel including doctors, assistant medical officers, and nurses working in the ED during the study duration. Those on leave during the study period were excluded. A total of 430 personnel was randomly selected.

A validated questionnaire was utilised to collect the study data. This questionnaire comprised three domains: knowledge, attitude, and practice. A score of more than 60% in each domain was considered to indicate adequate KAP. The 60% cut-off point was chosen based on a previous study.[6] The questionnaire was distributed to all personnel, and of the 430, 427 responded (99.0%).

Socio-demographic characteristics were summarised by using descriptive statistics. The level of KAP among emergency department medical personnel was also summarised using descriptive statistics. The associated factors and the level of KAP was analysed using multiple logistic regression.

RESULTS

The sociodemographic data obtained were expressed as n (frequency, %) for categorical variables tabulated as in Table 1. The 3 respondents excluded due to incomplete questionnaire responses. Of this, the majority of 427 respondents were aged 40 years or younger (91.1%, n=389). In relation to gender distribution, 55.0% (n=235) were males and 45.0% (n=192) were females. There was a variation in the education levels of the respondents. Most of the degree holders (166, n=38.9%) were doctors whereas diploma holders (231, n=54.1%) were assistant medical officers and nurses. Slightly more than half of the participants (55%, n=235) have had experience in a disaster incident, although specifics regarding the type and timing of these disasters were not provided. With regards to disaster training, most of them had undergone disaster response training (n=332, 77.8%). More than half had attended disaster drill exercise (n=187, 56%), 23% had participated in field stimulation, 9% had attended tabletop exercise, and the remaining

had attended didactic or functional exercise. Among this, some participants had received training or education continuously throughout their employment.

Table 1: Descriptive statistics among participants (n=427)

Variables	N (%)
Age	
<30	203 (47.5)
30-40	186 (8.9)
>40	38 (43.6)
Gender	
Male	235 (55.0)
Female	192 (45.0)
Education level	
Certificate	13 (3.0)
Diploma	231 (54.1)
Degree	166 (38.9)
Master	17 (4.0)
ED experience	
<1 year	83 (19.4)
1-4 years	166 (38.9)
5-10 years	111 (26.0)
>10 years	67 (15.7)
Experience disaster response	
No	192 (45.0)
Yes	235 (55.0)
Training for disaster response	
No	95 (22.2)
Yes	332 (77.8)

Abbreviation: ED, Emergency Department

Regarding the level of KAP among ED medical personnel**,** we found that most participants demonstrated adequate knowledge (n=391, 91.6%) and positive attitude (n=334, 78.2%), while more than half exhibited adequate practice (n=261,61.1%). Over 80% of respondents answered correctly regarding disaster definition and disaster management in the knowledge domain. The majority of the respondents also recognised that disasters increased the risk of developing communicable diseases among the affected communities and agreed that population displacements can cause social burdens to inhabitants.

In terms of attitude, more than 80% of respondents agreed that it is important for them to understand disaster management. Most of them expressed willingness to be involved during disaster response efforts. Additionally, more than 80% believed that collaboration among medical and health personnel is needed in managing disaster victims. However, half of the respondents felt that assisting disaster victims with their basic needs is not their responsibility. Furthermore, 80% of the respondents agreed that medical or health personnel should be educated about the long-term impact of disasters, such as mental health problems.

More than half knew the location of their disaster response plan and agreed that it could be easily accessed and 70% had read their institution's disaster response plan and almost half of them had read the plan apart from their institution. More than 90% were willing to be involved in disaster training and more than 75% were prepared to be involved in any disaster response. More than half were familiar with the field triage system that is used during disasters. Most of them stated that their institutions had disaster education or training conducted regularly and if conducted, most of them agreed it involved other agencies as well such as fire rescue teams.

A simple logistic regression test was conducted to determine the association between KAP and the variables. These results are summarised in Tables 2, 3 and 4. Experience in disaster response and training for disaster response were found to be the only associated factors towards adequate knowledge among participants, with 2.04 times the odds of having adequate knowledge compared to participants without experience in disaster response (95% CI:1.02, 4.11) and 3.16 times the odds of having adequate knowledge compared to participants without training for disaster response (95% CI: 1.57, 6.38) (Table 2). This current study also revealed that there was no significant association between all related variables studied towards attitude (Table 3).

Table 2: Association between socio-demographic characteristics and knowledge

Variables	Regression coefficient, b	Crude Odd Ratio (95% CI)	Wald statistics (df)	p value
Age				
<30	0	1		
31-40	0.66	1.93 (0.91,4.11)	2.95	0.086
>40	0.35	1.42 (0.40,4.996)	0.30	0.587
Gender				
Male	0	1		
Female	0.02	1.02 (0.52,2.03)	0.004	0.948
Education level				
Certificate	0	1		
Diploma	-0.58	0.56 (0.07,4.45)	0.30	0.582
Degree	0.99	2.68 (0.29,24.85)	0.76	0.385
Master	18.72	134622903.57 (0.00,0.00)	0.00	>0.95
ED experience				
<1 year	0	1		
1-4 years	0.00	1.00 (0.41,2.44)	0.00	>0.95
5-10 years	0.46	1.59 (0.55,4.56)	0.73	0.393
>10 years	0.28	1.32 (0.41,4.25)	0.22	0.639
Experience disaster response				
No	0	1		
Yes	0.71	2.04 (1.02,4.1)	4.01	0.042
Training for disaster response				
No	0	1		
Yes	1.15	3.16 (1.57,6.3)	10.31	0.001

Table 3: Association between socio-demographic characteristics and attitudes (427)

Variables	Regression coefficient, b	Crude Odd Ratio (95% CI)	Wald statistics	p value
Age				
<30	0	1		
31-40	0.26	1.29 (0.79,2.10)	1.05	0.305
>40	-0.002	0.998 (0.44,2.25)	0.00	>0.950
Gender				
Male	0	1		
Female	0.27	1.31 (0.82,2.09)	1.29	0.257
Education level				
Certificate				
Diploma	0	1		
Degree	0.69	2.00 (0.63,6.37)	1.38	0.241
Master	1.13	3.08 (0.94,10.11)	3.44	0.064
	0.41	1.50 (0.33,6.92)	0.27	0.603
ED experience				
<1 year	0	1		
1-4 years	0.37	1.45 (0.78,2.70)	1.40	0.236
5-10 years	0.38	1.50 (0.74,2.87)	1.20	0.273
>10 years	0.14	1.15 (0.55,2.42)	0.14	0.713
Experience disaster response				
No	0	1		
Yes	0.07	1.07 (0.67,1.69)	0.08	0.780
Training for disaster Response				
No	0	1		
Yes	0.02	1.03 (0.59,1.78)	0.01	0.931

Abbreviation: ED, Emergency Department

Table 4: Association between socio-demographic characteristics and practice (427)

Variables	Regression coefficient, b	Crude Odd Ratio (95% CI)	Wald statistics (df)	p value
Age				
<30	0	1		
31-40	0.47	1.60 (1.06,2.40)	5.10	0.024
>40	1.76	5.82 (2.18,15.47)	12.37	<0.001
Gender				
Male	0	1	11.86	0.001
Female	-0.69	0.50 (0.34,0.74)		
Education level				
Certificate	0	1		
Diploma	0.62	1.86 (0.60,5.72)	0.57	0.282
Degree	-0.15	0.86 (0.28,2.66)	0.58	0.857
Master	1.03	2.79 (0.58,13.31)	0.80	0.199
ED experience				
<1 year	0	1		
1-4 years	0.44	1.55 (0.91,2.63)	2.60	0.107
5-10 years	0.74	2.10 (1.18,3.76)	30	0.012
>10 years	2.03	7.63 (3.35,17.40)	23.35	<0.001
Experience disaster Response				
No	0	1		
Yes	1.32	3.76 (2.49,5.65)	40.02	<0.001
Training for disaster response				
No	0	1		
Yes	2.46	11.68 (6.62,20.61)	72.01	<0.001

Abbreviation: ED, Emergency Department

In Table 4, there was a significant association between age, gender, years of ED experience, experience in disaster response, and training in disaster response towards practice. Participants aged 31 to 40 years old had 1.6 times the odds and those aged age over 40 years old had 5.82 times the odds of exhibiting adequate practice compared to participants aged under 30 years old (OR=1.60, 96% CI:1.06, 2.40, p=0.024 and OR=5.82, 96% CI: 2.18, 15.47, p<0.001). Female participants showed 50% lower odds of exhibiting adequate practice compared to male participants (OR=0.50, 96% CI: 0.34, 0.74, p=0.001). Additionally, participants with more than 10 years of ED experience, experience in disaster response, and training in disaster response were associated with adequate practice, with odds of 7.63 times, 3.76 times, and 11.68 times, respectively, compared to participants with less than 1 year of ED experience (OR=7.63, 96% CI:3.35, 17.40, p<0.001), no experience in disaster response (OR=3.76, 96% CI: 2.49, 5.65, p<0.001), and no training experience in disaster response (OR=11.68, 96% CI: 6.62,20.61, p<0.001).

DISCUSSION

The medical personnel in Emergency Departments (ED) are frontline workers with important roles and responsibilities if any disaster occur. Therefore, this team needs to be highly skilled and capable of managing emergency situations, especially in a disaster situation and saving lives.[7]

This study showed that the majority of ED personnel in the 12 hospitals in Peninsular Malaysia possess adequate knowledge. A similar Malaysian study conducted in the East Coast region also reported similar findings.[5] On an international scale, a study conducted in China showed that nurses had an average level of KAP,[8] while a study in Nigeria found that the majority had good and fair knowledge about disaster preparedness.[4] In contrast, a study in Australia concluded that respondents had a knowledge score of less than 50%.[9] Conversely, a study in Saudi revealed that their physicians and nurses had a satisfactory level of knowledge in disaster preparedness.[10]

In terms of knowledge, our study found an exceptionally high score (91.6%) compared to similar studies performed elsewhere. This might be attributed to the inclusion of medical officers, assistant medical officers, and nurses in our study, whereas other studies mainly focused on nurses and healthcare workers. More than half of the respondents were assistant medical officers who probably have more exposure to prehospital care including disasters. However, from our study, they were no association between knowledge and level of education. Another reason was the high-risk environment in the East Malaysia, which faces the South China Sea and thus frequent threats of floods, landslides, and drought every year.[11] From this study we found that more than half of the respondents (67%) were from central and east coast states, which are more prone to disaster occurrences. This regional exposure probably contributed to the higher level of knowledge observed in our study participants.

Our study revealed that most of the respondents had positive attitude towards disaster preparedness and it corresponds with a previous Malaysian study[5] and another study in Yemen.[12] However a study in Egypt revealed that only 37.5% of the respondents had a positive attitude towards disaster preparedness.[13] The possible reason for this result in the Egyptian study was because Egypt is not typically considered a disaster-prone country, so this leads to less exposure to disasters.

Most studies have shown that health personnel often have inadequate practice towards disaster preparedness. A previous Malaysian study showed that less than half of respondents had adequate practice towards disaster preparedness,[6] which was similar to a study in South Africa.[14] The majority of participants in Saudi Arabia agreed on the need for frequent disaster simulations in their hospitals as these simulations will increase knowledge and improve practice in disaster preparedness.[10] Compared to other studies, we found that training and education were very important factors in determining the level of practice. Additionally, the willingness to be involved in disaster response and training also played an important role in this regard.

Education and training play important roles in disaster preparedness and disaster management. Surprisingly, the duration of ED experience does not correlate with knowledge and attitude as expected. One would expect that the longer one works in the ED, the more knowledge they would have about disaster management. However, this study found that participants who had experienced disaster response and undergone training in disaster response exhibited adequate knowledge of disaster preparedness, similar to a study conducted in China.[15] Contrarily, another study showed that Australian hospital staff were under-prepared to respond to disasters because of a lack of education, insufficient simulation exercises, and limited disaster experience.[16]

Based on our study, no association was found between the attitude of medical personnel and variables. A study conducted among nurses working in emergency areas and community health nurses in Saudi Arabia showed a higher positive attitude towards disaster preparedness among nurses attending disaster-related education.[17] This finding was similarly observed among nurses in emergency departments in Malaysia, with the positive attitude attributed to their involvement in both disaster response and disaster-related education.[6] However, the findings of our study contradicted these previous studies. In our opinion, this discrepancy may be due to our study mainly involving specialist hospitals, with only one non-specialist hospital included, which could probably be the main reason for no association with attending disaster-related education. More studies are needed to explore this issue.

Another important domain in this study is practice. In our study, practice refers to the use of ideas and beliefs rather than performance towards disaster management. Our study revealed significant associations between years of experience in ED, experience in disaster response, and training in disaster response towards practice. A study conducted in the United States of America demonstrated a lack of adequate training in disaster and terrorism response for emergency medical service (EMS) providers.[18] According to the study, continuous medical education (CME) and simulation exercises improved their skills and

care during disaster management.[18,19] Another study in Japan concluded that years of ED experience correlate with disaster preparedness level, as well as disaster education and training.[20]

Training is one of the most important factors associated with practice. With correct practice, the medical personnel can develop the right attitudes and improve our knowledge regarding disaster management. To achieve this, they need to establish a proper training setup such as regular CME to educate the staff and regular exercise to improve knowledge and preparedness levels in case of disaster. To assist in meeting these training needs, a comprehensively written emergency preparedness curriculum may be used. Moreover, additional studies on a larger sample size should be conducted to provide data related to the necessity for such training among all ED staff, including paramedics.

CONCLUSION

The level of knowledge, attitude, and practice (KAP) was satisfactory among emergency department medical personnel in the 12 hospitals in Malaysia regarding disaster preparedness. Experience in disaster response and training in disaster response emerged as significant predictors of knowledge and practice in this area. Therefore, workshops focusing on theories and practices of disaster preparedness should be carried out periodically to prepare all ED staff for potential disasters. Preparedness is one of the stages of disaster management that can be addressed at our level. Thus, improving our KAP regarding disaster management is very important not only for our own preparedness in case of disasters but also to reduce the overall impact of disasters on the healthcare system. Policy makers and the hospital management must realise that continuous education and training of staff is important to prevent disastrous losses due to disasters.

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ORIGINAL ARTICLE

Gender and Ethnic Differences in Stress and Lifestyle Factors Post COVID-19 Lockdown Among Medical Students

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ABSTRACT

INTRODUCTION: Lifestyle choices can significantly impact students' stress levels, especially during the COVID-19 lockdowns. It is not known whether the management of lifestyle behaviours and stress factors post COVID-19 lockdown differs between genders and ethnicities in Malaysia. **MATERIALS AND METHODS:** A cross-sectional study was conducted among 345 medical students in a private Malaysian University willing to participate. The demographic details were collected after obtaining their consent for participation. Lifestyle and stress questionnaires were administered online, and multiple logistic regression analyses were used to analyse their lifestyle and stress factors post COVID-19 lockdown. **RESULTS:** Male students tend to have a strict exercise regime (p<0.0001) and reported low alcohol consumption (p=0.002). Female students did less exercise (p=0.007) and experienced an increase in muscular aches (p<0.0001). They also tend to bring work home at night (p=0.032), have insufficient hours to do all duties (p=0.038), and have altered appetites (p=0.001). Both Indian (p=0.011) and Chinese (p=0.006) participants can still cope with the present working environment. Indian respondents tend to get sick more frequently than other ethnicities (p=0.043). Malay (p=0.007) and Chinese (p=0.024) respondents are less likely to experience muscular pain. Chinese students are less likely than other ethnicities to have sick parents (p=0.027), while Malay students have family members with illnesses like high blood pressure and diabetes (p=0.019). **CONCLUSION:** Developing targeted student support learning such as stress management workshops, time management training, and comprehensive wellness programs tailored to different genders and ethnicities could reduce stress and promote a healthier lifestyle.

Keywords
Gender, Ethnicity, Lifestyle, Stress, Lockdown.

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INTRODUCTION

Medical students frequently suffer high amounts of stress because of their intensive training, which can lead to burnout and mental health concerns.[1] Social isolation, independent study, and continuous cognitive workload have added significant educational challenges during the COVID-19 pandemic.[2] The closing of universities had overwhelmed healthcare students' education as lessons were shifted to online delivery and clinical placements were cancelled.[3] Higher academic load and lack of social support can heighten the stress levels of undergraduate students.[4] Stress can promote unhealthy lifestyle choices and increase the risk of chronic diseases.[4] The pandemic has disrupted many students' daily routines, leading to increased sedentary behaviour and poor eating habits,[5] and these were associated with heightened anxiety and depression.[3] Adopting a healthy lifestyle is related to decreased odds of depression, anxiety, and stress.[6] Developing efficient support systems requires an understanding of how these hardships impact various student groups.

There is limited data on the intersection of gender and ethnicity on stress factors and lifestyle behaviours post COVID-19 lockdown among medical students in Malaysia. Ethnic background can influence lifestyle choices, resource availability, and coping techniques.[6]

A pre-pandemic study in Malaysia reported Chinese students were more prone to higher stress levels compared to other ethnicities probably due to the stronger commitment to strive for excellence.[8] Indian students reported lower coping skills than other ethnicities.[8] During the pandemic, female students are more likely to report higher levels of stress and anxiety compared to their male counterparts,[9] and this was similarly observed in a Malaysian cohort.[10] Examining how gender and ethnicity interact with lifestyle choices will provide insights into the broader health consequences for medical students in the post COVID-19 lockdown, which may affect patient care in the future. This understanding is critical for establishing focused educational strategies and mental health interventions that address the specific requirements of varied student populations, thereby improving their educational experience and well-being. As a result, the current research paper investigates the impact of gender and ethnicity on lifestyle and stress factors post COVID-19 lockdown among medical students at a private Malaysian University.

