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EDITORIAL

Molecular Markers in Colorectal Carcinoma – Transforming Prognostication and Therapy in Malaysia.

Colorectal cancer (CRC) remains a formidable health challenge in Malaysia, contributing to 13.5% of all newly diagnosed cancers (2012-2026), ranking as the second most common malignancy. Alarmingly, survival outcomes remain poor, with a median survival of just 24 months and a 5-year survival rate of only 18.4% [1]. These sobering statistics underscore the urgent need for precision oncology strategies to improve patient outcomes. As a molecularly heterogeneous disease, CRC has distinct genetic and epigenetic alterations influencing tumour behaviour, treatment response, and prognosis. The advent of next-generation sequencing (NGS) and immunohistochemistry (IHC) has enabled the classification of CRC based on molecular subtypes, facilitating precision oncology. The evolution of molecular pathology classification systems from The Cancer Genome Atlas (TCGA, 2012), Consensus Molecular Subtypes (CMS, 2015), Colorectal Intrinsic Subtypes (CRIS, 2016), Single Cell Intrinsic CMS (iCMS, 2022) and to the latest Pathway Derived Subtypes (PDS, 2024) has revolutionised our understanding of CRC biology [2]. This editorial note discusses briefly a few molecular markers in CRC, their prognostic significance, and clinical implications for personalised therapy.

RAS/RAF Mutations (KRAS, NRAS, BRAF): KRAS and NRAS mutations are detected in 40-50% and 1.2-4.2% of CRC, respectively. Survival of KRAS and BRAF V600E mutation in the microsatellite stable (MSS) CRC, is better than in the microsatellite instability-high (MSI-H) CRC [3]. KRAS and NRAS mutations predict resistance to anti-epidermal growth factor receptor (anti-EGFR) therapy. Emerging data suggest that KRAS/BRAF wild-type MSS tumours may derive benefits from EGFR inhibition, reinforcing the need for routine molecular testing [4].

Microsatellite Instability-High (MSI-H)/Mismatch Repair Deficient (dMMR): MSI-H/dMMR tumours occur in ~15% of sporadic CRCs and exhibit a favourable prognosis in their early stages. MSI-H tumours display high tumour mutational burden, making them exquisitely sensitive to treatment with immune checkpoint inhibitors (pembrolizumab, nivolumab) [5]. Hence, MSI-H testing is important to identify patients for these immunotherapies, which will dramatically improve survival outcomes [4,5].

***TP 53* and Adenomatous Polyposis Coli (APC) Mutations:** *TP53* is mutated in 60% of CRC, with most being missense substitutions at position R175 or R273. *TP53* mutations correlate with aggressive tumour behaviour, metastasis, resistance to 5-fluorouracil, and dismal survival, underscoring their role as a poor prognostic marker [6]. APC mutations are seen in 70-80% of CRC, are early events in CRC, and drive the canonical (β-catenin-dependent) Wnt signaling pathway activation. Recent evidence suggests APC and *TP53* mutations help to predict cetuximab sensitivity, offering new avenues for personalized therapy and better patient outcomes [6].

Human Epidermal Growth Factor Receptor 2 (HER2) Amplification: CRC with HER2 amplification is seen in 3-5%, are associated with aggressive behaviour, brain metastasis and worse outcomes. Dual HER2 blockade (trastuzumab and pertuzumab) has

shown promise in metastatic HER2 CRC, mirroring advances in breast and gastric cancers [7].

While molecular diagnostics have transformed CRC management, several challenges persist in Malaysia, notably, limited access to NGS and biomarker testing in routine practice, and high costs of targeted therapies. To bridge these limitations, the molecular testing facilities in public hospitals should be expanded, and there should be integration of molecular biomarkers into the national CRC treatment protocols. Molecular stratification, guided by KRAS, BRAF, MSI, *TP53*, APC, and HER2 status, is essential for optimizing outcomes.

Keywords: *BRAF, Colorectal carcinoma, KRAS, MSI-H, Precision oncology.*

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SYSTEMATIC REVIEW

Enhancing Hand Hygiene Compliance among ICU and NICU Visitor Families: The Impact of Advanced Nursing Roles, the Barriers and Challenges: A Review.

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Abstract
Proper hand hygiene is crucial for preventing,, infections in intensive care units (ICUs) and neonatal intensive care units (NICUs). Despite the awareness among healthcare personnel and visitors of its importance, compliance with regulations is often inadequate. Advanced nurse educators and infection control professionals can significantly improve these habits. This review investigates whether advanced nursing positions improve hand hygiene among ICU and NICU families, as well as visitors, focusing on enhancing hand hygiene programs, identifying effective solutions, recognising practice shortcomings, and providing recommendations. The methodology involved a search of databases, including PubMed, CINAHL, Scopus, and Google Scholar, using relevant keywords related to hand hygiene and advanced nursing roles. The analysis included research on visitor hand hygiene in ICUs and NICUs, specifically focusing on advanced nursing responsibilities. Only articles published in English were selected. Out of the initial 1,430 articles, 36 met the inclusion criteria. The study found that advanced nurse roles had a positive effect on hand hygiene adherence in the ICU and NICU. Effective strategies included educational programs, proactive engagement, and regular follow-up. Challenges, such as nurse workloads, were also identified. Continuous training, family involvement, and infection control programs were highlighted as important for improving hand hygiene behaviours. Through structured programmes and education, as well as advanced nursing roles, nurses can significantly lower infection rates and improve patient outcomes. To improve hand hygiene in critical care, comprehensive interventions, and strong leadership should be prioritised.

Keywords: *Advanced Nursing Roles, Hand Hygiene Compliance, ICU and NICU, Infection Control, Visitor Education*

Introduction

Hand hygiene is a critical component in preventing healthcare-associated infections (HAIs), particularly in high-risk areas such as Intensive Care Units (ICUs) and Neonatal Intensive Care Units (NICUs) [1]. These units house patients who are extremely vulnerable to infections due to their compromised health conditions. Despite the well-documented importance of hand hygiene, compliance rates among healthcare workers and visitors often remain suboptimal. This underscores the need for effective strategies to enhance hand hygiene practices [1].

Nurses play an integral role in healthcare settings, not only providing direct patient care but also acting as educators and role models for other healthcare staff and visitors. Advanced nursing roles, including those of nurse educators, infection control specialists, and clinical nurse leaders, have been increasingly recognized for their potential to influence hand hygiene behaviours positively [2]. Through educational interventions, monitoring and feedback, and the implementation of evidence-based practices, nurses can significantly enhance hand hygiene competence among healthcare workers and visitors alike [3-4].

The objective of this review is to examine the impact of advanced nursing roles on enhancing hand hygiene competence among families visiting patients in ICU and NICU settings. By synthesizing findings from previous research, this review aims to highlight effective strategies employed by nurses, identify gaps in current practices, and provide recommendations for future initiatives.

Methodology

Literature search and selection criteria

To ensure a comprehensive review of the impact of advanced nursing roles on enhancing hand hygiene competence among ICU and NICU visitor families, a systematic literature search was conducted. The search aimed to identify relevant studies published in peer-reviewed journals.

Search Strategy

The literature search was conducted using several electronic databases, including PubMed, CINAHL, Scopus, and Google Scholar. The search terms included combinations of the following keywords: "hand hygiene," "ICU," "NICU," "nurse," "advanced nursing roles," "infection control," "visitor education," and "hand hygiene compliance." Boolean operators (AND, OR) were used to refine the search results and ensure a broad yet focused retrieval of relevant literature.

Inclusion Criteria

This review focuses on studies examining hand hygiene practices among visitors, family members, and relatives in ICU settings. Specifically, it investigates the contributions of nurses, particularly those in advanced roles such as nurse educators, infection control specialists, and clinical nurse leaders. To be included in this review, studies must examine visitor hand hygiene practices. They could use various research methodologies, including quantitative or qualitative approaches like randomised controlled trials, observational studies, and descriptive studies. Only studies published in English were considered.

Exclusion Criteria

Studies were excluded if they did not focus on hand hygiene or were unrelated to ICU/NICU settings. In addition, studies that only focused on healthcare workers' hand hygiene practices without involving visitor families were also excluded. Furthermore, non-peer-reviewed articles, such as conference abstracts, opinion pieces, and editorials, were excluded as well.

Selection Process

The initial search yielded 1,430 articles. After removing duplicates, 100 articles remained. The titles and abstracts of these articles were screened for relevance, resulting in 215 articles deemed eligible for full-text review. The PRISMA chart results indicate that 36 articles constituted the

final review following a thorough evaluation of the full texts.

Data Extraction and Analysis

Data from the selected studies were extracted using a standardized literature review matrix form. This form captured key information, including study design, sample size, intervention details, outcomes measured, and key findings. The extracted data were then analysed to identify common themes, effective strategies, and gaps in the literature. This systematic approach to literature search and selection ensured that the review included high-quality studies that provide valuable insights into the impact of advanced nursing roles on enhancing hand hygiene competence among families visiting ICUs.

Results

The review identified four key themes which are: 1) the impact of advanced nurse roles on hand hygiene compliance, 2) the engagement of relatives, visitors, and families in hand hygiene and infection prevention in ICUs, 3) barriers to hand hygiene compliance and 4) nurse-led interventions and structured programmes. These themes highlight the critical areas where hand hygiene practices can be improved and the importance of nursing leadership in promoting compliance.

The impact of advanced nurse roles on hand hygiene compliance

The impact of advanced nursing roles on enhancing hand hygiene competence among families visiting ICUs is a critical aspect of healthcare. Nurses play a crucial role in influencing hand hygiene practices among staff and visitors, which ultimately affects patient safety and infection control [5]. Research has shown that a high nursing workload is associated with poor adherence to hand hygiene, emphasizing the need for effective management strategies to support nurses in maintaining proper hand hygiene practices [6]. Additionally, the knowledge, attitudes, and practices of hand hygiene among nursing students are essential. They represent the future nursing workforce, and their training significantly influences their future hand hygiene practices [7-8].

The engagement of relatives, visitors, and families in hand hygiene and infection prevention in ICUs

In addition, patient involvement in promoting hand hygiene among nurses is vital. Patient engagement can have a positive impact on nurses' adherence to hand hygiene protocols [9]. In the context of NICUs, Family-Centered Care has been found to influence clinician-parent collaborations and shape the culture within NICUs, highlighting the importance of involving families in promoting hand hygiene practices [10-11]. Furthermore, the implementation of infection control link nurse programs has proven effective in improving compliance with hand hygiene among nurses, underscoring the significance of structured programs in enhancing hand hygiene practices [12-13].

Barriers to hand hygiene compliance

It is important to consider the barriers that nursing staff face when it comes to hand hygiene performance. Addressing these barriers is crucial for improving hand hygiene practices [14]. Furthermore, research has shown that multimodal interventions are effective in increasing nursing students' adherence to hand hygiene. This highlights the value of comprehensive approaches in promoting proper hand hygiene practices [15]. Additionally, the impact of hospital design and unit admission on staff, family, and patient satisfaction emphasizes the need for a holistic approach to promoting hand hygiene within healthcare facilities [16-17].

Nurse-led interventions and structured programmes

Advanced nursing roles play a crucial role in improving hand hygiene practices among ICU and NICU visitor families. Studies have

demonstrated that interventions such as interactive training in small groups [18] and implementing infection control link nurse programs and educational interventions significantly enhance hand hygiene practices among healthcare workers [19]. These interventions typically involve multifaceted approaches, including role modelling, in-service training, and implementing the WHO's Multimodal Hand Hygiene Improvement Strategy [11-12]. Immediate verbal feedback, continuous monitoring, and providing feedback have also been identified as effective strategies for improving hand hygiene compliance [20-21]. Factors that influence the sustainability of hand hygiene adherence include strong leadership, collaboration, and proactive education by healthcare professionals [22]. Context-based multimodal interventions are recommended for improving hand hygiene adherence among nursing students [14]. Educational interventions and continuous training are crucial for enhancing hand hygiene practices among healthcare workers and visitors, ultimately reducing the risk of healthcare-associated infections [23-24].

Discussion

Impact of advanced nurse roles on hand hygiene compliance

Nurses are crucial in influencing hand hygiene practices among staff and visitors, which has important implications for patient safety and infection control [4]. Research consistently shows that a heavy nursing workload is associated with poor adherence to hand hygiene, highlighting the need for effective management strategies to support nurses in maintaining proper hand hygiene practices [5]. It is also important to consider the knowledge, attitudes, and practices of hand hygiene among nursing students, as they represent the future nursing workforce, and their training significantly impacts their hand hygiene practices [6-7].

Advanced nurse roles are essential in promoting hand hygiene compliance among patients' relatives, family members, and visitors in ICUs. These roles involve implementing structured programs, educational initiatives, and active engagement strategies to enhance infection prevention practices. Involving patients and family members in infection control through education and participation has been proven effective in preventing the transmission of healthcare-associated infections [25].

Additionally, using theoretical models to study hand hygiene behaviour among hospital patients and visitors has resulted in positive outcomes, such as a reduction in infections like methicillin-resistant *Staphylococcus aureus* (MRSA) [26].

Moreover, involving carers in hand hygiene compliance is recognised as a crucial aspect of infection control in healthcare settings [27]. Educating parents and caregivers about the importance of hand hygiene practices can significantly impact compliance rates and help reduce the risk of healthcare-associated infections [28]. Additionally, empowering patients through active participation in infection control measures has been shown to improve adherence to hygiene standards and enhance patient safety [29].

Furthermore, the use of persuasive messaging and newly implemented system interventions has proven effective in enhancing handwashing compliance among visitors in hospital settings. This underscores the essential role of hand hygiene in infection control [26]. Research has also identified key factors that predict compliance with hand hygiene practices, including effective communication from hospital management, peer performance, and stress reduction. These factors can significantly impact overall compliance rates among healthcare workers and visitors in intensive care units (ICUs) [2]. In conclusion, the impact of advanced nurse roles on hand hygiene compliance among patients' relatives, family members, and visitors in ICUs is significant. By implementing structured programs, educational initiatives, and active engagement strategies, healthcare facilities can enhance infection prevention practices, reduce the risk of healthcare-associated infections, and create a

safer healthcare environment for everyone involved.

Relatives, visitors and family engagement in hand hygiene and infection prevention in ICUs

The role of patient involvement in promoting hand hygiene among nurses is extremely important. Patient engagement has the potential to positively impact nurses' adherence to hand hygiene protocols [8]. In neonatal intensive care units (NICUs), Family-Centered Care has been found to influence collaborations between clinicians and parents and shape the culture within NICUs, highlighting the significance of involving families in promoting hand hygiene practices [9].

Engaging relatives, visitors, and families in hand hygiene and infection prevention practices in intensive care units (ICUs) is critical for maintaining a safe healthcare environment. Hand hygiene compliance is a fundamental aspect of infection control, especially in ICUs where patients are vulnerable to healthcare-associated infections (HAIs) [30]. Hospital infections pose a significant risk in healthcare settings, and hand hygiene serves as the primary measure to control the transmission of these infections [30]. Implementing structured programmes that emphasize the importance of hand hygiene can significantly contribute to reducing pathogen transmission and preventing HAIs [31].

Educational initiatives play a vital role in promoting hand hygiene compliance among healthcare workers and visitors. Knowledge, attitude, and practice regarding hand hygiene are essential components in preventing and reducing HAIs [32]. Involving healthcare professional students and workers in educational programmes can deepen their understanding of the importance of hand hygiene in preventing infections. [33]. Additionally, interventions such as infection control procedures and practices, including hand hygiene between patients and before entering ICUs, are essential to minimize the transmission of infections [34].

Furthermore, patient and family engagement in safety practices, including hand hygiene, is advocated to ensure a Patient-Centered Care approach to care [35]. Providing education to parents on the importance of hand hygiene can empower them to advocate for infection prevention measures in healthcare settings [28]. Flexible visitation policies supported by family education can also contribute to reducing anxiety among family members while promoting adherence to infection control practices in ICUs [36]. In conclusion, promoting hand hygiene compliance among relatives, visitors, and families in ICUs through educational initiatives, structured programs, and active engagement is crucial for preventing healthcare-associated infections and creating a safe healthcare environment.

Nurse-Led interventions and structured programmes

The implementation of infection control link nurse programmes has been shown to effectively enhance nurses' compliance with hand hygiene, highlighting the importance of structured programs in improving hand hygiene practices [12–13]. Additionally, multimodal interventions are effective in promoting nursing students' adherence to hand hygiene, emphasising the need for comprehensive approaches [15].

Nurse-led interventions and structured programmes are essential for promoting hand hygiene and infection prevention among relatives, family members, and visitors in ICUs. These interventions are critical for improving compliance with hand hygiene guidelines and reducing the risk of healthcare-associated infections. Educational interventions, such as providing nursing students with comprehensive knowledge of hand hygiene procedures and continuous evaluation, have been proven effective in enhancing infection prevention practices [38].

The implementation of infection control link nurse programmes has been identified as an effective strategy for improving compliance with

standard precautions and hand hygiene among healthcare workers, including nurses [12]. These programmes involve multifaceted interventions, such as adopting the World Health Organisation's Multimodal Hand Hygiene Improvement Strategy, modelling proper hand hygiene practices, and providing in-service training on hand hygiene [12]. Nurse-led educational interventions have also been shown to enhance nurses' knowledge, attitude, and adherence to hand hygiene practices in ICUs [18]. Furthermore, environmental factors play a significant role in hand hygiene compliance. Studies have emphasized the importance of factors such as the availability and accessibility of washbasins and alcohol-based hand rubs in influencing hand hygiene compliance among healthcare workers and visitors in ICUs [39]. In addition, the use of technology, such as Internet of Things management systems, can contribute to improving hand hygiene compliance in healthcare settings [40]. In conclusion, nurse-led interventions, structured programmes, and educational initiatives are crucial components in promoting hand hygiene and infection prevention among relatives, family members, and visitors in ICUs. By implementing these strategies, healthcare facilities can improve compliance with hand hygiene guidelines, reduce the risk of healthcare-associated infections, and create a safer environment for patients, visitors, and healthcare workers.

Barriers to Hand Hygiene Compliance

Barriers to hand hygiene compliance among relatives and family members in intensive care units (ICUs) are multifaceted and can significantly impact infection control practices. Numerous studies have identified various obstacles that contribute to subpar hand hygiene compliance in healthcare settings. These barriers include limited resources, patient overcrowding, staff shortages, allergic reactions to hand sanitisers, lack of awareness and knowledge, failure to recognise hand hygiene opportunities during patient care, and environmental constraints [10, 41, 13]. The COVID-19 pandemic has also influenced hand hygiene behaviours among healthcare workers, potentially affecting the compliance of family members and visitors in adhering to hand hygiene protocols [42]. Despite efforts to improve hand hygiene compliance, studies have shown that rates remain relatively low in ICUs [43].

Additionally, factors such as forgetfulness, lack of focus, and prioritisation of other tasks have been identified as significant obstacles to adequate hand hygiene practices in hospitals [26]. Environmental factors, including the availability and accessibility of washbasins and alcohol-based hand rubs, also play a pivotal role in shaping hand hygiene compliance among healthcare workers and visitors in ICUs [39]. It is crucial to address the barriers to hand hygiene performance among nursing staff as well, as this is integral to improving hand hygiene practices [14]. Furthermore, the impact of hospital design and unit admission on the satisfaction of staff, family, and patients underscores the need for a comprehensive approach to promoting hand hygiene within healthcare facilities [16-17]. In summary, effectively addressing these barriers through targeted interventions, education, and enhancement of environmental resources is essential for bolstering hand hygiene compliance among relatives and family members in ICUs, thereby reducing the risk of healthcare-associated infections.

Challenges and Limitations in hand hygiene practices

Nurses have a critical role in influencing hand hygiene practices among staff and visitors. This role has a significant impact on patient safety and infection control [5]. However, due to heavy nursing workloads, there is often a decrease in adherence to hand hygiene protocols [6]. This highlights the need for effective management strategies and support systems to help nurses maintain proper hand hygiene practices while managing their demanding responsibilities. Additionally, it is crucial to prioritise the

education and training of nursing students, as they are the future workforce whose practices will shape infection prevention efforts [7-8].

Recommendations

To address the urgent need for improved hand hygiene compliance among healthcare professionals, particularly nurses, current literature offers several strategic recommendations. Firstly, nursing education programmes should be enhanced by incorporating evidence-based curricula that provide comprehensive training in hand hygiene protocols and infection prevention strategies. Including practical demonstrations and simulations will reinforce the application of theoretical knowledge. Secondly, fostering interprofessional education initiatives between nursing and allied healthcare disciplines is essential for promoting a holistic approach to infection control. Collaborative efforts, such as interdisciplinary simulations and team-based learning activities focused on hand hygiene practices, can facilitate this synergy. Thirdly, continuous professional development programmes are crucial for keeping nurses updated on evolving best practices and technological advancements in infection prevention. Workshops, webinars, and online courses covering emerging topics, such as new hand hygiene products and strategies for mitigating healthcare-associated infections, should be included in these programmes.
Additionally, healthcare organisations must prioritise supportive work environments by implementing effective workload management strategies and ensuring the availability of hand hygiene resources throughout patient care areas. Leadership commitment to infection control, along with clear accountability mechanisms and regular performance evaluations, plays a pivotal role in fostering a culture of hand hygiene compliance among healthcare professionals.

Conclusion

Advanced nursing roles play a pivotal part in enhancing hand hygiene competence among family visitors in the ICU and NICU. This review aims to evaluate whether advanced nursing positions contribute to improved hand hygiene practices within these groups, focusing on the development and enhancement of hand hygiene programmes. It also seeks to identify effective strategies, address existing practice shortcomings, and provide actionable recommendations. By prioritising evidence-based education, fostering interdisciplinary collaboration, and promoting continuous professional development, healthcare facilities can overcome challenges such as resource limitations and environmental constraints. These efforts are crucial for cultivating a robust culture of infection prevention, ultimately leading to improved patient well-being and enhanced healthcare outcomes.

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Authors' contribution:
SAAB wrote the manuscript, and conduct data collection.
KTA review of the manuscript.
SA wrote the initial draft of the manuscript and conduct data collection.
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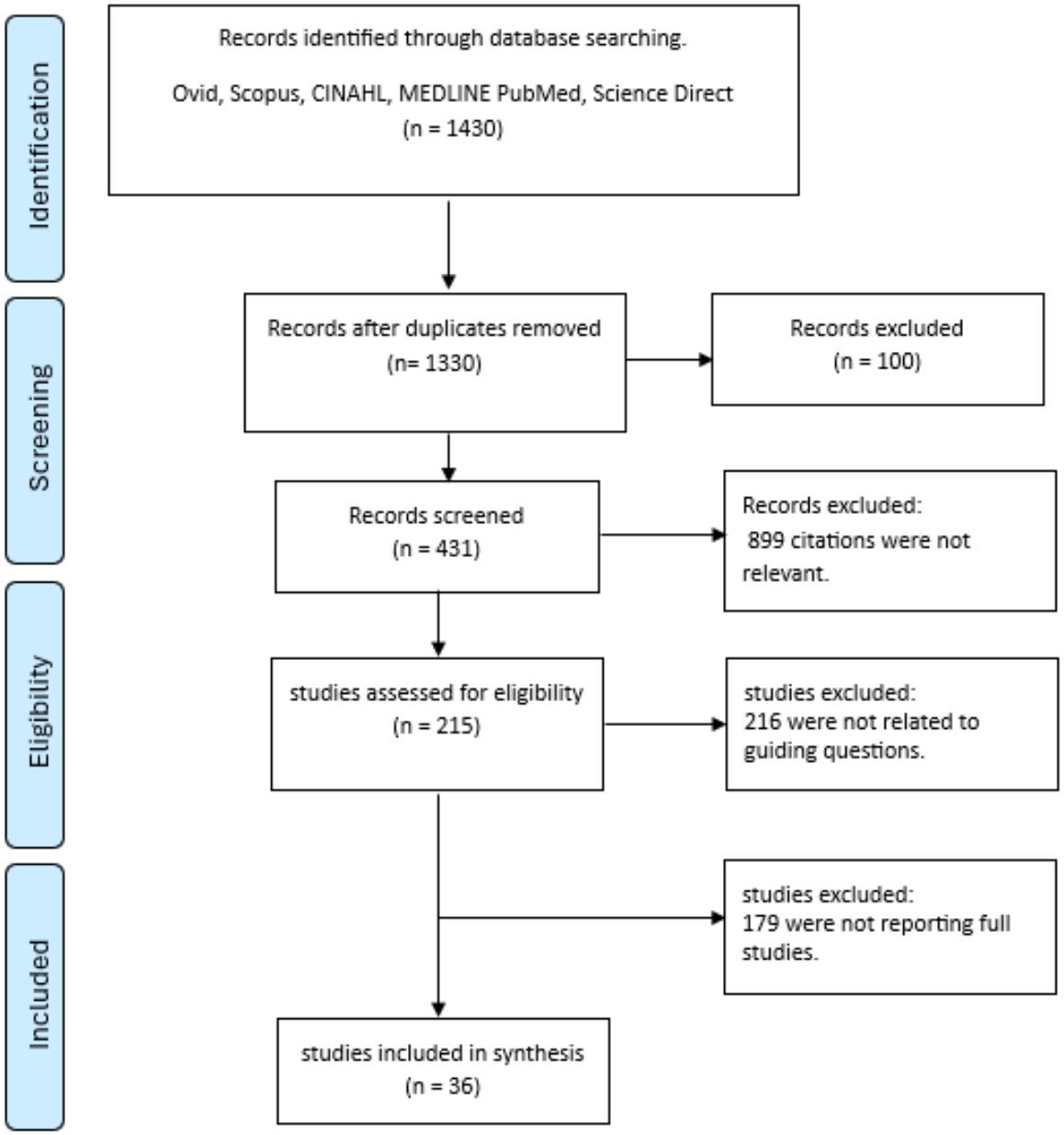

Figure 1. Flow diagram of search strategy

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REVIEW ARTICLE

Endothelial Dysfunction and Pregnancy-Induced Hypertension: A Bibliometric Analysis (2000–2024).

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Abstract

Background: This bibliometric analysis examines the evolving landscape of research on endothelial dysfunction and pregnancy-induced hypertension (PIH), focusing on trends, influential contributors, and key themes. Endothelial dysfunction in PIH significantly impacts maternal and foetal health, yet gaps remain in understanding its mechanisms and management.

Objective: The study aims to provide a comprehensive overview of over two decades of publications on endothelial dysfunction and PIH to guide future research and clinical practice.

Study design: Data were retrieved from Scopus, covering 397 publications over 25 years. Bibliometric measures, including citation metrics, co-authorship networks, and term co-occurrence maps, were analysed using the Scopus analytics tool and VOSviewer software. Key metrics included total citations, h-index, and term clustering, offering insights into publication trends, influential contributors, and thematic areas.