MATERIALS AND METHODS

Study Design

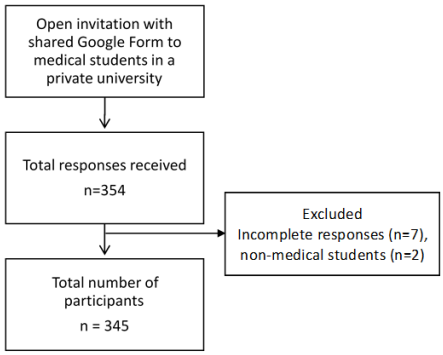

Figure 1: Flowchart of study design in recruitment of participants

The purpose of the survey was to investigate if there are differences in gender and ethnicity in the lifestyle behaviours and stress factors post COVID-19 lockdown among medical students. Lifestyle behaviour encompasses the dietary habits, sleeping patterns, and physical activities performed. Lifestyle choices are important as they can impact the stress levels of students. Stress is a significant underlying cause of mental and physical illnesses. The instrument used in this study aligns closely with the construct and measures the lifestyle and stress factors mentioned above. Two reviewers independently validated the questionnaire to ensure the questions were relevant, clear, and understandable for respondents. In the stress questionnaire, question number 20 (My sex drive is lower, can experience changes to the menstrual cycle) was removed as it can be misinterpreted as applying only to the female respondents. Overall, basic evidence for validity in this study included alignment with the construct and content validity by expert reviews.

Participant Recruitment and Data Collection

A cross-sectional study was conducted between June to September 2022 at a private Malaysian university. The timeline indicated the physical return of the students to campus after the COVID-19 lockdown was lifted in early 2021. The students, regardless of age or gender, who agreed to participate in the study and are well-versed in English were included in this study. The questionnaire was administered online (Google Form) to collect data from the students. Students who are not from the medical program are excluded from this study. A final total of 345 medical students participated in this study.

The final online survey consisted of three sections: (1) demographics; (2) lifestyle behaviours[11] with 15 items; and (3) stress factors[12] with 24 items. The format of the questionnaire on lifestyle behaviour was multiple options with no order, while the stress factors were in a dichotomous (yes/no) format. The purpose and objective of the study were explicitly described to the students via an information sheet, and they were informed that participation was voluntary. It was emphasized that all collected data would remain confidential. The questionnaire was distributed to the respondents only after receiving written informed consent. The survey took about 10-15 minutes to be completed. We acknowledge the potential biases introduced by using an online questionnaire, such as limited participation by less tech-savvy or less English-proficient students. These were mitigated by including the contact number and email of the person in charge to address any queries. Self-reported bias is reduced as participants have the right to not share their identity and remain anonymous. Measures to maintain confidentiality are ensured by restricting access to the respondents' data.

Data Analysis and Statistical Methods

Multiple logistic regression analyses were used to determine the correlation between gender and ethnicity with lifestyle and stress factors. Odds ratios (ORs) and 95% confidence interval (CI) were also identified in this study. The analysis was conducted using statistical tests in the SPSS software (version 29.0). Data is expressed as number of respondents and/or percentages. Heat maps and stacked bar charts were constructed using GraphPad Prism (version 10.2.2).

RESULTS

Demographic characteristics

On average, the age of the participants was 20.73 years. There were more female respondents (55.7%) compared to male respondents (44.3%) in this study. The majority of the participants were of Indian ethnicity (65.2%) (Table 1).

Table 1: Demographic characteristics of questionnaire respondents (N=345)

Characteristics	Frequency (%)
Age (years), mean ± SD	20.73 ± 1.797
Gender	
Male	153 (44.3)
Female	192 (55.7)
Race	
Chinese	75 (21.7%)
Indian	225 (65.2%)
Malay	30 (8.7%
Others	15 (4.3%)

Health and Lifestyle behaviour

Health and lifestyle behaviour were assessed on various parameters such as meal frequency, fitness, smoking habits, and alcohol consumption (Figure 2 and 3; Table 2 in Supplementary Page). Results show that female participants hardly exercise (OR=2.43, 95% CI: 1.27-4.65; p=0.007), while the male participants were more likely to follow a strict exercise regime (OR= 0.177, 95% CI: 0.07-0.44; p<0.0001). It is not surprising that the female respondents also felt unfit compared to males (OR= 3.45; 95% CI: 1.62-7.33; p=0.001), and the majority felt they could be fitter (OR= 2.00, 95% CI: 1.15-3.47; p=0.014). They also spend more time watching television or online surfing (OR= 3.97, 95% CI: 2.19-7.21; p<0.0001), or feel that they do not have any free time (OR= 3.12,95% CI: 1.47-6.63; p=0.003). Male respondents tend to report low alcohol consumption (OR= 0.47, 95% CI: 0.29-0.76; p=0.002).

Both parents of Chinese participants were more likely to be healthy (OR = 0.07, 95% CI: 0.01-0.73; p=0.027), while Malay participants have family members with illnesses like high blood pressure and diabetes (OR= 9.12, 95% CI 1.43-58.00; p=0.019). Both Indian (OR= 6.21, 95% CI: 1.51-25.49; p=0.011) and Chinese (OR= 10.16, 95% CI: 1.92-53.81; p=0.006) participants can still cope with the present working environment. More Malay respondents fell ill in the last 3 to 6 months (OR= 7.36, 95% CI: 1.00-54.15; p=0.05), or last year (OR= 9.24, 95% CI: 1.15-74.05; p=0.036), while Indian respondents tend to get illness in the last month (OR= 4.71, 95% CI: 1.05-21.12; p=0.043).

Stress Factors

Stress factors were assessed on various parameters such as ability to manage workload, appetite, mood swings, and pain complaints (Figure 4 and 5; Table 3 in Supplementary Page). Female respondents were more likely to bring work home at night (OR= 1.75, 95% CI: 1.05-2.91; p=0.032). Despite this, they still felt like they did not have enough time to complete their work (OR= 1.79, 95% CI: 1.03-3.09; p=0.038). They also experienced a change in their appetite (OR= 2.2, 95% CI: 1.40-3.45; p=0.001) and felt that they had impaired concentration and memory (OR= 1.69, 95% CI: 1.10-2.61; p=0.017). Female participants reported increased muscular aches and pains (OR= 2.53, 95% CI: 1.62-3.97; p<0.0001), while Malay (OR= 0.14, 95% CI: 0.03-0.59; p=0.007) and Chinese (OR= 0.23, 95% CI: 0.07-0.83; p=0.024) participants were less likely to have such pain. There was no interaction between both ethnicity and gender in this stress factor.

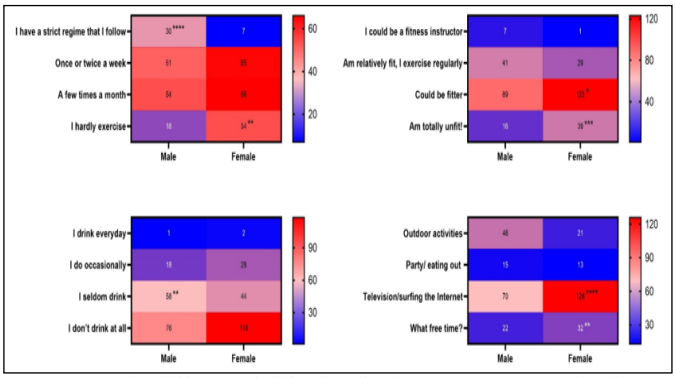

Figure 2: Gender differences in lifestyle behaviours post COVID-19 lockdown among medical students.
Heat maps show the number of responses from male and female students. Asterisks mark significant p-values
(*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001)

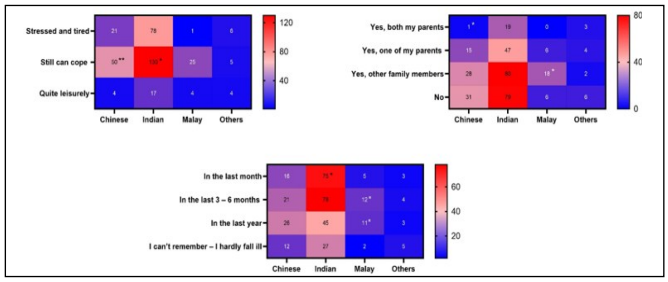

Figure 3: Ethnic differences in lifestyle behaviours post COVID-19 lockdown among medical students.
Heat maps show the number of responses between students of different ethnicities. Asterisks mark significant p-values (*p<0.05, **p<0.01)

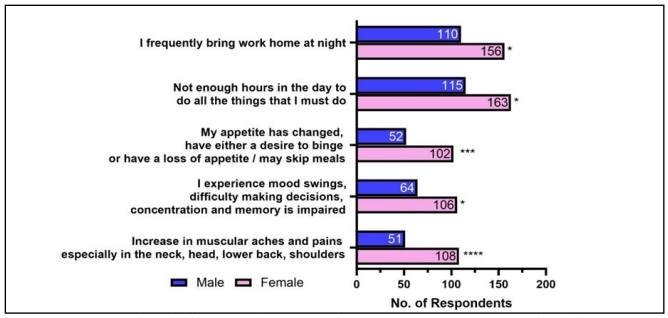

Figure 4: Gender differences in stress factors post COVID-19 lockdown among medical students.
Stacked bar charts show the number of responses between male and female students. Asterisks mark significant p-values
(*p<0.05, ***p<0.001, ****p<0.0001)

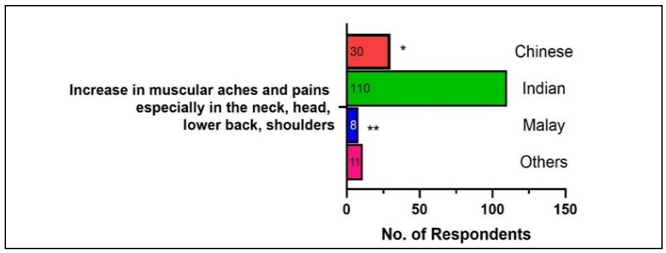

Figure 5: Ethnic differences in stress factors post COVID-19 lockdown among medical students. Stacked bar charts show the number of responses between students of different ethnicities. Asterisks mark significant p-values (*p<0.05, **p<0.01)

DISCUSSION

The present survey evaluated gender and ethnicity differences in lifestyle and stress factors post COVID-19 lockdown among medical students. We found that the female participants did less physical activity (OR=2.43, 95% CI: 1.27-4.65; p=0.007) and experienced increased muscular aches and pains (OR=2.53, 95% CI: 1.62-3.97; p<0.0001) compared to males. This is supported by another finding whereby the majority of the female respondents also felt they were unfit and could be fitter. Women were found to participate less in physical activity due to gender roles, cultural standards, lack of motivation and social support.[13] Perceived stress was associated with physical inactivity, and the effects were stronger in female students.[4] In our study, more male participants follow a strict exercise regime (OR=0.177, 95% CI: 0.07-0.44; p<0.0001), and consumed less alcohol (OR=0.47, 95% CI: 0.29-0.76; p=0.002). However, during the lockdown, physical activity was reportedly decreased and alcohol consumption increased especially in men.[14] Male college students experienced much lower perceived stress levels than females,[15] which could be related to the use of self-distraction to cope with stress.[16] Females tend to use emotion-focused approaches that brings about short-term relief of stress,[15] like spending their free time watching television or surfing the Internet as seen in our study. Those who engaged in less physical activity had reduced scores in mental health and well-being, in addition to profound generalized anxiety.[17] This however was not seen in our study. The mental conditions of the female medical students were not affected, most likely because this survey was conducted after the national Movement Control Order (MCO) were lifted and there were no barriers to partake in physical activity.

Time management has been a major issue among students in higher education.[9] Students may feel overwhelm with the crammed daily schedules and increased pressure to maintain academic performance. The constant stress can influence students' mental and physical health, which became even more noticeable during the COVID-19 pandemic.[18] We found that the majority of the female participants seem to struggle with time management, which may lead to feeling stressful. They felt that they hardly have any free time (OR=3.12, 95% CI: 1.47-6.63; p=0.003) and were more likely to bring work home at night. Despite this, they still felt like they do not have enough time to complete their work. Without establishing an effective time management, students may feel less motivated to learn, leading to procrastination, stress, and anxiety,[9,19] The stressful environment may have contributed to appetite change and concentration and memory impairment observed among the female students in our study. As a result, students reported increased levels of stress and anxiety disorders compared to pre-pandemic.[20]

We found that both Indian (OR= 6.21, 95% CI: 1.51-25.49; p=0.011) and Chinese (OR= 10.16, 95% CI: 1.92-53.81; p=0.006) participants reported that they can still

cope with the present working environment. In a study conducted on a Malaysian cohort before the pandemic, Chinese students were reportedly more prone to higher stress levels compared to other ethnicities, while Indian students reported lower coping skills than other ethnicities.[8] The reason for this is still not certain, as factors like parental expectations[21] and socioeconomic status[22] may affect students' behaviour. Regardless, there is a clear ethnic disparity in perceived stress levels, which warrants further investigations in order to implement appropriate coping strategies in learning.

Leading a healthy lifestyle habits are essential to prolong quality of life and prevent disease. Our study found that both parents of Chinese participants were more likely to be healthy (OR=0.07, 95% CI:0.01-0.73; p=0.027), while Malay participants have family members with illnesses like high blood pressure and diabetes (OR= 9.12, 95% CI 1.43-58.00; p=0.019). Ethnic groups have varying lifestyle behaviours that can be attributed to cultural, socio-economic, and environmental factors.[23] Chinese individuals were more likely than Malays to achieve higher healthy lifestyle scores[23]. This is most likely due to the better diet quality intake[24] and better level of health literacy[25] compared to other ethnicities, resulting in healthier lifestyle. It is interesting to find a similar health pattern in different ethnicities in our cohort, where Indian respondents tend to get sick in the last month, while Malay respondents reported falling ill significantly less often. This may be corroborated by another finding of our study, where Malay (OR=0.14, 95% CI: 0.03-0.59; p=0.007) and Chinese (OR=0.23, 95% CI: 0.07-0.83; p=0.024) participants were less likely to have such increased muscular aches and pains compared to Indian respondents. Compared to Malay and Chinese participants, Indian individuals engaged in less physical activity,[26] although this was not found significantly different in our study. Indian respondents reported the lowest self-efficacy scores, and this was related to their high pain score compared to other ethnicities.[27] The pain they are experiencing can make them reluctant to perform tasks. In contrast, Chinese groups prefer not to verbalize pain and use peer support to manage functional activities, while Malay respondents reported the highest score in physical health-related quality of life.[27]

LIMITATIONS

This study has several limitations. This study is confined to data collected from a single private university with origins in India, which means it only represents the student population at this specific institution. This study does not represent the general populations of Malaysians, where the major ethnic group is Bumiputera (which include Malay and indigenous people), followed by ethnic Chinese and Indians. This study is cross-sectional and comparisons to the effects of lifestyle and stress factors before lockdown were not possible. A prospective cohort study among several universities may be useful to understand the long-term effect of the pandemic on stress and lifestyle behaviours between the gender and ethnicity of medical students. This study did not investigate whether the students were in lockdown by themselves or with others as this may have affected their responses. This study did not examine the socioeconomic status of the students or its potential impact on lifestyle and stress levels as a confounding variable. The pandemic may have disproportionately affected families from lower socioeconomic backgrounds due to financial insecurity and limited access to healthcare. The findings of our study may be influenced by bias, as participants were enrolled in a medical course and are potentially more health-conscious compared to the general student population.

RECOMMENDATIONS

Students' stress levels can be mitigated by promoting healthy lifestyle behaviours such as physical activity, a healthy diet, and low-risk use of alcohol and cigarettes. Campus administrators can prioritize healthier food options in the cafeteria and provide opportunities and spaces for sports, physical activities, and walkability on campus. Stress management workshops and nutrition and wellness campaigns can be encouraged to advocate a healthier lifestyle. These interventions can be uniquely tailored to male and female students. Policymakers can allocate resources to acknowledge and educate mental health and well-being on campus and in social media, such as providing access to mental health counselling services and peer support groups. It is important to intervene at a college level where the learning spaces are safe and welcoming to foster sustainable behaviours as students

progress to their professional life. Organization is essential to keep up with tasks and accomplish them on time. This skill is indeed important when undergraduate students are in complete charge of their schedule due to the sudden closure of universities and campus libraries during the pandemic. Students' preference for organization was shown to promote perceived control over time, thereby reducing stress and anxiety.[9] Actionable persuasive strategies to assist students in organizing tasks, study space, and realizing the benefits of organization can be implemented especially for female students. This includes goal-setting, self-monitoring, and social learning strategies.[9] It is also important to devote particular attention to Indian students in terms of managing their physical and mental health. Simultaneously, motivation and encouragement by peers and senior role models to take on important challenges can contribute to higher self-esteem.

CONCLUSION AND FUTURE DIRECTIONS

Overall, our findings clearly show a difference in lifestyle behaviours and stress factors between genders and ethnicities post COVID-19 lockdown. This may probably impact the overall performance of the students during assessments, which will be particularly important during the clinical rotations where social competencies are fundamental. Hence, early interventions on lifestyle and stress factors can be addressed especially in the campus setting. Integrating casual physical activities and conducting stress management workshops tailored to male and female students can foster a healthier environment. Training and support on time management is crucial to reduce stress and anxiety. Comprehensive health campaigns and wellness programs focusing on different ethnic perspectives could be beneficial to the students. Future research comprising several universities in Malaysia is needed to understand the long-term effect of the pandemic on stress and lifestyle behaviours between different genders and ethnicities of medical students.

INSTITUTIONAL REVIEW BOARD (ETHIC COMMITTEE)

Ethical approval for this study was obtained from the University Research Ethics Committee (MUCM/FOM/REC-12/2022). Informed consent was obtained from all respondents before answering the questionnaire. Data confidentiality was respected by ensuring restricted access to personal data and anonymized when sharing to protect participants' identities.

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SUPPLEMENTARY MATERIAL

Table 2: Health and lifestyle behaviour of medical students post COVID-19 lockdown

Health and Lifestyle-related Behaviour	Total N (%) 345 (100)	Gender		Race			
		Male	Female	Chinese	Indian	Malay	Others
Frequency of eating out (per week)							
0 – 2	114 (33)	-	-	-	-	-	-
3 – 5	174 (50.4)	ns	ns	ns	ns	ns	ns
> 5	57 (16.5)	ns	ns	ns	ns	ns	ns
Frequency of meals (per day)							
1	15 (4.3)	-	-	-	-	-	-
2	112 (32.5)	ns	ns	ns	ns	ns	ns
3	204 (59.1)	ns	ns	ns	ns	ns	ns
> 3	14 (4.1)	ns	ns	ns	ns	ns	ns
Frequency of snacks							
No	32 (9.3)	ns	ns	ns	ns	ns	ns
Once in a while, usually `healthy' snacks	49 (14.2)	ns	ns	ns	ns	ns	ns
Sometimes	225 (65.2)	ns	ns	ns	ns	ns	ns
All the time – I thrive on snacks!	39 (11.3)	-	-	-	-	-	-
Frequency of exercise							
I have a strict regime that I follow	37 (10.7)	<0.0001	ns	ns	ns	ns	ns
Once or twice a week	116 (33.6)	ns	ns	ns	ns	ns	ns
A few times a month	120 (34.8)	-	-	-	-	-	-
I hardly exercise	72 (20.9)	ns	0.007	ns	ns	ns	ns
Fitness							
I could be a fitness instructor	8 (2.3)	ns	ns	ns	ns	ns	ns
Am relatively fit, I exercise regularly	70 (20.3)	-	-	-	-	-	-
Could be fitter	212 (61.4)	ns	0.014	ns	ns	ns	ns
Am totally unfit!	55 (15.9)	ns	0.001	ns	ns	ns	ns
Personal illnesses							
Yes, and it's quite serious	2 (0.6)	ns	ns	ns	ns	ns	ns
Yes, but it's under control	21 (6.1)	ns	ns	ns	ns	ns	ns
I don't think so (but I'm not very sure)	195 (56.5)	-	-	-	-	-	-
Nope – I have regular check-up	127 (36.8)	ns	ns	ns	ns	ns	ns
Family Members with illnesses							
Yes, both my parents	23 (6.7)	ns	ns	0.027	ns	ns	ns
Yes, one of my parents	72 (20.9)	ns	ns	ns	ns	ns	ns
Yes, other family members	128 (37.1)	ns	ns	ns	ns	0.019	ns
No	122 (35.4)	-	-	-	-	-	-
Tobacco use							
Yes, I smoke at least a pack a day	0	ns	ns	ns	ns	ns	ns
Yes, I smoke around half a pack a day	5 (1.4)	ns	ns	ns	ns	ns	ns
I'm a social smoker	26 (7.5)	ns	ns	ns	ns	ns	ns
No	314 (91)	-	-	-	-	-	-
Alcohol consumption							
I drink everyday	3 (0.9)	ns	ns	ns	ns	ns	ns
I do occasionally	46 (13.3)	ns	ns	ns	ns	ns	ns
I seldom drink	102 (29.6)	0.002	ns	ns	ns	ns	ns
I don't drink at all	194 (56.2)	-	-	-	-	-	-
Duration of sleep (hours per day)							
7 – 8	62 (18)	-	-	-	-	-	-
5 – 6	234 (67.8)	ns	ns	ns	ns	ns	ns
< 5	49 (14.2)	ns	ns	ns	ns	ns	ns
Present working mood							
Stressed and tired	106 (30.7)	ns	ns	ns	ns	ns	ns
Still can cope	210 (60.9)	ns	ns	0.006	0.011	ns	ns
Quite leisurely	29 (8.4)	-	-	-	-	-	-
Activities during free time							
Outdoor activities	67 (19.4)	-	-	-	-	-	-
Party/ eating out	28 (8.1)	ns	ns	ns	ns	ns	ns
Television/surfing the Internet	196 (56.8)	ns	<0.0001	ns	ns	ns	ns
What free time?	54 (15.7)	ns	0.003	ns	ns	ns	ns
Mental conditions							
Yes but it's in the past	53 (15.4)	ns	ns	ns	ns	ns	ns
Yes – quite often	49 (14.2)	ns	ns	ns	ns	ns	ns
Yes- only once in a while	158 (45.8)	ns	ns	ns	ns	ns	ns
Never	85 (24.6)	-	-	-	-	-	-
Frequency of previous illness							
In the last month	99 (28.7)	ns	ns	ns	0.043	ns	ns
In the last 3 – 6 months	115 (33.3)	ns	ns	ns	ns	0.05	ns
In the last year	85 (24.6)	ns	ns	ns	ns	0.036	ns
I can't remember – I hardly fall ill	46 (13.3)	-	-	-	-	-	-
Body size							
Average	167 (48.4)	-	-	-	-	-	-
On the slender side	74 (21.4)	ns	ns	ns	ns	ns	ns
Slightly plump	82 (23.8)	ns	ns	ns	ns	ns	ns
Very overweight or obese	22 (6.4)	ns	ns	ns	ns	ns	ns

ns=not significant, -=reference, p-values (bolded) <0.05 is considered as significant

Table 3: Stress factors of medical students post COVID-19 lockdown

Stress factors	Total N (%)	Gender		Race			
		Male	Female	Chinese	Indian	Malay	Others
I frequently bring work home at night							
Yes	266 (77.1)	ns	0.032	ns	ns	ns	ns
No	79 (22.9)	-	-	-	-	-	-
Not enough hours in the day to do all the things that I must do							
Yes	278 (80.6)	ns	0.038	ns	ns	ns	ns
No	67 (19.4)	-	-	-	-	-	-
I deny or ignore problems in the hope that they will go							
Yes	174 (50.4)	ns	ns	ns	ns	ns	ns
No	171 (49.6)	-	-	-	-	-	-
I do the jobs myself to ensure they are done properly							
Yes	281 (81.4)	ns	ns	ns	ns	ns	ns
No	64 (18.6)	-	-	-	-	-	-
I underestimate how long it takes to do things							
Yes	225 (65.2)	ns	ns	ns	ns	ns	ns
No	120 (34.8)	-	-	-	-	-	-
I feel that there are too many deadlines in my work / life that are difficult to meet							
Yes	188 (54.5)	ns	ns	ns	ns	ns	ns
No	157 (45.5)	-	-	-	-	-	-
My self confidence / self esteem is lower than I would like it to be							
Yes	146 (42.3)	ns	ns	ns	ns	ns	ns
No	199 (57.7)	-	-	-	-	-	-
I frequently have guilty feelings if I relax and do nothing							
Yes	246 (71.3)	ns	ns	ns	ns	ns	ns
No	99 (28.7)	-	-	-	-	-	-
I find myself thinking about problems even when I am							
Yes	224 (64.9)	ns	ns	ns	ns	ns	ns
No	121 (35.1)	-	-	-	-	-	-
I feel fatigued or tired even when I wake after an adequate sleep							
Yes	212 (61.4)	ns	ns	ns	ns	ns	ns
No	133 (38.6)	-	-	-	-	-	-
I often nod or finish other peoples sentences for them when they speak slowly							
Yes	127 (36.8)	ns	ns	ns	ns	ns	ns
No	218 (63.2)	-	-	-	-	-	-
I have a tendency to eat, talk, walk and drive quickly							
Yes	172 (49.9)	ns	ns	ns	ns	ns	ns
No	173 (50.1)	-	-	-	-	-	-
My appetite has changed, have either a desire to binge or have a loss of appetite / may skip meals							
Yes	154 (44.6)	ns	0.001	ns	ns	ns	ns
No	191 (55.4)	-	-	-	-	-	-
I feel irritated or angry if the car or traffic in front seems to be going too slowly/ I become very frustrated at having to wait in a queue							
Yes	146 (42.3)	ns	ns	ns	ns	ns	ns
No	199 (57.7)	-	-	-	-	-	-
If something or someone really annoys me I will bottle up my feelings							
Yes	178 (51.6)	ns	ns	ns	ns	ns	ns
No	167 (48.4)	-	-	-	-	-	-
When I play sport or games, I really try to win whoever I play							
Yes	172 (49.9)	ns	ns	ns	ns	ns	ns
No	173 (50.1)	-	-	-	-	-	-
I experience mood swings, difficulty making decisions, concentration and memory is impaired							
Yes	170 (49.3)	ns	0.017	ns	ns	ns	ns
No	175 (50.7)	-	-	-	-	-	-
I find fault and criticize others rather than praising, even if it is deserved							
Yes	41 (11.9)	ns	ns	ns	ns	ns	ns
No	304 (88.1)	-	-	-	-	-	-
I seem to be listening even though I am preoccupied with my own thoughts							
Yes	242 (70.1)	ns	ns	ns	ns	ns	ns
No	103 (29.9)	-	-	-	-	-	-
I find myself grinding my teeth							
Yes	94 (27.2)	ns	ns	ns	ns	ns	ns
No	251 (72.8)	-	-	-	-	-	-
Increase in muscular aches and pains especially in the neck, head, lower back, shoulders							
Yes	159 (46.1)	ns	<0.0001	0.024	ns	0.007	ns
No	186 (53.9)	-	-	-	-	-	-
I am unable to perform tasks as well as I used to, my judgment is clouded or not as good as it was							
Yes	136 (39.4)	ns	ns	ns	ns	ns	ns
No	209 (60.6)	-	-	-	-	-	-
I find I have a greater dependency on alcohol, caffeine, nicotine or drugs							
Yes	68 (19.7)	ns	ns	ns	ns	ns	ns
No	277 (80.3)	-	-	-	-	-	-
I find that I don't have time for many interests / hobbies outside of work							
Yes	168 (48.7)	ns	ns	ns	ns	ns	ns
No	177 (51.3)	-	-	-	-	-	-

ns=not significant, -=reference, p-values (bolded) <0.05 is considered as significant

ORIGINAL ARTICLE

Effect of Tualang Honey Supplementation in Weight Reduction and Dyslipidaemia in High Cholesterol Diet- induced Obese Rats

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ABSTRACT

INTRODUCTION: Obesity is a key risk factor for many chronic diseases. Malaysia records the highest prevalence of obesity in Southeast Asia. Tualang honey has been proven to treat many chronic diseases but its effect on weight reduction has yet to be well-studied. This study aimed to investigate the effects of Tualang honey (TH) supplementation on body weight and lipid profile in a 12% high cholesterol diet (HCD) induced obesity rat model. **MATERIALS AND METHODS:** Forty male Sprague-Dawley rats were assigned to five groups (n=8): Group 1 (normal diet), Group 2 (normal diet + TH 3.0 g/kg), Group 3 (12% HCD), Group 4 (12% HCD + TH 3.0 g/kg), and Group 5 (12% HCD + Orlistat 10 mg/kg). Diets were administered for 12 weeks, followed by treatments for six weeks. Body weight was measured weekly, and blood was collected for lipid analysis at the end of the study. **RESULTS:** We demonstrated a significantly lower final body weight of rats in Group 2 (328.25 ± 25.49 g) compared to Group 1 (409.13 ± 16.33g) ($p<0.001$) and in Group 4 as compared to Group 3 (343.88 ± 44.24 g vs 471.00 ± 19.55g, $p<0.001$). The administration of TH also significantly reduces the cholesterol (Med=1.8 mmol/L, IQR=0.7 vs Med=3.2 mmol/L, IQR=0.8, $p<0.05$) and triglyceride level (Med=0.9 mmol/L, IQR=0.3 vs Med=1.5 mmol/L, IQR=1.0, $p=0.001$) in Group 4 compared to Group 3. **CONCLUSION:** Tualang honey supplementation has been shown to reduce body weight and improve lipid profiles in 12% HCD-induced obese rats.

Keywords
Obesity, tualang honey, high cholesterol diet, dyslipidaemia, body weight

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INTRODUCTION

Obesity and overweight are pathological states marked by an elevated body mass index (BMI) and/or increased fat accumulation.[1] A BMI of 25 kg/m² or more is classified as overweight, whereas obesity is indicated by a BMI of 30 kg/m² or above.[2] Currently, obesity has risen to epidemic levels globally, with its prevalence expected to continue rising across both developed and developing countries due to shifts in dietary patterns and reduced physical activity.[3] As global standards of living improve, overweight and obesity have become prominent and pressing nutritional issues in many regions.

Research has shown that from 1975 to 2015, global obesity rates rose significantly, from 3.2% to 10.8% among men and from 6.4% to 14.9% among women.[4] With this accelerated increase in prevalence, it is projected that by 2025, more than 18% of men and 21% of women worldwide becoming overweight or obese.[5] Among South Asian countries, Malaysia ranks highest in overweight and obesity rates, with 64% of men and 65% of women being classified as either overweight or obese.[6] These statistics highlight a growing health and economic burden, as the rising obesity rates directly contribute to an increase in obesity-related health complications. Recent studies have demonstrated that obesity and excess body weight are correlated with elevated mortality rates and are contributors to numerous health complications, including cardiovascular problem, liver disease, kidney failure, and diabetes mellitus (Figure 1).[7]

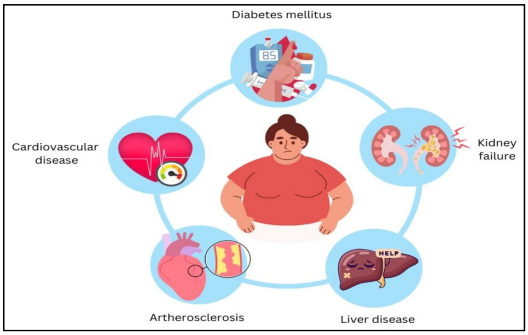

Figure 1: Health complications related to obesity.

Obesity management primarily involves lifestyle interventions, including dietary adjustments and exercise. Pharmacological treatments, such as orlistat, and surgical procedures like bariatric surgery are also employed as therapeutic strategies.[8] However, these methods are often associated with potential risks and adverse effects. Consequently, there has been growing interest in exploring natural products, such as honey, as alternative approaches for managing obesity due to their potential to minimize side effects.[9] In modern contexts, honey is valued as a nutritious supplement with recognized medicinal benefits. As reported by the Food and Agriculture Organization of the United Nations (FAO), honey production in Asia rose substantially, from 600 tonnes in 2007 to nearly 1,000 tonnes in 2017. In 2021, the amount of honey produced is nearly 1.8 million tonnes, reflecting a notable increase in honey consumption.[10]

Honey is a natural mixture composed of numerous constituents, including both simple and complex sugars, water, organic acids, proteins, vitamins, and minerals, as well as amino acids, phenolic acids, and flavonoids.[11] It has been shown to offer varieties of physiological benefits, such as antibacterial, anticancer, anti-inflammatory, and antioxidant effects.[12] By the late 20th century, honey gained popularity as a weight management aid, either alone or paired with other nutritious foods. Various studies have also demonstrated anti-obesity effects of honey, [13–15] with its active compounds, such as phenols and flavonoids, believed to impact fat metabolism by stimulating lipolysis and inhibiting lipogenesis.[16]

One of the most recognized honey varieties is Tualang honey (TH), which was selected as the primary focus of this study. It is produced by the rock bee (*Apis dorsata*), which builds its hives high in the branches of the Tualang tree (*Kompassia excelsa*). This wild, multi-floral honey is renowned in Malaysia for its medicinal properties. TH contains over 200 components, including various sugars such as fructose, glucose, maltose, and sucrose, along Zwith organic acids, vitamins, minerals, proteins, phenolic acids, flavonoids, enzymes, and other bioactive compounds.[17] TH stands out from other honey varieties lies on its notably high concentration of flavonoids and phenolic acids, which contribute to its antioxidant and anti-inflammatory effects.[18] These properties are particularly important in the context of obesity, where oxidative stress[19] and chronic inflammation[20] are key mechanisms driving the development of metabolic complications. Oxidative stress can lead to cellular damage, while prolonged inflammation has been closely associated with insulin resistance and lipid metabolism disturbances. TH, known for its antioxidant and anti-inflammatory qualities, helps to reduce oxidative stress by neutralizing free radicals and preventing cellular damage and may help to reduce chronic inflammation, which is commonly associated with obesity and metabolic disorders.

Additionally, the natural sweetness of TH may help to regulate appetite and reduce overall calorie intake.[21] Its consumption has also been suggested to promote satiety, which could support weight management efforts. Furthermore, TH may positively regulate gut microbiota composition, which plays a vital role in metabolic health and obesity prevention.[22] While TH has been widely investigated for its beneficial effects in several metabolic disorders, studies focusing on its role in obesity management remain limited.

In addition, in human studies, body mass index (BMI) is a widely accepted measure of obesity, however, its applicability in animal models, particularly rodents, is limited due to species-specific differences in body composition and shape. Unlike BMI, the Lee Obesity Index (LOI) was specifically developed for rodents and accounts for variations in body size and shape. This makes LOI a more accurate and reliable tool for assessing obesity in rats, as it better reflects the body fat percentage in rodents subjected to dietary-induced obesity.[23]

Therefore, by utilizing LOI, this study aimed to assess the impact of Tualang honey's antioxidant and anti-inflammatory effects on weight reduction in rats with obesity induced by a high-cholesterol diet.

MATERIALS AND METHODS

Animals

In this study, forty male Sprague-Dawley rats, each weighing between 200-250g, were selected as the experimental animal model. The rats were obtained from A-Sapphire Enterprise, located in Seri Kembangan, Selangor, Malaysia. They were individually housed in controlled conditions with a temperature of 22 ± 2ºC, a relative humidity of 60 ± 5%, and a 12-hour light/dark cycle. Food and water were provided *ad libitum*. The rats were acclimatized for a week period with a commercial rat pellet diet prior to the beginning of the experiment. All experimental procedures were approved by the Animal Care and Use Committee of the International Islamic University Malaysia (IIUM/504/14/2/IACUC).

Preparation of High Cholesterol Diet

The 12% high-cholesterol diet (HCD) was formulated by blending 1 kg of powdered commercial rat pellets (Gold Coin, Malaysia) with 120 grams of analytical-grade cholesterol powder (Nacalai-Tesque, Japan; Code 08721-75). To promote the absorption of cholesterol, 3 grams of cholic acid (Nacalai-Tesque, Japan; Code 08843-72) were incorporated into the mixture. To prevent oxidative modifications of the cholesterol, the high-cholesterol diet was freshly prepared daily.

Preparation of Tualang Honey and Orlistat

Tualang honey (TH) (AgroMas, Malaysia) was sourced from the Federal Agricultural Marketing Authority (FAMA), Kedah, Malaysia. A daily dose of 3.0g/kg[24] was prepared by dissolving the honey in warm water immediately before administration. The dose was calculated by converting the human equivalent dose to a rat equivalent using the Km factor method, based on the following formula:

Human Equivalent Dose (HED) = (Animal Km factor / Human Km factor) × Animal dose.[25]

Xenical Orlistat (Roche, Basel, Switzerland) was obtained from a local drugstore and was administered at a dose of 10 mg/kg[26] body weight, also freshly prepared in warm water before use.