Results: The analysis revealed an increasing trend in publications, being the United States and China as the most productive countries. Highly cited studies emphasised translational research linking clinical outcomes with mechanistic insights. Author keyword analysis highlighted research priorities including preeclampsia, hypertension, and oxidative stress. Co-occurrence maps revealed strategic and granular perspectives, highlighting angiogenesis, placental ischaemia, and long-term maternal health as critical themes. Limitations include reliance on Scopus data, which may exclude relevant studies indexed elsewhere.

Conclusion: This study uniquely synthesises bibliometric insights to map the progression of endothelial dysfunction and PIH research. It highlights influential contributors, emerging trends, and key gaps, offering valuable guidance for researchers and policymakers. The findings highlight the importance of integrating mechanistic research with clinical applications to improve outcomes for hypertensive disorders in pregnancy.

Keywords: *Bibliometrics, Data Visualisation, Endothelial Dysfunction, Hypertension, Pregnancy-Induced, Preeclampsia.*

Introduction

Endothelial dysfunction is central to the pathophysiology of pregnancy-induced hypertension (PIH), including gestational hypertension, preeclampsia, and eclampsia, which are linked to severe maternal and neonatal complications and long-term cardiovascular risks [1,2]. It disrupts the balance of vasodilatory and vasoconstrictive factors, leading to placental perfusion impairment, systemic inflammation, and vascular remodelling [3]. Recent research highlights the nitrate-nitrite-nitric oxide pathway's potential in mitigating oxidative stress and identifies microvascular dysfunction as a contributor to adverse outcomes and maternal vascular risks [1,2]. The role of inflammatory and metabolic biomarkers in PIH further emphasises the interplay between systemic inflammation and vascular health [4]. Longitudinal studies, such as the EPOCH study, reinforce the association of hypertensive pregnancies with persistent vascular risks [5].

Although recent studies have explored elements of endothelial dysfunction and its role in pregnancy-induced hypertension, there is a lack of comprehensive, systematic bibliometric studies that map the evolving trends, collaborative networks, and thematic shifts across this multidisciplinary field. Furthermore, patterns of research output, collaboration networks, and emerging themes remain underexplored, highlighting a need for a comprehensive bibliometric review that integrates these dimensions over the period from 2000 to 2024.

Historical background and recent developments

The understanding of endothelial dysfunction in pregnancy-induced hypertension (PIH) has evolved significantly over the past two decades. Early studies laid the groundwork by identifying endothelial dysfunction as a central mechanism in preeclampsia, linking it to inflammation, metabolic changes, and long-term cardiovascular risks [6,7]. Recent advancements have expanded this foundation, identifying novel biomarkers, mechanisms, and therapeutic approaches [8]. Sun et al. explored inflammatory and metabolic biomarkers, proposing gene therapy as a novel intervention for PIH [9]. Tyrmi et al. added insights into genetic predispositions for preeclampsia, further refining disease risk prediction [10].

Previous studies on bibliometric analysis of endothelial dysfunction and PIH

There is a scarcity of bibliometric analyses specifically related to endothelial dysfunction and PIH (Table 1). Wei et al. conducted a bibliometric study on endothelial dysfunction in sepsis, highlighting knowledge structures in critical care settings but lacking relevance to hypertensive pregnancy disorders [11]. Alam and Islam performed a bibliometric analysis on the role of the placenta in PIH emphasising placental function but offering limited insights into endothelial biomarkers, oxidative stress, and therapeutic targets [12]. Similarly, Kahraman and Yıldırım identified global research trends in PIH but focused primarily on publication patterns rather than mechanistic or translational insights [13]. Shen et al. focused on thematic trends in the management of pre-eclampsia but did not extensively cover endothelial dysfunction as a unifying mechanism [14]. Collectively, these studies demonstrate a fragmented approach, focusing on isolated aspects such as sepsis, placental dysfunction, or clinical management, and limited integration of endothelial dysfunction and hypertensive disorders of pregnancy.

The objective of this bibliometric analysis is to provide a comprehensive perspective by mapping the interconnected research domains of clinical, molecular, and experimental studies, illustrating how endothelial dysfunction serves as a central mechanism linking PIH pathophysiology, long-term maternal health risks, and potential therapeutic targets by systematically examining trends, key themes, and research contributions in the study of endothelial dysfunction and pregnancy-induced hypertension over the past 25 years. This study will address the following research questions:

1. What are the publication trends regarding endothelial dysfunction and PIH?
2. Who are the most prolific authors in the field, and what are the key themes and topics in their research?
3. What are the most influential institutions in this field?
4. What are the most active countries in the field?
5. What are the most highly cited documents in the field of endothelial dysfunction and PIH?
6. What are the most common keywords and themes in the literature in this field?
7. What are the patterns of co-authorship in the field of endothelial dysfunction and PIH?
8. What are the key themes and topics that emerge from co-occurrence analyses of author keywords and title/abstract terms?

Methods

Search strategy and data collection

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart (Figure 1) to conduct our analysis. On 1st December 2024, we gathered data from the Scopus database publications from 2000 to 2024. Our study included "articles" and "reviews", and we limited our search to "English" language publications. We conducted our search by utilising specific keywords in the article titles and abstract. This method assumed that all the retrieved articles are relevant to the topic of our study. The keyword search strings used were as follows:

(TITLE-ABS-KEY (endothelial AND function OR endothelial AND dysfunction AND hypertension) AND TITLE-ABSKEY (pregnancy AND induced AND hypertension OR gestational AND hypertension) OR TITLEABSKEY (postpartum AND hypertension)) AND PUBYEAR > 1999 AND PUBYEAR < 2025 AND (LIMITTO (PUBSTAGE , "final")) AND (LIMIT-TO (SUBJAREA , "MEDI") OR LIMIT-TO (SUBJAREA , "BIOC") OR LIMIT-TO (SUBJAREA , "PHAR") OR LIMIT-TO (SUBJAREA , "NURS") OR LIMIT-TO (SUBJAREA , "IMMU") OR LIMIT-TO (SUBJAREA , "CHEM") OR LIMIT-TO (SUBJAREA , "NEUR")) AND (LIMIT-TO (DOCTYPE , "ar") OR LIMIT-TO (DOCTYPE , "re")) AND (LIMIT-TO (LANGUAGE , "English"))

A total of 472 articles were initially identified by the Scopus database.

Data screening

In order to ensure the reliability of our bibliometric analysis, only peer-reviewed journal articles were included in this study. This selection criterion was implemented to ensure the relevance and adherence to scholarly standards, as well as transparency for readers [15]. Papers from conference proceedings, books, book chapters, and other non-journal publications were excluded from our analysis. All irrelevant publications were also excluded. Following these criteria, a total of 397 scientific journal articles and reviews were chosen for the bibliometric analysis. These selected articles provide a comprehensive overview of the literature on endothelial dysfunction and PIH research spanning from 2000 to 2024. Publication-related data were exported in comma-separated values (.csv) format for further analysis.

Data analysis

The analysis utilised bibliometric measures to evaluate research trends, key contributors, and thematic patterns in the field of endothelial dysfunction and PIH. Key bibliometric measures included publication output trends, citation analysis to identify influential research, co-citation analysis to uncover clusters of related studies, and keyword co-occurrence analysis to determine dominant themes and research focus shifts over time. Additionally, author and institutional productivity were assessed to highlight leading contributors, while geographic patterns were mapped to evaluate regional research activity and collaborations. These

measures provided a quantitative basis for understanding research development, key contributions, and emerging trends within the field. We used the Scopus database as the primary data source, as well as leveraging its Analyse function to process metadata such as author names, affiliations, keywords, and citations. This allowed for an exploration of research trends, influential papers, and key institutional and geographic contributions. Furthermore, VOSviewer was used to visualise the findings, mapping keyword co-occurrences, and co-citation networks. VOSviewer also facilitated the identification of research themes, key collaborations, and geographic patterns, enhancing the analysis by providing intuitive visual insights into the complex relationships within the data.

Results

Publication profiles and trends

We retrieved a total of 287 original articles and 110 reviews. All were journal articles written in English. These articles were published in 159 different journals. Most of the publications covered Medicine (79.1%), Biochemistry, Genetics and Molecular Biology (35.8%), and Pharmacology, Toxicology and Pharmaceutics (12.6%) as the topics. Overall, the number of publications per year has increased over time with a slight temporary decrease in 2019. The highest number of publications was in 2018 with 39 articles published that year. The number of citations per year has also increased over time with a peak of 1683 in 2024 (Figure 2).

Citation metrics

A total of 397 papers have been published in this period, collectively garnering 14,484 citations, which translates to an average of 579.36 citations per year. This steady annual citation rate reflects the relevance of the research on endothelial dysfunction and PIH as well as its ongoing contribution to medical and scientific advancements. Furthermore, the average number of C/P of 38.5 underscores the substantial impact of individual studies. An *h*-index of 67 indicates that at least 67 papers have received 67 or more citations each.

Highly cited documents

Table 5 lists highly cited documents highlighting landmark studies that have significantly shaped the understanding of endothelial dysfunction and pregnancy-induced hypertension. The most cited paper, Zhou et al., has garnered 393 citations, presenting ground-breaking findings on how angiotensin receptor agonistic autoantibodies induce preeclampsia in pregnant mice [16]. Notably, Redman and Staff with 270 citations, explores preeclampsia biomarkers and syncytiotrophoblast stress, has the highest annual citation rate of 27.00 among earlier studies [17]. More recent contributions include Dimitriadis et al., with 224 citations and an exceptional annual citation rate of 112.00 [18].

Publications by authors and institutions

Granger J.P. from the University of Mississippi School of Medicine is the most productive author with 11 publications, a total of 1,283 citations, and a high *h*-index of 10. Mitchell B.M. and Chiasson V.L., both from Texas A&M University School of Medicine, demonstrate substantial productivity with 9 and 7 publications, respectively, and high citation counts (430 and 355). Notably, authors like Sandrim V.C. (Brazil) and Hannan N.J. (Australia) also contribute significantly. However, their average citations per publication (C/P) are lower compared to leading authors from the United States, highlighting potential disparities in research impact (Table 2).

As depicted in Table 3, institutional contributions to the field are led by the University of Mississippi School of Medicine and the University of Mississippi Medical Center, both in the United States, with each producing 24 publications and achieving the highest total citations of 1,785 and 1,694 citations, respectively. These institutions also exhibit strong citation metrics, with average C/P

exceeding 70 and an *h*-index of 19. Brazilian institutions, such as Universidade de São Paulo and Universidade Estadual Paulista Júlio de Mesquita Filho, show notable contributions with 13 publications each. Australian representation is seen with the University of Melbourne, which contributes 11 publications with a C/P of 66.55.

Publication by countries

The United States had the highest number of publications with 125 articles and an *h*-index of 51, which suggests the significant impact and quality of the research contributions. China followed with 40 publications, and the United Kingdom ranked third with 38 publications. The United States was also the most cited country with 6572 citations. It should be noted that the top 10 most productive countries spanned five continents, namely North America, Asia, Europe, South America, and Australia, as seen in Figure 3.

Publications by source titles

The analysis highlights Hypertension as the most prominent source title for research on endothelial dysfunction and pregnancy-induced hypertension, with 28 publications contributing a total of 1,901 citations. Other notable source titles include Hypertension in Pregnancy, which has produced 11 publications with 170 citations. The American Journal of Hypertension and the American Journal of Obstetrics and Gynecology each contribute 9 publications, but the latter exhibits a significantly higher citation count of 782 versus 605, and stronger impact metrics. Finally, the American Journal of Physiology: Heart and Circulatory Physiology adds nine publications with a cumulative 361 citations and maintains a solid reputation, reflected in its SJR of 1.45 and Q1 status (Table 4).

Top keywords

The analysis of author keywords reveals the dominant themes and research focuses within the field of endothelial dysfunction and PIH. The most frequently used keyword, "pre-eclampsia," appears in 37.3% of publications, highlighting its centrality to the topic. Closely associated terms include "pregnancy-induced hypertension" (12.6%), "gestational hypertension" (10.2%), and "preeclampsia" (8.9%), demonstrating the broader spectrum of hypertensive conditions. Key physiological mechanisms such as "endothelial dysfunction" (15.7%), "oxidative stress" (12.3%), and "nitric oxide" (9.5%) highlight their significance in disease pathophysiology. Molecular biomarkers, including "sFlt-1" (6.8%), "PlGF" (5.4%), and "soluble endoglin" (4.7%), reflect increasing research interest in predictive and diagnostic approaches. Additionally, terms like "cardiovascular disease" (8.1%), "metabolic syndrome" (6.2%), and "postpartum" (5.9%) emphasise the long-term maternal implications of PIH.

Co-authorship by author

The co-authorship network visualisation (Figure 4) reveals distinct clusters of researchers collaborating on hypertensive pregnancy disorders. The red cluster features authors from University of Mississippi Medical Center, indicating strong internal collaboration on mechanistic studies. The yellow cluster highlights regional collaborations. The blue cluster centres around influential authors such as Granger, JP and Palei, AC, reflecting work on translational and vascular research. The green cluster shows international collaborations. Notably, Granger, JP acts as a bridge, connecting clusters and facilitating interdisciplinary research.

Co-authorship by countries

The network visualization map of co-authorship by countries highlights the United States as the central hub, reflecting its dominant role in global research output and international collaborations on endothelial dysfunction and PIH (Figure 5). Strong connections are observed with countries like the United Kingdom, Brazil, Australia, Canada, and China, indicating productive partnerships. Regional clusters showcase collaborative efforts across North America, Europe, Latin America, and Asia-Pacific regions.

Smaller nodes like Greece, Italy, and Sweden reflect more localised collaboration.

Co-occurrence analysis of author's keywords

We conducted a comprehensive analysis of author keywords utilising co-occurrence patterns. Employing a threshold of at least 5 occurrences, we identified 43 significant keywords out of a pool of 853. The network depiction of these keywords is visualised in Figure 6, as well as their relationships, with circle sizes corresponding to occurrence frequencies. Notably, the keyword "pre-eclampsia" stands out with the largest circle, indicative of its frequent appearance. This visualisation reveals the presence of six distinct clusters, each centered around a primary keyword that denotes high occurrence rates within the publications. Cluster themes include preeclampsia and its associated factors, role of oxidative stress and nitric oxide dysregulation in vascular smooth muscle and endothelial damage in hypertensive states. pregnancy-related hypertensive disorders with links to cardiovascular disease, severe preeclampsia subtypes as well as metabolic and postpartum factors.

Co-occurrence analysis of terms based on title and abstract

The network visualisation of terms from titles and abstracts reveals interconnected themes in hypertensive pregnancy disorder research (Figure 7). The red cluster emphasises clinical outcomes, focusing on maternal cardiovascular risks. The blue cluster highlights molecular mechanisms, particularly endothelial dysfunction and angiogenic imbalance. The green cluster centers on experimental research, exploring vascular mechanisms in animal models. The integration of clinical, molecular, and experimental dimensions underscores endothelial dysfunction as a unifying mechanism, with increasing attention on the long-term implications for maternal and foetal health.

Discussion

The bibliometric analysis highlights significant progress in understanding endothelial dysfunction and pregnancy-induced hypertension (PIH), with a strong focus on nitric oxide pathways, oxidative stress, and biomarkers like sFlt-1. Mechanistic studies and translational advancements, such as dietary interventions and cellular models, align with the field's precision medicine goals [24-26]. Zhou et al. (2008) is the most cited study due to its pivotal discovery of angiotensin receptor agonistic autoantibodies (AT1-AA) as a key driver of pre-eclampsia, providing strong experimental evidence in a pregnant mouse model. This research established a crucial link between immune dysregulation, endothelial dysfunction, and hypertensive pregnancy disorders, significantly advancing the understanding of pre-eclampsia pathophysiology. Its impact extends beyond obstetrics, influencing cardiovascular and immunological research by highlighting autoantibody-mediated vascular dysfunction. Furthermore, it has shaped biomarker discovery and therapeutic development, particularly in immunomodulation and targeted interventions for pregnancy-induced hypertension, solidifying its status as a foundational study in the field [16]. The surge in publications on endothelial dysfunction and PIH in 2018 was likely driven by increased global focus on maternal health, advancements in biomarker research, and emerging therapeutic interventions. Initiatives such as the Global Strategy for Women's, Children's and Adolescents' Health (2016–2030) prioritised maternal mortality reduction, driving research interest [27].

Research is predominantly driven by high-income countries like the United States, reflecting concentrated resources and expertise. However, as emphasised by Barbosa et al. and Björkman et al., addressing regional disparities in PIH prevalence and management requires research in diverse settings [1-2]. The co-occurrence maps provide complementary perspectives on research

into endothelial dysfunction and PIH. The map, based on author keywords, highlights broad research themes, focusing on clinical outcomes and mechanisms [28-29]. In contrast, the map derived from titles and abstracts delves deeper into specific mechanisms, animal models, and long-term outcomes.

In real-world contexts, these findings emphasise the importance of incorporating endothelial dysfunction markers into routine antenatal care and improving maternal health policies. Integrating endothelial dysfunction biomarkers into routine antenatal care could enhance early detection and risk stratification for hypertensive pregnancy disorders. The incorporation of endothelial stress markers into existing risk assessment models could improve clinical decision-making and guide the timing of delivery [17]. Biomarkers such as sFlt-1 and PlGF are already being explored for predictive screening, but emerging candidates like methylglyoxal and inflammatory markers provide additional insights into vascular dysfunction [30]. Regular monitoring of these biomarkers could facilitate personalised interventions, such as antioxidant or nitric oxide-based therapies, to mitigate vascular impairment [31].

Future research should prioritise addressing the geographic disparities in PIH studies. Research into cost-effective interventions, such as dietary modifications or biomarker-based diagnostics, is crucial for global impact [24,30]. Additionally, longitudinal studies, are essential to elucidate the long-term cardiovascular effects of PIH on women. Methodologically, the field would benefit from integrating advanced techniques such as 3D *in vitro* models and omics approaches to uncover new therapeutic targets [25]. Moreover, expanding research on epigenetic factors could offer insights into intergenerational impacts of PIH and endothelial dysfunction [32].

Strengths and limitations

This bibliometric analysis provides a comprehensive overview of research trends in endothelial dysfunction and PIH, highlighting key clinical and mechanistic advancements while identifying critical research gaps. However, its reliance on Scopus, focus on English-language publications, exclusion of older foundational studies, and disproportionate representation of high-income countries may limit its coverage and relevance, particularly for low-resource settings.

Conclusion

This bibliometric analysis provides a comprehensive overview of research trends, key contributors, and thematic developments in the field of endothelial dysfunction and PIH over the past 25 years. The findings highlight the dominance of terms like preeclampsia, hypertension, and nitric oxide in the research landscape, reflecting both a clinical and mechanistic focus. Highly cited works have emphasised pivotal themes such as oxidative stress, angiogenesis, and vascular dysfunction, demonstrating their relevance to understanding and managing endothelial dysfunction and PIH. Moreover, leading institutions and authors from the United States, Brazil, and Australia have been instrumental in advancing this body of knowledge, highlighting international collaboration. While the analysis successfully identifies major trends and contributors, several limitations, such as reliance on the Scopus database and the exclusion of non-English publications, may have constrained the breadth of findings. Future research should address these gaps by integrating multiple databases and exploring emerging areas like long-term cardiovascular risks and precision medicine. This study contributes to the field by mapping the intellectual structure of research on endothelial dysfunction and PIH, offering insights for targeted interventions, interdisciplinary collaborations, and policy development such as standardised screening protocols.

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Disclosure statement
The authors report no conflict of interest.

Author contributions
HRI - responsible for conceptualization, methodology, validation, formal analysis, data curation, writing - original draft, writing - review & editing, visualization, and project administration. MMZ - responsible for conceptualization, writing - review & editing, and validation. KZ - responsible for writing - review & editing, and data curation

Table 1. Summary of previous studies

Author	Title	Domain/Search Strategy	Data Source & Scope	TDE	Bibliometric Attributes Examined
Wei et al. (2024)[11]	Evolutionary trend analysis and knowledge structure mapping of endothelial dysfunction in sepsis: a bibliometrics study	(TS = (sepsis OR (severe sepsis) OR (septic shock) OR (endotoxemia) OR SIRS OR (systematic inflammatory response syndrome))) AND TS = ((endothelium OR (endothelial cell*) OR endothelia OR (vascular endothelium) OR (vascular endothelial cell*)))	Web of Science Core Collection (WoSCC)	4,536	- citation tendencies - active institutions - active authors - frequently cited publications - references co-citation network - references with citation bursts - keywords
Alam, M. S., & Islam, M. M. (2022)[12]	Bibliometric Study of Placenta in Pregnancy-Induced Hypertension	"Placenta," "Pregnancy," and "Hypertension" in the "Title."	PubMed	298	- prolific authors, affiliations, journal sources, and country - co-authorship analysis - co-occurrence keyword analysis
Kahraman, E., & Yıldırım, E. (2020)[13]	A bibliometric study: Hypertension during pregnancy	"pregnancy" and "hypertension" as keywords	Web of Science Core Collection (WoSCC)	2120	- citation counts - active countries - productivity count
Shen et al. (2023)[14]	Research hotspots and thematic trends in the management of pre-eclampsia: a bibliometric analysis from 2000 to 2022	(TS= (pregnan*) OR TS= (gestation)) AND TS= (*eclampsia) AND (TS= (management*) OR TS= (treatment*)) AND LA= (English)	Web of Science	1525	- titles, publication dates, authors, institutions, countries, and keywords of all articles

TDE=Total documents examined

Table 2. Most Productive Authors

Author's Name	**Affiliation**	**Country**	**TP**	**NCP**	**TC**	**C/P**	***h***
Granger J.P.	University of Mississippi School of Medicine	United States	11	11	1283	116.6	10
Mitchell B.M.	Texas A&M University School of Medicine	United States	9	9	430	47.8	8
Sandrim V.C.	Universidade Estadual Paulista "Júlio de Mesquita Filho"	Brazil	8	8	156	19.5	6
Chiasson V.L.	Texas A&M University School of Medicine	United States	7	7	355	50.7	6
Hannan N.J.	Mercy Hospital for Women	Australia	7	7	423	60.4	6

Notes: TP=total number of publications; NCP=number of cited publications; TC=total citations; C/P=average citations per publication; h=h-index

Table 3. Most productive institutions with minimum of 10 publications

Affiliation	**Country**	**TP**	**NCP**	**TC**	**C/P**	***h***
University of Mississippi Medical Center	United States	24	23	1694	70.50	19
University of Mississippi School of Medicine	United States	24	23	1785	74.38	19
Universidade de São Paulo	Brazil	13	13	701	53.92	11
Universidade Estadual Paulista Júlio de Mesquita Filho	Brazil	13	12	182	14	7
Harvard Medical School	United States	12	12	633	52.74	10
University of Melbourne	Australia	11	11	732	66.55	8

Notes: TP=total number of publications; NCP=number of cited publications; TC=total citations; C/P=average citations per publication; and h=h-index.

Table 4. Most active source titles

Source Title	TP	TC	Publisher	Cite Score	SJR 2024	SNIP 2024
Hypertension	28	1901	Lippincott Williams & Wilkins	20.1	Q1	2.73
Hypertension in Pregnancy	11	170	Taylor & Francis Inc	2.5	Q2	0.6
American Journal of Hypertension	9	605	Oxford Univ Press	5	Q2	0.86
American Journal of Obstetrics and Gynecology	9	782	Mosby-Elsevier	13.2	Q1	3.4
American Journal of Physiology Heart and Circulatory Physiology	9	361	Amer Physiological Soc	8.2	Q1	1.45

Notes: TP=total number of publications; TC=total citations; CiteScore = average citations received per document published in the source title; SJR = SCImago Journal Rank measures weighted citations received by the source title; SNIP = source normalised impact per paper measures actual citations received relative to citations expected for the source title's subject field.