Animal Experimental Design

The study was conducted in two phases: the induction phase (12 weeks) and the treatment phase (6 weeks). Following a one-week acclimatization period, their initial bodyweight was measured, and the rats were randomly assigned to five groups, with eight rats per group.

Group 1 served as the control and was provided with standard commercial rat pellets and drinking water, with no treatment administered throughout the study. Group 2 also received a standard commercial rat pellet diet, but was treated with Tualang honey (TH) during the treatment phase. Groups 3, 4, and 5 were given with a high-cholesterol diet (HCD) during the induction phase to induce obesity. Group 3 did not receive any treatment during the treatment phase, however Groups 4 and 5 were treated daily via oral gavage with TH (3.0g/kg) and Orlistat (10mg/kg), respectively.

At the end of the experimental period, the rats were fasted overnight and their final weight were recorded before sacrifice. Blood was collected via retro-orbital bleeding and centrifuged for 10 min at 2500 x g for serum separation and stored at -80°C until further biochemical obesity-related parameters analysis.

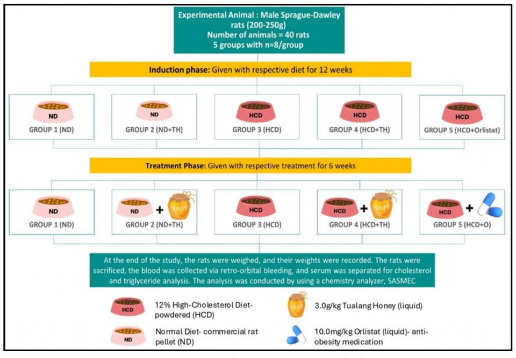

Figure 2: Animal experimental design.

Assessment of Obesity Parameter

The Lee obesity index (LOI) was calculated following the method described in previous studies, with a value greater than 315 indicating obesity.[27] To compute the LOI, the

cube root of the body weight (in grams) was divided by the naso-anal length (in centimetres), and the resulting value was multiplied by 1000.

Lipid Profile Analysis

Lipid profile measurements were conducted on the serum samples, including total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-c), and low-density lipoprotein cholesterol (LDL-c). These parameters were analysed using the Cobas Integra 400 Plus Analyser (Roche, Switzerland) at the Sultan Ahmad Shah Medical Centre (SASMEC), Kuantan, Malaysia.

Statistical Analysis

Data that followed a normal distribution were analysed using one-way analysis of variance (ANOVA), with post-hoc comparisons performed using the Tukey test. Results are presented as the mean ± standard deviation. For non-normally distributed data, the Kruskal-Walli's test was applied, followed by the Dunn-Bonferroni test, and results are reported as the median with interquartile range. A p-value<0.05 was considered statistically significant.

RESULTS

Bodyweight, Lee Obesity Index and Adipose Tissue Weight

Table 1 presents significant differences across the dietary and treatment groups. Initial bodyweights were comparable among all groups, indicating no significant baseline differences (p>0.05). At the end of the study, rats in the HCD-only group (Group 3) had the highest final bodyweight and bodyweight gain percentage, significantly greater than those in the other groups (p<0.05). In contrast, the normal diet group (Group 1) showed significantly lower final bodyweight and bodyweight gain percentage compared to Group 3 (p<0.05). Additionally, rats on a normal diet with TH (Group 2) had significantly lower final bodyweight and bodyweight gain percentage compared to Group 1 (p<0.05). Among the HCD groups receiving treatment, both Group 4 and Group 5 had significantly lower final bodyweight and bodyweight gain percentage compared to Group 3 (p<0.05).

Table 1: Comparison of Bodyweight, Adipose tissue weight and Lee Obesity Index results among the rat groups

Groups	Group 1 ND only	Group 2 ND + TH	Group 3 HCD only	Group 4 HCD + TH	Group 5 HCD + Orlistat
Initial bodyweight (g)	210.5 ± 23.1	196.0 ± 23.7	191.6 ± 13.3	191.0 ± 18.2	192.5 ± 17.7
Final bodyweight (g)	409.1 ± 16.3	328.3 ± 25.5[a]	471.0 ± 19.5[a]	343.9 ± 44.2[b]	351.0 ± 27.1[b]
Bodyweight gain (%)	96.4 ± 23.1	70.5 ± 30.4	146.3 ± 9.7 [a]	82.8 ± 37.4[b]	84.9 ± 19.5[b]
Lee's Obesity Index	304.8 ± 16.3	294.3 ± 20.3	335.3 ± 11.3[a]	302.8 ± 8.2[b]	308.4 ± 7.4[b]
Adipose Tissue Weight (g)	15.7 ± 2.1	12.3 ± 1.7[a]	19.8 ± 2.2[a]	11.9 ± 1.7[b]	12.3 ± 1.7[b]

Normal distributed data was presented as mean ± standard deviation.
a. Significant difference when compared to Group 1 (p < 0.05).
b. Significant difference when compared to Group 3 (p < 0.05).

Lee Obesity Index (LOI), a measure of obesity in obese-animal model, was also highest in Group 3 compared to Group 1 (p<0.05). Nevertheless, when supplemented with TH, rats in Group 2 showed significantly lower LOI compared to Group 1 (p<0.05). Similar with Group 4, when treated with TH, those rats exhibit significantly lower LOI compared to Group 3 (p<0.05). However, there is no significance different of LOI between the HCD-treated groups, Groups 4 and 5 (p>0.05).

As for the weight of adipose tissue, the HCD-treated group, Groups 4 and 5 showed significantly lower adipose tissue weights (p<0.05) compared to Group 3. Similarly, adipose tissue weight in Group 2 which was treated with TH is significantly lower compared to Group 1 (p<0.05).

Lipid Profile Parameters

Table 2 presents the lipid profile results across the groups. Total cholesterol levels were significantly higher in rats receiving the HCD (Group 3) compared to those on the normal diet (Group 1) (p<0.05). In contrast, rats in the HCD groups receiving treatment (Groups 4 and 5) had significantly lower total cholesterol levels compared to Group 3 (p<0.05). A similar trend was observed for triglyceride levels, with Group 3 exhibiting significantly higher levels compared to Groups 1, 4, and 5 (p<0.05). No significant difference was observed between the TH and Orlistat treatments in the HCD groups (Groups 4 and 5, p>0.05). Nevertheless, there were no significant differences among the groups in LDL-c and HDL-c levels.

Table 2: Lipid profile result for each group

Groups	Group 1 ND only	Group 2 ND + TH	Group 3 HCD only	Group 4 HCD + TH	Group 5 HCD + Orlistat
Total cholesterol (mmol/L)	1.8 (0.2)	1.4 (0.1)[b]	3.2 (0.8)[a]	1.9 (0.7)[b]	1.9 (0.4)[b]
Triglyceride (mmol/L)	0.8 (0.4)	0.7 (0.2)[b]	1.5 (1.0)[a]	0.9 (0.3)[b]	0.9 (0.4)[b]
HDL-c (mmol/L)	1.0 (0.2)	0.9 (0.4)	0.9 (0.2)	1.3 (0.2)	1.3 (0.4)
LDL-c (mmol/L)	0.3 (0.3)	0.4 (0.3)	0.8 (0.2)	0.5 (0.3)	0.7 (0.6)

Non-normal distributed data was presented as median (interquartile range)
a. Significant difference when compared to Group 1 ($p < 0.05$).
b. Significant difference when compared to Group 3 *($p < 0.05$).*

Gross of Adipose Tissue

Figure 3 shows the visceral adipose tissue deposition in rats across five experimental groups, demonstrating differences influenced by dietary interventions. Group 1 exhibits minimal adipose tissue deposition around the abdominal cavity. In contrast, Group 3 shows markedly excessive visceral fat accumulation, characterized by prominent fat accumulation surrounding the intestines and organs. Groups 2, 4 and 5 reveal varying degrees of fat reduction compared to Group 3. Notably, Group 4 which was supplemented with TH has displayed a substantial decrease in visceral adiposity, while Group 5 also shows reduced fat deposition.

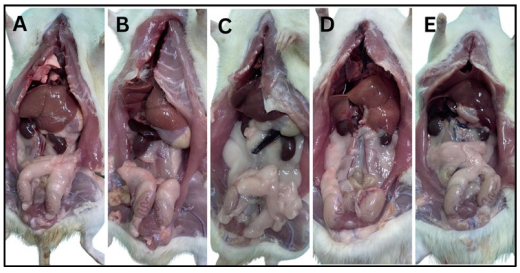

Figure 3: Gross anatomical representation of the rat's adipose tissue among the five groups; A (Group 1- showing minimal fat accumulation), B (Group 2- displaying reduced visceral fat deposition compared to Group 1), C (Group 3- demonstrating excessive visceral fat accumulation, indicative of obesity development), D (Group 4- showing a marked reduction in visceral fat compared to Group 3), E (Group 5- decreased visceral fat deposition, comparable to Group 4).

DISCUSSION

A high-cholesterol diet was used in research to induce obesity and dyslipidaemia in animal models, as it promotes excessive fat accumulation and disrupts lipid metabolism, leading to conditions associated with metabolic syndrome and cardiovascular disease. In this study, we investigated the effect of Tualang honey (TH) supplementation on body weight and lipid profile in a 12% high-cholesterol diet (HCD)-induced obesity rat model and observed that HCD-alone group led to significant increases in body weight, Lee Obesity Index (LOI), and unfavourable lipid profiles, which aligns with previous studies using similar dietary models to induce obesity and related metabolic disorders.[24] The HCD model employed in this study effectively induced obesity in rats, as evidenced by significant weight gain and an increased LOI in the HCD-only group. These results are in line with previous research, which shows that high-fat diets lead to increased adiposity, weight gain, and metabolic disturbances, confirming the effectiveness of the diet in inducing obesity within this timeframe.[28,29] In contrast, TH supplementation significantly reduced body weight, bodyweight gain percentage, and LOI in HCD-fed rats, suggesting that TH has a beneficial impact on body weight regulation in an obesity-rat model. These results align with findings from other studies, where supplementation of honey for six weeks has improved the anti-obesity parameters in high-fat diet induced obese rats.[30]

The weight-modulating effects of TH may be largely attributed to its unique composition. TH contains 35–40% fructose and 30–35% glucose, sugars that differ significantly from refined sugars in metabolic effects.[31] Unlike sucrose, the fructose in honey is absorbed more gradually, leading to a lower glycaemic response and reduced insulin spikes, which can reduce fat storage and appetite.[21] This was further proven by a study that observed rats fed honey, rather than sucrose, showed reduced weight gain and lower body fat percentage over the study period.[32] The moderate absorption rate of honey's sugars may help regulate blood glucose levels and avoid excessive insulin release, factors associated with obesity prevention.[21]

In this study, obese rats treated with TH (Group 4) showed significantly lower final bodyweight. Additionally, TH is rich in polyphenolic compounds and flavonoids such as quercetin, kaempferol, and luteolin, which have been shown to possess anti-obesity effects.[33] A study has demonstrated that rats on an high-fat diet treated with Gelam and Acacia honey for 4 weeks exhibited significantly lower weight gain compared to the untreated group.[34] Their findings suggested that honey's polyphenol content may inhibit fat deposition and adipogenesis.[34] This

was further explained by another study that stated flavonoid-rich honey reduced weight gain in rats on a high-fat diet, presumably via improving fat oxidation and energy expenditure.[35]

The weight and accumulation of adipose tissue in rats which were supplemented with TH (Group 2 and 4) is significantly lower compared to rats in Groups 1 and 3. The findings may be attributed to the antioxidant properties of TH, which can exert its effect on body weight and adiposity. Obesity is associated with elevated oxidative stress, which can impair mitochondrial function and fat oxidation, leading to fat accumulation.[36] A study had suggested that honey's antioxidant activity helps to combat oxidative damage in obese individuals, which could indirectly support weight management.[37] Findings from the current research suggest that TH's antioxidants, including phenolic acids and flavonoids, help to counter oxidative stress and may enhance mitochondrial function, thus supporting metabolic health and reducing fat storage.

TH also showed significant effects on lipid profile parameters. In Group 3, we observed elevated total cholesterol, triglycerides, and LDL-c, with a reduction in HDL-c, which align with the dyslipidaemia profile typically seen in high-fat or high-cholesterol diets. TH supplementation in Groups 2 and 4, significantly reduced total cholesterol, triglycerides, and LDL-c, while increasing HDL-c levels, indicating an overall improvement in lipid profile.

The findings were in accordance with previous research which suggests that Kelulut honey significantly lowered LDL-c and total cholesterol levels in high-fat diet-induced models, lending further support to TH's potential in cholesterol management.[38] Another study proposed that Acacia tree honey (*Desi kikar*) may reduce triglyceride, total cholesterol, and LDL levels in albino mice.[39] Studies suggest that the lipid-modulating effects of TH are likely due to its bioactive compounds, such as phenolics and flavonoids, which are known to influence cholesterol metabolism and enhance reverse cholesterol transport.[40] This was further supported by another study which demonstrated that polyphenols inhibit HMG-CoA reductase, a crucial enzyme in cholesterol biosynthesis, resulting in decreased circulating cholesterol levels.[41]

Other experimental data further confirm these recent findings, where supplementation of Gelam honey in Sprague-Dawley rats improved lipid profiles and reduced oxidative stress markers, supporting honey's role in managing lipid dysregulation.[42] This aligns with the findings of the present study, which indicate that TH can mitigate HCD-induced dyslipidaemia and support healthier lipid profiles. Among the benefits highlighted from previous study is the honey's ability to facilitate weight loss and reduce blood triglyceride levels in obese rats.[39] In this study, the triglyceride-lowering effect of TH is also noteworthy, as elevated triglycerides are associated with increased cardiovascular risk. The high flavonoid content in TH may activate lipoprotein lipase, which is involved in triglyceride breakdown, facilitating triglyceride clearance and contributing to a more favourable lipid profile.[43]

Human subjects have also been studied to see how different honey variations affect their lipid profiles. Previous study found that consuming honey for 48 days improved lipid profiles in obese adult participants.[44] In addition, a study has discovered that patient with diabetic neuropathy supplemented with probiotic honey for 12 weeks has significant improvement in their lipid profile while not causing weight gain in overweight or obese participants.[45] Furthermore, a clinical study revealed that the supplementation of honey in human subjects led to a reduction in serum total cholesterol and LDL-c, accompanied by an increase in HDL-c, suggesting that honey's lipid-modulating effects are applicable across species.[46]

The effects observed with TH in this study were comparable to those of Orlistat, a pharmacological anti-obesity agent, suggesting that honey may offer similar benefits through natural mechanisms that improve metabolism and lipid utilization. A study comparing the effect of Pauttika honey and Orlistat has shown that both have exerted similar effects in reducing fat accumulation in obesity.[47] These current findings suggest that TH may be a promising natural intervention for managing diet-induced obesity and dyslipidaemia.

This aligns with a growing interest in using natural products to manage metabolic diseases since natural interventions often have fewer side effects than pharmaceuticals.

However, further clinical studies are required to verify the effects of TH in human. Additionally, long-term studies could also evaluate the sustainability of honey's benefits and any potential side effects associated with prolonged consumption. Although the present study demonstrated a significant reduction in adipose tissue weight following TH supplementation, it is recommended that future studies utilize body composition analysis methods, such as DEXA scan, to further validate whether the weight reduction is specifically due to fat loss rather than changes in muscle or water content. Moreover, gut microbiome dysbiosis has been strongly associated with obesity and high-fat diets,[22,48] while antioxidant supplementation has demonstrated the potential to improve gut microbiota composition and mitigate obesity-related effects.[49] Therefore, exploring this connection further is encouraged to develop a more comprehensive strategy for managing obesity and its associated health complications.

CONCLUSION

Tualang honey supplementation has been shown to reduce body weight and improve lipid profiles in 12% HCD-induced obese rats.

CONFLICT OF INTEREST

There are no conflicts of interest among the authors.

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ORIGINAL ARTICLE

Antiaging activities of *Muntingia calabura* Leaf Aqueous Extracts (MCE) on Testicular Histology, Spermatogenic Proliferation, and Testosterone Level of D-Galactose-Induced Mice Model

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ABSTRACT

INTRODUCTION: Male aging may disrupt spermatogenesis and induce intratesticular redox imbalance, leading to testicular damage. *Muntingia calabura* leaf extracts (MCE) have potent antioxidant activity, but *in vivo* reports in the male reproductive system aging are limited. This research aimed to determine the effects of MCE on testicular histology and testosterone levels in the D-galactose-induced aging mice model. **MATERIALS AND METHODS:** Plasma and testicular tissue obtained from 20 male *Mus musculus* strain Balb/C which were divided into 5 groups: normal; aging; aging+ *Muntingia calabura* leaf aqueous extracts (MCE) 35 mg/kg; aging+MCE 70 mg/kg; and aging+vitamin C 28 mg/kg. Treatments were scheduled orally for 4 weeks; aging condition was induced using oral 500 mg/kg D-galactose for 6 weeks before treatments. Plasma testosterone was determined using ELISA, seminiferous tubules' diameter, spermatogenesis score, and Leydig cell number were examined with routine staining, and the nuclear expression of Ki-67 was performed via immunohistochemistry. **RESULTS:** The MCE-treated aging group had higher seminiferous tubules' diameter, spermatogenesis score, Leydig cells' number, and percentage of cells expressing Ki-67 compared with the untreated group ($p < 0.005$), and the optimum dose was 70 mg/kg. However, testosterone levels of the MCE group did not significantly differ from those of others. **CONCLUSION:** Administration of MCE in D-galactose-induced aged mice improved seminiferous tubule diameter, spermatogenesis score, Leydig cells' count, and spermatogenic cell proliferation, but not testosterone level.

Keywords
Muntingia calabura, testosterone, aging, spermatogenesis, seminiferous tubule.

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INTRODUCTION

Aging is a normal mechanism, but occasionally prematurely happens due to DNA damage, which leads to cell regeneration failure.[1] This process is commonly induced by oxidative stress due to a disturbed balance of reactive oxygen species (ROS) formation and antioxidant system. Excessive ROS leads to lipid peroxide accumulation in the cell membrane and disrupts its functions and the declining cell viability.[2] ROS also reacts with polyunsaturated fats and forms malondialdehyde (MDA), a reactive aldehyde that is toxic for cells and tissues, decreasing tissues and organ functions and accelerating senescence.[3]

Senescence signs are visible in many organ systems, including the reproductive system.[4] Aged male reproductive system is characterized by a decrease in testicular volume, weight, and testicular density, which may disrupt the spermatogenesis.[5] While normal testicular tissue is essential for spermatogenesis, aging can induce testicular microstructural changes.[6] These changes include an increase in weight and thickness of tunica albuginea, thickening of the seminiferous tubule basement membrane, and also accumulation of collagen tissue and thickening of tunica propria of the testicles due to a reduction in testicular perfusion due to occlusion and

thickening of testicular blood vessels.[5,7,8] As the age progresses, intra-testicular antioxidant productions are declining.[6] This condition leads to an increased risk of testicular damage.[9,10]

Rodent models were frequently used in laboratory aging research. Naturally aged animals are the most ideal condition for mimicking natural aging in humans, but, due to problems concerning animals' lifespan, the chemical-induced aging models were also beneficial, for example, the D-galactose-induced aging models.[11] Inducing aging conditions using D-galactose was popular because it has many advantages such as being easy to apply, being low-cost, producing a high-survival animal, and having fewer side effects throughout the aging period.[12,13] In inducing male testicular aging models, D-galactose-induced male aging models were reported successfully to reproduce the aging mechanism.[14,15] Administering 50–500 mg/kg D-galactose daily for 6–8 weeks induced aging characteristics such as reduced testosterone and structural changes on the testis and spermatogenesis similar to those of aged control individuals aged 16 to 24 months.[16,17] Since one human year is nearly identical to nine mouse days when comparing their respective lifespans, therefore the animals in this study were equivalent to humans aged 52.60–78.90 years.[18]

Muntingia calabura (Jamaican cherry) is widely distributed in the tropics and subtropics, and is traditionally used as a gastric pain remedy. Leaves extracts of *M. calabura* have been reported to contain carbohydrates, protein, polyphenols, flavonoids, ascorbate acid, α-tocopherol, and chlorophylls.[19,20] *M. calabura* leaf extracts also have a potent antioxidant activity through 1,1-Diphenyl-2-picrylhydrazyl (DPPH) and lipid peroxidase formation inhibitions.[21] This antioxidant activity has been confirmed in vitro and it is highly possible that this extract also has anti-aging properties. *M. calabura* leaf extracts *in vivo* exploration in Indonesia is quite narrow.[22,23] Based on this condition, in this study, we try to determine the potential usage of *M. calabura* leaves extracts as an antiaging agent, mainly in the male reproductive systems aging. In this research, we evaluated the antiaging properties of *M. calabura* leaf aqueous extract (MCE) on the male reproductive system, mainly on seminiferous tubules' diameter, spermatogenesis score, Leydig cells' number and expression of Ki-67 as a marker for the proliferation of spermatogenic cells and testosterone levels of D-galactose-induced aged mice.[24]

MATERIALS AND METHODS

Research Design

This study used a combination of pre-and post-test and the post-test only with a control design, conducted at the Integrated Research Laboratory, Islamic University of Indonesia in May-August 2021.

Experimental Intervention

This research is a continuation of previous research that studied the antiaging activities of MCE on D-galactose-induced *Mus musculus* Balb/c.[25] Research specimens were obtained from 20 male *Mus musculus* Balb/C, aged 12 weeks, and weighed 25 + 5 g. The sample size was determined using the Research equation.[26] Mice were grouped into normal control (I, received aquadest); aging control (II, received aquadest); aging group received MCE 35 mg/kg (III); aging group received MCE 70 mg/kg (IV); and aging group received vitamin C 28 mg/kg (V or positive control).[25] Aging conditions in Group II-V were induced with 500 mg/kg D-galactose orally (Sigma-Aldrich, USA) daily for 6 weeks.[9,17] After aging conditions were confirmed from elevated plasma MDA level, animals received scheduled treatment with 1 ml working solution (reconstituted with distilled water with a ratio of 1:1) orally for 4 weeks. The extract preparation used of *M. calabura* leaf collected from Sleman Region (GPS coordinate -7°.68751, 110°.41423), which was deposited and identified by Faculty of Mathematics and Natural Sciences, Islamic University of Indonesia (Register Number 02/UII/Jur.Far/det/I). After washing, air-dried and milled into powder; about 1,000 g of the powder was macerated with 5 l of distilled water for 24 hours and then filtered using filter paper. All filtrates from 3 × 24 hours were evaporated to obtain crude extract (Figure 1).

Retro-orbital blood samples were taken before and after treatment, while testicular tissues were taken after the animals' sacrifice via ketamine injection followed by

decapitation. The experimental protocols were approved by the Health and Medical Research Ethics Committee, Faculty of Medicine, Islamic University of Indonesia (Reg. Number 32/Ka.Kom.Et/70/KE/I).

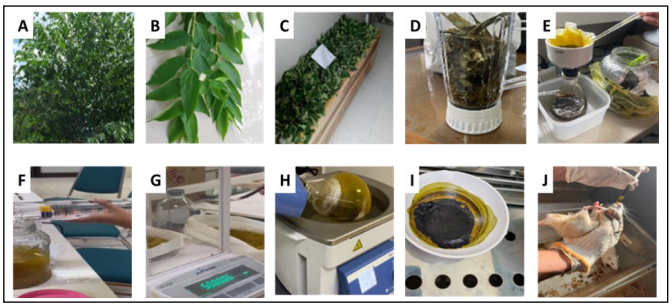

Figure 1. Preparation of *Muntingia calabura* leaves extract and administration to mice (A) *Muntingia calabura* tree; (B) Fresh leaves of *Muntingia calabura*; (C) Temperature and humidity controlled drying of collected leaves; (D) Pulverization of dried leaves; (E) Measurement of the ground material; (F) Maceration of leaves; (G) Filtration; (H) Evaporation; (I) Concentrated extract; (J) Administration of MCE via oral gavage

Sample Collection and Analyses

Blood samples were placed in containers, then centrifuged at 4,000 rpm (15 min), and retrieved plasma was stored at −20°C for further examination. Testosterone concentration was determined using ELISA (DRG® Testosterone, EIA-1559). Right testicles were placed in 10% buffer formalin and then processed into a paraffin block. The blocks were sectioned with a microtome of 5 µm thickness, deparaffinized, and stained for Hematoxylin-Eosin and analysed for spermatogenesis scores, Leydig's cells count (characterized by polygonal cells with eosinophilic cytoplasm and a large round nucleus with a prominent nucleolus), and seminiferous tubule's diameters.[27,28]

Table I: Johnsen's score on spermatogenesis[27]

Score	Criteria
Score 10	Complete spermatogenesis
Score 9	Moderately disturbed spermatogenesis, numerous late spermatids, disordered epithelium
Score 8	Less than 5 spermatozoa within a tubule, a small number of late spermatids
Score 7	No spermatozoa, no late spermatids, numerous early spermatids
Score 6	No spermatozoa, no late spermatids, a small number of early spermatids
Score 5	No spermatozoa or spermatids, plenty of spermatocytes
Score 4	No spermatozoa or spermatids, a small quantity of spermatocytes
Score 3	Spermatogonia only
Score 2	No spermatogenic cells, Sertoli cell only
Score 1	No seminiferous epithelium

Immunohistochemistry

After deparaffinized and processed in graded ethanol, the 5 µm tissue slices were incubated in H_2O_2 3% to eliminate nonspecific staining. After antigen retrieval process, the slides were incubated with Ki-67 primary antibody (Abcam, ab279653) at 4℃ overnight. The sections were incubated with secondary antibodies and then counterstained with Haematoxylin Meyer. The Ki-67 nuclei protein showed as brown-yellow particles and presented in percentage of KI-67 positive cells. All photomicrographs were taken with Olympus® CX23 (Olympus, Japan) assembled with Optilab® Viewer (Miconos, Indonesia). The quantification of all histology parameters was performed on 5 separate fields using Image Raster software (Miconos, Indonesia) by 2 observers blinded to the treatments.

Statistical Analysis

Data were reported in means and standard deviations and analysed with SPSS v.26.00 Statistics. Saphiro Wilk tests were conducted to assess data normality. For normally distributed data, the mean was compared using one way ANOVA and Tukey HSD for post hoc comparison. For non-normally distributed data, the mean was compared using Kruskal-Wallis followed by Mann-Whitney test. Wilcoxon signed-rank test was used to compare paired data (pre- and post- treatment). All tests were conducted in a 95% confidence interval.

RESULTS

Spermatogenesis Score and Morphological of Seminiferous Tubules

Examination of testicular tissue in the low magnification exhibited the normal control group had an intact seminiferous tubule with optimum epithelial thickness. The interstitial components of the normal control group occupy a small part of the field (Figure 2, Panel I, A). The aging control showed a dominant interstitial compartment with scanty distribution of seminiferous tubules and variable size of seminiferous tubules (Figure 2, Panel I, B). Most seminiferous tubules in the aging group had small diameters and thin epithelium layers. The aging group received 35 mg/kg MCE showed a dominant interstitial

compartment but thicker epithelium (Figure 2, Panel I, B). The aging group received 70 mg/kgBB MCE and vitamin C has a minimal interstitial compartment and thick epithelium (Figure 2, Panel I, D and E). The untreated aging group had the lowest diameter. While the aging group received MCE 70 mg/kg and vitamin C, showed a higher seminiferous tubule diameter, and did not significantly differ from the normal control. However, the MCE 35 mg/kg treated group still had lower diameters compared with the MCE 70 mg/kg and vitamin C group (Figure 3, A).

Higher magnification (400x) revealed thick epithelium with complete spermatogenesis which is made up of different spermatogenic cell phases, from spermatogonia, spermatocytes, spermatids, and spermatozoa (score: 10). The aging control group showed thin epithelium, cellular depletion, and minimal spermatogenesis (Figure 2, panel II B). Since the most common cells are immature sperm cells, the aging control group only reached a score of 6 in Johnsen's spermatogenesis scores (Figure 3, B). The treatment with MCE 35 mg/kg resulted in a similar histological appearance to the aging control group (Figure 2, Panel II C). However, the aging group received MCE 70 mg/kg showed thicker epithelium (Figure 2, Panel II D) and higher spermatogenesis score (score: 8-10, Figure 3B); vitamin C-treated group showed spermatogenesis score 9-10, but the score of both groups still lower compared with normal control. The treatment with MCE 70 mg/kg and vitamin C showed higher diameter and Johnsen's score compared with an untreated aging group ($p < 0.05$, Figure 3B).

Ki-67 Expression

The expression of Ki-67 in the seminiferous epithelium is related to actively proliferating and spermatogenic cells. The normal control group showed abundant cells expressing Ki-67 (Figure 2, Panel III A), mainly expressed in spermatogonia and spermatocytes, whereas the aging control showed a smaller number of cells (Figure 2, Panel III B). The aging group treated with MCE 70 mg/kg and vitamin C showed quite high levels of expression (Figure 2, Panel III D and E). The treatment with MCE 70 mg/kg and vitamin C showed a significant improvement in the percentage of Ki-67 positive cells, compared with an untreated aging group. Nevertheless, the aging group that received MCE 70/kg still had lower levels of Ki-67 expression than the normal control group ($p<0.05$, Figure 3C).

Leydig Cells' Count

The normal control group showed abundant interstitial cells of Leydig which produced testosterone. The aging group had the lowest number of Leydig cells, while the aging group received MCE 70 mg/kg and vitamin C showed an increased number of Leydig cells. The aging group received MCE 35 mg/kg showed an elevated number of Leydig cells, but did not significantly differ from the aging group. The number of Leydig cells in the aging group received vitamin C was similar to normal control, however, the MCE 70 mg/kg still had a lower number of Leydig cells ($p<0.05$, Figure 3D).

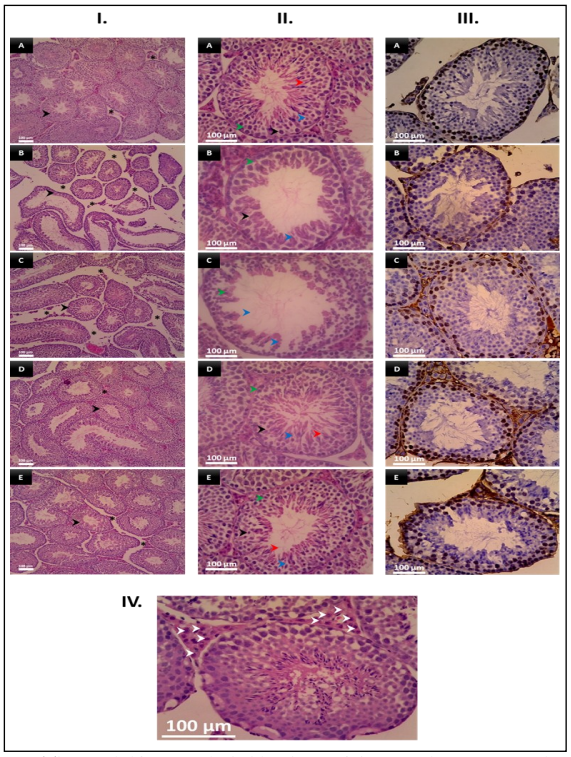

Figure 2. The seminiferous tubule histology of the experiment groups in various examinations. A: healthy control; B: aging control; C: Aging + MCE 35 mg/kg; D: Aging + MCE 70 mg/kg; E/ positive control: Aging + vitamin C 28 mg/kg. Panel I: The architecture of seminiferous tubules. The normal group showed thick epithelium and a small portion of interstitial space. While the aging group showed a reduced number of seminiferous tubules with small diameter and thin epithelium, but wide interstitial tissue. Bar indicated 100 µm in 100x magnification; Panel II: The seminiferous epithelium cells observation, spermatogonia (green arrow), spermatocytes (black arrow), spermatozoa (red arrow), and spermatids (blue arrow), bar indicated 100 µm in 400X magnification; Panel III: Nuclear expression of Ki-67 (brown-coloured) with Ki-67 immunohistochemistry staining. The Ki-67 expression was higher in the healthy control compared to the aging control group. Bar indicated 100 µm in, 100X magnification; Panel IV: Interstitial cell of Leydig (arrowheads) in the testicular interstitial tissue. Bar indicated 100 µm in, 400X magnification. MCE = *Muntingia calabura* leaves aqueous extract.

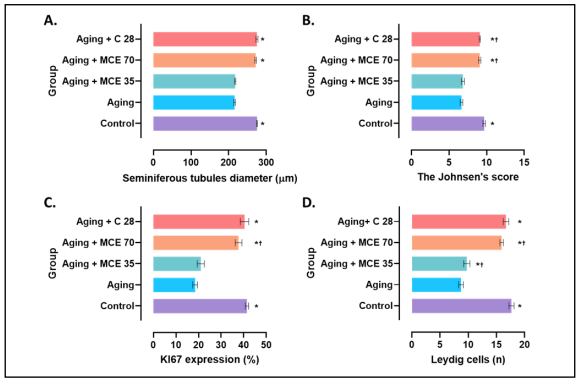

Figure 3: Seminiferous tubule parameters; (A) Comparison of tubules' diameter. The aging group and aging + MCE 35, exhibit the smallest seminiferous diameter, compared to the rest of the experimental groups; (B) Johnsen's spermatogenesis scores. The control group has the highest Johnsen's score. (C) Comparison of Ki-67 positive cell percentages. The control group shows the highest Ki-67 positive cell percentages among the experimental groups, followed by the positive control group. (D) The number of Leydig cells for each experimental group. Signifier symbol: *p < 0.05 compared with the aging group, †p < 0.05 compared with a control group (Analysis of Variance and post hoc Tukey Honestly Significant Difference analyses).

Testosterone Level

Table II presented the mean levels of testosterone. Overall, the increase in testosterone level is 0.87 ± 4.26 ng/mL. In the control group, pre-treatment testosterone levels ranged from 0.17-0.27 ng/mL with a mean of 0.24 ± 0.05 ng/mL. At the end of the research period, we noted an insignificant increase of about 3.21 ± 5.87 ng/mL compared with the pre-test testosterone level.

Pre-treatment testosterone of aging control was 3.37 ± 5.91 ng/mL. Post-treatment measurement reveals a decrease in testosterone level, about 2.58 ± 5.22 ng/mL, which was the lowest testosterone level among groups. The mean pre-treatment testosterone levels of the aged group received 35 mg/kg of MCE were 0.43 ± 0.02 ng/mL. During treatment periods, the testosterone levels rose by about 0.54 ± 0.78 ng/mL, and at the end of treatment periods, post-treatment testosterone levels for this group were 0.96 ± 0.80 ng/mL. Before being treated with MCE 70 mg/kg, the mean value of testosterone levels of group IV was 0.52 ± 0.04 ng/mL. Post-treatment testosterone levels were 3.31 ± 4.89 ng/mL, which means there was an increase in testosterone level, for about 2.79 ± 4.86 ng/mL. Pre-treatment testosterone levels of the aged group treated with 28 mg/kg of vitamin C were 0.51 ± 0.11 ng/mL. After vitamin C treatment, the testosterone levels decreased to 0.90 ± 0.65 ng/mL, reducing 0.39 ± 0.62 ng/mL of testosterone levels. Kruskall-Wallis's analysis revealed a significant difference in pre-treatment testosterone levels (p-value= 0. 025), but no significant difference in testosterone escalations (p-value= 0. 734) and post-treatment testosterone levels (p-value= 0. 282). In post-hoc analysis, only Group IV that has a significantly different testosterone level, compared with the control group (p-value= 0. 282).