Table 5. Top 10 highly cited articles

No.	Authors	Title	Cites	Cites per Year
1	Zhou et al. (2008)[16]	Angiotensin receptor agonistic autoantibodies induce pre-eclampsia in pregnant mice	393	23.12
2	Khan et al. (2005)[7]	A high-fat diet during rat pregnancy or suckling induces cardiovascular dysfunction in adult offspring	304	15.20
3	Williams (2003)[19]	Pregnancy: A stress test for life	283	12.86
4	Redman & Staff (2015)[17]	Preeclampsia, biomarkers, syncytiotrophoblast stress, and placental capacity	270	27.00
5	Rodie et al. (2004)[20]	Pre-eclampsia and cardiovascular disease: Metabolic syndrome of pregnancy?	241	11.48
6	Giorgini et al. (2016)[21]	Air pollution exposure and blood pressure: An updated review of the literature	226	25.11
7	Dimitriadis et al. (2023)[18]	Pre-eclampsia	224	112.00
8	Torrens et al. (2006)[22]	Folate supplementation during pregnancy improves offspring cardiovascular dysfunction induced by protein restriction	194	10.21
9	LaMarca et al. (2005)[6]	Role of endothelin in mediating tumor necrosis factor-induced hypertension in pregnant rats	184	9.20
10	Brownfoot et al. (2016)[23]	Metformin as a prevention and treatment for preeclampsia: Effects on soluble fms-like tyrosine kinase 1 and soluble endoglin secretion and endothelial dysfunction	177	19.67

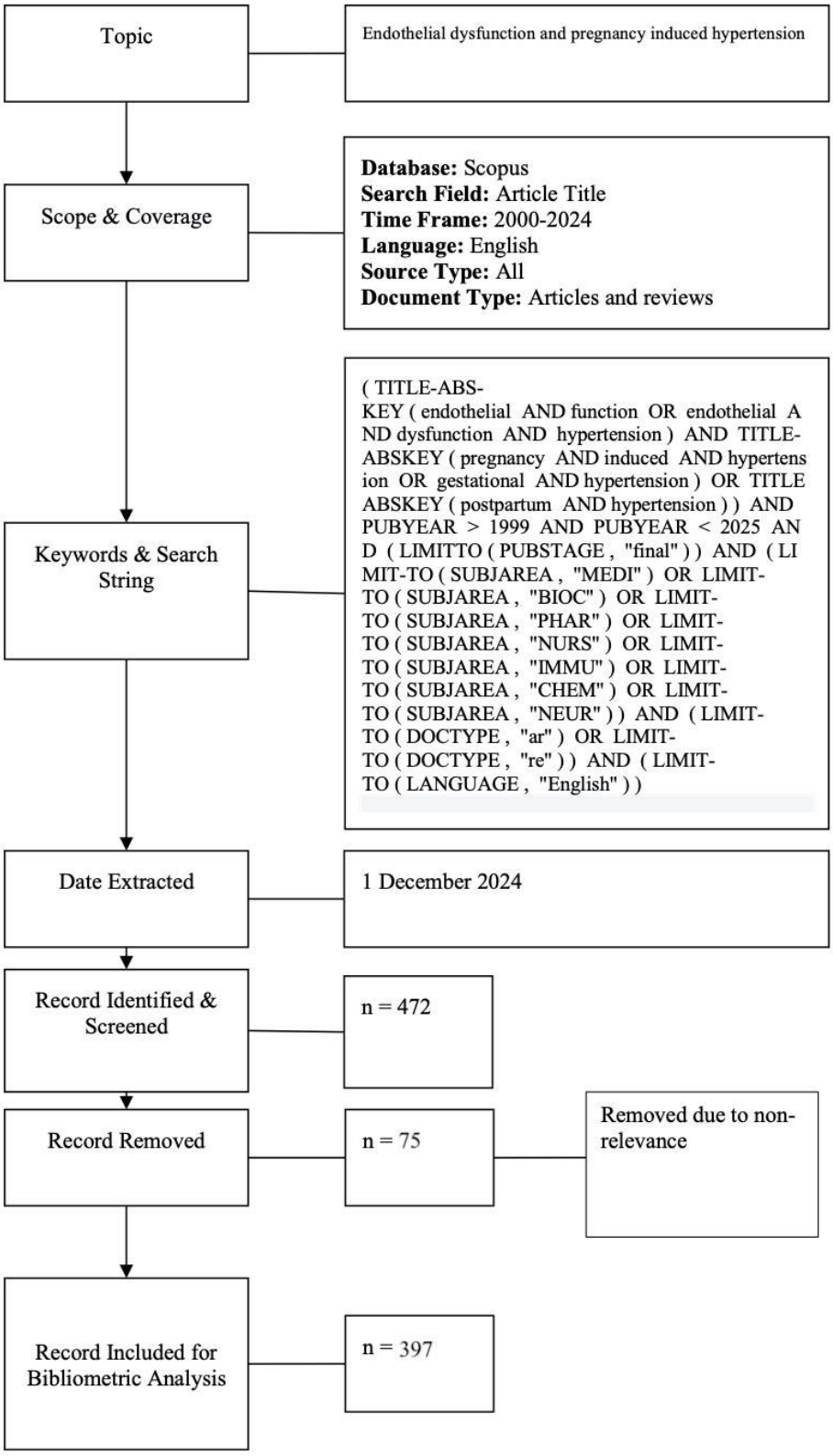

Figure 1. Flow diagram of the search strategy

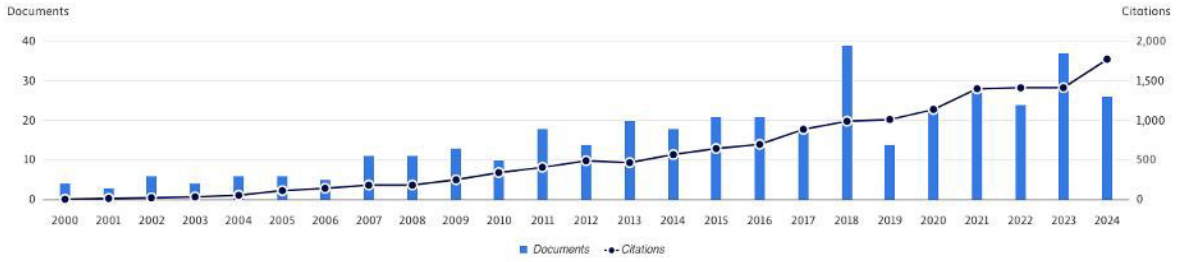

Figure 2. Total publications and citations by year of publications on endothelial dysfunction and pregnancy-induced hypertension research (2020-2024)

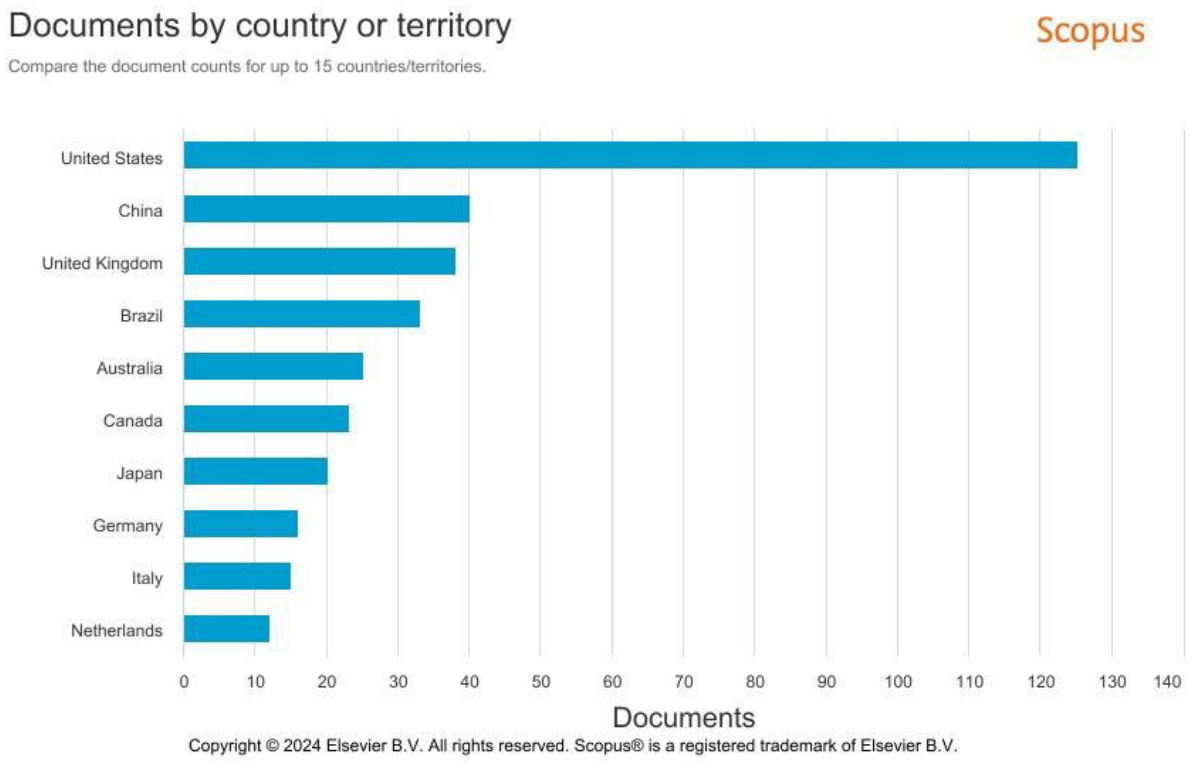

Figure 3. Top 10 countries contributing to publications on endothelial dysfunction and pregnancy-induced hypertension research over the past 25 years

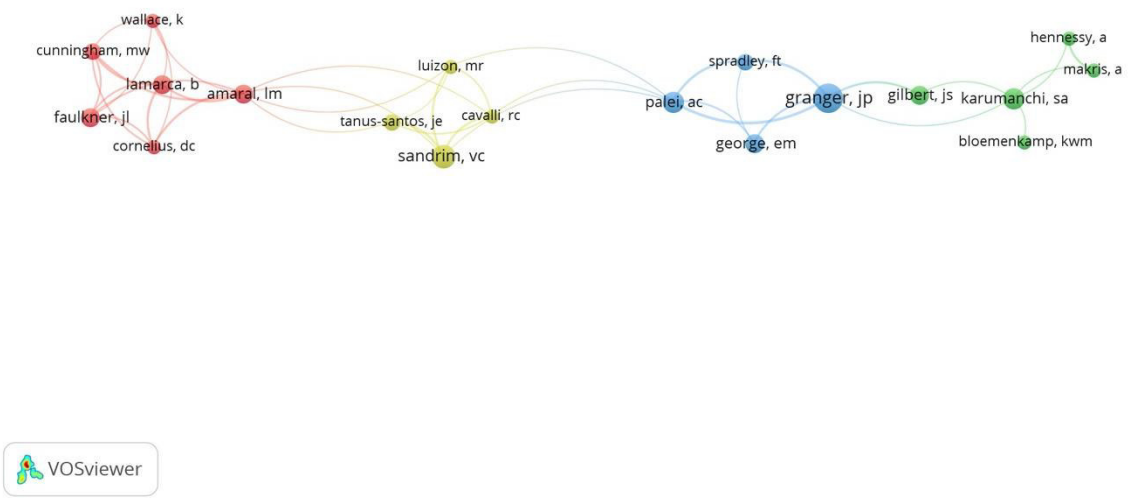

Figure 4. Network visualisation map of the co-authorship by authors of publications on endothelial dysfunction and pregnancy-induced hypertension research (2020-2024)

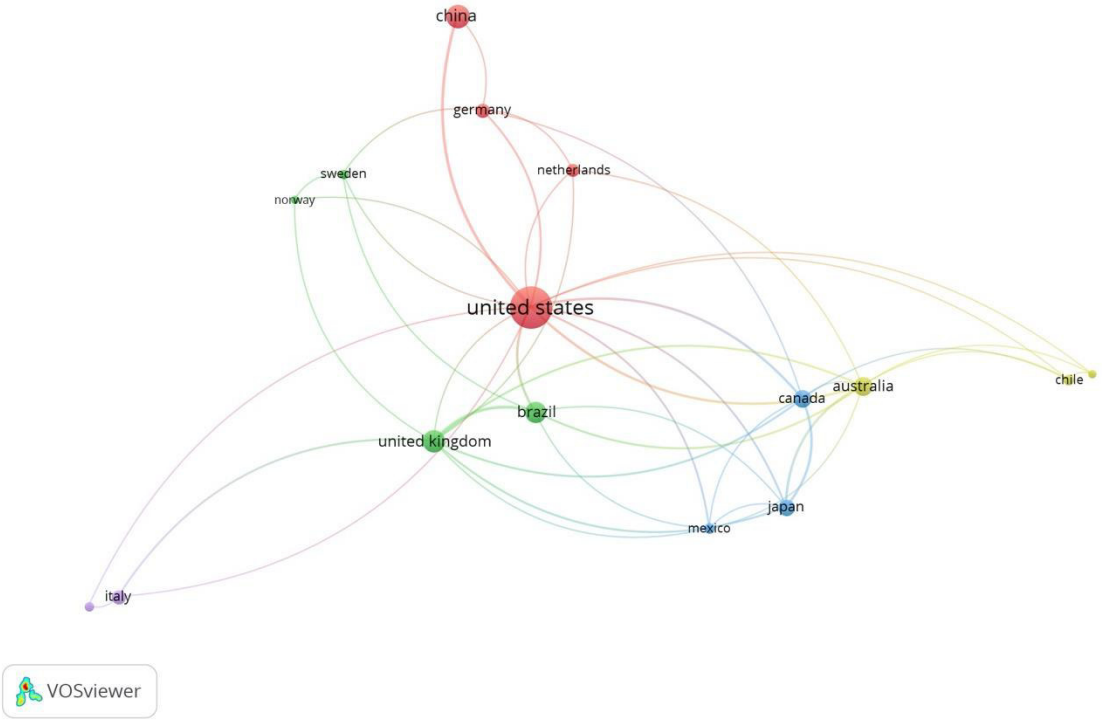

Figure 5. Network visualisation map of the co-authorship by countries of publications on endothelial dysfunction and pregnancy-induced hypertension research (2020-2024)

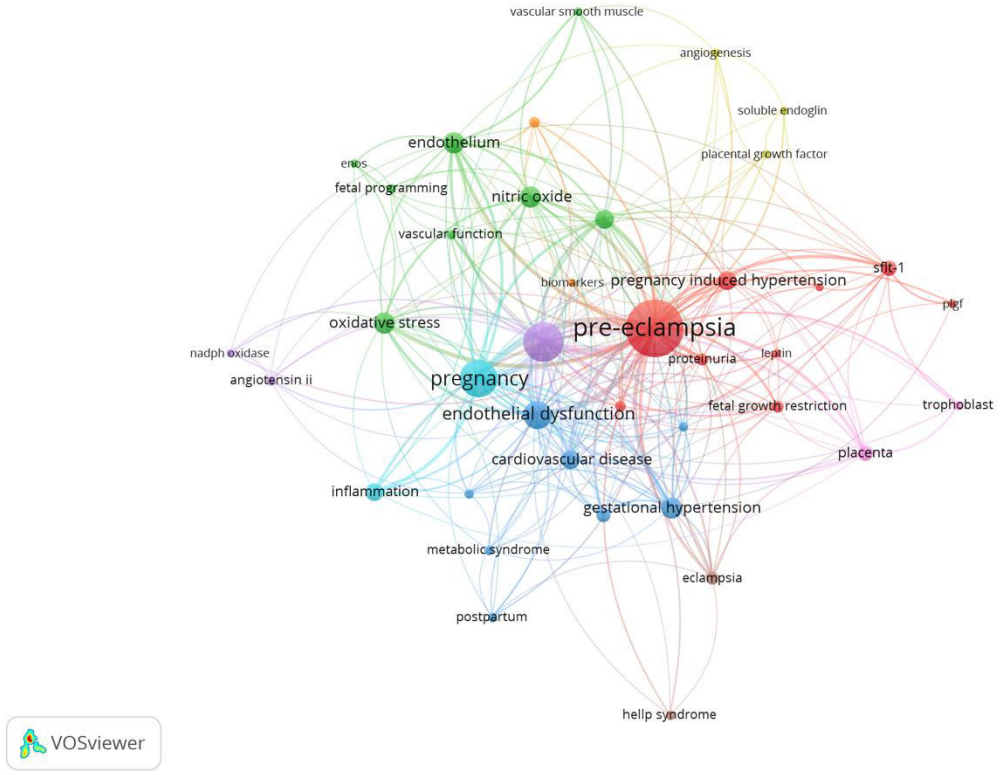

Figure 6. Network visualisation of the author's keywords of publications on endothelial dysfunction and pregnancy-induced hypertension research (2020-2024)

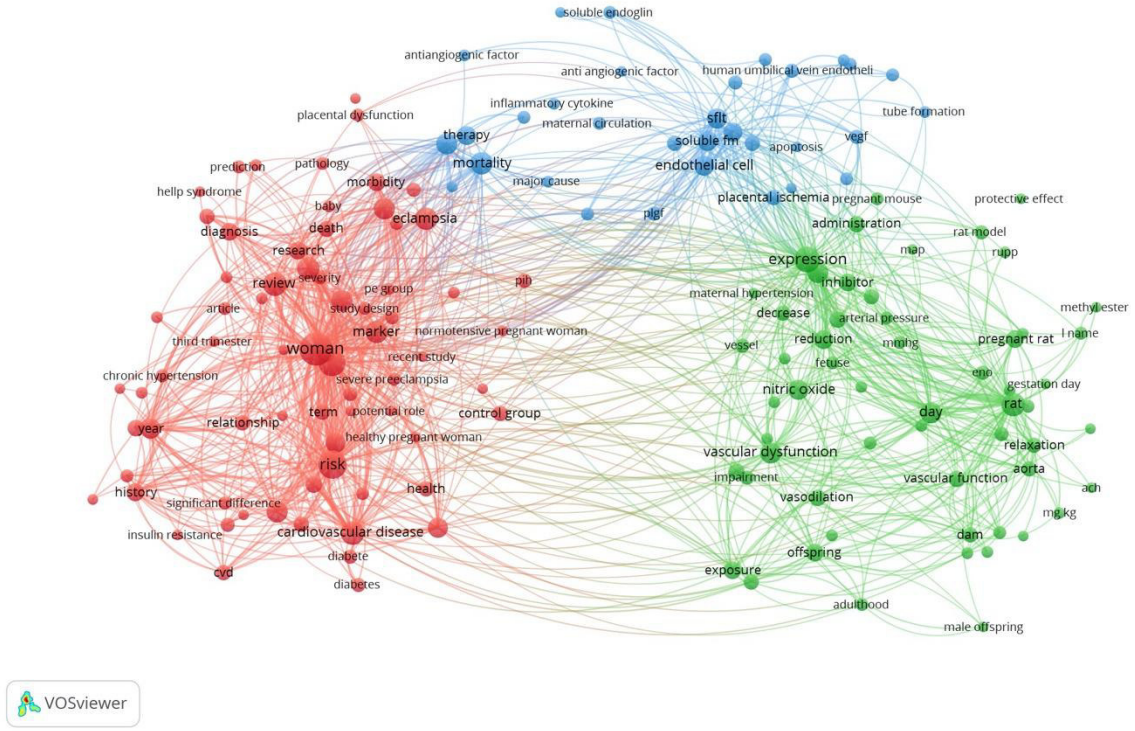

Figure 7. Network visualisation of a term co-occurrence network based on title and abstract fields of publications on endothelial dysfunction and pregnancy-induced hypertension research in the past 25 years

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REVIEW ARTICLE

Islamic Ethics in Nursing: A Scoping Review of Clinical Fiqh Principles and Practice.

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Abstract

Introduction: Clinical Fiqh, an application of Islamic jurisprudence in healthcare, is essential in guiding nursing practice, particularly in ensuring ethical decision-making and holistic patient care. Despite its importance, there is limited research assessing nursing students' knowledge, attitudes, and practices (KAP) regarding Clinical Fiqh principles. **Objective:** This scoping review examines existing literature on the integration of Clinical Fiqh principles in nursing education and practice. **Methodology:** A systematic search was conducted using Scopus, PubMed, ProQuest, and SpringerLink databases. The review adhered to the PRISMA guidelines, selecting studies published between 2015 and 2024. Inclusion criteria focused on articles discussing Clinical Fiqh in nursing education and students' knowledge, attitudes, and practices (KAP) related to Islamic jurisprudence in healthcare. Studies not available in full text or unrelated to the research objectives were excluded. **Results:** Seventeen articles were identified for analysis, revealing key themes aligned with the knowledge, attitudes, and practices (KAP) framework, offering insights into students' understanding of Clinical Fiqh principles, their perceived importance, and application challenges in clinical settings. Findings indicate that while nursing students recognise the importance of Clinical Fiqh principles, gaps remain in their formal education, affecting their ability to apply them in clinical settings. Structured educational interventions, experiential learning, and competency-based assessments were suggested to enhance integration into nursing curricula. **Conclusion:** This review highlights the need for a structured approach to incorporating Clinical Fiqh into nursing education, ensuring culturally competent and ethically sound care. Future research should focus on developing standardised curricula, assessing the impact of Clinical Fiqh education on clinical competencies, and bridging the knowledge-practice gaps.

Keywords: *Clinical Fiqh, cultural competence, ethical nursing practice, holistic care, Islamic jurisprudence, nursing education.*

Introduction

Clinical Fiqh, derived from Islamic jurisprudence (Fiqh), is fundamental in ensuring that healthcare services align with Islamic ethical and legal principles. In nursing, Clinical Fiqh provides guidelines on ethical decision-making, patient care, and religious accommodations in healthcare settings, particularly for Muslim patients. These principles, rooted in the Qur'an and Sunnah, address key aspects such as modesty, end-of-life care, ritual purity, and dietary considerations, fostering a holistic approach to patient well-being. Integrating Clinical Fiqh into nursing education is particularly relevant in Muslim-majority regions, where culturally and religiously competent care is crucial for patient satisfaction and adherence to treatment plans [1,2]. However, despite its importance, there is a notable gap in nursing curricula regarding the structured teaching of Clinical Fiqh, potentially affecting the preparedness of nursing graduates in to address the religious needs of patients [3,4].

Existing research indicates that while spiritual care is recognised as an essential component of holistic nursing, many nursing students feel inadequately trained to provide it effectively [5]. Studies on religious competence in healthcare suggest that integrating faith-based knowledge into nursing education enhances students' ability to deliver compassionate, patient-centred care [6,7]. Furthermore, embedding Clinical Fiqh into nursing curricula supports ethically sound decision-making, especially in managing complex clinical issues like reproductive care, pain control, and terminal illness management [8]. Despite these potential benefits, limited empirical research has been conducted to evaluate the level of knowledge, attitudes, and practices (KAP) of nursing students regarding Clinical Fiqh, making it imperative to assess current educational gaps and propose strategies for improvement [9,10].

This scoping review aims to systematically explore the existing literature on integrating Clinical Fiqh principles in nursing education and practice. By analysing relevant studies, this review seeks to identify knowledge gaps, examine the impact of Clinical Fiqh education on nursing students' competencies, and propose recommendations for curriculum enhancement. Given the increasing emphasis on culturally competent care, the findings of this review may contribute to developing educational strategies that better equip nursing students to address the religious and ethical needs of Muslim patients, ultimately improving the quality of care in diverse healthcare settings [11,12]. To the best of our knowledge, this is one of the first scoping reviews that systematically examines the intersection of Clinical Fiqh principles and nursing education, addressing a significant gap in existing literature.

Materials and methods

This scoping review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure transparency and rigor. The framework adopted for this review follows Arksey and O'Malley's methodological approach, which consists of five key stages: (1) identifying the research question, (2) searching for relevant studies, (3) selecting studies based on inclusion and exclusion criteria, (4) charting the data, and (5) synthesising the findings [13]. The primary research question guiding this review was: What are the existing studies on the knowledge, attitudes, and practices (KAP) of nursing students regarding Clinical Fiqh principles, and how are these principles integrated into nursing education? This review aims to explore available literature, identify gaps, and propose recommendations for improving the integration of Clinical Fiqh in nursing education.

A comprehensive literature search was conducted using Scopus, PubMed, ProQuest, and SpringerLink, which were selected due to their extensive coverage of healthcare, medical education, and nursing research. A structured Boolean search strategy was used to refine the search and maximise the retrieval of relevant literature. The following keywords and Boolean operators were applied:

(nursing students OR nursing undergraduates) AND (Islamic legal principles comprehension)

AND (spiritual care OR religious care nursing) AND (nursing education OR nursing curriculum OR Islamic education nursing) AND (knowledge OR understanding OR comprehension) AND (attitudes OR perceptions OR behavior) AND (practices OR application)

These keywords were chosen based on common terminologies used in Islamic nursing ethics, spiritual care, and nursing education, ensuring a broad spectrum of relevant literature was considered.

To further enhance the search, truncation and wildcards were used where applicable to capture variations of words, such as "nurs*" to include nursing, nurses, and nurse practitioners. Additionally, subject headings (MeSH terms) were utilised in PubMed to refine the search related to Islamic jurisprudence in healthcare.

The SPIDER (Sample, Phenomenon of Interest, Design, Evaluation, Research type) framework was employed to structure the search strategy systematically. This approach ensures that relevant qualitative and quantitative studies are included.

The inclusion criteria for study selection were as follows: (1) studies focusing on Clinical Fiqh principles in nursing education or practice, (2) studies involving nursing students as the primary population, and (3) studies involving educators or other healthcare professionals were included only if their focus pertained directly to the integration or impact of Clinical Fiqh in nursing education. Studies solely focused on medical students or other professions without clear implications for nursing education were excluded (4) articles published in English, and (5) full-text availability. Articles were excluded if they did not specifically address Clinical Fiqh, were conceptual or opinion papers lacking empirical data, or focused solely on healthcare professionals other than nursing students. The screening process was conducted in two stages: first, titles and abstracts were reviewed independently by two researchers, and second, full-text articles were assessed for eligibility. Discrepancies in selection were resolved through discussion.

To ensure consistency in selecting relevant Clinical Fiqh principles, we focused on rulings explicitly tied to nursing care and patient management. These included principles governing ritual purity (taharah), prayer and fasting exemptions for ill patients (rukhsah), gender-sensitive care, modesty in clinical procedures, end-of-life considerations, and spiritual accommodations. These categories were chosen based on their recurrence across preliminary literature, relevance to nursing education and practice, and alignment with the broader goals of holistic and ethical care in Islamic contexts. Only studies that directly addressed one or more of these domains in relation to nursing students or curricula were included in the final synthesis.

A standardised data extraction form was used to collect key information from the selected studies, including author(s), year of publication, study design, sample population, research objectives, methods, key findings, and limitations. The findings were analysed using thematic synthesis, grouping studies under the KAP framework—Knowledge of Clinical Fiqh principles, Attitudes towards its integration in nursing education, and Practices related to its implementation in clinical settings. This structured approach provided a comprehensive understanding of how Clinical Fiqh is integrated into nursing curricula and impacts students' competencies in delivering culturally competent care.

To ensure the quality and credibility of the included studies, the Critical Appraisal Skills Programme (CASP) checklist was used to assess each article's methodological rigor. The CASP tool provides a structured approach to evaluate different study designs, including qualitative, cohort, and mixed-methods research. Two reviewers independently appraised each article using the relevant CASP checklist focusing on research clarity, methodological appropriateness, data collection and analysis, ethical considerations, and overall research value.

Discrepancies in assessment were resolved through discussion. While no studies were excluded based on appraisal outcomes—consistent with tscoping review methodology—the CASP evaluation helped contextualise the strengths and limitations of the current body of literature.

Results

A total of 2,342 articles were identified through the initial database search. After removing duplicates and irrelevant studies, 2,083 articles remained for screening. Based on title and abstract screening, 148 articles were deemed relevant, and 17 met the full inclusion criteria for this scoping review. These studies varied in design, including cross-sectional surveys, qualitative explorations, and mixed-method studies, with sample populations primarily consisting of nursing students, educators, and healthcare professionals involved in nursing education. The findings from these studies were synthesised into three major themes: (1) knowledge of Clinical Fiqh principles among nursing students, (2) attitudes toward the integration of Clinical Fiqh in nursing curricula, and (3) practices related to Clinical Fiqh in clinical settings.

Knowledge of Clinical Fiqh Principles Among Nursing Students

Several studies indicated varying levels of knowledge among nursing students regarding Clinical Fiqh principles. While students exhibited a basic understanding of Islamic ethical guidelines, gaps were identified in specific rulings related to patient care, such as guidelines on ritual purity (taharah), exemptions in prayer and fasting for sick patients (rukhsah), and ethical decision-making in complex medical cases. The findings also revealed that students with prior exposure to Islamic education or those enrolled in structured courses on Clinical Fiqh demonstrated higher levels of competency and confidence in applying these principles. However, in institutions where Clinical Fiqh was not formally incorporated into the nursing curriculum, students reported limited understanding and uncertainty in integrating these concepts into clinical practice.

Attitudes toward the integration of clinical Fiqh in nursing curricula

The reviewed studies highlighted positive attitudes among nursing students toward integrating Clinical Fiqh into nursing curricula. Many students recognised its relevance in enhancing culturally competent care, particularly for Muslim patients. They perceived the inclusion of Clinical Fiqh as an essential component of holistic nursing education, ensuring that spiritual, ethical, and religious considerations are addressed in patient care. However, some studies noted resistance among educators and curriculum developers, primarily due to a lack of standardised teaching materials and concerns about balancing religious-based content with contemporary nursing education requirements. The findings suggest faculty training and structured curriculum development are necessary to facilitate effective integration.

Practice related to clinical Fiqh in clinical settings

Despite an overall positive attitude toward Clinical Fiqh, the practical application of its principles in clinical settings remained inconsistent. Many students reported challenges in applying Islamic nursing ethics in real-life scenarios, particularly in environments where institutional policies and cultural diversity may conflict with Islamic jurisprudence. Key areas of concern included accommodating Muslim patients' religious practices, providing spiritual care in end-of-life situations, and navigating ethical dilemmas such as organ donation, medical interventions, and gender-sensitive care. Some studies also identified a lack of confidence among students in addressing patients' religious needs, emphasising the need for structured training and mentorship programs to bridge the gap between theoretical knowledge and practical implementation.