Table II: Testosterone level of *Mus musculus* Balb/c

Testosterone level			**Testosterone level range**		**Mean ± SD (ng/mL)**	
Pre-treatment (group I-V)			0.17-12.23		1.01 ± 2.64	
Post-treatment (group I-V)			0.36-12.29		1.88 ± 3.33	
Testosterone escalation (post-pre)			-10.40-12.02		0.87 ± 4.26	
	Pre-treatment testosterone levels (ng/mL) *		Post-treatment testosterone levels (ng/mL)		Testosterone escalations (ng/mL)	
	Range	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD
Group I	0.17 - 0.27	0.24 ± 0.05	0.42 - 12.29	3.46 ± 5.90	0.16 - 12.02	3.21 ± 5.87
Group II	0.28 - 12.23	3.37 ± 5.91	0.38 - 1.83	0.79 ± 0.69	-10.40 - 0.24	-2.58 ± 5.22
Group III	0.41 - 0.45	0.43 ± 0.02	0.49 - 2.16	0.96 ± 0.80	0.07- 1.71	0.54 ± 0.78
Group IV	0.49 - 0.57	0.52 ± 0.04**	0.52 - 10.63	3.31 ± 4.89	0.02 - 10.06	2.79 ± 4.86
Group V	0.42 - 0.66	0.51 ± 0.11	0.36 - 1.82	0.90 ± 0.65	-0.06 - 1.31	0.39 ± 0.62

*p< 0.05 on Kruskal Wallis test; **p< 0.05 on Mann-Whitney post hoc, compared to the control group (Group I). I: healthy control, II: aging control, III; Aging + MCE 35 mg/kg, IV: Aging + MCE 70 mg/kg, V: Aging + vitamin C 28 mg/kg. MCE: *Muntingia calabura* extract. SD: standard deviation

DISCUSSION

Spermatogenesis is a complex process involving the mitotic division of the spermatogonia, to the formation of mature and motile sperm cells. Optimal spermatogenesis also required many factors, including the role of the interstitial compartment of the testis, mainly the testicular vascularization and the interstitial cell of Leydig.[29] However, the spermatogenesis process was disrupted in aged males. Sperm cell death rises with age, and spermatogenesis impairment is primarily shown in spermatocyte meiosis and spermatogonia mitosis, which leads to fewer sperm cells and sperm distortion.[5, 6, 30]

In this study, we use D-galactose to induce testicular aging in mice. Oral gavage of D-galactose was successful in elevating plasma MDA concentration compared with the normal group, and 4 weeks of MCE treatment and vitamin C significantly reduced plasma MDA levels, also, the testosterone level of the aging control group was decreased after six weeks of D-galactose induction.[17,25]

Chronic administration of D-galactose can induce aging conditions in the male reproductive system.[9,17]

D-galactose can cause a decrease in testicular weight and volume, poor quality of sperm analysis (including sperm count, motility, and morphology of sperm cells), lower testosterone levels, also a decrease in spermatid and spermatozoa gene expression markers, a downregulation of testosterone synthesis, which progresses to impaired spermatogenesis.[9,31] They reported that 6-8 weeks administration of oral low-dose-D-galactose accelerates aging conditions in the male reproductive system, and the condition resulting from this method of induction resembles natural aging with similar changes in reduced sperm count, reduced ratio of testicular weight/body weight with parenteral administration. Animals that received oral administration of D-galactose also had a reduced activity of superoxide dismutase and increased level of testicular lipid peroxidation.[12] The reduced testicular mass might be caused by testicular tubular size reduction, spermatogenesis failure, and reduction of Leydig cell activity.[9] Animals that received D-galactose had disturbed seminiferous epithelial structure and decreased number of spermatogenic cells; enlarged congested blood vessels and cellular exudates in the interstitial compartments.[32] Our study also established D-galactose as a method for inducing male reproductive system aging based on the decreased level of testosterone, decreased diameter of seminiferous tubule, decreased spermatogenesis score and percentage of spermatogenic cell expressed KI-67, which is widely known as a marker for cellular proliferation.

We reported that administration of MCE 70 mg/kg improved the testicular morphology of the D-galactose aging mice model and improved the rate of KI-67 positive cells. However, although groups receiving MCE 70 mg also exhibit a higher number of interstitial cells of Leydig, the testosterone level of this group did not significantly differ from the aging control group. These results might reveal the potency of the antiaging properties of MCE on testicular aging conditions induced by D-galactose.

Many research reports that all parts of *M. calabura* comprise active compounds including proteins, carbohydrates, polyphenols, flavonoids, ascorbic acid, α-tocopherol, and chlorophyll. These chemicals are recognized for their antioxidant properties and possess the ability to inhibit oxidative stress.[19] *M. calabura* contains polyphenol compounds such as gallocatechin, epigallocatechin, catechin, flavonols, naringenin, quercetin, and gallic acid which are reported to have antioxidant capacity.[33] *M. calabura* leaf extracts are reported to have antioxidant activity which was examined on reducing the level of DPPH, 2,2'-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid (ABTS) radicals, and also iron reduction.[34] *M. calabura* leaf extracts are known to have the capability to inhibit DPPH and also have intracellular antioxidant activity.[35,36] The antioxidant capacities of the MCE have corresponded to total phenols.[34] The antioxidant capacity of *M. calabura* is relevant to the high number of flavonoids and phenolic constituents.[37] Total phenols and flavonoids analysis using colorimetric methods reported that total phenols and flavonoids detected in the MCE were 2.19 + 0.12 mgGAE/g and 2.43 + 0.24 mgQE/g respectively.[38] Also, the presence of myrcene, thymol, α-terpinol, linalool, geraniol, nerol, citronellol, eugenol, α-lonone, β-sitosterol, α-amyrin, lupelol, α-tocopherol, and β-carotene were reported in aqueous leaf extract.[20] Studies on the antiaging potency of MCE in the male reproductive system are scarce. *M. calabura* leaf extract might be slowing down the aging process by inhibiting free radicals including Advance Glycation End products (AGEs) and ROS.[39] Also, the polyphenolic compounds of MCE have antiglycation activity through inhibition of receptors for AGEs signaling, and inhibiting glycosylation.[40]

In vitro research reported that *M. calabura* fruit is a promising candidate for an antiaging agent for skin rejuvenation. Besides having antiradical activity, the *M. calabura* fruit lyophilisate was also reported to have anti-aging activity on the inhibition of elastase with IC50 of 21.67 and collagenase and with IC50 of 180.61 μg/mL.[36] Both enzymes were known to be responsible for collagen and elastic fiber degeneration in aging. Therefore, the inhibitions of those enzyme activities were subjects for anti-aging research.[41] The lyophilisate of the *M. calabura* fruit also preserves and augments fibroblast's viability in vitro and also increases the amount of procollagen-1-propeptide N-terminal (P1NP), a marker for

fibrogenesis.[36,42]

Nonetheless, the MCE administration did not result in an improvement and elevation of serum testosterone levels. The fluctuation of testosterone levels creates conditions in this research. The mean testosterone levels before (1.01 ± 2.64 ng/mL) and after treatment (1.89 ± 3.33 ng/mL) are within the normal limit. However, if we examine the average value of testosterone levels per group, either before or after treatment, most of the groups had lower testosterone levels than normal mice testosterone levels, which range from 1.5-2.0 ng/mL.[43] There are variations in testosterone levels of normal male mice, for instance, normal male mice's testosterone levels range between 2.8-9.5 ng/mL, and the mean testosterone level is 6.6 + 1.9 ng/mL or serum testosterone levels range in the lower level (44.80 ng/dl or 0.45 ng/mL).[44] Previous study reported a significant difference in *Mus domesticus* testosterone levels at the beginning of the study (0.24-37.7 ng/mL with a mean of 5.62 ng/mL) and when the study was completed (0.19-60.1 ng/mL with a mean of 11.2 ng/mL).[45] Repeated measurements of individual mice testosterone levels, indicating a significant fluctuation, range from 1.1-32 ng/mL with an increase of 2-5-fold and the coefficient of variation reaches 82% in everyone.[46,47] In addition, there were differences in the range and mean of testosterone levels as measured by different methods and tools, therefore the normal testosterone levels of test animals were likely to be strongly influenced by measurement methods and tools or materials used.[48]

We suspect that the testosterone levels in the stored sample used in this study were changed due to the storage process. There is a change in testosterone levels by 23.9% in blood samples which are stored at 22°C for a day.[49] In contrast, other research reported duration of storage time did not affect the testosterone levels of the measured samples, valid measurements are still feasible.[50] This phenomenon should be carefully examined in the next research to achieve conclusive results.

CONCLUSIONS

Administration of *M. calabura* leaf extract improved the testicular histology (diameter of the seminiferous tubule, spermatogenesis score, Leydig cells' count, and spermatogenic cell proliferation) in D-galactose-induced aging mice model but showed no significant effect on testosterone levels.

CONFLICT OF INTEREST

None to declare.

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ORIGINAL ARTICLE

Impact of Spiritual Well-Being on The Quality of Life Among the Muslim Elderly

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ABSTRACT

INTRODUCTION: Increasing elderly population will have an impact on increasing demand for long-term health care. As a person gets older, there is increase in their health problems. The challenges facing the health authorities is to increase life expectancy of people through improving the quality of life of the elderly. Spirituality has become an important aspect of improvement of health related quality of life. This study aims to identify the relationship between spiritual well-being and the quality of life of the elderly living in nursing homes. **MATERIALS AND METHODS**: This study is a crossectional study conducted in Central Java Province, Indonesia. The sample size was 131 Muslim elderly people living in nursing homes. Study respondents were recruited randomly with criteria of being able to communicate and having good cognitive function. Spiritual well-being was measured using the Spiritual Assessment Scale (SAS) and the Quality of life (QOL) was measured using the WHOQOL-OLD. **RESULT**: The spiritual well-being of the respondents was mostly low. The QOL of the respondents was mostly low. The results of the Pearson correlation test showed that all three aspects of spirituality had a relationship with all the three domains of QOL. Religious practices have a very strong relationship with psychological functioning (p=0.000, r=0.793). **CONCLUSION:** The higher the spiritual well-being, the higher the QOL of the elderly living in nursing homes. The results of this research can be used by nurses in nursing homes to determine interventions to improve spiritual well-being in the elderly.

Keywords
Elderly, Nursing Home, Quality of Life, Spiritual Well-being.

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INTRODUCTION

Worlwide the elderly population is increasing. In 2022, the elderly population aged over 60 years was 771 million or 10% of the total population of the world. By 2050 the population of the elderly is expected to reach 16%, and increase to 24% by 2100.[1] Indonesia is a developing country with an elderly population growth that exceeds that of the world. In 2022 the number of elderly people will reach 10.48%, and is estimated to increase to 25.28% in 2100.[2] Therefore, the increasing elderly people in Indonesia needs attention.

Although aging is a normal occurrence, it is also associated with decreased biological, psychological and social functioning.[3] Thus, the increase in the elderly population will have an impact and increasing demand for long-term health care.[4] With increasing age the elderly will experience disabilities, unable to carry out daily activities and the absence of a family support system.[5] Additionally, the main challenge of public health today is increasing life expectancy.[6] The elderly nowadays have a better quality of life to live independently and the body functions optimally.

From another perspective, as a person gets older, the risk of health problems will increase and life satisfaction may also decrease.[7] The experiencing of life satisfaction reflects that elderly people are in good condition, in terms of subjective well-being and quality of life (QOL).[8] Thus, that the main goal for the elderly is not to have a longer life, but to have a more significant QOL.

QOL is currently a concern because it provides many benefits. The World Health Organization (WHO) defines QOL as a subjective evaluation inherent in their

cultures, social and environments. It is considered a multidimensional phenomenon, overall QOL is associated with good health.[9]

Holistically, worsening of the QOL of the elderly is based on aspects of decreased physical functioning, psychological, social isolation and independence.[10] Declining health will have a negative impact and affect the ability of the elderly to maintain their independence. So that the QOL of the elderly is easily threatened.[11]

In recent years, spirituality has been thought as an important component of QOL. Spirituality is needed in achieving a balance to maintain good health and well-being.[12] Spirituality is proven to able to overcome chronic diseases by reducing anxiety and depression.[13] Spirituality can be a source of adaptation to stressors in life.[14] Spirituality has a positive correlation to better self-health assessments.[15]

WHO announced that health needs of the elderly should include spiritual well-being in addition to physical, mental and social domains.[16] According to the WHO, besides physical, mental and social health, spiritual well-being is an important component. Spiritual well-being, though, is a dynamic state.and this is seen in a person who lives in harmony with himself, fellow humans, the environment and God.[17]

A person who has spiritual well-being will be able to integrate the meaning and purpose of life through connectedness with oneself, others, nature and the creator.[18] Studies show that seniors with stronger spiritual well-being will have better health conditions compared to their peers whose faith is weaker.[12] Although it is known that spiritual needs are important, the elderly often report their spiritual and existential needs are not met.[19]

Based on research, there are differences between the elderly who live in nursing homes and those who live with their families in terms of physical health, emotional health, social relationships and all dimensions in QOL.[20] Seniors living in nursing homes are at lower levels of QOL.[20] Elderly people in nursing homes experience decreased body function, are unable to carry out activities independently and experience severe dependency. This causes the elderly to not able to carry out religious practices independently and experience dependency.[21]

Elderly people in nursing homes also lose social contact with relatives and friends thus resulting in their social status and self-confidence decreasing. This will hinder the elderly from finding spiritual meaning from the experience of illness. The elderly people in Western countries may feel they do not believe in the existence of God and do not have faith in God's power.[22] Elderly people in nursing homes often experience reactive depression because they feel lonely having to live far from their families and are dissatisfied with their new environment. This condition prevents elderly people from feeling spiritual satisfaction, feeling not close to God and feeling anxious about life.[23]

The first step taken to evaluate the QOL of the elderly is to require comprehensive data on the quality of life of the elderly in Indonesia that should be measured. Although such efforts are one of the important challenges ahead, the elderly living in nursing homes are a priority. Because they are the most vulnerable group of the elderly.[24]

Therefore, this research was conducted to analyze the relationship between spiritual well-being and the QOL of elderly people living in nursing homes in Central Java Province, Indonesia.

MATERIALS AND METHODS

The study design used cross-sectional. The sample of respondents were Muslims, elderly aged who are domiciled in the Nursing Home of Central Java Province, Indonesia. Inclusion criteria were senior respondents aged 60 years and over, living in a nursing home in Central Java Province, Indonesia who were able to communicate and having good cognitive function based on the SPMSQ (Short Portable Mental Status Questionnaire) examination with results of 0-8. The exclusion criterion are those elderly who experience total dependence based on Barthel Index examination

with results of 0-61. There were 131 respondents in this study. Sampling began with preparing a sample frame containing the names of prospective respondents, preparing a table of random numbers and taking randomly using simple random sampling techniques.

The research instrument used was the Spiritual Assessment Scale (SAS) questionnaire to measure spiritual well-being, and the WHO Quality of Life Older (WHOQOL-OLD) questionnaire. The SAS questionnaire was chosen because it was able to measure the construct of spiritual well-being, containing 21 question items consisting of three subscales: 7 items of personal beliefs, 7 items of spiritual satisfaction and 7 items of religious practice. The questionnaire was prepared using a Likert scale with five answer categories in order to reduce bias. This questionnaire is easy to use because it takes about three to 4 minutes for the elderly to complete. The SAS instrument has been translated into Indonesian and a validity test was carried out with r table results of 0.371-0.821 and a reliability test with Cronbach's alpha results of 0.899 899.[25]

The WHOQOL-BREF questionnaire was selected because it was developed through extensive international cooperation, has been applied across cultures and comparisons of results are acceptable. WHOQOL-BREF contains 26 questions capable of measuring QOL, consisting of four domains of physical, psychological, social and environmental health. WHOQOL-BREF is available in Indonesian and a validity test was carried out with r table results of 0.390-0.798 and a reliability test with Cronbach's alpha results of 0.941.[26]

Data collection was carried out as follows: firstly, researchers informed the purpose of the study to the respondents and asked for willingness to participate. Respondents who were willing were then had to sign an informed consent. Secondly, at the time of data collection, if there are doubts, respondents are accompanied by data collectors and supervisors to help read questionnaires. Data collectors and supervisors were given two days of training on the purpose of research and filling in instruments before use. Pre-test trials are also conducted prior to actual data collection. Thirdly, the time needed to fill out the questionnaire was about 30 minutes. At the time of data collection, respondents were allowed a 10 minutes break after filling out the first questionnaire. This is to prevent fatigue. Finally, researchers checked the completeness of the fields to make sure all questions have been filled.

Univariate analysis uses descriptive analysis to determine the characteristics of the respondents, spiritual well-being and QOL. Descriptive analysis is presented in percentage form. Bivariate analaisis uses the Pearson correlation to determine the relationship between the independent variable and the dependent variable. As well as analyzing the closeness of relationships between variables.

RESULTS

Demographic Characteristics of Respondents

Table I: The profile of respondents (n=131)

Variabel	Gender	Frequency	Persentase
Gender	Male	57	44
	Female	74	56
Age			
60-74	Male	33	25
	Female	48	37
75-90	Male	24	18
	Female	23	17
>90	Male	1	1
	Female	2	2
Educational level			
Elementary school	Male	34	26
	Female	52	40
Junior high school	Male	19	15
	Female	21	16
Senior high school	Male	4	3
	Female	1	1
Lama Tinggal, tahun			
<1	Male	12	9
	Female	7	5
1-2	Male	30	23
	Female	28	22
2-5	Male	8	6
	Female	24	18
>5	Male	7	6
	Female	15	11
Medical report Barthel Indeks			
Independent	Male	30	53
	Female	33	45
Slight dependency	Male	15	26
	Female	27	36
Moderate dependency	Male	12	21
	Female	14	19

Most of the respondents in this study were women (74) (56%) and aged 60-74 years 48 female (37%), most had elementary school graduation education (52 female) (56.5%). Most have lived in nursing homes for 1-2 years

(30 females) (23%). Based on the results of medical records using the Barthel index, most elderly people (33 females) (45%) were able to carry out daily activities independently.

Table II: Spirituality of the Elderly in Nursing Homes (n=131)

Variable	Category	Frequency (n)	Percentage (%)
Personal faith	Low	106	81
	Medium	22	17
	High	3	2
Spiritual satisfaction	Low	86	65
	Medium	43	33
	High	2	2
Religious practice	Low	98	75
	Medium	24	18
	High	9	7

Most respondents had low beliefs as many as 106 respondents (81%), had low spiritual satisfaction as many as 86 respondents (65%) and low religious practices as many as 98 respondents (75%).

Table III: Quality of Life for the Elderly in Nursing Homes (n=131)

Variable	Category	Frequency (n)	Percentage (%)
Physical function	Low	107	82
	Medium	21	16
	High	3	2
Psychological function	Low	91	70
	Medium	33	25
	High	7	5
Social function	Low	77	59
	Medium	50	38
	High	4	3
Environment	Low	105	80
	Medium	22	17
	High	4	3

Most respondents (107) (82%) had low physical function, had low psychological function as many (91) (70%), had low social relationships (77) (59%) and low environment (105) (80%).

Table 3, the results of the Person Correlation test found that all aspects of spirituality have a relationship with the three domains of QOL. Aspects of spirituality include personal beliefs, spiritual satisfaction, and religious practice. The domain of quality of life includes physical functioning, psychological functioning, and social relationships. Religious practice had a particularly strong relationship with psychological functioning (p=0.000, r=0.793).

Table IV: Correlation Test of Spiritual Wellbeing Person on Quality of Life of Elderly in Nursing Home (n=131)

Variable		Physical function						Psychological						Social relations						Environment					
		L		M		H		L		M		H		L		M		H		L		M		H	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Personal faith	L	91	69	14	11	1	1	86	66	20	15	0	0	76	58	27	21	3	2	96	73	9	7	1	1
	M	14	11	7	5	1	1	5	4	12	9	5	4	1	1	20	15	1	1	9	7	11	8	2	2
	H	2	2	0	0	1	1	0	0	1	1	2	2	0	0	3	2	0	0	0	0	2	2	1	1
Spiritual satisfaction	L	79	60	6	5	1	1	75	57	10	8	1	1	67	51	17	13	2	2	79	60	6	5	1	1
	M	28	21	14	11	1	1	16	12	22	17	5	4	10	8	31	24	2	2	26	20	14	11	3	2
	H	0	0	1	1	1	1	0	0	1	1	1	1	0	0	2	2	0	0	0	0	2	2	0	0
Religious practice	L	90	69	8	6	0	0	86	66	12	9	0	0	73	56	24	18	1	1	93	71	5	4	0	0
	M	13	10	10	8	1	1	5	4	19	15	0	0	3	2	19	15	2	2	11	8	12	9	1	1
	H	4	3	3	2	2	2	0	0	2	2	7	5	1	1	7	5	1	1	1	1	5	4	3	2

Note: L (low), M (moderate), H (hight)

Variable	Physical function		Psychological function		Social relations		Environment	
	p	r	p	r	p	r	p	r
Personal faith	0,003	0,261	0,000	0,624	0,000	0,464	0,000	0,562
Spiritual satisfaction	0,000	0,402	0,000	0,545	0,000	0,490	0,000	0,406
Religious practice	0,000	0,485	0,000	0,793	0,000	0,517	0,000	0,694

DISCUSSION

The provision of care in nursing homes aims to improve the QOL of the elderly living there.[27] This study aimed to analyze the relationship between spiritual well-being and QOL of the elderly living in nursing homes in Central Java Province, Indonesia. This study shows that most elderly from physical, psychological and social domains have a low QOL. This result is similar with research conducted in Taiwan that the majority of elderly living in nursing homes have a low QOL.[28]

Several other studies have also shown that the QOL of the elderly in various provinces in Indonesia is also the same in the low category.[29,30] The causative factor, physically, has an average of three chronic diseases. Chronic diseases will decrease the QOL among the elderly population. Psychologically, the elderly experience stress because they move to a nursing home. Their tendency is to have no social activities and family support.[31]

Based on the results of medical records, 47 elderly people (35.9%) have a body mass index in the underweight category. Most elderly people had comorbidities, 8 elderly

people have had stroke and are dependent, 46 elderly people had controlled hypertension and take medication regularly, 13 elderly people had DM and are independent in their daily lives. Some elderly people had psychological problems, 4 elderly people experienced loneliness and often cried when they remember their families, 6 elderly people experience social isolation and do not want to interact.

The QOL theory explains that quality of life is influenced by physical conditions, psychological conditions and social relationships.[10] Physical health problems and disease severity will cause the elderly to experience obstacles and dependence in carrying out daily activities, experiencing dependence on medication and care. Psychologically, the elderly are more sensitive and focused on themselves, the presence of severe stressors in life causes the elderly to experience anxiety, stress and depression.[32] Social problems cause the elderly to not want to socialize with friends and withdraw. According to the theory of spiritual well-being in illness, the ability of the elderly to find spiritual meaning in the experience of illness will affect spiritual well-being in illness, and ultimately will have an impact on the quality of life.[33]

In recent years, spiritual well-being has become an attraction to be enhanced in healthcare settings. Spirituality is believed to have an important role in the lives of the elderly. Spirituality is a personal belief, used to interpret life events, evaluate, find meaning and purpose in life, and establish relationships with self-transcendence.[34]

Spirituality is related to health, well-being and QOL.[12] Spirituality has three aspects, namely personal belief, spiritual satisfaction and religious practice.[17] The results showed that the three aspects of elderly spirituality of respondents in this study were in the low category. Based on the results of the Person correlation test, the three aspects of spirituality are related to the three domains of quality of life. The relationship is very strong in religious practice and psychological functioning.

The results of this study are in line with previous reports, which showed that high spirituality improves QOL.[16] Spiritual well-being is an important part of HRQOL.[35] Spirituality can reduce physical and mental disorders, this causes the quality of life to improve.[36] In fact, spirituality is able to produce tranquility when the elderly feel lonely.[37] Spirituality helps the elderly cope with new environments, especially when moving from a family environment to a nursing home.[38] Therefore, spirituality has an important role to play in the lives of the elderly, as it can support the challenges associated with aging.

In several countries, spirituality has an influence on medical decisions.[39-41] Occupational therapy, for example, elements of spirituality are incorporated into the body, mind and spirit of individuals through a holistic approach. Spirituality has been included as part of end-of-life care for the elderly to die peacefully.[42]

Spirituality has certain consequences for the elderly. Many elderly people cling to their beliefs or even become more religious with age.[43] When the health of the elderly declines, they try to better prepare for death such as gathering the whole family to leave the last message and ask for prayers to die peacefully.[44]

Seniors living in nursing homes have specific spiritual needs, according to their religion. Religious practices such as worshiping, prayer, meditation and other needs are largely unknown, and have yet to be investigated. Based on the results of this study, it is recommended for elderly caregivers in nursing homes to pay more attention and try to improve their QOL by fulfilling his spiritual needs. Nurses create deep connections and share spiritually.

At the beginning of entering the nursing home, it is recommended that each elderly person be assessed for their spiritual level and needs, and an assessment of the QOL is carried out. Furthermore, periodic assessments are carried out to determine goals and

follow-up. Measuring the QOL of the elderly using the Whooqol-old instrument needs to consider the medical records or health status of the elderly. Elderly people who are able to carry out activities independently will have a better QOL, compared to elderly people who experience mild or moderate dependence.[45]

The findings of this study and available literature show that the QOL of the elderly who live in nursing homes is lower than those who live with their families, it is advisable to care for the elderly at home. The elderly who stay at home will enjoy intimacy and spiritual atmosphere in the family to maintain their functional and psychological abilities. Even if the elderly had to live in nursing homes, families are regularly scheduled to visit and provide spiritual support. A comprehensive spiritual model from the Indonesia government seems to need to be designed for seniors living in nursing homes. As part of the commitment to improve the QOL of the elderly.

CONCLUSION

Aspects of spirituality including personal beliefs, spiritual satisfaction and religious practice have a relationship with the three domains of quality of life, namely physical functioning, psychological functioning and social relationships. The relationship is very strong in religious practice and psychological functioning. For further research, a more comprehensive spiritual service model design can be developed to improve the spiritual well-being of elderly people living in nursing homes.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

INSTITUTIONAL REVIEW BOARD (ETHIC COMMITTEE)

This study was approved by the health research ethics committee at the Nursing Faculty, Sultan Agung Islamic University with the number 1108/A.1-KEPK/FIK-SA/X/2022.

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CASE REPORT

A Rare Complex Pleural Effusion in Post Trauma Patient: A Case Report

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Keywords
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ABSTRACT

Pleural effusion is common in routine medical practice and can be due to many different underlying diseases including infections, malignancy, connective tissue disease, heart failure and liver failure. However, a complex pleural effusion such as post-traumatic pleural effusion (PTPE) is an uncommon clinical entity. A precise diagnosis of PTPE can be facilitated by the efficient use of computed tomography (CT) and ultrasound. The PTPE may be successfully managed by pigtail drainage and intrapleural fibrinolysis (IPF), highlighting the significance of prompt intervention in attaining favorable results for patients with PTPE.

INTRODUCTION

Pleural effusions, defines as an accumulation of fluid within the pleural cavity, can stem from a wide array of causes, such as infections, malignancies, connective tissue disorders, heart failure, and liver disease. However, a post traumatic pleural effusion (PTPE) is a rare cause of pleural effusion. Although the exact pathophysiology of PTPE is still unknown, few studies found that there is an activation of classical complement pathway as part of the body's defence mechanism the behind PTPE. Once triggered, the pathway forms complexes that cause inflammation thus lead to the formation of pleural effusion.[1,2] Thus, understanding the PTPE is essential for clinicians navigating the complexities of pleural pathology, ensuring timely and effective management strategies for affected patients.

CASE REPORT

A 45-year-old male with no known medical illness had a motor vehicle accident (MVA) after his motorbike skidded. During the MVA, his left chest wall was hit by his motorbike's handle. Immediately after the trauma, the patient started to feel pain of his left chest wall. However, he did not seek any medical treatment as he was able to tolerate the pain. On day 3 post trauma, the patient went to Emergency Department (ED) due to worsening of left chest wall pain as well as he started to experience difficulty in breathing. Upon arrival at the ED, he appeared tachypneic with respiratory rate (RR) of 30 breath per minute. There was no chest wall deformity or skin changes and the lung examination revealed reduced air entry over left lower zone. His immediate blood investigations shown hemoglobin: 14.4g/dL, white cell counts: 13.6x10^3/L, platelet count: 346mg/L and C-reactive protein (CRP): 245mg/L. His chest radiography (CXR) showed blunted left costophrenic angle with a homogenous opacity at the left lower zone. A repeated CXR on day 5 post trauma revealed worsening of the homogenous opacity over the left hemithorax.

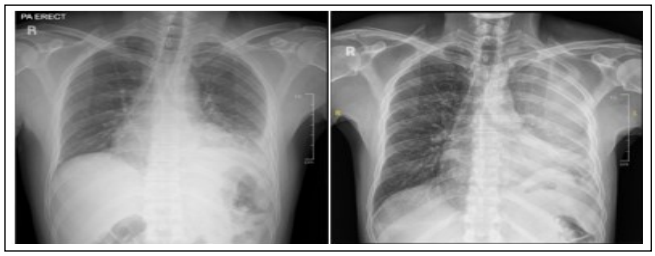

Figure 1 *:* Comparison of CXR on day 3 post trauma (left) and CXR on day 5 post trauma (right). The latter CXR showed worsening of homogenous opacity over the left hemithorax

Ultrasound thorax which was performed on day 6 post trauma shown multiloculated septation and minimal debris within the pleural effusion with a maximum thickness measuring 4.9 cm. Thus, a diagnosis of complex left pleural effusion was made. In view of complex pleural effusion, patient was sent for computed tomography (CT) of thorax which revealed left encysted pleural effusion with adjacent collapsed consolidation.

Figure 2: Ultrasound showed multiseptations and debris within effusion

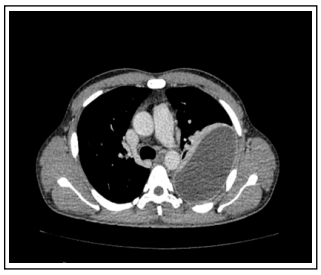

Figure 3: CT Thorax revealed left encysted pleural effusion (red arrow)

Subsequently on day 10 post trauma, an ultrasound guided pigtail drainage was inserted over the left pleural effusion area. The pleural fluid analysis result revealed that LDH: 1136 IU/L, pH: 5, protein: 49g/L, glucose: 2.9 and it was suggestive of exudative pleural effusion (pleural fluid protein: 49/serum protein: 63=0.78). Otherwise, the pleural fluid AFB/MTB was negative and the pleural culture and sensitivity shown no growth. Pleural fluid eosinophil count was not done as the service is not available in our center. In addition, the pleural fluid cytology was also not sent during this admission.

In view of minimal drainage noted after 3 days of pigtail insertion, intrapleural fibrinolysis therapy (IPFT) with streptokinase was given in 3 divided doses to break the multi-septation of the pleural effusion. A CXR done on day 3 post IPF showed improvement of pleural effusion with no evidence of hydropneumothorax. Hydropneumothorax was our concern as there was massive presence of bubbles in the drainage tube. The pigtail drainage was successfully removed on day 5 post IPF and the patient was discharged well. During the subsequent follow-up, there was no evidence of recurrence of pleural effusions.

Figure 4: Pigtail drainage and serous content of the pleural fluid drained

DISCUSSION

Post traumatic pleural effusion (PTPE) is a rare cause of pleural effusion. It is postulated that the PTPE is primarily due to an immune complex reaction which triggers the classical complement pathway causing an inflammation and subsequently resulted in pleural effusion.[1,2] The typical symptoms of PTPE are pleuritic chest pain and shortness of breath and the onset of the symptom varies between an individuals. Patients with PTPE may exhibit a range of signs and symptoms, and the commonest clinical feature is delayed appearance of respiratory symptoms which usually occur around 4 to 6 weeks after the trauma.[2,3] However, there is a reported case that the PTPE patients might develop the symptoms soon after the trauma.[4] In our case report, our patient developed the symptoms of dyspnea and pleuritic chest pain after day 3 of post trauma.

Few modalities can be used in diagnosing PTFE including chest x-ray (CXR), ultrasound thorax and computed tomography (CT) of thorax. CXR only can show the presence of fluid in the pleural cavity but unable to differentiate between hemothorax and pleural effusion. In ultrasound, a simple pleural effusion will appear to be anechoic without intervening echogenic findings while complex pleural effusions are likely to have debris, septations and loculations. Interestingly, in hemothorax, there is presence of "hematocrit sign' or "plankton sign" which can be seen in an ultrasound.[5] A CT thorax of hemothorax may show significant higher attenuation value and pleural fluid over aortic blood (P/A) ratios compared to pleural effusion. These findings is due to presence of iron in the hemoglobin which caused higher tissue density of blood and higher attenuation value in hemothorax.[6]

Managing complex pleural effusions presents a clinical challenge that often requires a multifaceted approach with various treatment modalities. These effusions can be complex due to factors such as multi-loculation and septation, which complicate effective drainage and resolution of the fluid accumulation. The available treatment options ranging from thoracocentesis in the form of tube placement to intrapleural fibrinolytics therapy (IPFT) and surgical interventions such as video-assisted thoracoscopy (VATS) and open thoracotomy with pleural rub.[7] In our case, the patient underwent pigtail drainage of the pleura first followed by IPFT streptokinase insertion mainly to break down fibrin clots

and fibrinous material within the pleural space in order to facilitate the drainage of the effusion. A newer agents such as alteplase demonstrate greater efficacy and a similar adverse effect profile compared to traditional agents.[8] In our case, a streptokinase was used as IPFT agent in view of no alteplase available in the centre. IPFT is reported to be safe and has a high success rate in in resolving complex pleural effusion without the need for surgery.[9] This case highlights the effectiveness of IPF as a less invasive option in managing challenging pleural effusions.

CONCLUSION

In conclusion, PTPE can manifest with variable timing of symptoms, ranging from early onset to delayed presentation. Early detection of PTPE is crucial in patient who present with dyspnea and pleuritic chest pain in which an early treatment will improve the outcomes. Management of complex pleural effusions often necessitates a tailored approach combining drainage techniques like pigtail catheter placement with interventions such as IPFT to surgical interventions such as VATS or open thoracotomy. Our case report proved that an IPFT is effective in resolving PTPE without a need for surgical intervention. Thus, our findings highlight IPFT role as a minimally invasive treatment option in challenging cases.

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CASE REPORT

Aspergillus ochraceus: A Rare Cause of Paranasal Fungal Ball

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Keywords
Aspergillus, *Aspergillus ochraceus,* fungal ball, non-invasive sinusitis

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ABSTRACT

Infection of paranasal sinuses is not uncommon. Fungal ball of the paranasal sinuses is a non-invasive form of paranasal sinus infection that has been documented to be more frequently caused by *Aspergillus fumigatus* than by other *Aspergillus* species and typically affects immunocompetent individuals more than those who are immunocompromised. Here, we report the first case of *Aspergillus ochraceus* (*A. ochraceus*) in an immunocompromised patient with post-trauma maxillary implant who presented with transient ischemic attack and incidental findings of fungal ball within the right maxillary sinus from the Computed Tomography (CT) scan. *A. ochraceus* is a species under the *Aspergillus* section *Circumdati,* a widely distributed fungus which is pathogenic to humans that can lead to various clinical implications. *A. ochraceus* was detected from paranasal tissue sent for culture. The laboratory culture findings were further supported by histopathological evidence of fungal hyphae and matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF) identification.

INTRODUCTION

Paranasal fungal ball (FB) is categorized under non-invasive fungal rhinosinusitis (FRS) and is chronic in nature.[1] FB is the most common type of non-invasive FRS, and its incidence has increased in recent years. The infection is caused mainly by *Aspergillus* species with *Aspergillus fumigatus* being the most common cause of sinus fungal balls. Other causative agents, including *Mucor sp*, *Bipolaris sp*, and *Alternaria sp,* have been reported.[2,3] *A. ochraceus* has previously been reported as the cause of osteomyelitis, chronic granulomatous disease, and invasive pulmonary aspergillosis.[4,5,6] However, there is a lack of data documenting *A. ochraceus* as the agent in non-invasive FRS. Here, we report a case of *A. ochraceus,* a rare species of *Aspergillus* causing paranasal fungal ball post-surgical maxillary implant.