Discussion

This scoping review highlights the current landscape of Clinical Fiqh integration in nursing education, revealing significant gaps in knowledge, attitudes, and practices (KAP) among nursing students. The findings indicate that while students acknowledge the importance of Islamic ethical principles, their ability to apply Clinical Fiqh concepts in clinical settings remains limited. This aligns with previous studies suggesting that nursing curricula in many institutions lack structured content on Islamic jurisprudence, leading to inconsistent levels of preparedness among graduates [1,2]. Furthermore, while some universities, such as IIUM, have pioneered the integration of Clinical Fiqh into their programs, there is still a need for standardised guidelines to ensure a uniform and evidence-based approach to incorporating Islamic ethical principles in nursing education [3,4].

The attitudinal aspect of Clinical Fiqh education among nursing students presents a mixed perspective. Many students express positive attitudes toward including Islamic principles in nursing curricula, recognising their relevance to culturally competent care [5,6]. However, faculty resistance, lack of instructional materials, and concerns over balancing religious-based content with standard nursing education hinder effective implementation [7]. Some studies report a lack of confidence among educators in teaching Clinical Fiqh, suggesting that faculty development programs and interdisciplinary collaboration between nursing educators and Islamic scholars could enhance teaching methodologies [8]. Addressing these concerns through curriculum restructuring, interactive teaching methods, and case-based learning could bridge the gap between theory and practice, equipping nursing students with theoretical knowledge and practical skills to effectively integrate Clinical Fiqh into patient care [9].

Despite recognising Clinical Fiqh's importance, its practical application in clinical settings remains inconsistent. Many nursing students struggle with implementing Islamic nursing ethics due to institutional constraints, diverse patient populations, and uncertainty in handling ethical dilemmas involving Muslim patients [10,11]. Areas such as ritual purification (taharah), prayer accommodations, end-of-life care, and religious exemptions (rukhsah) for patients remain challenging, especially in non-Muslim majority healthcare settings where institutional policies may not fully support Islamic practices [12]. To mitigate these challenges, practical training in culturally competent care, hospital policy adjustments, and greater collaboration between healthcare institutions and Islamic scholars could give nursing students the confidence and competency to integrate Clinical Fiqh principles into patient care [14].

Moving forward, integrating Clinical Fiqh into nursing curricula requires a multifaceted approach. First, structured educational interventions, such as case studies, simulation-based learning, and mentorship programs, should be incorporated to strengthen nursing students' practical application of Islamic ethical principles [15]. Second, research on effective pedagogical strategies and competency-based assessments is crucial to measuring the impact of Clinical Fiqh education on nursing students' preparedness and confidence in delivering culturally and ethically competent care [16]. Finally, collaborative efforts among policymakers, nursing educators, and healthcare institutions must develop standardised guidelines for integrating Clinical Fiqh into nursing education and practice, ensuring that future nursing graduates are equipped to meet Muslim patients' spiritual and ethical needs [17].

In increasingly multicultural healthcare environments, understanding Clinical Fiqh principles equips nurses to provide care that respects religious sensitivities and promotes cultural safety. For example, nurses trained in these principles are better prepared to support Muslim patients during Ramadan by understanding exemptions (rukhsah) from fasting due to illness. They can also accommodate prayer routines, ensure modesty in physical

examinations, and provide gender-concordant care where feasible. These culturally congruent practices can enhance trust, patient satisfaction, and adherence to treatment.

Furthermore, in mixed-faith settings, nurses must balance Islamic practices with institutional protocols and the diverse needs of other patients. Therefore, collaboration with hospital administrators and chaplaincy teams, along with clear policies for spiritual care, can facilitate respectful implementation of Islamic values without compromising standard clinical guidelines. Educating nurses in these areas not only benefits Muslim patients but strengthens holistic and ethical nursing care in pluralistic societies.

Study strengths and limitations

This study offers several notable strengths:

a) Novel Focus on Clinical Fiqh in Nursing Education: To the best of our knowledge, this is one of the first scoping reviews to systematically explore the intersection between Clinical Fiqh principles and nursing education. This unique focus addresses a significant gap in the literature on Islamic ethics in healthcare.

b) Rigorous Methodological Framework: The study adhered to the PRISMA guidelines and adopted the Arksey and O'Malley scoping review framework, ensuring a structured and transparent review process. The use of the SPIDER framework for search strategy design also enhanced the precision of study selection.

Despite these strengths, the study is not without limitations:

a) Heterogeneity of Study Populations: Although the initial inclusion criteria focused on nursing students, some included studies also involved nurses, educators, or medical students. While these were deemed relevant to the study's objectives, this variation may affect the specificity of conclusions drawn about nursing student experiences.

b) Limited Empirical Evidence: Many of the included studies were qualitative or descriptive in nature, and few employed longitudinal or experimental designs. As such, causal inferences about the impact of Clinical Fiqh education on nursing competencies are limited.

Conclusion

This scoping review highlights the growing need to integrate Clinical Fiqh principles into nursing education to enhance students' knowledge, attitudes, and practices (KAP) in providing culturally and ethically competent care. While nursing students recognise the importance of Clinical Fiqh, the findings suggest significant gaps in their practical application, particularly in areas such as ritual purification, religious exemptions, and ethical decision-making in clinical settings. Despite some progress in incorporating Islamic nursing ethics in selected institutions, a lack of standardised guidelines and structured teaching approaches remains a barrier to practical implementation.

To address these challenges, curriculum development efforts should prioritise structured educational interventions, including case-based learning, experiential training, and competency-based assessments. Faculty development programs, interdisciplinary collaboration between nursing educators and Islamic scholars, and institutional support are crucial for bridging the gap between theoretical knowledge and practical implementation. These measures will enhance students' ability to apply Clinical Fiqh principles in patient care and ensure that nursing graduates are better equipped to provide holistic, patient-centered care that aligns with Islamic ethical standards.

Future research should focus on evaluating the impact of Clinical Fiqh education on nursing students' competency levels, developing evidence-based teaching frameworks, and

exploring effective pedagogical strategies for integrating Islamic ethics into nursing curricula. Furthermore, collaborations between policymakers, educators, and healthcare institutions are essential to establish standardised guidelines and accreditation frameworks for Clinical Fiqh education. By strengthening the integration of Islamic ethical principles in nursing, the profession can move toward a more inclusive, culturally competent, and ethically grounded approach to healthcare delivery.

Implication for nursing practice

Integrating Clinical Fiqh principles in nursing education has significant implications for nursing practice, particularly in enhancing culturally competent, ethical, and holistic patient care. By equipping nursing students with a clear understanding of Islamic ethical guidelines, including ritual purification (taharah), religious exemptions (rukhsah), and end-of-life care, nurses will be better prepared to respect and accommodate the religious needs of Muslim patients in diverse healthcare settings. This, in turn, promotes patient-centred care, improves nurse-patient communication, and fosters trust between healthcare providers and Muslim communities. Additionally, integrating Clinical Fiqh into hospital policies, nursing protocols, and professional training programs will ensure a more inclusive approach to healthcare, reducing ethical dilemmas related to religious accommodations in patient care. Moving forward, interdisciplinary collaboration between nursing educators, Islamic scholars, and healthcare policymakers is essential to develop standardised guidelines and competency-based training programs that enable nurses to deliver care that is both clinically sound and religiously sensitive, ultimately improving patient satisfaction, health outcomes, and the overall quality of nursing care.

Recommendations for future research

Several studies highlighted the urgent need for more targeted research on integrating Clinical Fiqh and Islamic ethics within nursing education. Given that many nurses and students lacked knowledge of fundamental Islamic ethical concepts such as *Maqasid al-Shari'ah* and *Qawaid al-Fiqhiyyah*, future research should focus on developing structured training modules and evaluating their impact on students' knowledge, attitudes, and practices. Studies also recommended exploring longitudinal outcomes to assess how exposure to Islamic nursing professionalism and spiritual care training influences professional commitment, ethical decision-making, and compassionate care over time. Further, comparative research is needed to examine the effectiveness of different pedagogical strategies—such as passive, reflective, and case-based approaches—in enhancing students' spiritual care competency and ethical sensitivity. Since religious students were shown to report higher competence in providing spiritual care, future investigations should explore how personal religiosity influences clinical practice and patient interactions. Additionally, mixed-methods and multi-center studies are encouraged to comprehensively understand barriers and facilitators to implement Clinical Fiqh education across culturally diverse and secular institutions. Finally, collaboration between nursing scholars, Islamic ethicists, and curriculum developers is essential to produce standardised, culturally grounded, empirically validated educational frameworks.

Conflict of interest

The authors have conflict of interest in this study.

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Authors' Contributions

FTA conceptualised the study, led the literature search, and contributed to the drafting of the

manuscript. MFMI was responsible for the methodological framework, data extraction, and critical review of the manuscript. SZS contributed to data analysis, interpretation of the findings, and editing of the final manuscript. All authors reviewed and approved the final version of the manuscript.

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Table 1. Sample, Phenomenon of Interest, Design, Evaluation, Research Type (SPIDER) Framework Table

Component	Description
Sample	Nursing students
Phenomenon of Interest	Islamic legal principles comprehension
Design	Interviews and questionnaires
Evaluation	Experiences
Research Type	Qualitative and quantitative studies

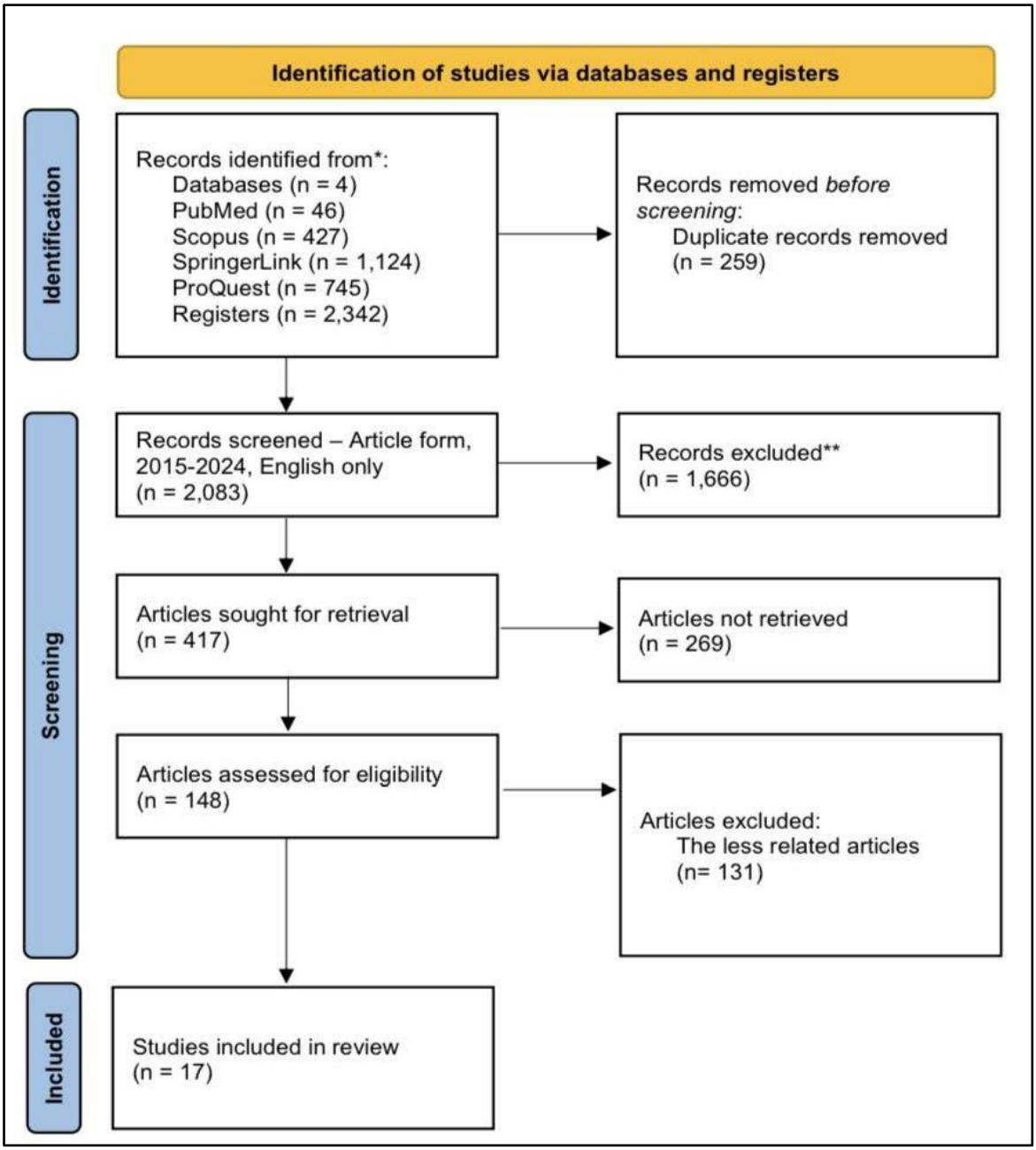

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Table

Table 2. Summary of Literature Review

Title, Author, Year	Research Method	Objective/Question	Variables & Tools	Participants	Findings	Limitations
Integration of Islamic Values in Undergraduate Nursing Program (Nurumal et al., 2019)	Expository Analysis	To address the importance of integrating Islamic values in nursing education	Not applicable	Not applicable	Islamic nursing professionalism is essential for safe nursing, ethical values, and compassionate care	Not stated
Perception of Islamic Nursing Ethics among Nurses in Pahang (Ismail et al., 2022)	Quantitative	To examine nurses' perceptions of Islamic nursing ethics	Dependent: Perception; Independent: Demographics; Descriptive statistics (questionnaire)	118 Muslim RNs in Malaysia *Nurses included due to direct focus on Islamic nursing ethics in a nursing context	Many nurses lacked knowledge of Islamic nursing ethics; 63.6% never heard of Maqasid al-Shari'ah and Qawaid al-Fiqhiyyah.	Not stated
Nurse Students' Perspectives on Spiritual Care Education (Cooper & Chang, 2016)	Qualitative	To explore the impact of a spiritual care subject in an undergraduate nursing program	Dependent: Students' perception; Independent: Spiritual care education; Thematic analysis (interviews)	6 second-year nursing students in Australia	Students felt better prepared to provide spiritual care after completing the course.	Not stated
Maqasid Al-Shari'ah as a Complementary Framework for ICN Code of Ethics (Ismail et al., 2022)	Analytical	To present Islamic nursing ethics with Maqasid al-Shari'ah applications	Not applicable	Not applicable	Explores how Islamic principles align with ICN Code of Ethics for Nurses	Not stated
Spiritual Education and Nursing Competencies	Quasi-experimental	To assess the impact of a spiritual education course on	Dependent: Spiritual competencies; Independent: Spiritual	92 nursing students in Taiwan	Significant improvement in spiritual health, professional	Convenience sampling limits generalizability; No

(Chiang et al., 2020)		nursing competencies	education; Chi-square test, self-report questionnaire		commitment, and caring behavior	clinical performance assessment.
Effectiveness of Islamic Input in Medical Practice (Ramli et al., 2022)	Prospective Cohort	To measure the impact of Islamic education on medical students' knowledge, attitude, and practice	Dependent: KAP; Independent: Sociodemographics; One-way ANOVA (MMSQ tool)	102 medical students from IIUM (International Islamic University Malaysia) *Medical students included due to relevance to Islamic ethics education	Knowledge, practice, and attitude improved significantly after training	Small sample size (72% response rate); Mixed-method design needed for a more comprehensive evaluation
Nursing Students' Compassion Competencies and Spirituality (Dincer & Ciftci, 2024)	Descriptive	To explore the relationship between compassion competencies and spirituality	Dependent: Spiritual perception; Independent: Compassion competency; Pearson correlation	263 nursing students in Turkey	Positive relationship between spiritual care competency and compassion level	Not stated
Development of a Spiritual Care Education Matrix (Ross et al., 2022)	Analytical	To develop the EPICC framework for spiritual care education	Not applicable	Not applicable	Identifies facilitators and barriers to implementing spiritual care education	Not stated
Spiritual Care Competencies in Brazilian Nursing Students (Alvarenga et al., 2024)	Mixed-method	To explore nursing students' knowledge, preparedness, and obstacles in spiritual care	Dependent: Competency in spiritual care; Independent: Demographics; Descriptive stats, Mann-Whitney test	106 nursing students in Brazil	65% never provided spiritual care; Religious students felt more competent	Limited representation of students from different curricula and religious backgrounds
Perceptions of Spirituality and Competency in Middle Eastern Nursing	Cross-sectional	To assess spirituality perceptions and	Dependent: Spiritual care competency; Independent: Sociodemograp	785 nursing students from five Middle	Positive attitude towards spirituality, but	Self-reported bias; Limited generalizabil

Students (Al Qadire et al., 2024)		competency predictors	hics; Multiple linear regression	Eastern countries	moderate competency in providing care	ity due to convenience sampling
Spiritual Care Competencies in European Nursing Students (Ross et al., 2018)	Longitudinal	To examine how students' perceptions of spiritual care evolve over time	Dependent: Spiritual perception; Independent: Demographics; Paired t-tests, ANOVA	3,175 European nursing students	Competency improved over time due to patient care experiences	High attrition rate; Predominantly Christian students limit religious diversity
Spirituality and Nursing Students' Learning (Laochai et al., 2024)	Qualitative	To explore how spirituality is promoted in nursing education	Dependent: Spiritual learning; Independent: Teaching methods; Thematic analysis	9 nursing educators in Thailand *Nursing educators included due to relevance to Islamic ethics education	Identifies four themes: spirituality, learning, engagement, and mentorship	Findings are limited to educators' perspectives, not students
Teaching Spiritual Care in Nursing (Booth & Kaylor, 2018)	Qualitative	To understand students' perspectives on spirituality in nursing	Dependent: Spiritual care competence; Independent: Prior hospital experience; Thematic analysis (interviews)	11 nursing students	Identifies themes: knowledge, confidence, diversity, and maturity	Not stated
Spiritual Care in Undergraduate Nursing Education (Willet et al., 2024)	Integrative Review	To analyse strategies for preparing nursing students in spiritual care	Not applicable	Not applicable	Three teaching approaches identified: passive, reflective, and combinatory.	Focused only on English-language studies, limiting perspectives
Competence in Spiritual Care and Spiritual Intelligence (Ahmadi et al., 2021)	Cross-sectional	To assess the relationship between spiritual competence and intelligence	Dependent: Spiritual care competency; Independent: Spiritual intelligence; Pearson correlation	510 Iranian nursing students	Positive correlation between spiritual intelligence and spiritual care competence	Self-reported bias; No long-term follow-up

Nursing Students'Perceptions of Spiritual Care in Turkey (Kalkim et al., 2018)	Descriptive-correlational	To describe nursing students' perceptions of spirituality and competence	Dependent: Spiritual care competence; Independent: Demographics; ANOVA, correlation	325 Turkish nursing students	Students' perception of spiritual care accounted for 14% of competency	Small sample size; Limited generalizability

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REVIEW ARTICLE

Integrating Clinical Fiqh into Nursing Education: A Scoping Review on Student Satisfaction and Ethical Nursing Practice.

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Abstract

Introduction: Integrating Clinical Fiqh into nursing education is a novel approach that aligns nursing practice with Islamic ethical and legal principles. However, student satisfaction with this curriculum remains unexplored, particularly in the context of preparing culturally competent nurses. This scoping review examines the available literature on integrating Clinical Fiqh in nursing education and evaluates student satisfaction with its inclusion. **Objective:** This scoping review aims to explore nursing students' satisfaction with the integration of Clinical Fiqh in their curriculum and identify the influencing factors that impact their learning experiences. It seeks to assess how this integration contributes to professional and ethical competencies in nursing practice. **Methodology:** A systematic search was conducted using Scopus, SpringerLink, and PubMed databases to identify relevant studies published between 2019 and 2024. The review followed the PRISMA framework, applying inclusion criteria such as peer-reviewed articles in English and studies focusing on Islamic ethics in healthcare education. The Joanna Briggs Institute (JBI) Critical Appraisal Tool was used to evaluate the validity and reliability of selected studies. **Results:** The findings highlight limited literature on Clinical Fiqh integration in nursing curricula. Preliminary evidence suggests that students value its inclusion for fostering ethical decision-making, cultural competency, and patient-centred care. However, challenges such as teaching methods, faculty expertise, availability of learning resources, and clinical practice integration influence overall satisfaction levels. The review also identifies gaps in research regarding the long-term impact of Clinical Fiqh education on nursing practice. **Conclusion:** This review underscores the significance of incorporating Clinical Fiqh in nursing education to enhance ethical and culturally sensitive care. The findings contribute to the ongoing discourse on religious ethics in healthcare and provide insights for improving curriculum design. Future studies should explore longitudinal impacts and comparative assessments across institutions to strengthen evidence-based recommendations for Islamic nursing education.

Keywords: *Clinical Fiqh, cultural competence, curriculum integration, Islamic ethics, nursing education, student satisfaction.*

Introduction

Nursing education plays a crucial role in shaping competent and ethical healthcare professionals. The integration of cultural and religious perspectives in nursing curricula is essential, particularly in multicultural and Muslim-majority societies where religious beliefs influence healthcare decisions. Clinical Fiqh, an emerging discipline within Islamic medical ethics, provides nursing students with a framework for ethical decision-making in alignment with Shariah principles. It encompasses Islamic jurisprudential guidelines on healthcare practices, including patient care, bioethics, and end-of-life issues [1]. Including Clinical Fiqh in nursing education will enhance students' ability to deliver culturally competent and ethically sound care, ensuring alignment with Islamic principles while maintaining professional standards [2]. However, the impact of this integration on nursing students' learning experiences and satisfaction remains underexplored.

Student satisfaction is a key indicator of curriculum effectiveness, influencing learning outcomes, engagement, and motivation. A well-integrated nursing curriculum must align with students' expectations, professional competencies, and the realities of clinical practice [3]. Previous studies highlight the importance of incorporating ethical and religious perspectives to improve patient care outcomes [4]. However, research focusing on Clinical Fiqh in nursing education is limited, with most literature addressing broader Islamic bioethics in healthcare [5]. Assessing nursing students' satisfaction with this integration is crucial for evaluating its effectiveness, identifying potential challenges, and refining the curriculum to support their academic and professional development [6].

This scoping review explores nursing students' satisfaction with integrating Clinical Fiqh into their curriculum and identifies the key factors influencing their perceptions. By systematically reviewing existing literature, this study seeks to bridge the knowledge gap in Islamic nursing education and contribute to curriculum development strategies that enhance student engagement and competency in culturally responsive care. The findings will provide insights into the benefits and limitations of Clinical Fiqh integration and offer recommendations for its optimisation in nursing education [7].

Materials and methods

This scoping review followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to ensure a structured and comprehensive review of existing literature [8]. The search strategy was designed to identify relevant studies examining nursing students' satisfaction with the integration of Clinical Fiqh in their curriculum. Three major electronic databases—Scopus, SpringerLink, and PubMed—were systematically searched. A combination of keywords was used, including "(nursing students OR undergraduate nursing students OR nurse trainee OR student nurse) AND (satisfaction OR fulfilment OR enjoyment OR contentment) AND (clinical fiqh OR Islamic jurisprudence OR Islamic law OR Islamic ethics OR Shariah-compliant healthcare) AND (curriculum OR syllabus OR academic framework OR study plan OR educational program)." Boolean operators (AND, OR) were applied to refine the search results. The initial search yielded 128,399 articles. After removing duplicates and non-relevant studies, 121,960 articles remained. Further screening of abstracts and applying inclusion criteria—such as full-text availability, peer-reviewed status, English language, and a publication date between 2019 and 2024—narrowed the selection to 1,201 articles. A final round of screening resulted in 23 articles being included for comprehensive review. These selected articles helped identify key themes and issues related to nursing students' satisfaction with integrating Clinical Fiqh into nursing curricula.

The inclusion criteria for this review were full-text availability, peer-reviewed status, and studies published between 2019 and 2024 in

English. The selected studies had to focus on nursing students' satisfaction with integrating Clinical Fiqh or Islamic ethics in nursing curricula. Studies that were not fully accessible or did not specifically address Clinical Fiqh in nursing education were excluded. The study selection process adhered to the PRISMA flowchart, consisting of four phases: identification, screening, eligibility, and inclusion. The selected studies were critically appraised using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist to assess methodological quality and reliability.

A standardised data extraction form was used to collect information on author details, year of publication, study design, sample size, research setting, key findings, and study limitations. Thematic analysis identified recurring patterns in nursing students' perspectives on Clinical Fiqh integration, focusing on teaching methodologies, faculty expertise, learning resources, institutional support, and practical applications in clinical settings. The SPIDER framework was applied to guide the study selection process, as outlined in Table 1.

Descriptive statistics, including frequencies and percentages, were used to summarise relevant quantitative data. Thematic synthesis was applied to qualitative findings, ensuring a structured analysis of key themes emerging from the review. Investigator triangulation was employed, with multiple reviewers independently screening and analysing selected articles. Any discrepancies in study selection or data extraction were resolved through discussion. Ethical considerations were maintained throughout the research process, as only publicly available data were used, and no human participants were involved.

Results

This scoping review identified 23 studies that examined nursing students' satisfaction with integrating Clinical Fiqh into their curriculum. The studies varied in research design, including qualitative interviews, cross-sectional questionnaire-based surveys, and mixed-methods approaches. The thematic analysis revealed key areas influencing student satisfaction, including teaching methodologies, faculty expertise, availability of learning resources, cultural and institutional support, and clinical practice integration. The selected studies were conducted in different academic and clinical settings, primarily in Muslim-majority countries, with sample sizes ranging from small focus groups to more extensive surveys of nursing students.

Impact of teaching methodologies and faculty expertise

Teaching methodologies played a significant role in determining students' engagement with the Clinical Fiqh curriculum. Studies suggested active learning approaches, such as case-based discussions, role-playing, and problem-based learning, were more effective in fostering critical thinking and ethical decision-making than traditional lecture-based instruction [11,12]. Nursing students were more satisfied when instructors demonstrated Islamic jurisprudential knowledge and practical clinical experience [2,6,13]. Some studies indicated that when Clinical Fiqh was taught using real-life clinical scenarios, students developed a deeper appreciation for its relevance to nursing practice [5,6]. However, challenges emerged in institutions where faculty members lacked expertise in nursing and Islamic jurisprudence, leading to variations in content delivery and student engagement [4,10,13].

Availability of learning resources and institutional support

The availability of learning resources was another determinant of student satisfaction. Studies indicated that access to well-structured textbooks, case studies, and online materials improved students' comprehension of Clinical Fiqh concepts [2,6,13]. Some institutions provided digital platforms and e-learning modules facilitating self-directed learning, enhancing students' ability to apply theoretical concepts in

practice [5,11,12]. However, several studies highlighted the lack of standardised reference materials, leading to inconsistent content delivery across different institutions [2,6,10]. Institutional support also influenced students' experiences, with universities that embedded Clinical Fiqh within a well-defined academic framework reporting higher student engagement and satisfaction levels [6,13,14]. Integrating Clinical Fiqh into university-wide courses on Islamic ethics and professionalism enhanced students' interdisciplinary understanding of ethical nursing practice [1,4,15].