CASE REPORT

Mr. AK, a 70 year-old gentleman with underlying diabetes mellitus, hypertension, and ischemic heart disease, also had a history of motor vehicle accidents in 2009 and sustained bilateral maxillary bone fractures, which required screw implants in both maxillae. He presented with numbness and weakness of the right side of his body and subsequently had a fall. Upon examination, he was stable, with reduced power and sensation noted over the right upper limb with no other significant neurological deficit. He was treated as transient ischemic attack, as CT brain reported no intracranial bleeding, however, an incidental finding of mucosal thickening was noted in the right maxillary sinus along with calcification. He was referred to the Otorhinolaryngology team for suspicion of right maxillary fungal sinusitis. Otherwise, he was asymptomatic, except for mild allergic rhinitis symptoms precipitated by cold environments. Nasoendoscopy showed no evidence of fungal material or necrotic mucosa at the osteomeatal complex area. Subsequently, he underwent Functional Endoscopic Sinus Surgery with the removal of bilateral infected maxillary implants. Intraoperative findings showed a blackish fungal ball within the right maxillary sinus

with healthy surrounding sinus mucosa. No evidence of invasive fungal sinusitis was seen.

The tissue from the paranasal sinus was sent for fungal culture. It was inoculated on Sabouraud Dextrose Agar (SDA) and incubated at 20-25°C. After 4 days of incubation, small mould colonies, which became more prominent by Day 10, were noted on the SDA. Initially, the colonies appeared irregular; they appeared velvety, then fluffy to cottony. The colonies were creamy to yellowish orange and appeared white at the reverse plate. (see Figure 1). Microscopically, the hyphae are long, septate hyaline with smooth conidiophores. There is a presence of vesicles, biseriate, and radiates covering most of the vesicle. The conidia are spherical with rough surfaces. (see Figure 2). Based on these findings, it was identified as *Aspergillus* species. The isolate was sent for further identification using Vitek® MS Flexprep and identified as *Aspergillus ochraceus* (99.6%). The tissues were also sent for histopathological examination, which was reported as necrotic tissue debris with residual intact fungal hyphae seen.

Mr. AK continued postoperative six-monthly follow-ups under the Otorhinolaryngology Clinic. Nasoendoscopic findings revealed minimal granulation tissue and crusting over the right osteomeatal complex, resolved with frequent nasal irrigation. No major postoperative complications were observed, and no recurrence of the fungal ball was seen upon the visit.

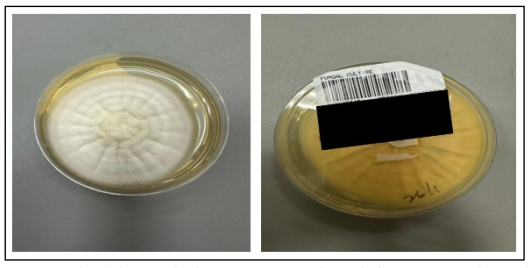

Figure 1: Colonial morphology on SDA plate (left), reverse plate (right)

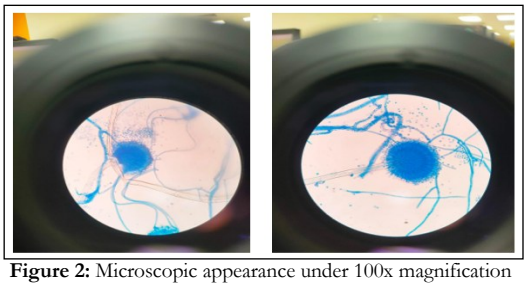

Figure 2: Microscopic appearance under 100x magnification

DISCUSSION

Fungal ball (FB), also known as a mycetoma, is a non-invasive fungal growth occurring in the paranasal sinuses, commonly in the maxillary sinus.[2,3] This condition typically affects immunocompetent individuals and remains localized within the sinus without invading the mucosa, bone, or blood vessels.[1,2,3,7] However, deterioration of host immunity not only increases susceptibility to FB but also raises the risk of progression to invasive fungal sinusitis.[7,8] *Aspergillus fumigatus* has been implicated as the primary causative agent in many studies; in this case, we highlight the first case of *Aspergillus ochraceus* as a rare cause of non-invasive FB in a diabetic patient post maxillary implant. Although *A. ochraceus* is less common in clinical infection compared to *A. fumigatus*, it has been proven recently to cause severe disease that can lead to fatality in immunosuppressed state.[6]

Aspergillus ochraceus, a species under the *Aspergillus* section *Circumdati*, is known to produce ochratoxin (mycotoxin), a widely distributed fungus that is typically found in soil, decaying organic matter, and various food products.[9] Ochratoxin is associated with nephrotoxicity in humans,[9] in FRS the direct effect of the toxin is still unknown. This fungus is pathogenic to humans by evidence from several studies causing various clinical infections.[4,5,6] Hakamikard et al. reported dissemination of *A. ochraceus* infection from the pulmonary to the brain in a patient with an underlying immunosuppressed state due to SARS-CoV-2 infection, which implied that the fungus not only causes invasive diseases but also has the propensity to disseminate to other organs.

Paranasal FB is caused by either colonization of inhaled spores through a sinus ostium or is often associated with orthodontics procedures.[2] Foreign body introduction during orthodontic procedures, such as wires or brackets, has been implicated as a source for fungal colonization.[2] In our patient, maxillary implant placed due to a fracture could be the nidus for fungal colonisation and growth. However, inhalation of spores could also be a source of transmission in this case since the fungus is ubiquitous. When the spores are inoculated into anaerobic sinuses

through inhalation or a foreign body, they then germinate and lead to the growth of hyphae in the sinus cavities. In an immunocompetent individual, a robust local immune response, particularly macrophage and neutrophil activation, is observed to control the infection and prevent further spread.[3] It does not usually invade mucosa, bone, or blood vessels; however, in an immunocompromised host, FB can progress to a more invasive form, which involves the invasion of hyphae into blood vessels that can lead to vasculitis with thrombosis, haemorrhage, and tissue infarction.[1,2,3] Studies have shown that diabetes is one of the indicators for patients to develop invasive FRS.[2,3,7] Diabetes, especially when poorly controlled, impairs immune function that disrupts both innate and adaptive immunity, making individuals unable to mount effective responses to fungal invasion. Therefore, they are not only vulnerable to infections but also at risk of aggressive disease progression.[2,3,7] In this case, the patient was asymptomatic which is common in cases of maxillary FB,[2] however, the fact that he is diabetic increases the risk of progression to invasive FRS should warrant careful consideration. Furthermore *A. ochraceus* itself has proven to be pathogenic causing severe clinical implications.

The diagnosis of FB relied on a combination of imaging, histopathology, and mycology studies. CT scans most often reveal heterogeneous opacities in the sinus, containing calcification or metallic densities,[2,3] which is consistent with our patient's findings. Specimens from the affected tissues should be biopsied and sent to the laboratory for further identification. FB was observed intraoperatively during the right middle meatal antrostomy with the removal of bilateral impacted maxillary implant surgery, and the specimen was sent to the lab for further identification and confirmation. Several studies mentioned that histopathological examination is more sensitive than fungal culture; this is attributed to the poor viability of fungi.[1,2,7] Histopathology distinguishes acute fulminant (invasive) sinusitis from chronic forms based on the presence of direct tissue or vascular invasion by fungi. It assists in clinical decisions based on the nature and fungal involvement.[10] In our patient, the histology result was consistent with the findings of FB, which showed fungal hyphae without tissue invasion. Culture is to complement the histological findings and further confirm the causative fungal agent. In this case, we managed to grow a mould typical of *Aspergillus* species under the microscope. However, the colony was atypical in terms of its unique colour. Morphologically, *A. ochraceus* is described as a species with rough-walled stipes, biseriate conidial heads with yellow to ochre conidia, and sclerotia that do not turn black.[9] Microscopically, it appears as globose vesicles, biseriate conidiophores with ampulliform phialides.[9] In this case, conventional methods such as observing the colony morphology and microscopy are insufficient to identify the species of *Aspergillus*. Therefore, further identification was carried out by using mass spectrometry (VITEKMS FLEXPREP), an automated mass spectrometry microbial identification system that uses Matrix-Assisted Laser Desorption Ionization Time-of-Flight (MALDI-TOF) technology. It is a preferred method of choice due to its rapid results and accurate identification of organisms at species and genus levels.

In terms of therapeutic management, the main highly effective treatment is to perform directed endoscopic surgery to correct the obstruction and to extract the fungus ball.[2,3,7] The fact that this is non-invasive means that the use of antifungals has shown no apparent benefit. However, glucocorticoids are commonly used during the perioperative period to reduce inflammation.[2,3]

CONCLUSION

FB is considered a benign condition; however, with waning immunity and due to the pathogenic nature of *A. ochraceus*, the condition may progress to an invasive form, which could lead to serious complications. Therefore, early detection and management can improve patient care and outcomes. We highlight the use of additional modalities laboratory methods such as MALDI-TOF is necessary to aid in the identification of the species of Aspergillus genus.

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CASE REPORT

Atypical Cystic Carcinoma: A Rare Malignancy of The Lower Eyelid

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Keywords
Adenoid cystic carcinoma, Lower Eyelids, Rare Case

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ABSTRACT

Adenoid cystic carcinoma (ACC) is a rare malignancy of the secretory glands, most commonly originating in the lacrimal gland but rarely involving the eyelids. ACC is known for its aggressive behaviour, high recurrence rate, and potential for metastasis, leading to a poor prognosis. Histopathological examination is essential for the diagnosis, and early detection with complete excision offers the best chance for a favourable outcome. This case highlights the importance of comprehensive management to reduce the recurrence risk and improving patient survival. The authors present a 56-year-old man with ACC of the left lower eyelid, who underwent surgical excision followed by reconstruction, ensuring tumour-free margins.

INTRODUCTION

A rare type of eyelid malignancy that occurs includes sebaceous cell carcinoma, and malignant melanoma, including adenoid cystic carcinoma (ACC).[1,3] ACC is a subtype of cancer of the secretory glands. ACC of the eye generally manifests in the lacrimal gland, but it can also develop from Moll glands, sweat glands on the eyelids, or accessory lacrimal glands covering of the conjunctiva. ACC is rare in its prevalence but has local and regional recurrence rates and high levels accompanied by metastases. Appropriate, fast management and enforcement of the diagnosis through histopathological examination is an important stage in determining the therapy, and prognosis, preventing recurrence and metastasis so that patients get better results.[2,4,5] ACC involving the lower eyelids is a rare presentation, as most cases originate in the lacrimal gland. The importance of early diagnosis and complete surgical excision of the mass after histopathological confirmation is to improve prognosis. Reconstructive surgery plays a role in restoring function after tumour excision. Whilst the need for long-term follow-up is to monitor for recurrence or metastasis. This case report aims to explain the diagnosis and management of cases of ACC on the inferior eyelid with the involvement of the punctum and canaliculi.

CASE REPORT

A 56-year-old man with the main complaint of a lump on the lower eyelid of his left eye which he felt has become enlarged for the last 3 years. The lump was initially the size of a green bean and grew bigger until it was the size of a marble. The lump was reddish in color, sometimes accompanied by itching and lumpiness. The lump never bled or festered. No lymph node enlargement was observed in the head, neck, or axillary regions. The patient had no history of malignancy, chronic diseases such as diabetes or hypertension, immunosuppression, or prior radiation exposure. There were no known exposure to carcinogens, chemicals, or UV radiation. Additionally, no systemic symptoms, including weight loss, night sweats, or fatigue, were reported. Examination of the left eye (Figure 1) showed that in the lower eyelid there was a mass measuring 2 x 1.5cm which affected the inferior punctum and covered the medial canthus area. The mass had an uneven surface, was soft in consistency, had firm boundaries with a fixed base. It also had a partly red and yellowish central mass. The mass did not bleed, and no pus or ulcers were present, and there was also madarosis. A thorax x-ray examination performed before surgery showed that there were no visible active pulmonary TB

Figure 1: Mass on the lower eyelid

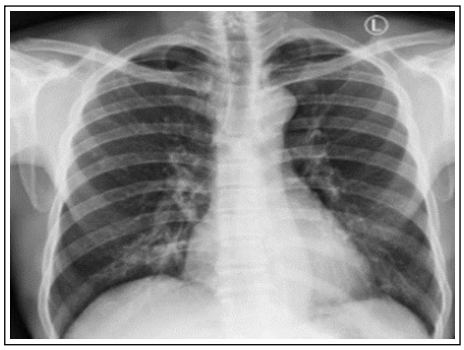

Figure 2: No mass in the pulmonary

The patient was planned for a wide excision of the inferior eyelid mass with reconstruction of the eyelid defect using the Tenzel semicircular flap technique to preserve function and cosmesis and placement of a silicone tube to maintain the patency of the remaining inferior canaliculi. The results of histopathological examination (Figures 3 and 4) showed adenoid cystic carcinoma in the lower palpebra of the left eye. The base of the incision and the 4-1 thread border are not yet free of malignant tumor cells. Incision margins 1-2, 2-3 and 3-4 were free of malignant tumor cells. Since one surgical margin was positive for tumour cells, re-excision was planned. Regular clinical assessments every 3-6 months for the first 2 years was planned, following that, annual follow-up.

Figure 3: Macroscopic mass

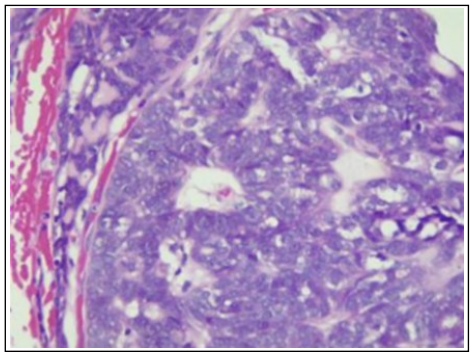

Figure 4: Microscopic cribriform pattern seen in ACC. Basaloid cells with hyperchromatic nuclei, small gland-like spaces filled with eosinophilic material. No perineural invasion is a hallmark of aggressive behaviour. (400x H&E)

DISCUSSION

Adenoid cystic carcinoma is a rare secretory gland cancer with an incidence of 4-5 cases per 100,000 individuals. Epidemiological data shows that ACC is only 1% of all cancers and are located in the head and neck area. ACC is a type of malignancy with relatively slow clinical progression; however, it has high local and regional recurrence rates. ACC cases often metastasize including distant metastases such as lung metastases or liver. ACC that occurs in the eye area generally affects the lacrimal gland including the lacrimal system which has a histological structure resembling the saliva gland. ACC can also appear in other glands such as sweat glands, glands of Moll and other accessory glands scattered in the eyelids and conjunctiva. Manifestations of ACC on the inferior eyelid with involvement of the punctum and canaliculi are not common. The mass that arises can be a primary tumour or secondary tumours due to metastases from other organs.[1,6,7] In our patient the mass presented on the inferior eyelid and involved the punctum and inferior canaliculi. It has progressively grown in size for the last 3 years. The lump which sometimes felt itchy has an irregular surface that indicates one of the clinical signs of malignancy. The patient is likely a case of primary ACC because no other local or regional mass other than the inferior eyelid was found.

Signs and symptoms that can be found in cases of ACC resemble malignancy of the outer eyelid. The clinical manifestation of ACC may present as a firm, nodular lesion, which is typically painless, with possible madarosis. The mass located in the lacrimal system can cause epiphora. Other accompanying symptoms depend on the

location and size of the mass. Manifestations in the lacrimal glands can cause ptosis.[2,8] Our patient's tumour mass was located in the inferior palpebra accompanied by inferior punctum distension. The mass measured 2x1.5cm, had an uneven surface, was soft in consistency, had firm boundaries with a fixed base. It also had a partly red and yellowish central mass. The mass did not bleed, and no pus or ulcers were present, and there was also madarosis. Making a definite diagnosis in ACC cases is through examination of histopathology of the tumour. The results of histopathological examination on ACC of our patient showed epithelial cells basaloid with pleomorphic nuclei (Figure 4). Histologically there are three types of ACC, namely tubular, solid, and cribriform with the most common type being cribriform.[9] In the patient the results of histopathological examination showed group tumour masses that were hyperplastic. Tumour cells with round oval shapes, pleomorphic nuclei, hyperchromatic, coarse chromatin, abnormal mitoses were found to form cribriform and cystic structures and solidify diffusely. This histopathological description aligns with the characteristic features of ACC.

ACC is a malignant tumour with a generally poor long-term prognosis. Although ACC is a slow-growing epithelial malignancy, it has a high tendency for recurrence and metastasis. The estimated survival rates for ACC patients are 68% at 5 years, 52% at 10 years, and 28% at 20 years. Early detection, accurate diagnosis and appropriate therapy is necessary for the management of patients with ACC to ensure a better prognosis. Definitive therapy for ACC is excision of the mass until the excision margins are free of tumour cells. Excision of the mass with a frozen section is recommended to ensure the excision area is completely tumour free. Other more aggressive measures such as exenteration can be considered depending on the size and distribution of the mass. Approach to the management with globe-sparing interventions can be carried out and should be accompanied by adjuvant radiotherapy.[4,9-10] Our patient underwent a wide excision of the mass until the margins were tumour-free. The tumour mass in the patient appeared to be localized with clear boundaries so the intervention chosen is wide excision which maintains the integrity of the eyeball. Frozen section is performed intraoperatively to ensure that the excision margin is free from tumour mass.

ACC commonly originates in the lacrimal gland, but our case involves the lower eyelid, which is an extremely rare site for this malignancy. Most ACC cases of the eyelid affect the upper eyelid or tarsal region, making this presentation unique. Eyelid involvement poses challenges in achieving clear surgical margins while maintaining function and cosmesis. This case demonstrates that precise surgical excision with reconstruction can achieve both oncologic control and good cosmetic outcomes. Many ACC cases present late with perineural invasion and distant metastases (e.g., lungs, bones), but this patient had no lymph node involvement or distant spread, making early intervention highly effective.

Since ACC of the lower eyelid is rare, this case alerts clinicians to consider ACC in differential diagnoses of persistent, firm eyelid masses, ensuring timely biopsy and histopathological confirmation. Early detection and wide excision with tumour-free margins remain the gold standard for improving survival. This case highlights surgical precision in balancing oncologic safety and functional/cosmetic reconstruction. The need for collaboration among ophthalmologists, pathologists, oncologists, and reconstructive surgeons is reinforced to achieve optimal patient outcomes. Given the rarity of eyelid ACC, this case adds valuable clinical data to enhance future guidelines and treatment protocols. It highlights the need for long-term follow-up and consideration of adjuvant therapy in selected cases.

CONCLUSION

ACC is managed by complete tumour removal. A multidisciplinary approach is needed to manage patients with ACC to achieve a better prognosis for functional and aesthetic outcomes.

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