Clinical practice integration and application of clinical Fiqh

Clinical practice integration was a key theme across the reviewed studies. Nursing students who had the opportunity to apply Clinical Fiqh principles during their clinical rotations demonstrated increased confidence in handling ethically sensitive situations, such as patient modesty, end-of-life care, and religious accommodations in healthcare settings [2,5,6,13]. Some students reported that their knowledge of Islamic medical ethics helped them navigate complex patient care scenarios, mainly when working with Muslim patients who required religiously sensitive interventions [1,4,14,15]. However, studies noted that some clinical placements lacked structured guidance on implementing Clinical Fiqh principles, resulting in inconsistencies in how students applied their theoretical knowledge in real-world nursing scenarios [6,10,13]. The findings from this review emphasise the need for refining curriculum strategies, enhancing faculty training, and improving resource availability to ensure effective Clinical Fiqh integration in nursing education [2,5,6,13].

Discussion

Integrating Clinical Fiqh into nursing education enhances ethical and culturally competent nursing practice. This scoping review found that nursing students expressed satisfaction with including Clinical Fiqh in their curriculum, particularly in how it prepared them to navigate religious and ethical dilemmas in healthcare settings. Similar findings have been reported in studies on Islamic medical ethics, where healthcare professionals equipped with Islamic jurisprudential knowledge demonstrated improved ethical decision-making and culturally sensitive patient care [1,9,10]. However, the review also identified challenges, including variations in teaching methodologies, faculty expertise, and the availability of structured learning resources, influencing students' overall satisfaction with the subject. Addressing these issues is crucial to optimising the integration of Clinical Fiqh into nursing education and ensuring its effectiveness in preparing future nurses for diverse clinical environments.

The teaching methodology used to deliver Clinical Fiqh content was a key factor influencing student satisfaction. Studies in this review indicated that interactive and case-based teaching approaches were more effective than traditional lecture-based methods. This aligns with existing nursing education literature, emphasising the importance of active learning strategies in improving student engagement and knowledge retention [3,11,12]. Problem-based learning, role-playing, and real-life clinical case discussions enhanced students' ability to apply Clinical Fiqh principles in practice. However, in institutions where faculty members lacked expertise in Islamic jurisprudence and nursing, students experienced inconsistent content delivery. Previous studies have highlighted the importance of faculty training in Islamic ethics and clinical education to bridge this gap [4,13,14]. Strengthening faculty competencies through professional development programs and interdisciplinary collaboration between Islamic scholars and nursing educators may enhance the effectiveness of Clinical Fiqh instruction.

The availability of structured learning resources was another determinant of student satisfaction. This review found that students

accessing well-structured textbooks, case studies, and digital learning materials reported a better understanding of Clinical Fiqh principles. Similar findings have been reported in studies on Islamic bioethics, where access to comprehensive educational resources was associated with improved student engagement and competency in applying ethical principles in healthcare [5,15]. However, a lack of standardised reference materials across institutions led to inconsistencies in content delivery. This gap suggests the need to develop a unified Clinical Fiqh curriculum that incorporates standardised textbooks, e-learning platforms, and case-based modules to ensure consistency in instruction across nursing programs. Institutions should consider incorporating Clinical Fiqh topics into broader courses on professional ethics and cultural competence to reinforce students' interdisciplinary understanding of ethical nursing practice.

Clinical practice integration was one of the most significant themes identified in this review. Nursing students who had opportunities to apply Clinical Fiqh principles during their clinical placements demonstrated increased confidence in addressing religiously sensitive patient care situations, such as maintaining patient modesty, addressing end-of-life concerns, and accommodating religious practices in healthcare settings. These findings are consistent with research on cultural competence in nursing education, which suggests that real-world application of ethical principles enhances students' preparedness for professional practice [6,16]. However, some clinical settings lacked structured guidance on how students should apply Clinical Fiqh principles, leading to inconsistencies in practice. This highlights the need for nursing institutions to collaborate with healthcare facilities in developing structured guidelines for integrating Clinical Fiqh principles into clinical training. Simulation-based training, mentorship programs, and clinical case discussions can effectively reinforce students' application of Clinical Fiqh in real-world settings [7,17,18,19].

This review highlights the benefits and challenges of integrating Clinical Fiqh into nursing curricula. While students generally recognise its value in preparing them for ethically and culturally competent nursing practice, inconsistencies in teaching methodologies, faculty expertise, and resource availability must be addressed to maximise its impact [20]. Strengthening faculty training, developing standardised educational resources, and enhancing clinical practice integration can improve the effectiveness of Clinical Fiqh instruction in nursing education. Future research should explore longitudinal outcomes to assess the long-term impact of Clinical Fiqh training on nursing graduates' ethical decision-making and professional practice in diverse healthcare settings.

Conclusion

Integrating Clinical Fiqh into nursing education represents a significant step toward developing ethically grounded and culturally competent healthcare professionals. This scoping review found that nursing students generally appreciate the inclusion of Clinical Fiqh in their curriculum, as it enhances their understanding of Islamic ethics and provides practical guidelines for addressing religious and ethical challenges in healthcare settings. However, the effectiveness of this integration depends on various factors, including teaching methodologies, faculty expertise, the availability of structured learning resources, and opportunities for clinical application. Addressing these factors ensures that Clinical Fiqh contributes meaningfully to nursing students' professional development and preparedness for real-world practice.

Despite the positive reception of Clinical Fiqh in nursing education, this review highlights the need for further improvements in curriculum design and implementation. The inconsistencies in teaching methods, faculty training, and access to standardised learning materials suggest a more

structured and unified approach is necessary. Institutions should consider incorporating interactive teaching strategies, strengthening faculty development programs, and providing well-defined educational resources to enhance students' learning experiences. Furthermore, improving clinical practice integration through structured guidelines, mentorship programs, and simulation-based training can help bridge the gap between theoretical knowledge and real-world application. These steps will ensure that nursing students are adequately prepared to navigate ethical dilemmas in diverse clinical settings while upholding Islamic values in their practice.

Future research should explore the long-term impact of Clinical Fiqh education on nursing graduates' professional competency and ethical decision-making. Longitudinal studies examining how Clinical Fiqh training influences nursing practice in various healthcare environments would provide valuable insights for refining the curriculum. Comparative studies across different institutions could also help identify best practices for effective integration. By addressing the gaps identified in this review, nursing educators and policymakers can strengthen the role of Clinical Fiqh in shaping a new generation of healthcare professionals who are clinically proficient and ethically and culturally competent in providing holistic patient care.

Implications for nursing practice

Integrating Clinical Fiqh in nursing education enhances culturally competent care by equipping nurses with the knowledge to navigate religious and ethical considerations in clinical practice. It enables nurses to provide holistic, patient-centred care that respects Islamic principles, particularly in healthcare settings, patient modesty, end-of-life care, and religious accommodations. This integration also strengthens ethical decision-making by guiding nurses in addressing moral dilemmas related to informed consent, life-sustaining treatments, and biomedical ethics from an Islamic perspective. Additionally, Clinical Fiqh fosters professionalism and sensitivity in nurse-patient interactions, improving trust and communication with Muslim patients and families. By incorporating these principles, nursing practice aligns more effectively with the values and beliefs of diverse patient populations, ultimately improving patient satisfaction and healthcare outcomes.

Conflict of interest

The authors have conflict of interest in this study.

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Authors' Contributions

NJ conceptualised the study, led the literature search, and contributed to the drafting of the manuscript. MFMI was responsible for the methodological framework, data extraction, and critical review of the manuscript. SZS contributed to data analysis, interpretation of the findings, and editing of the final manuscript. All authors reviewed and approved the final version of the manuscript.

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Table 1. SPIDER Framework for Study Selection

SPIDER	Initial Terms
Sample	Nursing students
Phenomenon of Interest	The satisfaction levels of nursing students with the nursing curriculum or subject
Design	Qualitative interviews and questionnaire-based studies
Evaluation	Subjective assessments of advantages, challenges, and overall satisfaction with Clinical Fiqh
Research Type	Qualitative and quantitative studies

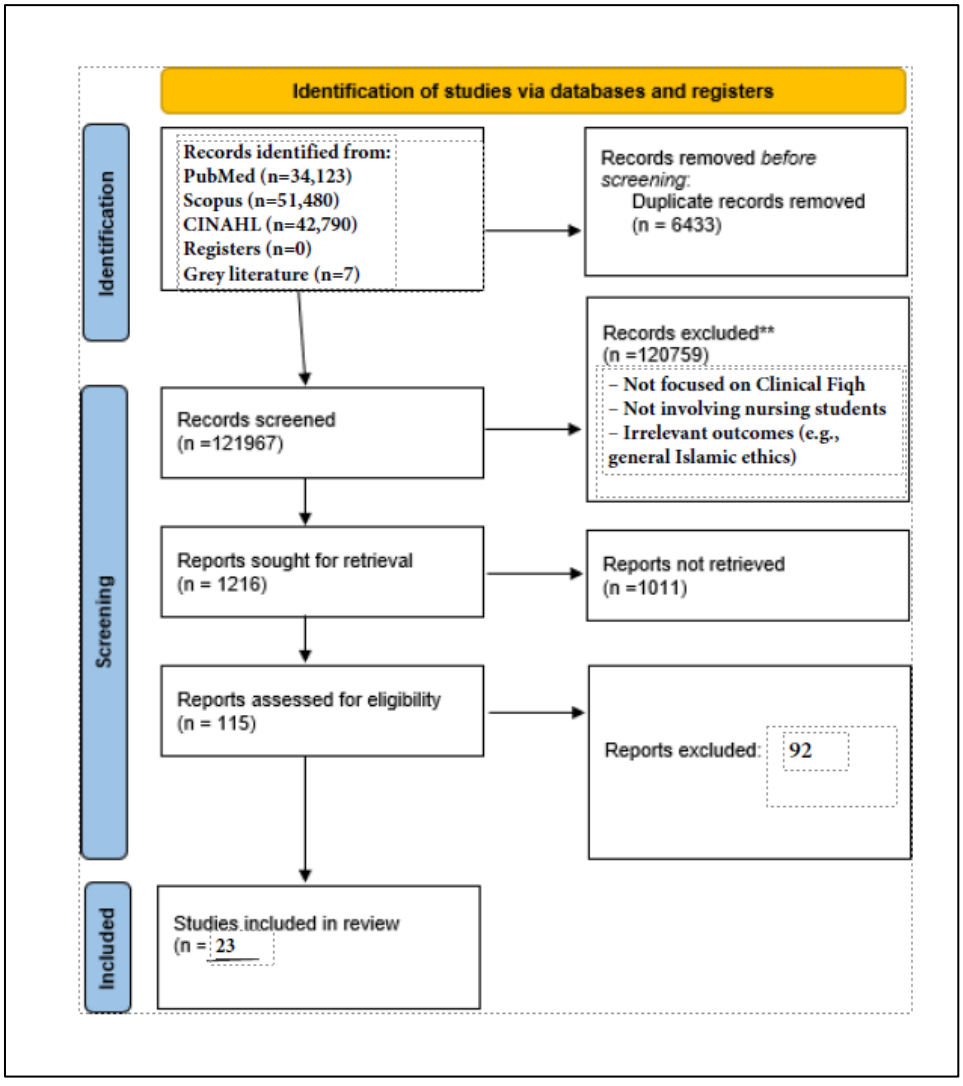

Figure 1. PRISMA flow table

Table 2. Summary of Literature Review

Title, Author, Year	Research Method	Objective	Variables & Analysis	Participants	Findings	Limitations
1.Ratings of performance in multisource feedback: comparing performance theories of residents and nurses. Tariq, M., et al. (2022)	Qualitative research	Explore performance theories of assessors when evaluating residents	DV: Performance assessment of residents, IV: Performance theories, Inductive thematic analysis	14 nurses & 15 residents, varying experience & roles	7 key themes on performance theories with overlaps and differences	Single-center study, limited perspectives, only residents & nurses assessed
2. A meta-analysis of nursing students' knowledge and attitudes about end-of-life care. Wang, W., et al. (2022)	Meta-analysis	Synthesise nursing students' knowledge and attitudes about end-of-life care	DV: Knowledge and attitudes, IV: Demographics, gender, academic year, AHRQ appraisal	9749 nursing students across 26 studies from 13 countries	Insufficient knowledge on end-of-life care, positive attitudes noted	Cross-sectional design, convenience sampling, lack of grey literature
3. Competencies expected of undergraduate nursing students: A scoping review. Purabdollah, M., et al. (2023)	Scoping review	Identify core competencies for undergraduate nursing students	DV: Nursing core competencies, IV: Population, Summative content analysis	43 studies selected from 15,875 articles	5 core themes: individualised care, nursing process, administration, readiness, professional development	Exclusion of non-English articles, cultural contextualisation needed
4. Setting agenda for medical education research in Pakistan. Ali, S., & Sethi, A. (2021)	Mixed-method study	Identify research priorities in medical education in Pakistan	DV: MER priority areas, IV: Demographics, Thematic analysis & SPSS	140 faculty, students, policymakers	20 research priorities in 8 themes; top 3: faculty development, assessment, communication	Purposive sample, regional imbalance in representation
5. Missed nursing care among nursing students: A scoping review. Abawaji, M. A., et al. (2024)	Scoping review	Explore nursing students' perspectives on missed care during clinical placements	Not stated, Thematic content analysis	9 studies from 7 countries	Themes: negligence of patient rights, teamwork issues, leadership inefficiencies	Limited to English studies, possible language bias, non-generalizable
6. Intercultural readiness of nursing students:	Integrative review method	Synthesise research on cultural	DV: Readiness of nursing students, IV: Educational	14 studies screened from	Themes: Increasing knowledge	Selection bias, limited range of

An integrative review of evidence examining cultural competence educational interventions. O'Brien, E., et al. (2021)		competence educational interventions	interventions, Thematic analysis	624 research articles	and commitment to culturally competent care	interventions reviewed
7. Predictors of nursing student satisfaction as a key quality indicator of tertiary students' education experience: An integrative review. Cant, R., et al. (2023)	Integrative review method	Explore and report elements affecting nursing student satisfaction	Not stated, Statistical analysis of student satisfaction surveys	22 studies, primarily quasi-experimental	Five dimensions of student satisfaction: Faculty, learning environment, curriculum, social interaction, development	Small sample sizes, potential bias in measurement tools
8. Peer Teaching Strategy and Its Effect on Self-efficacy, Collaborative Behavior, and Performance of Nursing Students at Nursing College, King Khalid University. Alqarni, A. S., et al. (2023)	Quasi-experimental design	Assess effect of peer teaching on self-efficacy, collaboration, and performance	DV: Peer teaching strategy, IV: Self-efficacy, collaboration, performance, Various assessment tools	36 fourth-year nursing students	Peer teaching improved students' self-efficacy and collaboration	Small sample size, limited generalizability
9. Exploring the formal assessment discussions in clinical nursing education: an observational study. Aase, I., et al. (2022)	Exploratory qualitative study	Explore characteristics of formal assessment discussions in clinical education	DV: Formal assessment discussions, IV: Clinical education setting, Thematic analysis	12 nursing students, 12 RN mentors, five nurse educators	Themes: Variability in structuring, constrained feedback dialogue, and limited assessment criteria	Researchers' background may have influenced analysis
10. Clinical preceptorship in Ghana in the era of COVID-19 pandemic: an interventional study. Enyan, N., et al. (2022)	Mixed methods with non-randomized interventional study	Investigate nurse preceptors' perceptions of digital technology use in preceptorship	DV: Nurse preceptors' perceptions, IV: Factors influencing use of digital tools, Statistical analysis & thematic approach	45 nurse preceptors with min. 3 years of experience	Perceived usefulness of technology increased post-intervention; self-efficacy improved	Small sample size, limited to one region in Ghana

11. Intercultural readiness of nursing students: An integrative review. O'Brien, E., et al. (2021)	Integrative review	Review educational interventions for cultural competence in nursing	DV: Cultural competence, IV: Educational interventions, Thematic analysis	14 studies screened from 624 articles	Themes: Increasing cultural competence, confidence, and commitment	Selection bias, limited range of interventions reviewed
12. Predictors of nursing student satisfaction: An integrative review. Cant, R., et al. (2023)	Integrative review	Explore factors influencing nursing student satisfaction	Not stated, Statistical analysis of surveys	22 studies, primarily quasi-experimental	Factors: Service quality, faculty, learning environment, curriculum, social interaction	Small sample sizes, potential bias in measurement tools
13. Peer Teaching Strategy and Its Effect on Nursing Students. Alqarni, A. S., et al. (2023)	Quasi-experimental	Examine the impact of peer teaching on student learning outcomes	DV: Peer teaching, IV: Self-efficacy, collaboration, performance, Various assessment tools	36 fourth-year nursing students	Peer teaching improved students' self-efficacy and collaborative behavior	Small sample size, limited generalizability
14. Exploring formal assessment discussions in clinical nursing education. Aase, I., et al. (2022)	Exploratory qualitative study	Investigate formal assessment discussions in clinical education	DV: Assessment discussions, IV: Clinical education, Thematic analysis	12 nursing students, 12 RN mentors, five nurse educators	Themes: Variability in structuring, constrained dialogue, limited assessment criteria	Researchers' background may have influenced analysis
15. Clinical preceptorship in Ghana during COVID-19: An interventional study. Enyan, N., et al. (2022)	Mixed methods, non-randomized intervention	Assess nurse preceptors' perceptions of digital technology use	DV: Nurse preceptors' perceptions, IV: Digital technology, Statistical & thematic analysis	45 nurse preceptors with min. 3 years of experience	Preceptors' confidence in using digital tools improved significantly post-training	Small sample size, limited to one region in Ghana
16. Preceptors' and nursing students' experiences with peer learning. Jassim, T., et al. (2022)	Qualitative study	Explore experiences with peer learning in primary healthcare	DV: Experiences of preceptors and students, IV: Peer learning strategy, Content analysis	7 preceptors, 10 nursing students	Peer learning stimulated professional identity, but the learning environment had challenges.	Physical constraints in the learning environment affected peer learning.

17. A unique lens: What nurses assess about residents. Dunbar, K., et al. (2022)	Qualitative study	Identify behaviors that nurses are best positioned to assess in residents	DV: Understanding of resident behaviors, IV: Nurses' and residents' perspectives, Thematic analysis	5 focus groups with 20 residents & 17 nurses	Nurses assess interprofessional collaboration, communication, and patient advocacy.	Single hospital setting, limited generalizability
18. Islamic Jurisprudence on Harm in Medical Confidentiality. Muhsin S. M. (2023)	Not stated	Analyse conflicts in medical confidentiality from an Islamic perspective	DV: Confidentiality conflicts, IV: Islamic ethical principles, Not stated	Not stated	Islamic law supports confidentiality but allows breaches for significant harm prevention.	Not stated
19. Perception of Islamic Nursing Ethics among Nurses in Pahang, Malaysia. Ismail, M. F. M., et al. (2022)	Quantitative study	Examine nurses' perceptions of Islamic nursing ethics in Malaysia	DV: Perception of Islamic nursing ethics, IV: Demographics & competency, Questionnaire	118 registered nurses from two hospitals in Pahang	Nurses reported moderate knowledge of Islamic nursing ethics; ethical dilemmas occur frequently	Not stated
20. Effectiveness of Islamic Input in Medical Practice (IIMP). Musa, R., et al. (2022)	Prospective cohort study	Evaluate IIMP's effect on knowledge, attitude, and practice among medical students	DV: Effectiveness of IIMP, IV: Demographics, Paired t-test analysis	102 IIUM medical students	IIMP significantly improved knowledge, attitude, and practice in students	Small sample size, only 72% response rate
21. Integration of Islamic Values in Nursing Program. Nurumal, M.S., et al. (2019)	Expository analysis	Discuss the role of Islamic values in nursing education	DV: Impact of Islamic values, IV: Nursing program, Not stated	Not stated	Islamic values in nursing education improve professionalism and ethical conduct.	Not stated
22. Ethical Reasoning and Professional Values among Nursing Students. Hajilo, P., et al. (2021)	Cross-sectional study	Investigate ethical reasoning and professional values among nursing students	DV: Ethical reasoning & professional values, IV: Demographics, Questionnaire	125 final-year nursing students	No significant relationship between ethical reasoning and professional values	Not stated

23. Undergraduate nursing student satisfaction in Namibia. Tomas, N. & Muronga, H. (2022)	Cross-sectional survey	Assess student satisfaction with a nursing program in Namibia	DV: Student satisfaction, IV: Socio-demographics, support, services, Logistic regression	147 undergraduate nursing students	Most students were satisfied with faculty & curriculum, but dissatisfied with access to services.	Limited investigation of transport & accommodation services

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REVIEW ARTICLE

Pharmacokinetic Properties of Amikacin in Asian Neonates and Infants: A Narrative Review.

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Abstract

Amikacin (AMK) is among the narrow therapeutic index drugs that are still being used in neonates for early-onset and late-onset sepsis. The pharmacokinetic and pharmacodynamic properties of drugs in neonates vary across ages, especially in premature babies. Neonates exhibit differences in body composition and organ function, which can influence drug disposition and response. Although much literature has discussed the pharmacokinetics of AMK in neonates, this review aims to explore the pharmacokinetic properties of AMK in Asian neonates and infants. Seven articles were included in this review, with evaluation conducted on Malaysian, Japanese, Pakistani, Indian, Korean, and Thai neonates. Overall, 702 neonates were included in these studies, consisting of both preterm and term neonates, with one study focusing exclusively on low-birth-weight neonates. This review highlights that a high dose of AMK with once-daily dosing shows a better option for achieving therapeutic concentrations. Nevertheless, variability in pharmacokinetic profiles across neonatal age was observed. Factors affecting these pharmacokinetic changes need to be addressed during the initiation of AMK therapy in neonates to ensure optimal outcomes.

Keywords: *Amikacin, Asian, Neonates, Pharmacokinetic.*

Introduction

Aminoglycosides (AMGs), such as amikacin (AMK) and gentamicin (GEN), are among the narrow therapeutic index drugs that are still being used in neonates for early-onset and late-onset sepsis. They inhibit protein synthesis in susceptible bacteria by binding to 30S ribosomal subunit. AMGs have excellent coverage against most gram-negative organisms, including *Pseudomonas aeruginosa* and some *Mycobacterium* spp. They demonstrate concentration-dependent bacterial killing and have a post-antibiotic effect [1].

Blood concentration monitoring of AMK is routinely performed for dose optimization. The recommended blood sampling time is at a steady state dose (usually after 24 hours), requiring two samples for estimation of minimum concentration (Cmin) and maximum concentration (Cmax). Pre-dose sampling and post-distributional sampling are routinely done. Alternatively, two post-distributional samples, taken at least two half-lives apart can be used. Achievement of a therapeutic Cmax indicates the efficacy of AMK, while a supratherapeutic Cmin exposes patients to toxicity [2].

Nephrotoxicity and ototoxicity are the most mentioned adverse events related to AMG use. Nephrotoxicity is reversible with early detection and timely discontinuation of AMGs. Meanwhile, vestibular and auditory toxicity might occur at high doses due to the presence of oxidative free radicals, which damage the hair cells in the cochlea. This toxicity can become permanent with prolonged use of AMG. Routine hearing tests are currently performed in infants nowadays [1].

Pharmacokinetic and pharmacodynamic properties of drugs in neonates vary across ages, especially in premature babies. Neonates exhibit differences in body composition and organ function, which can influence drug disposition and response to drugs. Developmental and physiological changes continue to fluctuate throughout the first year of life [2]. Although much literature has discussed the pharmacokinetics of AMK in neonates, this review aims to explore the pharmacokinetic properties of AMK in Asian neonates and infants.

Materials and methods

Literature search

A literature search was performed using several research databases, including PubMed and Scopus, in August 2024. Relevant papers and reports within the subject area of pharmacokinetic properties of AMK were searched using a combination of the following sets of keywords: 1) Amikacin AND 2) neonate OR infant AND 3) pharmacokinetic OR 4) volume of distribution OR 5) clearance OR 6) ototoxicity OR 7) nephrotoxicity. No cut-off points of search years were applied. The selection criteria for articles were as follows; articles had to be written in English and focus on the AMK pharmacokinetics in Asian neonates and infants. Articles that were short reports, letters, written in languages other than English, or without full-text availability were excluded.

Results

Out of 124 retrieved literatures, only seven were eligible. 116 articles were excluded as the subjects were not from Asian population, and one article was published in Korean language. No duplication of articles was detected.

The retrieved literature evaluated neonates from Malaysia, Japan, Pakistan, India, Korea, and Thailand. Overall, 702 neonates were included in these studies, comprising both preterm and term neonates, with one study focusing exclusively on low-birth-weight neonates.

Amikacin dosing regimens:

A retrospective study conducted in a neonatal intensive care unit (NICU) of a Korean hospital compared standard reference-based dosing with a

revised pharmacokinetic dosing guide. The study showed that the achievement of the target Cmax (20-30 mg/L) was significantly higher in the revised pharmacokinetic dosing guide (*p*-value <0.001), while there is no significant difference in Cmin between the two groups (*p*-value = 0.086). The standard reference-based dosing ranges from 18 mg/kg every 48 hours (for neonates aged ≤7 days and gestational age (GA) of ≤27 weeks) to 15 mg/kg every 24 hours (for neonates aged ≤7 days and GA of ≥34 weeks). Doses were adjusted based on GA, postconceptional age (PCA), and postnatal age (PNA). In contrast, the revised dosing regimens were computed at 13 mg/kg for all PCA with a range of dosing intervals from every 48 hourly (neonates aged <7 days and GA of ≤29 weeks) to every 24 hours (neonates aged <7 days and GA of ≥37 weeks) [3].

Another study conducted in a tertiary hospital in the East Coast Region of Malaysia demonstrated a statistically significant association between AMK dose and the achievement of the target Cmax. Preterm neonates were prescribed with a mean ± SD AMK dose of 8.12 ± 2.24 mg/kg/day, while term neonates with 8.46 ±2.44 mg/kg/day. Neonates who started with a dose of less than 15 mg/kg/day were unable to achieve therapeutic Cmax of at least 20 mg/L. In contrast, those with adequate Cmax had a mean (± SD) AMK dose of 9.39 ± 3.01 mg/kg/day. The Cmin observed was <5 mg/L in most subjects (95.2%), regardless of the dosing regimen [4].

A study on AMK pharmacokinetics in premature neonates in a Thailand Hospital evaluating the Cmax and Cmin after initiating AMK dosing based on GA. Doses were divided into three groups: ≤30 weeks GA: 18 mg/kg every 48 hours; 31-33 weeks GA: 16 mg/kg every 48 hours; 34-36 weeks GA: 15 mg/kg every 24 hours. The reported mean (± SD) Cmin of total dose was 1.77 + 1.6 mg/L with no significant difference of Cmin among groups (p-value = 0.29). Most subjects achieved a concentration of <2 mg/L. The mean (± SD) for Cmax of all neonates was 25.29 + 6.46 mg/L, which is within therapeutic range, with no significant difference between groups as well (p-value = 0.343). A high peak concentration of >30 mg/L was most frequently reported in neonates <30 weeks GA (57.14%) [5]. The summary of the effects of dosing regimens on the attainment of Cmax and Cmin is presented in Table 1.

Pharmacokinetic (PK) Properties:

Yusof, NN et.al. (2024) analyzed the PK properties of 129 preterm and 100 term neonates. The elimination rate constant (Ke) for preterm and term neonates was similar with values of 0.11 ± 0.04 /hour and 0.12 ± 0.03 /hour, respectively. Preterm neonates tend to have a larger volume of distribution (Vd) and longer half-life (t½) (mean ± SD: 0.80 ± 0.52 L/kg and 8.18 ± 5.02 hours) compared to term neonates (mean (±SD): 0.76 ± 0.52 L/kg and 6.47 ± 3.9 hour) [4].

AMK clearance was significantly affected by PCA and PNA, showing an increasing trend as subjects aged. AMK clearance in neonates with PCA ≥ 37 weeks and PNA ≥ 8 days was fourfold higher than in neonates PCA ≤ 29 weeks and PNA ≤ 7 days. In contrast, Vd values did not show any significant differences among the subgroups [3].

The reported means (± SD) of Ke showed an increasing trend with GA; with 0.067 ± 0.023 /hour (≤30 weeks GA), 0.082 ± 0.030 /hour (31-33 weeks GA), and 0.094 ± 0.035 /hour (34-36 weeks GA). The corresponding clearance per body weight were 0.044 ± 0.018 L/kg/hour, 0.053 ± 0.016 L/kg/hour, and 0.058 + 0.022 L/kg/hour, respectively. The mean (± SD) of t½ was 8.90 ± 5.41 hours, shorter across GA, with Vd of 0.659 ± 0.231 L/kg. No significant variation was seen across groups [5]. The findings of the overall pharmacokinetic profile are summarized in Table 2.

Nephrotoxicity and Ototoxicity of Amikacin:

Endo, A et.al. (2022) defined acute kidney injury (AKI) as a ⩾ 1.5-fold or ⩾ 26.5 umol/L increase in serum creatinine, or urine output <0.5 mL/kg/hour for 6 hours. In a retrospective chart

review, AMK was dosed according to body weight: <1 kg: 20 mg/kg every 48 hours (EOD) and ≥ 1 kg: 15 mg/kg once daily (OD). Nephrotoxicity was observed in 21% of subjects receiving 15 mg/kg OD and 58% of subjects with a dose of 20 mg/kg EOD. The reported Cmax of subjects with and without nephrotoxicity was 33.5 mg/L and 29.9 mg/L, respectively, with the Cmin of 4.2 mg/L and 2.4 mg/L, respectively. This study also reported that an increment of serum creatinine was seen in EOD group on the day of AMK concentration measurement, regardless of concurrent indomethacin therapy initiation [6].

Ototoxicity was observed in 16 % subjects in the EOD dosing group while 5% in the OD group. No significant difference was seen between the groups regarding Cmax and Cmin (p = 0.815 and 0.592, respectively). The reported median (IQR) Cmax was 31.0 (27.3-34.6) mg/L for EOD group while 31.5 (27.5-36.6) mg/L for OD group, with Cmin of 1.8 (1.2-6.3) mg/L and 3.1 (2.1-4.3) mg/L, respectively. However, the total AMK dose administered was higher in EOD group compared to OD group (82.7 mg/kg and 73.5 mg/kg). Endo, A et.al. (2019) previously reported that a higher Cmin was associated with a higher risk of ototoxicity, with a cut-off value of 10 mg/L (p = <0.05) [6-7].

One study found no significant difference in serum creatinine and creatinine clearance among premature neonates across postnatal ages on Day 1 of AMK administration (p value= 0.718 and 0.161, respectively). However, a significant difference was observed in serum creatinine and creatinine clearance measured within 2 days after discontinuation of AMK (p-value= 0.017 and 0.016, respectively). A better renal profile was observed in neonates with GA 34 -36 weeks [5].

Factors that might affect the variability of Amikacin PK properties:

Endo, A et.al. (2019) examined the characteristics of neonates with a Cmin of ≥10 mg/L. Neonates with supratherapeutic Cmin neonates had a low body weight (LBW) with a mean of 0.742 kg, while those with therapeutic Cmin had a mean body weight of 1.415 kg. The overall test result was statistically significant (p = <0.05). The researchers further analyzed the volume of distribution (Vd), calculated using measured post-dose concentration and dosage, and found a significant difference between the two groups (≥10 mg/L group:0.37 L/kg, < 10 mg/L group: 0.55 L/kg, p-value = <0.05) [7]. A population pharmacokinetic modeling conducted by Saikumar Matcha et.al. (2023) also identified creatinine clearance and body weight as significant covariates influencing the pharmacokinetic properties of AMK in neonates [8].

Prematurity has been identified as a contributing factor to variability in Vd and t½, as reported in Malaysian neonates. Prolonged t½ and larger Vd were observed in neonates with GA of < 37 weeks. The study also reported that preterm neonates had a mean ± SD body weight at 1.62 ± 0.50 kg, while term neonates' mean body weight was 3.06 ± 0.57 kg [4]. A comparative study conducted at a Military Hospital in Pakistan evaluated the risk of toxicity in premature infants. Subjects were administered AMK at a dose of 15 mg/kg OD and trough concentrations were taken after 72 hours of therapy. Serum creatinine was measured at two points: on admission and on the third day. Preterm neonates with GA of 29 - 36 weeks had significantly higher median (± IQR) of Cmin at 11.33 (1.5-42.6) mg/L compared to term neonates (8.5 (2.8-33.0) mg/L, p-value = >0.01). This finding was consistent with a higher frequency of toxic concentration observed in preterm neonates. Additionally, a positive correlation was found between AMK Cmin and serum creatinine at day 3 (r = 0.48; p = <0.05). Serum creatinine at Day 3 of AMK therapy in term neonates was significantly lower compared to preterm neonates with mean ± SD of 61.4 ± 22.8 µmol/L versus 76.0 ± 28.9 µmol/L (p = 0.002) [9].

Ke was significantly seen in an increasing trend following increasing GA (p-value = 0.003) with mean ± SD of 0.0094 ± 0.035 /hour. Following this trend, the t½ was shown to be shorter in older GA neonates, with no statistical significance (p = 0.057). The Vd appeared similar across groups (mean ± SD: 0.659 ± 0.231), while the clearance per body weight was significantly differ across groups (mean ± SD: 0.058 ± 0.022; p = 0.02). There was a significant correlation between GA and Ke, clearance, and t½ (r = 0.529, 0.44 and 0.367, respectively, p <0.05). Correlation of Ke and clearance was proportionate to GA while t½ was inversely proportional to GA. Significant correlation between Ke and PNA also has been reported (r = 0.529, p <0.05) [5].

Discussion

AMK has been widely used in neonates as standard therapy for nosocomial infections. Dosing of 15 mg/kg once daily showed achievement of therapeutic Cmax and Cmin. This finding is consistent with research conducted by Abdel-Hady et.al. (2011) and Langhendries, J. P. et al (1993). These studies employed a similar study design, randomizing neonates into two groups: Group 1 received 15 mg/kg once daily dosing, while Group 2 received AMK dose at 7.5 mg/kg twice daily. Cmax achievement was higher in Group 1 compared to Group 2, with mean (± SD) of 27.7 (± 6.6) mg/L and 23.06 (± 3.30) respectively. Additionally, Group 1 showed lower Cmin than Group 2 (4.6 ± 2.5 and 2.75 ± 1.19 mg/L, respectively). Although the reported Cmin was significantly lower in the OD group, yet, all subjects in both studies were reported with Cmin of <10 mg/L. The researchers concluded that once daily dosing revealed an acceptable high peak concentration with no toxic trough concentrations [10,14].

Hughes, KM et.al. (2017) reported that the desired Cmax of 20 - 35 mg/L was achieved in neonates with AMK dose of 12 mg/kg. Higher AMK doses were reported with supratherapeutic concentrations of more than 35 mg/L, although there was no significant difference in achieving the Cmin target between the two groups [11]. This finding was consistent with the study conducted by the Korean researchers [3]. Both studies had similar baseline demographics. However, the Korean study had an uneven distribution of subjects between groups and used different subgroup divisions.

The elimination half-life and clearance of AMK were shown to be affected by GA, PCA and PNA, with an increasing trend as neonates approached term. Conversely, the half-life decreased across age groups. Preterm infants exhibited a longer elimination half-life compared to term babies. Prematurity and ill infants tend to have lower glomerular filtration rates, leading to slower clearance of drugs, including aminoglycosides. These variations in pharmacokinetic profiles across neonates were all consistent with other published studies, however, with slight differences in the reported values possibly due to dissimilar study designs, sample sizes, and regional variations [11-14].

Serum creatinine levels and urinary excretion of marker enzymes for proximal tubular kidney damage were shown to increase in neonates on AMK therapy, regardless of the dosing regimen. Similar findings have been reported in several studies, with complete recovery of renal function over time [10,14,16]. It should be noted that these studies were designed to observe nephrotoxicity in neonates with GA of ≥ 34 weeks. Additionally, all studies had small sample sizes, and larger sample sizes may be required to yield more robust outcomes.

Treatment with AMK, compared to no treatment, was shown to have an increased risk of developing hearing loss in neonates [15]. However, several studies found no evidence of ototoxicity in neonates receiving AMK therapy, suggesting that it appears to be safe even in very low birth weight neonates in the absence of other

risk factors, such as a family history of hearing loss [16-17]. Nevertheless, although most studies excluded factors that could contribute to hearing loss, the sample sizes limited the generalizability of these findings.

Conclusion

High dose with once daily dosing shows a better option for achieving therapeutic concentrations. However, variability in pharmacokinetic profiles across neonatal age groups has been observed. Factors affecting these pharmacokinetic changes need to be addressed during the initiation of AMK in neonates, to ensure optimal outcomes. Future research involving multicenter studies with larger sample sizes and diverse demographic baselines is necessary to optimize AMK treatment in neonates.

Conflict of interest

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Authors' Contributions

SNN and SM performed the literature search and manuscript preparation. All authors agreed and approved the manuscript for publication.

Table 1. Dosing regimen effects on the attainment of Cmax and Cmin

First Author (Year)	Dosage Design	Outcome on attainment of Cmax and Cmin				p-value
An SH (2014)	Standard reference-based dosing (Group 1) versus Revised-pharmacokinetic dosing guide (Group 2) (n = 107 versus 74)	Cmax (Definition: 20 – 30 mg/L)	Significant higher Cmax attainment in Group 2 (81.3% versus 50.7%)			<0.001
		Cmin (Definition: < 5 mg/L)	No significant difference between Group 1 and Group 2 (85.1% versus 87.5%)			0.621
Yusof NN (2024)	AMK dose adequacy of the current dosing regimen		Dose (mg/kg/day)			
			< 7.5	7.5 - 15	> 15	0.022
		Cmax ≥ 20 mg/L, n (%)	14 (6.1)	28 (12.2)	2 (0.8)	
		Cmax <20 mg/L, n (%)	99 (43.2)	82 (35.9)	4 (1.7)	
			Gestational Age (weeks)			
			< 37		≥ 37	
		Cmin ≥ 5 mg/L, n (%)	7 (5.4)		4 (4.0)	NA
		Cmin < 5 mg/L, n (%)	122 (94.6)		96 (96.0)	
Pomanong Aramwit (2008)	Pharmacokinetic properties of AMK in Thai premature neonates	Gestational Age (weeks)	≤ 30 (n = 7)	31 – 33 (n = 16)	34 – 36 (n = 14)	
		Dosing regime	18 mg/kg q48h	16 mg/kg q36h	15 mg/kg q24h	
		Cmax, mg/L (%) < 20	14.29	31.25	21.62	0.343
		20 – 30	28.57	71.43	54.05	
		> 30	57.14	14.28	24.33	
		Cmin, mg/L (%) < 2	57.14	93.75	42.86	0.290
		2 – 5	42.86	0	57.14	
		> 5	0	6.25	0	

NA: not available; q48h: every 48 hours; q36h: every 36 hours; q24h: every 24 hours

Table 2. Summary of PK Properties for Asian neonates

First Author (Year)	Locality	Study Population	PCA (weeks)	PNA (days)	n	Mean (± SD)		
						Vd (L/kg)	t½ (hour)	Ke (/hour)
AnSH (2014)	Korean	Preterm & Term neonates	≤ 29	0-7	8	0.60 ± 0.16	17.6 ± 4.8	0.044 ± 0.197
				>7	11	0.54 ± 0.07	9.8 ± 2.1	0.073 ± 0.017
			30-33	0-7	2	0.61 ± 0.14	12.3 ± 0.5	0.056 ± 0.002
				>7	15	0.61 ± 0.12	7.3 ± 3.2	0.112 ± 0.046
			34-36	0-7	6	0.47 ± 0.14	6.3 ± 1.4	0.114 ± 0.025
				>7	25	0.54 ± 0.14	5.2 ± 1.6	0.143 ± 0.037
			≥37	0-7	12	0.57 ± 0.16	7.4 ± 3.1	0.105 ± 0.035
				>7	55	0.55 ± 0.13	4.4 ± 2.4	0.179 ± 0.060
Yusof NN (2024)	Malaysian	Preterm & Term neonates	< 37	ND	129	0.80 ± 0.52	8.18 ± 5.02	0.11 ± 0.04
			≥ 37	ND	100	0.76 ± 0.52	6.47 ± 3.90	0.12 ± 0.03
Pomanong Aramwit (2008)	Thailand	Premature neonates	≤ 30	3.9 ± 2.62	7	0.684 ± 0.277	11.41 ± 3.95	0.067 ± 0.023
			31-33	4.96 ± 5.96	16	0.703 ± 0.247	10.65 ± 8.10	0.082 ± 0.030
			34-36	6.77 ± 5.14	14	0.616 ± 0.205	6.39 ± 1.51	0.115 ± 0.032

PCA = postconceptional age, PNA = postnatal age, t½ = half-life, Ke = elimination rate constant, V = volume of distribution, ND = No data

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REVIEW ARTICLE

Therapeutic Potential of Cajeput Oil in Muscle Health: a Mini-review through a Bibliometric Approach.

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Abstract
Cajeput oil has been used in traditional medicine for its anti-inflammatory, analgesic, and antimicrobial properties. Recently, there has been increased interest in investigating its potential benefits for muscle health, including its ability to alleviate muscle pain, promote recovery, and enhance overall muscular function. This review provides a comprehensive analysis of the existing literature on cajeput oil and its applications in muscle health. Through a bibliometric analysis of research trends, citation networks, and key themes within this field, the review identifies the primary bioactive compounds in cajeput oil, such as 1,8-cineole, α-terpineol, α-pinene, and their roles in improving muscle health. The review emphasises the growing body of evidence that supports the effectiveness of cajeput oil in reducing muscle inflammation and soreness, while also discussing the limitations and gaps in current research. Additionally, the analysis highlights the need for more robust clinical trials and interdisciplinary studies to fully understand the therapeutic potential of cajeput oil in muscle health. These findings provide a foundation for future research and underline the importance of integrating traditional knowledge with modern scientific approaches to promote muscle health and overall well-being.

Keywords: *Bibliometric analysis, Essential oil, Melaleuca cajuputi,, Muscle health.*

Introduction

The muscle is an essential body component that is responsible for movement by contracting and relaxing the muscle fibres [1]. Although muscle is important for movement, overuse can cause soreness or strain. Muscle soreness or myalgia is a condition where there is discomfort or pain in the muscle [2]. This condition can arise from various causes, such as overexertion, infection, and injury. Common treatments for muscle soreness include ice therapy, heat therapy, massage, nonsteroidal anti-inflammatory drugs, rest and recovery [3,4]. Apart from these treatments, some resorted to herbal ailments as topical treatments due to their therapeutic properties, including cajeput oil.

Cajeput oil, also spelt as cajuput oil, is a volatile oil extracted through steam distillation from the leaves and twigs of the cajeput tree, specifically *Melaleuca leucadendron* and *Melaleuca cajuputi* [5,6]. They are originally from Southeast Asia, Australia, and several tropical countries. The interest in these plants has been focused mainly on their essential oil, which is extracted from their leaves and branches. Cajeput oil has been traditionally used for several conditions, such as pain in muscles and joints. Hence, it has become very useful as a natural remedy [7]. Its analgesic properties can alleviate pain from strains and injuries of muscles. Furthermore, the anti-inflammatory nature of the oil decreases swelling and hastens the process of wound healing [8,9]. Cajeput oil is rich in bioactive compounds and is renowned for its diverse therapeutic properties, particularly its antiseptic, analgesic, and anti-inflammatory effects [10]. One of the most notable benefits of cajeput oil is its strong antioxidant activity. Research indicates that extracts from cajeput oil can effectively scavenge free radicals, thereby protecting cells from oxidative stress and potential damage. This antioxidant capacity is largely due to the plant's high levels of phenolic compounds, which are crucial in combating oxidative damage linked to various chronic diseases.

Traditionally, cajeput oil has been used in various medicinal applications. It is commonly employed to alleviate respiratory issues, such as coughs and congestion, making it a popular choice in herbal remedies for colds and flu. In addition to that, cajeput is recognised for its antibacterial and anti-inflammatory effects [11–13]. Studies have demonstrated its efficacy against several strains of bacteria, including *Staphylococcus aureus* and *Bacillus cereus*, commonly used as topical ointment [14,15]. Recent studies have highlighted the potential of cajeput oil in modern applications, suggesting that it could serve as an effective alternative in managing muscle-related conditions [15,16]. However, while its benefits are promising, further research is necessary to fully understand the pharmacological mechanisms and safety profiles associated with its use in muscle therapy. This review discusses the potential use of cajeput oil as a natural muscle relaxant and remedy for muscle soreness. Based on a bibliometric methodology, the following review also examines cajeput oil's phytonutrients, physiological characteristics, and potential health advantages in muscle therapy.

Bibliometric analysis of cajeput oil over the past 20 years (2003-2023)

A bibliometric analysis was conducted using the Web of Science© (WOS) (www.webofknowledge.com) database to examine the global literature on cajeput oil. The term '*melaleuca cajuputi*', 'gelam', 'tea tree', 'cajuput tree', '*M. leucadendron*' and 'Cajeput oil' were used in the "topic item," including the title, abstract, keywords, and keywords plus of articles indexed in the Web of Science Core Collection (Figure 1). The search was performed to include only the last twenty years (2003–2023), English language, and scientific articles. A total of 2099 publications were retrieved and extracted for publication numbers, top authors, affiliations, countries, and 50 most frequently used keywords.

Publication numbers and categories analysis

The examination of publications constitutes a performance analysis, offering distinct perspectives and intriguing data regarding the output. This analysis aids readers in comprehending the study field and its evolution over the years [17]. As shown in Figure 2, the number of publications involving cajeput oil has shown an increasing trend over the years, with notable peaks in 2008, 2012, and 2022. However, it has experienced some oscillations throughout the years, especially in 2005 to 2007, 2008 to 2010, and 2012 to 2014. These oscillations can be associated with the findings regarding the use of cajeput essential oil in the phytochemicals study. The year 2022 showed the highest number of publications recorded, with the findings regarding cajeput oil, either extracted or essential oil, used as an antimicrobial agent for many health applications [12,18], nanoparticles [19,20], and incorporation with other food products [21–23].

According to the WOS, the publication was allocated to 137 categories. For this review, only the five most relevant categories were presented, as illustrated in Figure 2, due to their high number of publications. It was noted that cajeput oil is quite versatile, given the large number of research areas it encompasses. The Food Science Technology category is highlighted among the others, presenting 266 publications throughout the 20 years, with an average of 10.07 publications yearly, associated with several applications of cajeput oil (essential oil) in foods. The Pharmacology Pharmacy category presented 242 publications with an average of 9.5 articles per year, researching cajeput oil predominantly for its health benefits toward both human and animal applications. The other three categories are related to biotechnology, microbiology, and plant sciences. The interest of these fields in cajeput oil is strongly associated with production, as the microbial route is preferable and more advantageous.

Analysis of highest-ranking authors, affiliations, countries, and keywords

Table 1 shows the most productive research, organisations, and countries responsible for the high number of publications concerning cajeput oil throughout the 20 years. This information forms what is known as bibliometric or science mappings. According to a study, these analyses involve thorough research into the characteristics of published literature, exploring the connections between research elements (such as authors, organisations, and countries) and their significance to science [24]. Additionally, they uncover emerging trends, highlight the academic impact of major works, and track the advancement of specific topics.

Thomas V Riley (Riley TV), Christine F Carson (Carson CF), and Catherine A. Hammer (Hammer CA) are the first (43 publications), second (38 publications) and third (30 publications) most productive authors, respectively focusing more the antimicrobial and antifungal effect of *Melaleuca* oil against multiple types of bacteria including *Staphylococcus aureus*, *Candida* sp., *Saccharomyces cerevisiae*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Malassezia species* and some *in vitro* work using cell culture analysis. Juergen Reichilng (Reichilng J), Matheus Dellaméa Baldissera (Baldissera MD) and Xingfeng Shao (Shao XF), with 23, 21 and 21 publications, respectively, research more on the antiviral properties of cajeput oil and its applications towards infected plants and farm animals.

According to Table 1, the most productive organisation in producing scientific articles related to cajeput oil is the University of Western Australia, which is the affiliation of the first, second and third most productive authors. Apart from that, several other universities and organisations from Australia were included in the list, including Southern Cross University, University of Queensland, and Queen Elizabeth II

Medical Centre. This also reflects Australia (323 publications) being the second most productive country in the field of cajeput oil, after China, with 397 publications. Apart from that, the United States of America, Brazil, Italy, and Malaysia are the top third, fourth, fifth and sixth most productive countries in producing research articles relating to cajeput oil.

To better understand the current research interests, a keyword analysis was conducted to identify trends associated with cajeput oil. The WOS database features two types of keywords: author keywords (AKs) and keywords plus (KP), both of which are significant in bibliometric studies [24,25]. In this analysis, we focus exclusively on the most frequently cited AKs to highlight the key trends emphasised by researchers. Analysis of the most cited keywords can uncover research's hot topics and trends by examining the frequency of specific terms [26]. This analysis can also provide insights into a subject's focus areas within a certain region or time period.

From 2003 to 2023, 9,794 different keywords were found in the 2,321 analysis publications. This review highlights the 50 most frequent keywords (Figure 3). The size of the nodes in Figure 3 represents the number of times the keywords are used. In contrast, the thickness of the lines connecting the nodes represents connections between the keywords. The terms 'tea tree oil', 'antimicrobial activity', 'antibacterial activity', and '*in vitro*' were identified as the most frequently cited author keywords, each appearing more than 40 times. This suggests that most articles concentrate on applying cajeput oil's antimicrobial and antibacterial properties to multiple research fields. Moreover, Figure 3 also showed the trends of recent popular keywords (in yellow), such as antioxidant, antibacterial, nanoparticles, electrospinning, nanoemulsion, and biofilm, highlighting the potential direction of cajeput oil research towards nanotechnology and antibacterial. In conclusion, the clusters identified, along with the bibliometric analysis described earlier, provide a foundation for identifying and prioritising key topics related to the therapeutic effects of cajeput oil on muscle health, which are further explored in this study.

Physicochemical and pharmacological analysis of cajeput oil relating towards muscle health

According to the literature from bibliometric analysis, most of the bioactivity studies of cajeput used different parts of the plant. A review from 2023 stated that the majority of the cajeput study used essential oils (80%), followed by leaves (40%), flowers (10%) and then stem (10%) [6,27]. Cajeput is renowned for its essential oil, which is rich in phytochemicals in the class of monoterpenes, sesquiterpenes, flavonoids, and phenolic compounds [5,27]. These bioactive components contribute to the oil's significant antioxidant, antibacterial, and anti-inflammatory properties, making it a valuable remedy in traditional medicine. The physicochemical content of cajeput oil varies depending on multiple factors, such as part of the plant, geographical location, and seasons [14,27]. Table 2 shows some of the commonly studied components of *Melaleuca cajaputi*.
Overall, there were slight variations in the proportions of the components but no significant differences in the major components, particularly 1,8-cineole. This monoterpenoid compound is also known as eucalyptol and is characterised by its colourless camphor-like odour [28]. This compound is crucial for assessing the quality of essential oil from cajeput oil leaves. Numerous studies have shown that 1,8-cineole is typically present in high cajeput oil leaf essential oil yields, ranging from 44.8 to 60.2% [5,27]. According to the study, many of these cajeput oil's constituents can be used to maintain muscle health. 1,8-cineole, apart from being the major compound in cajeput oil essential oil and primarily determining its biological activity, has anti-inflammatory and

analgesic (pain-relieving) properties that can help soothe muscle pain and inflammation [6].

A study by Nozohour et al. (2022) researched the use of 1,8-cineole on the effect of contraction and relaxation of the bovine ileum's smooth muscle [29]. The results from the findings show that the active compound significantly inhibits spontaneous muscle contractions and contractions induced by spasmogens such as carbachol, barium chloride, and potassium chloride bovine ileum, indicating muscle relaxation. The antispasmodic action of 1,8-cineole is mainly mediated through the blockade of calcium channels in smooth muscle. Inhibiting these channels, 1,8-cineole reduces calcium influx, which is necessary for muscle contraction. Calcium channels play an important role in muscle function: These channels promote excitation-contraction coupling in skeletal muscles, regulate cardiac contraction in cardiac muscles, and contribute to smooth muscle contraction. Modulations on these channels can reduce both spontaneous and stimulated contraction, thereby decreasing pain and promoting relaxation.

Another study on the effect of 1,8-cineole on tracheal smooth muscle indicated that it blocks the L-type voltage-gated calcium channels (VGCC) activity [30]. This blockade reduces calcium influx, which is necessary for muscle contraction. It also indicates that 1,8-Cineole has a dual-effect on muscle contraction. At lower concentrations, it induces muscle contraction, while at higher concentrations, it relaxes muscle contraction. Given its spasmolytic and myorelaxant properties, 1,8-cineole may have the potential for therapeutic use in respiratory conditions characterised by smooth muscle contraction, such as asthma or bronchospasm [30].

In an *in-vivo* study, 1,8-cineole showed a significant anti-inflammatory and analgesic effect in Albino Wistar rats [28]. In combination with flurbiprofen, it enhanced anti-inflammation and analgesia regarding the efficacy for inflammation and pain, so it played a very critical role in the management of muscle soreness. This mechanism involved the downregulation of pro-inflammatory cytokines, TNF-α and IL-4, which were the cytokines involved in muscle inflammation and perception of pain.

β-pinene is a bicyclic monoterpene that has a colourless, woody, pine-like aroma liquid. This compound is known to exhibit anti-inflammatory properties that can help to reduce swelling and pain in muscles [31]. It also has shown an analgesic effect in some studies, thus able to modulate pain perception, which somehow can help alleviate muscle spasms and cramps [31,32].

Another component that can help alleviate muscle pain is limonene. Limonene is an aliphatic hydrocarbon classified as a cyclic monoterpene. In a study using chronic musculoskeletal pain, mice models showed that D-limonene was able to reduce pain [33]. The study found that the compound possesses an antihyperalgesic effect, which reduces muscle pain through the reducing Fos protein (pain receptor). These actions can only be made possible by the anti-inflammatory, analgesic, and muscle relaxation action of limonene [33].

β-Caryophyllene, or (−)-β-caryophyllene, is a bicyclic natural sesquiterpene found in many essential oils, including cajeput oil. It possesses anti-inflammatory properties, which can be beneficial in alleviating muscle pain. In a study using liposomal β-caryophyllene, researchers assessed its effectiveness in reducing delayed onset muscle soreness in humans [34]. This randomised placebo-controlled study showed improvement in the treatment group compared to the placebo group. The improvements were seen in terms of muscle recovery, pain reduction, lower muscle fatigue, and better aerobic function, indicating the potential for liposomal β-caryophyllene to reduce muscle pain.

Another randomised placebo-controlled study used liposomal β-caryophyllene to evaluate its effect on delayed onset muscle soreness (DOMS) in healthy human subjects [35]. The treatment group that received liposomal β-caryophyllene showed a significant reduction in DOMS as compared to the placebo group. It was

demonstrated that the treatment improved aerobic function, reduced muscle fatigue, enhanced endurance, and improved muscle energy supply [35]. Additionally, the study indicated that liposomal β-caryophyllene reduced inflammation and enhanced neuromuscular activation, leading to improved muscle health. Other compounds, such as α-terpineol, have been shown to have anti-inflammatory and antioxidant effects, which can aid in muscle recovery and reduce soreness [5,27]. Besides, linalool, from the monoterpene alcohol, has been found to have muscle relaxant and analgesic effects, which can help alleviate muscle tension and pain [6].

Limitations and future planning

Cajeput oil is known for its ability to alleviate muscular aches and spasms, particularly in Southeast Asian countries like Malaysia, Indonesia, and Thailand. However, there are some important precautions to consider. This oil can irritate the skin or cause allergic reactions in some individuals, especially if it is not properly diluted with a carrier oil. Additionally, there is a concern that cajeput oil may interact with certain medications, such as those for diabetes. Therefore, anyone taking prescription or over-the-counter medications should consult a doctor before using them.

Despite its widespread availability and frequent claims of relieving muscle pain, cajeput oil has limited scientific literature to support these assertions. In contrast to other essential oils like eucalyptus, lemon, and peppermint, which have substantial research backing their benefits, cajeput oil presents an opportunity for further scientific exploration. While it is commonly used to relieve muscle pain in Southeast Asian countries and has shown potential benefits, more evidence is needed to validate these claims. Traditional uses of cajuput oil include applications as a muscle relaxant and for alleviating muscle pain; there is a lack of rigorous clinical studies specifically for these purposes, particularly in controlled environments. Most studies focus on its antioxidant and antibacterial properties rather than direct effects on muscle health or recovery [14]. Additionally, the variability in the chemical composition of cajuput oil based on extraction methods and geographical sources complicates the establishment of standardised dosages and formulations for therapeutic use [13]. Overall, these limitations highlight the need for targeted research to fully understand the potential benefits of *Melaleuca cajuputi* for muscle health.

Furthermore, this opens up opportunities for additional *in-vivo* and *in-vitro* studies to scientifically validate the effectiveness of cajeput oil in alleviating muscle pain. These studies could involve conducting large-scale randomised controlled trials to determine the safety, efficacy, and optimal dosage of cajeput oil for various muscle pain conditions. Investigating the underlying mechanisms responsible for the analgesic and anti-inflammatory properties of cajeput oil could also prove to be valuable. This research could lead to more scientific exploration, not only in this field but also in others. Overall, cajeput oil has untapped potential that warrants further investigation to enhance human health.

Conclusion

In summary, this mini-review explores the potential therapeutic benefits of cajeput oil for enhancing muscle health. Additionally, this mini-review utilises bibliometric analysis to observe the existing trends in cajeput oil literature. There is a growing body of literature on cajeput oil research each year. However, the bibliometric analysis also indicates a deficiency in literature focusing on the effects of cajeput oil on muscle health, highlighting the need for further scientific studies to expand our understanding beyond anecdotal evidence. Cajeput oil may enhance muscle health due to its phytochemicals, such as 1,8-cineole, limonene, and β-caryophyllene, which have anti-inflammatory and analgesic properties that can reduce muscle soreness. Despite claims in the market regarding the oil's

efficacy in relieving muscle pain, scientific evidence is still limited despite widespread consumer use, underscoring the necessity for additional scientific research in the future. Nevertheless, cajeput oil has huge potential to become one of the important ingredients that can be used to alleviate muscle soreness in the future, with enough scientific evidence.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Conflict of interest:

The authors have no conflict of interest to declare.

Authors' contribution:

M.F.Z: Formal analysis, Writing - Review & Editing M.A.A.M.: Software, Formal analysis, Methodology, Writing - Original Draft; M.N.M.B.: Review & Project planning; N.H.C.B.: Review & Project planning; P. M. R.: Writing - Review & Editing, Project administration.

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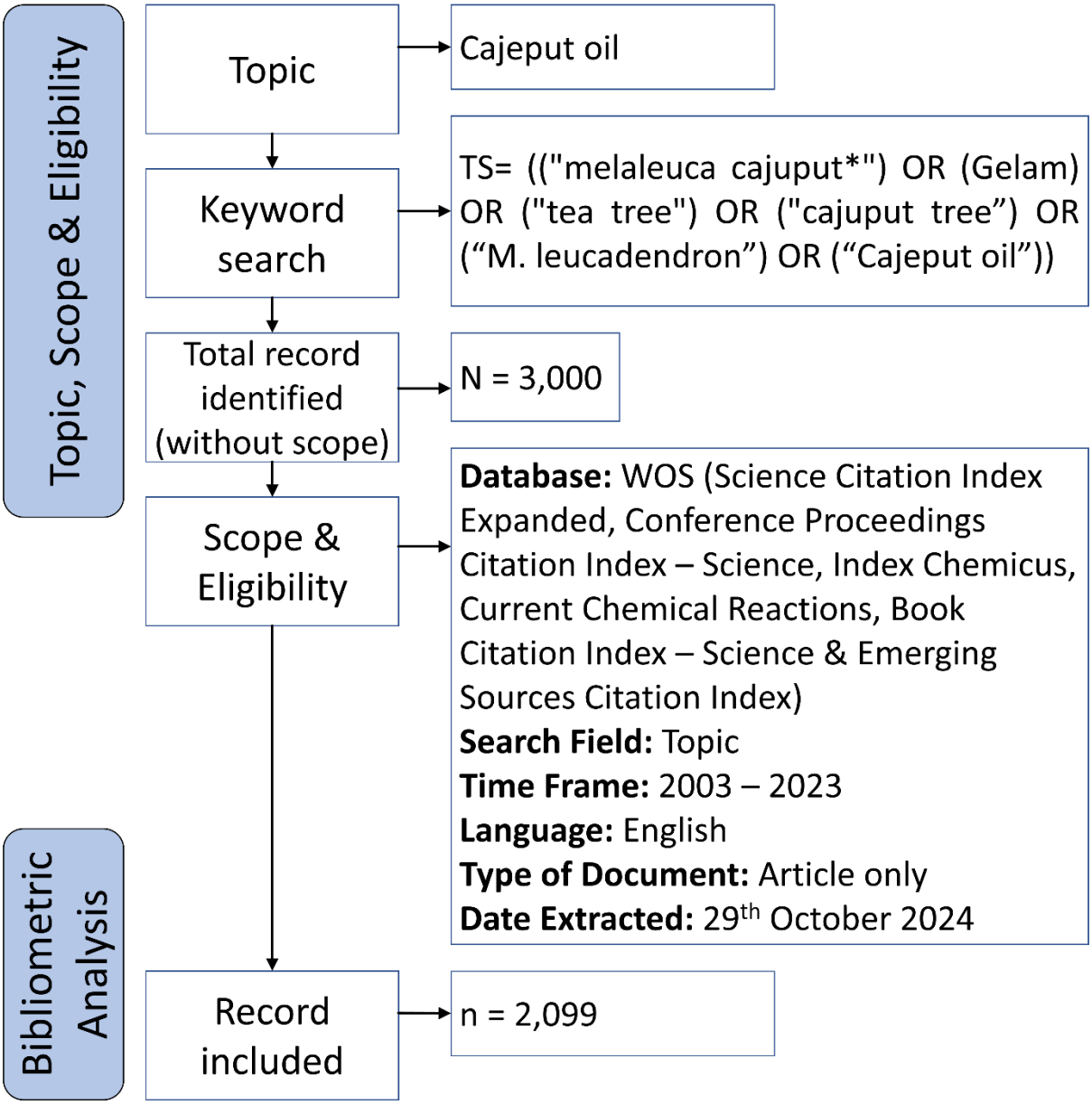

Figure 1. Flowchart for research structure on cajeput oil literature in the world focused on the WOS database.

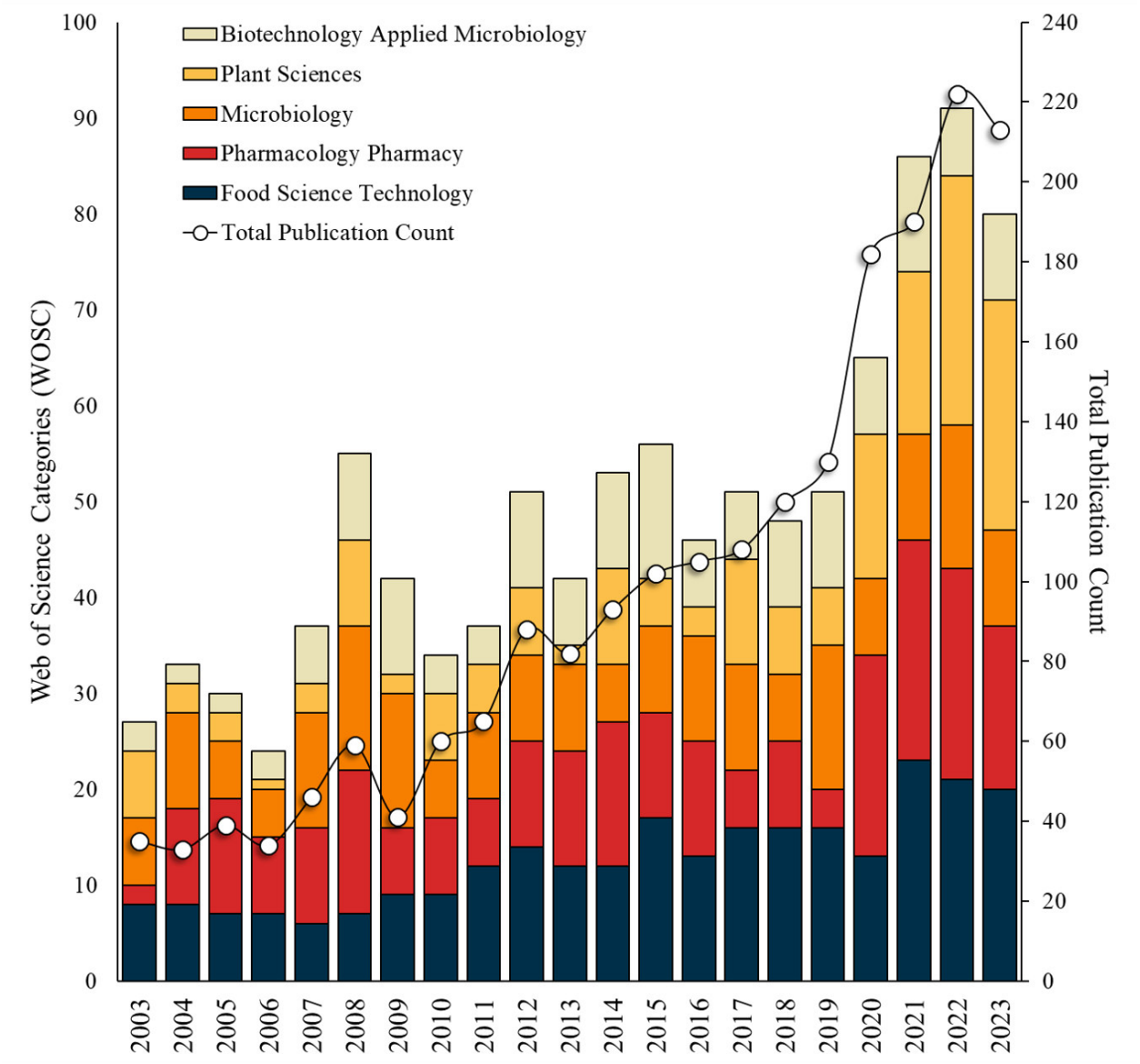

Figure 2. Number of publications and WOS categories

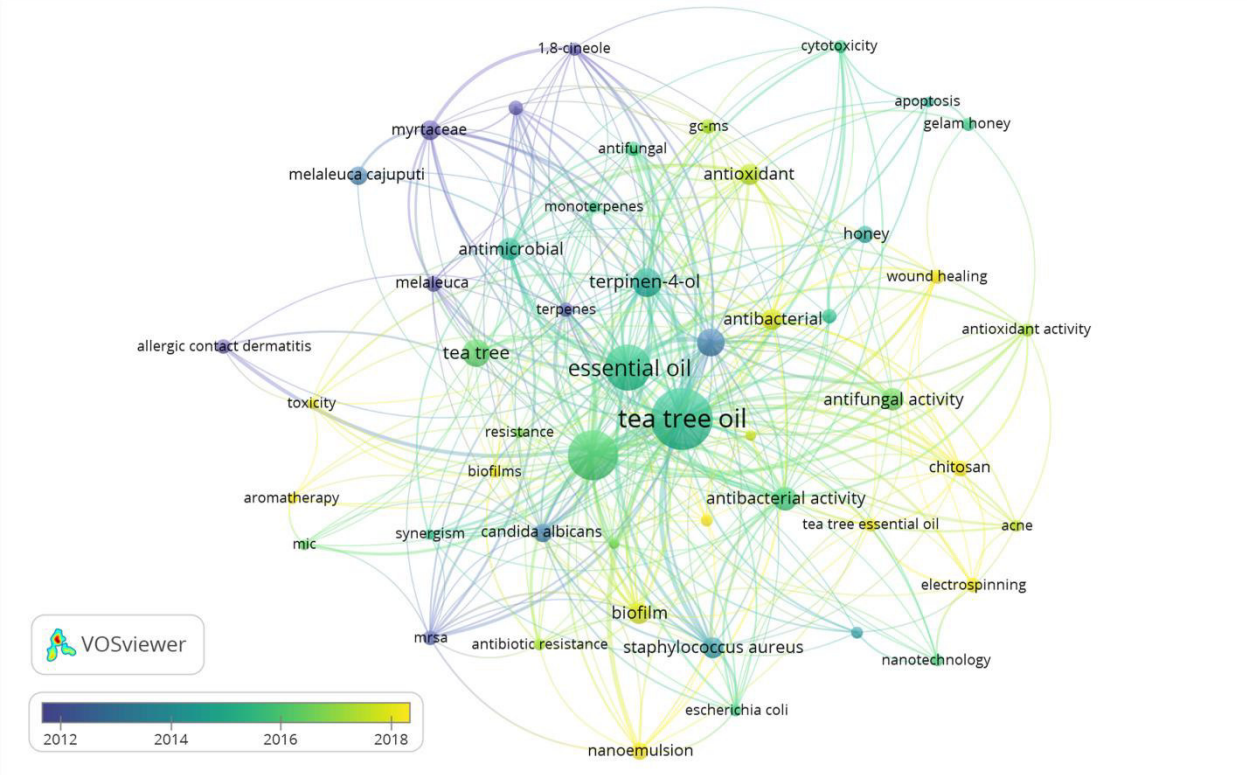

Figure 3. Network visualisation of top 50 most used keywords related to cajeput oil.

Table 1. Most productive researchers, organisations, and countries

Authors		
Names	Record count	% of 2,321
Riley TV	43	1.853
Carson CF	38	1.637
Hammer KA	30	1.293
Reichling J	23	0.991
Baldissera MD	21	0.905
Shao XF	21	0.905
Affiliations		
Names	Record count	% of 2,321
University of Western Australia	54	2.237
Egyptian Knowledge Bank (EKB)	51	2.197
Universidade Federal De Santa Maria	43	1.853
Southern Cross University	38	1.637
University of Queensland	33	1.422
Queen Elizabeth II Medical Centre	31	1.336
Country/region		
Names	Record count	% of 2,321
China	397	17.105
Australia	323	13.916
United States of America	248	10.685
Brazil	187	8.057
Italy	141	6.075
Malaysia	118	5.084

Table 2. Bioactive compound in cajeput oil [27,30].

Compound	Approximate proportion (%)	Properties	Reff
1,8-cineole (Eucalyptol)	44.8–60.2	Analgesic and anti-inflammatory actions, when applied locally, significantly reduce pain and inflammation. The warming sensation produced may improve blood circulation to the affected area, contributing to pain relief.	[27,30]
β-pinene	5.4–8.9	Possesses anti-inflammatory and analgesic effect	[27,30]
Limonene	4.5–13.5	Enhanced the general soothing effect of cajeput oil in the management of muscle pains.	[27]
α-terpineol	4–12.5	It has anti-inflammatory properties and thus can help reduce muscular pains and increase relaxation.	[30]
α-pinene	3–12	Alleviate muscle soreness and tension, hence beneficial for massage applications.	[27,30]
β-caryophyllene	3.8–7.6	Have analgesic and anti-inflammatory properties.	[30]
γ-terpinene	3.5–7.9	Have antinociceptive (pain-relieving), analgesic and anti-inflammatory properties.	[27]

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ORIGINAL ARTICLE

Assessment of Potential Drug-Drug Interactions between Nirmatrelvir/Ritonavir and Concomitant Drugs among Coronavirus Disease Patients in a Tertiary Care Hospital.

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Abstract
Background: Nirmatrelvir/ritonavir is indicated for the treatment of COVID-19infection. However, potential drug-drug interactions (pDDI) between nirmatrelvir/ritonavir and concomitant drugs require further investigation.
Objective: To assess the prevalence, management, and risk factors of pDDI between nirmatrelvir/ritonavir and concomitant drugs in patients with COVID-19 .
Methods: This cross-sectional study was approved by the Medical Research Ethics Committee of Malaysia. Inclusion criteria were COVID-19 patients aged ≥18 years, treated with nirmatrelvir/ritonavir between July and September 2022 in a tertiary care hospital in Selangor. Classification and management of pDDI were categorised according to the University of Liverpool COVID-19 Drug Interactions classification. The pDDI management in clinical practice was compared to the recommended classifications and categorised as 'compliant' or 'non-compliant. Patient characteristics were analysed descriptively. Binary logistic regression was used to identify pDDI risk factors.
Results: The study included 189 patients with a mean age ±SD of 56.76±18.68 years. Comorbidities and polypharmacy were observed in 147 (77.78%) and 73 (38.62%) patients, respectively. A total of 114 patients (60.32%) were reported to have at least one pDDI with nirmatrelvir/ritonavir. Most concomitant drugs had potential interactions with nirmatrelvir/ritonavir (n=152, 77.16%). Compliance with the recommended pDDI management was observed in 174 (88.32%) drug entries. Age (OR 1.04; 1.02-1.06; p=0.001), comorbidities (OR 8.87; 3.17-24.78; p<0.001), and polypharmacy (OR 6.76; 2.74-16.65; p<0.001) were significant risk factors of pDDI with nirmatrelvir/ritonavir.
Conclusion: Prevalence of pDDI among COVID-19 patients treated with nirmatrelvir/ritonavir was high and mainly compliant with the recommended pDDI management. Age, comorbidities, and polypharmacy were pDDI risk factors, warranting a case-by-case multidisciplinary approach to optimise treatment with nirmatrelvir/ritonavir.

Keywords: *Comorbidities, COVID-19, Drug interactions, nirmatrelvir and ritonavir drug combination, polypharmacy.*

Introduction

Within a month of its emergence, the coronavirus disease 2019 (COVID-19) was declared an international public health emergency by the World Health Organization (WHO). Alongside advancements in detection methods and prevention strategies, significant attention was given to developing treatment plans for COVID-19. This led to the United States Food and Drug Administration (USFDA) issuing an Emergency Use Authorization (EUA) for the unapproved product nirmatrelvir/ritonavir in December 2021. This combination is intended for the treatment of mild-to-moderate COVID-19 in adults and paediatric patients (12 years and older, weighing at least 40 kg) who have tested positive for SARS-CoV-2 and are at high risk of progressing to severe COVID-19, including hospitalization or death [1]. In this context, high-risk adults included those meeting any of the following criteria: aged ≥ 60 years, immunocompromised, having comorbidities, obese, current or former smokers, and unvaccinated or having received incomplete vaccination [2]. The treatment of COVID-19 with nirmatrelvir 300 mg/ritonavir 100 mg twice daily for 5 days in high-risk adult patients who experienced mild to moderate symptoms within 5 days of illness [2] began in Malaysia in April 2022 [3]. For patients with renal impairment (eGFR 30-60 mL/min), a renal-adjusted dose of nirmatrelvir 150 mg/ritonavir 100 mg twice daily for 5 days is recommended [2]. Nirmatrelvir is an inhibitor of the SARS-CoV-2 3CL-like protease, which prevents the cleavage of polyproteins necessary for viral genome replication. It is administered in combination with ritonavir, a medication that inhibits hepatic enzymes, thereby slowing the metabolism of nirmatrelvir and increasing its concentration [4]. However, the addition of ritonavir introduces the risk of potential drug-drug interactions (pDDI) due to its effects on cytochrome P450 3A4. Pharmacists were involved in procurement, supply, monitoring, pDDI management, and reporting adverse drug reactions of nirmatrelvir/ritonavir [3].

A few studies have evaluated the extent and nature of pDDI between nirmatrelvir/ritonavir and other drugs commonly prescribed to adult patients [5–7]. The prevalence of pDDI involving nirmatrelvir/ritonavir ranged between 16.2% and 68% , reported to be higher among the elderly patients and in the community settings [5-9]. An analysis of a large database in the US on pDDI between nirmatrelvir/ritonavir and commonly prescribed drugs to patients at high risk of developing COVID-19 complications showed that most drugs are unlikely to have pDDI with nirmatrelvir/ritonavir [10]. Age , gender , smokers , polypharmacy , history of solid organ transplant , and presence of co-morbidities were identified as the risk factors of developing pDDI between nirmatrelvir/ritonavir and other drugs [5,6].

Most existing evidence on pDDI with nirmatrelvir/ritonavir were derived from case reports and case series involving a certain drug , drug class , and specific group of patients [11-14]. The vast scarcity of evidence derived from real-world data on the prevalence, management, and risk factors of pDDI between concomitant drugs in COVID-19 patients treated with nirmatrelvir/ritonavir, both internationally and locally, led to the conception of this study. The study aimed to determine the prevalence, management and risk factors of pDDI between nirmatrelvir/ritonavir and concomitant drugs in COVID-19 patients. Understanding the prevalence and risk factors of pDDI in patients treated with nirmatrelvir/ritonavir could inform healthcare providers on better pDDI management strategies and optimise therapeutic outcomes for COVID-19 patients.

Materials and methods

Reporting considerations

The reporting of this study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [15]. During the preparation of this work, the authors used ChatGPT to improve readability and

language. After using the tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the article.

Study design and site

The retrospective study conducted at a 1261-bed tertiary care hospital in the central region of Peninsular Malaysia. During the COVID-19 pandemic, the study site provided inpatient and outpatient treatment to COVID-19 patients. Warning signs for considering inpatient treatment included: fever of more than 2 days, SPpO2 < 95% (at rest or after exertion), angina or chest pain, dehydration or not passing urine for more than 8 hours, inability to ambulate without assistance, or reduced level of consciousness [16]. The treatment for COVID-19 using nirmatrelvir/ritonavir started in June 2022 at the study site. The pharmacy department adhered to a consensus workflow for screening and supplying nirmatrelvir/ritonavir as well as providing patient counselling. Data from manual prescriptions for nirmatrelvir/ritonavir and concomitant drugs were entered into the Pharmacy Information System (PhIS) version 2.6.3.13. An assessment form was used to record patient's demographic and clinical characteristics, assess patient's eligibility criteria using a risk-stratified scoring system [17], record patient's current medications, and track medication counselling provision during the 5-day treatment with nirmatrelvir/ritonavir.

Sample size calculation

The sample size was calculated using the formula proposed in a previous study [18]. For the period of June to December 2022, a total of 1,479,401 cumulative COVID-19 cases were reported in the state of Selangor [19]. Among these cases, about 76% involved individuals aged 18 years and above (19), yielding the total cases among those eligible for nirmatrelvir/ritonavir treatment (age-wise) to be 1,124,345. From June to December 2022, a total of 9716 patients were prescribed with nirmatrelvir/ritonavir for the treatment of COVID-19 (unpublished data, Pharmacy Services Division, Selangor State Health Department, obtained with permission on 9 January 2023). Accordingly, the estimated prevalence of nirmatrelvir/ritonavir treatment for eligible patients was 0.86%.

Using 0.86 prevalence rate for patients prescribed with nirmatrelvir/ritonavir, precision value of 0.05, and a Z-value of 1.96, the formula yielded a minimum sample size of 185 patients.

Eligibility criteria

Adult patients diagnosed with COVID-19 and prescribed with nirmatrelvir/ritonavir as inpatients or outpatients at the study site between July and September 2022 were included in the study. Patients with incomplete or missing drug data were excluded. Additionally, patients who refused nirmatrelvir/ritonavir treatment after prescription issuance were also excluded from the study.

Data source

The nirmatrelvir/ritonavir treatment assessment forms as along with inpatient, outpatient, and discharge prescriptions, were used as source documents to obtain patient and drug data. The PhIS was used to retrieve additional information on medication counselling notes and to cross-verify the drug data.

Data collection

The data was collected using a structured, validated, and piloted data collection form, which included patient characteristics (age, weight, gender, ethnicity), renal function status, presence and types of comorbidities, and presence of COVID-19 X-ray changes. The COVID-19 X-ray changes were documented as present or not present. Prescribers considered features of severe pneumonia, multi-lobular involvement, or rapidly worsening chest X-ray [2] as COVID-19 X-ray changes.

The number and types of concomitant drugs were also recorded. Concomitant drugs included those that the patients were taking at the onset of and

during nirmatrelvir/ritonavir treatment. The presence of polypharmacy was determined if five or more concomitant drugs were prescribed to the patients [20]. Patients with at least one concomitant drug that has a pDDI with nirmatrelvir/ritonavir were classified as the pDDI group. In keeping with a previous study, patients with concomitant drugs that do not have a pDDI with nirmatrelvir/ritonavir or no concomitant drugs were classified as the non-pDDI group [6].

Potential drug-drug interaction was classified as; do not co-administer, potential interaction, potential weak interaction, or no interaction using established drug-drug interaction resources and references, in the following order, the University of Liverpool COVID-19 Drug Interactions checker [21], the Micromedex Drug Interactions checker, package insert, or literature review. For fixed-dose combination (FDC) drugs, pDDI were assessed for each drug in the FDC with nirmatrelvir/ritonavir, and the highest level of pDDI was assigned. The pDDI management as recommended by the University of Liverpool COVID-19 Drug Interactions checker was recorded which included withholding, dose reduction, or no dosage adjustment [21]. It is noteworthy that one drug may have more than one recommendation for pDDI management. For example, the pDDI between amlodipine and nirmatrelvir/ritonavir may be managed by a 50% dose reduction or withholding the drug, with advice to the patient to monitor for symptoms of hypotension [21]. The pDDI management in clinical practice was compared with the recommended pDDI management and classified as 'compliant' or 'non-compliant' [21-22].

The data were collected independently by two researchers who cross-checked each other's work. Any discrepancies were resolved through discussion between the researchers. In the event of disagreement, a senior pharmacist was consulted for clarification, and consensus was reached to finalize the decision.

Data analysis

Data were analysed using Microsoft Excel 2011 and SPSS 20.0 software. Mean and standard deviation (SD) were calculated for continuous variables. Frequencies and percentages were calculated for categorical variables. Univariable analysis was performed to screen for significant independent variables. The independent variables with a p-value < 0.25 and clinical significance were considered into the multivariable binary logistic regression.

Binary logistic regression was performed for the multivariable analysis. Forward, backward, forward stepwise and backward stepwise methods were applied. Multicollinearity and interaction test were conducted to ensure no correlation and interaction between independent variable in the final model. The preliminary main effect model was chosen based on the principle of the best model with the best fit, clinically plausible and statistically significant, using the Hosmer-Lemeshow test, classification table, and the area under the Receiver Operating Characteristic (ROC) curve. The adjusted odds ratio, regression coefficient, 95% confidence interval, Wald statistic was presented and p-values < 0.05 were considered statistically significant.

Results

During the study period, 191 patients were prescribed with nirmatrelvir/ritonavir. However, two patients were excluded due to missing drug data. Consequently, 189 COVID-19 patients prescribed and treated with nirmatrelvir/ritonavir during the study period were included in the study. The mean age (SD) was 56.76 (18.68) years (Table 1). The most reported comorbidities were hypertension (n=102, 53.97%), diabetes mellitus (n=73, 38.62%), and cardiovascular diseases (n=39, 20.63%).

Concomitant drug entries were recorded for 159 (84.13%) patients, involving 753 drug entries, which mostly involved atorvastatin (n=60, 7.97%), pantoprazole (n=56, 7.44%), and amlodipine (n=46, 6.11%). In total, 114 (60.32%)

patients were on 197 (26.16%) drug entries leading to pDDI with nirmatrelvir/ritonavir. The pDDI classified as do not co-administer, potential interaction, and potential weak interaction involved 10.15% (n=20), 77.16% (n=152), and 12.69% (n=25) drug entries, respectively. The pDDI was managed by withhold, dose reduction, and no dose adjustment in 55.84% (n=110), 18.27% (n=36), and 25.89% (n=51) drug entries, respectively (Table 2). The most common concomitant drugs involved in pDDI were atorvastatin (n=60, 30.46%), amlodipine (n=47, 23.85%), clopidogrel (n=18, 9.14%), simvastatin (n=14, 7.11%), and diphenhydramine (n=7, 3.55%). The comparison between the pDDI management in clinical practice and the recommended pDDI management is presented in Table 2. Compliance to the recommended pDDI management were observed in 174 (88.32%) drug entries.

Univariable analysis identified age, weight, elderly, obesity status, patient type (i.e. inpatient vs outpatient), presence of co-morbidities, number of co-morbidities, nirmatrelvir/ritonavir dosing, presence of COVID-19 x-ray changes, number of concomitant drugs, and polypharmacy as significant factors. Binary logistic regression analysis identified age (OR 1.04; 1.02-1.06; p=0.001), comorbidity (OR 8.87; 3.17-24.78; p<0.001), and polypharmacy (OR 6.76; 2.74-16.65; p<0.001) as pDDI risk factors (Table 3).

Discussion

The current study identified the prevalence, management and risk factors of pDDI involving nirmatrelvir/ritonavir and concomitant drugs prescribed to COVID-19 patients in tertiary care hospital using real-world data. The prevalence of pDDI between nirmatrelvir/ritonavir and concomitant drugs among COVID-19 patients identified in this study (60.32%) was lower than the rate reported in a local primary care setting [22], but comparable to a study conducted among hospitalised patients [7]. This could be explained by the high proportion of COVID-19 patients who received treatment as inpatient, whereby incidence of pDDI were reported to be higher in inpatients as compared to outpatients [23]. This is because hospital stays increase the likelihood of taking multiple drugs, which subsequently raises the risk of potential DDIs [24].

About 77% of the drug entries involved in pDDI were found to have potential interaction with nirmatrelvir/ritonavir. Almost 90% of pDDIs were managed in compliance with the recommended guidelines for pDDI management, leaving approximately 10% as non-compliant. A local study reported a higher non-compliance rate of 21.7% for recommended pDDI management [22]. This disparity may be attributed to differences in study settings but is primarily due to variations in the parameters used to calculate the proportion of non-compliance. In our study, the proportion was determined based on the number of non-compliant drug entries relative to the total number of drug entries. In contrast, the previous study [22], calculated non-compliance based on the types of non-compliant drugs relative to the total types of drugs. Nevertheless, the observed non-compliance can be explained by the application of clinical judgment in real-life pDDI management. This involves risk-benefit assessment by taking treatment goal, patient, and concomitant drug factors into consideration before withholding or reducing the dose of any drugs with pDDI, especially among those with multimorbidity and polypharmacy [25].

About 26% of the concomitant drugs prescribed to the COVID-19 patients posed a risk of pDDI with nirmatrelvir/ritonavir. This finding concurred with the rate reported in the US, whereby 30% of the top 100 drug-prescribed drug were expected to cause pDDI with nirmatrelvir/ritonavir [10]. Concomitant drugs with pDDI involving nirmatrelvir/ritonavir were mainly drugs for cardiovascular diseases. This finding highlighted the need for a specific decision-making algorithm for patients on cardiovascular drugs who needs nirmatrelvir/ritonavir as treatment for COVID-19 [25]. Statins are often involved in pDDI with

nirmatrelvir/ritonavir, but a previous study [6] found similar pDDI prevalence even without statins.

Age, comorbidity, and polypharmacy were identified as pDDI risk factors. Similar findings were reported in previous studies [5,6]. Elderly or people with comorbidity benefit the most from treatment with nirmatrelvir/ritonavir [26]. However, polypharmacy is frequently observed in the same population. Instead of depriving eligible patients from treatment with nirmatrelvir/ritonavir, anticipatory deprescribing practice, as proposed by Ross et al. may be considered to enhance the access and use of nirmatrelvir/ritonavir in eligible patients [8].

The strength of the study relies on the use of real-world data to assess pDDI in inpatient and outpatient setting, which is a typical scenario in most healthcare facilities in Malaysia and other countries. However, the study is limited by data to further assess the outcome of pDDI in patients treated with nirmatrelvir/ritonavir. Additionally, information on smoking status was not adequately captured in study source documents, making it impossible to assess if smoking status was a risk of pDDI in patients treated with nirmatrelvir/ritonavir. Future prospective studies could overcome incomplete or missing data issues. Moreover, future studies could explore the implementation and impact of personalised approaches such as disease-specific decision-making algorithms and anticipatory deprescribing practice in managing pDDI in nirmatrelvir/ritonavir patients.

Conclusion

The study revealed a high prevalence of potential drug-drug interactions among patients treated with nirmatrelvir/ritonavir, which were mainly compliant to the recommended pDDI management. Age, comorbidity, and polypharmacy were pDDI risk factors. A case-by-case approach is warranted in optimising treatment of COVID-19 patients with nirmatrelvir/ritonavir.

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Authors contribution

Both authors SB and KM contributed to conceptualisation, data management, synthesis and analysis, writing, reviewing, and finalizing the manuscript.

Declaration of conflicting interests

The authors declares that there is no conflict of interest.

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Table 1. Demographic and clinical characteristics of patients included in the study

Characteristics		With pDDI (n=114), n (%)	Without pDDI (n=75), n (%)	Total (n=189), n (%)	p-value
Age (years), mean ± SD		63.04 ± 14.79	47.2 ± 19.98	56.76 ± 18.68	<0.001
Weight (kg), mean ± SD		68.75 ± 15.94	73.14 ± 19.97	70.49 ± 17.73	0.095
Gender					
	Male	68 (59.65)	39 (52)	107 (56.61)	0.299
	Female	46 (40.35)	36 (48)	82 (43.39)	
Ethnicity					
	Malay	57 (50)	32 (42.67)	89 (47.09)	
	Chinese	25 (21.93)	21 (28)	46 (24.34)	0.71
	Indian	30 (26.32)	20 (26.67)	50 (26.46)	
	Others	2 (1.75)	2 (2.67)	4 (2.12)	
Elderly (≥60 years)					
	Yes	75 (65.79)	25 (33.33)	100 (52.91)	<0.001
	No	39 (34.21)	50 (66.67)	89 (47.09)	
Obese					
	Yes	16 (14.04)	21 (28)	37 (19.58)	0.019
	No	98 (85.96)	54 (72)	152 (80.42)	
Patient type					
	Inpatient	91 (79.82)	49 (65.33)	140 (74.07)	0.026
	Outpatient	23 (20.18)	26 (34.67)	49 (25.93)	
Immunocompromised					
	Yes	14 (12.28)	8 (10.67)	22 (11.64)	0.735
	No	100 (87.72)	67 (89.33)	167 (88.36)	
Presence of comorbidities					
	Yes	108 (94.74)	39 (52)	147 (77.78)	<0.001
	No	6 (5.26)	36 (48)	42 (22.22)	
Number of comorbidities					
	0	6 (5.26)	36 (48)	42 (22.22)	
	1	36 (31.58)	28 (37.33)	64 (33.86)	
	2	39 (34.21)	8 (10.67)	47 (24.87)	<0.001
	3	25 (21.93)	3 (4)	28 (14.81)	
	4	7 (6.14)	0 (0)	7 (3.7)	
	5	1 (0.88)	0 (0)	1 (0.53)	

Characteristics	With pDDI (n=114), n (%)	Without pDDI (n=75), n (%)	Total (n=189), n (%)	p-value
Paxlovid dosing				
Full-dose	69 (60.53)	63 (84)	132 (69.84)	0.001
Renal-adjusted dose	45 (39.47)	12 (16)	57 (30.16)	
Covid-19 X-ray changes				
Yes	39 (34.21)	19 (25.33)	58 (30.69)	0.195
No	75 (65.79)	56 (74.67)	131 (69.31)	
Polypharmacy				
Yes	65 (57.02)	8 (10.67)	73 (38.62)	<0.001
No	49 (42.98)	67 (89.33)	116 (61.38)	
Number of concomitant drugs, mean ± SD	5.25 ± 2.98	2.89 ± 2.12	3.85 ± 3.19	<0.001

pDDI: potential drug-drug interactions; SD: standard deviation

Table 2. Category of interaction and compliance to recommended intervention for drugs involved in potential drug-drug interaction with nirmatrelvir/ritonavir (drug entries, n = 197).

Drugs (number of drug entries)	**University of Liverpool COVID-19 pDDI classification** (21)	**University of Liverpool COVID-19 drug interactions recommendation** (21)	**Number of drug entries withheld (%)**	**Number of drug entries with dose adjusted (%)**	**Number of drug entries with no dose adjustment (%)**	**Number of compliance to recommended intervention (%)**
Atorvastatin (n=60)	Potential interaction	Avoid co-administration or use the lowest possible dose.	59(98.33)	1 (1.67)	0	60 (100)
Amlodipine (n=45)	Potential interaction	Reduce dose by 50% or take it every other day or withhold and advice patients to monitor for symptoms of hypotension.	14(31.11)	31(68.89)	0	45 (100)
Clopidogrel (n=18)	Potential interaction	Avoid co-administration.	5 (27.78)	0	13 (72.22)	5 (27.78)
Simvastatin (n=14)	Do not co-administer	Contraindicated – Withhold.	14 (100)	0	0	14 (100)
Diphenhydramine (n=7)	Potential weak interaction	No dosage adjustment is needed.	0	0	7 (100)	7 (100)
Felodipine (n=6)	Potential interaction	A dose reduction of 50% or taking the dose every other day could be considered, if necessary, to temporarily pause the antihypertensive drug if needed.	4 (66.67)	1 (16.67)	1 (16.67)	5 (83.33)
Dexamethasone (n=6)	Potential interaction	A dose reduction of 50% and the usual dose resumed 3 days after completing nirmatrelvir/ritonavir treatment.	2 (33.33)	0	4 (66.67)	0
Loratadine (n=5)	Potential weak interaction	No dosage adjustment is needed.	0	0	5 (100)	5 (100)
Losartan (n=4)	Potential weak interaction	No dosage adjustment is needed.	0	0	4 (100)	4 (100)
Diazepam (n=2)	Do not co-administer	Contraindicated – Withhold.	2 (100)	0	0	2 (100)
Midazolam (parenteral) (n=2)	Potential interaction	Administered with caution and close monitoring. Dosage reduction for midazolam should be considered if more than a single dose of midazolam is administered.	0	0	2 (100)	2 (100)
Rosuvastatin (n=2)	Potential interaction	Avoid co-administration or use the lowest possible dose.	2 (100)	0	0	2 (100)

Drugs (number of drug entries)	**University of Liverpool COVID-19 pDDI classification** (21)	**University of Liverpool COVID-19 drug interactions recommendation** (21)	**Number of drug entries withheld (%)**	**Number of drug entries with dose adjusted (%)**	**Number of drug entries with no dose adjustment (%)**	**Number of compliance to recommended intervention (%)**
Sodium Valproate (n=2)	Potential weak interaction	No dosage adjustment is needed.	0	0	2 (100)	2 (100)
Terazosin (n=2)	Potential interaction	No dosage adjustment is needed. Pause terazosin if hypotension occurs.	1 (50)	0	1 (50)	2 (100)
Theophylline (n=2)	Potential weak interaction	No dosage adjustment is needed.	0	0	2 (100)	2 (100)
Tramadol (n=2)	Potential interaction	No dosage adjustment is needed.	1 (50)	0	1 (50)	1 (50)
Alprazolam (n=1)	Potential interaction	Consider a lower dose.	1 (100)	0	0	0
Amlodipine/ Losartan (n=1)	Potential interaction	Reduce dose by 50% or take it every other day or withhold and advice patient to monitor for symptoms of hypotension[a]	1 (100)	0	0	1 (100)
Apixaban (n=1)	Potential interaction	Avoid co-administration or depending on apixaban dose, reduce dose by 50%.	1 (100)	0	0	1 (100)
Ciclosporin (n=1)	Do not co-administer	Dose reductions to 5-20% of the original dose with therapeutic drug monitoring if available. Otherwise use alternative COVID-19 treatment.	0	1 (100)	0	1 (100)
Digoxin (n=1)	Potential interaction	Risk/benefit evaluation or dosage adjustment based on the treatment indication and the patient's renal function.	0	0	1 (100)	1 (100)
Efavirenz (n=1)	Potential weak interaction	No dosage adjustment is needed.	0	0	1 (100)	1 (100)
Amlodipine/ valsartan (n=1)	Potential interaction	Reduce dose by 50% or take it every other day or withhold and advice patient to monitor for symptoms of hypotension[a]	0	1 (100)	0	1 (100)
Fluticasone/ salmeterol (n=1)	Do not co-administer	Contraindicated – Withhold[a].	1 (100)	0	0	1 (100)
Isosorbide mononitrate (n=1)	Potential weak interaction	No dosage adjustment is needed.	0	0	1 (100)	1 (100)
Ivabradine (n=1)	Do not co-administer	Contraindicated – Withhold.	1 (100)	0	0	1 (100)

Drugs (number of drug entries)	**University of Liverpool COVID-19 pDDI classification** (21)	**University of Liverpool COVID-19 drug interactions recommendation** (21)	**Number of drug entries withheld (%)**	**Number of drug entries with dose adjusted (%)**	**Number of drug entries with no dose adjustment (%)**	**Number of compliance to recommended intervention (%)**
Loperamide (n=1)	Potential interaction	No dosage adjustment is needed.	0	0	1 (100)	1 (100)
Losartan / Hydrochlorothiazide (n=1)	Potential weak interaction	No dosage adjustment is needed[a].	0	0	1 (100)	1 (100)
Piribedil (n=1)	Potential weak interaction	No dosage adjustment is needed.	0	0	1 (100)	1 (100)
Quetiapine (n=1)	Do not co-administer	Withold or reduced to one sixth of the original dose. Original dose to be resumed 3 days after nirmatrelvir/ritonavir completion.	0	1 (100)	0	1 (100)
Tamoxifen (n=1)	Potential weak interaction	No dosage adjustment is needed.	0	0	1 (100)	1 (100)
Valsartan (n=1)	Potential interaction	No dose adjustment, if hypotension occurs stop valsartan.	0	0	1 (100)	1 (100)
Valsartan / Hydrochlorothiazide (n=1)	Potential interaction	No dose adjustment if hypotension occurs stop valsartan.	0	0	1 (100)	1 (100)
Zolpidem (n=1)	Potential interaction	No dosage adjustment is needed.	1 (100)	0	0	0

pDDI: potential drug-drug interaction; [a]Fixed dose combination (FDC): Highest level of potential drug-drug interaction was assigned

Table 3. Binary logistic regression of risk factors for potential drug-drug interactions with nirmatrelvir/ritonavir.

Factors	**Adjusted Odds Ratio**	**95% CI**	**P-value**
Age (years)	1.04	1.02 - 1.06	0.001
Co-morbidities	8.87	3.17 - 24.78	<0.001
Polypharmacy	6.76	2.74 - 16.65	<0.001

CI: confidence interval; Hosmer & Lemeshow p-value of the model was 0.588, with 78.8% of the subjects are correctly classified by the model and area under the curve (AUC) of 0.869, denoting good model fit.

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ORIGINAL ARTICLE

Psychosocial Determinants and Treatment Outcomes in Adolescents with Major Depressive Disorder and Generalised Anxiety Disorder: A Preliminary Retrospective Analysis.

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Abstract
Mental health conditions such as anxiety and depression are prevalent among adolescents, yet evidence on psychosocial determinants and treatment responses remains limited. This retrospective study investigates the psychosocial determinants, prescribed treatments, and treatment outcomes in adolescents with major depressive disorder (MDD) and generalised anxiety disorder (GAD) at a Malaysian hospital. Data from 80 adolescents aged 10-19 years were analysed using descriptive statistics, Pearson's Chi-square tests, and logistic regression. Low self-esteem (16.5%) and dysfunctional family dynamics (15.4%) were identified as the most common determinants. Combined psychotherapy and pharmacotherapy were prescribed to 62.5% of patients, significantly improving symptom outcomes (p = 0.005). Disabilities were significantly associated with MDD and GAD diagnoses (p = 0.041), increasing the odds of developing these disorders by approximately 25-fold. The findings emphasise the need for integrated psychosocial and pharmacological interventions to optimise treatment outcomes, as well as the need for customised strategies in the care of adolescent mental health.

Keywords: Adolescents, *Generalised anxiety disorder, Major depressive disorder, Malaysia, Psychosocial.*

Introduction

Mental health disorders, particularly major depressive disorder (MDD) and generalised anxiety disorder (GAD), are significant public health concerns, especially among adolescents [1]. Adolescence, defined by the World Health Organization (WHO) as the age range of 10–19 years, is a critical developmental stage with rapid physical, emotional, and social changes [2]. During this period, individuals are highly susceptible to mental health challenges due to increased exposure to psychosocial stressors, including academic pressures, family conflicts, and peer dynamics [3]. Globally, after the COVID-19 pandemic, the prevalence of depression and anxiety among adolescents skyrocketed, with pooled prevalence rates of 25.2% for depression and 20.5% for anxiety [4].

In Malaysia, the situation is even more concerning. According to the 2017 National Health and Morbidity Survey, 18.3% of adolescents reported experiencing depression, while 39.7% faced anxiety symptoms [5]. These figures clearly show that there is a growing mental health crisis among Malaysian adolescents. Left untreated, mental health disorders in adolescence can lead to severe consequences, including academic failure, strained relationships, substance abuse, and an increased risk of suicide. These outcomes burden not only individuals but also society, with economic costs stemming from reduced workforce participation, decreased productivity, and increased government support expenditures [6].

Psychosocial factors, such as traumatic life events, dysfunctional family dynamics, peer rejection, and academic stress, are critical contributors to the onset and progression of MDD and GAD [7]. Dysfunctional family environments, for example, can disrupt an adolescent's emotional stability, leading to maladaptive coping mechanisms and exacerbating mental health issues [8]. Similarly, peer-related stressors, such as bullying and social isolation, can significantly impact an adolescent's self-esteem and psychological well-being [9]. Despite the established role of these factors, there is limited research in Malaysia exploring their influence on treatment outcomes in adolescents with MDD and GAD.

Another pressing issue is the lack of clinical practice guidelines (CPGs) for managing MDD and GAD in Malaysian adolescents. The absence of standardised management protocols creates inconsistencies in diagnosis and treatment, potentially affecting outcomes. Addressing this gap requires robust research to provide evidence-based recommendations tailored to the unique challenges faced by Malaysian adolescents.

This study seeks to bridge these gaps by conducting a retrospective analysis of psychosocial determinants and treatment outcomes among adolescents with MDD and GAD. Medical records from a tertiary care hospital were reviewed to identify key psychosocial factors, evaluate treatment patterns, and assess their effectiveness. The findings aim to inform clinical practice and policy development, ultimately contributing to improved mental health care for adolescents in Malaysia.

Materials and methods

Study design

The study employed a retrospective analysis, reviewing medical records of adolescent patients diagnosed with MDD and GAD within a specified timeframe (January to December 2023).

Study setting

The data was collected at Hospital Al-Sultan Abdullah (HASA), a newly operational tertiary care centre in Malaysia. HASA is located in an urban area and provides specialised services. The psychiatry clinic caters to a diverse patient population with varied socio-economic backgrounds, making it an ideal setting for studying adolescent mental health disorders.

Sample size calculation

The sample size was calculated using Cochran's formula with a confidence level of 95%, a standard deviation of 0.5, and a margin of error of 0.05 using a population size of 300, which was the number of adolescents registered to Child Psychiatry Clinic according to the census of child and adolescent clinic of HASA.

Initial sample size:

$$n_0 = \frac{z^2 \cdot p \cdot (1-p)}{e^2}$$

$$n_0 = \frac{1.96^2 \cdot 0.5 \cdot (1-0.5)}{0.005^2}$$

$$n_0 = 384.16$$

Finite population:

$$n = \frac{n_0}{1 + \frac{n_0 - 1}{population}}$$

$$n = \frac{384.16}{1 + \frac{384.16 - 1}{300}}$$

$$n \approx 168.37$$

$$n = 169$$

While the calculated sample size was 169, only 80 patients were included due to the limited population of adolescents diagnosed with MDD and GAD at this newly operational tertiary care hospital. This limitation reflects the specific focus of the study population and the challenges of recruitment within a single centre setting.

Inclusion and exclusion criteria

Patients were included if they were Malaysian citizens aged 10-19 years old diagnosed with MDD and/or GAD and had at least two recorded visits to the psychiatry clinic. A second visit is crucial for confirming a diagnosis of MDD or GAD, as it ensures comprehensive medical records, engagement in care, minimises bias, and enhances data reliability by allowing cross-verification of patient-reported factors and clinician observations. Patients who defaulted on treatment were excluded to ensure data reliability.

Data collection

A self-designed Data Collection Form (DCF) was used to extract anonymised data from the Hospital Information System (UniMEDS) on demographics, psychosocial determinants, treatments, and outcomes. The psychiatrists identified the determinants through history-taking with patients and caregivers during follow-ups , and these details were documented in the patients' records. Information on treatments (pharmacotherapy or psychotherapy) and improvement of symptoms were also included. To ensure patient privacy and confidentiality, all record reviews were conducted solely by a single investigator.

Statistical analysis

Descriptive statistics were used to summarise the sociodemographic characteristics. Pearson's Chi-square tests assessed associations between psychosocial factors and treatment outcomes. Logistic regression was conducted to examine the influence of various psychosocial determinants on the likelihood of MDD and GAD diagnoses. The analysis calculated odds ratios to quantify the strength of associations, with statistical significance defined at $P < 0.05$.

Results

The study population comprised 80 adolescents aged 11-18 years (mean age: 16.29 years, SD: 1.836). The youngest patient was 11 years old, and the oldest was 18. The majority were female (n = 65, 81.3%) and of Malay ethnicity (n=77, 96.3%), with a minority representation of Chinese adolescents (n=3, 3.8%). The majority of the patients' parents (65%) had a high education level, while 35% had an intermediate education level. In terms of household income, 60% of patients came from families earning above RM8000 per month, while 40% had family earning between RM3000 - RM8000 per month. Most patients (71.3%) lived with both parents, whereas only 2.5% lived with a single parent (Table 1).

The frequency of MDD and GAD was also recorded, and the percentage of adolescent patients with MDD, GAD, and MDD with GAD was 76.3%, 13.8%, and 10% respectively (Figure 1).

The majority of adolescents (96.3%) had more than one psychosocial determinant contributing to MDD and/or GAD, with the most common being low self-esteem (16.5%), dysfunctional family dynamics (15.4%), and academic pressures (11.9%). Other notable factors included family history of mental health problems (8.1%), isolation (7.7%), bullying (7.3%), and adjustment to a new school environment (6.5%). Less common determinants were traumatic events (5%), substance abuse (4.6%), excessive workload (3.8%), disability (1.5%), and least frequently, domestic violence and misuse of social media (both 0.4%) (Table 2).

A binary logistic regression was performed to examine the relationship between the psychosocial determinants and the likelihood of experiencing MDD and/or GAD. The model demonstrated adequate fit (-2 Log Likelihood = 43.188). The Cox & Snell R^2 and Nagelkerke R^2 values are 0.225 and 0.392 respectively, suggesting that the model explains between 22.5% and 39.2% of the variance in the dependent variable. The logistic regression analysis revealed that disability was significantly associated with the likelihood of experiencing the disorders. The coefficient for disability was 3.213 (p=0.041), suggesting that disabled individuals were 24.853 times more likely to have MDD and/or GAD (Table 3).

The majority of the patients (n=50, 62.5%) received combined psychotherapy and pharmacotherapy, while 27.5% received psychotherapy alone and 10% received pharmacotherapy alone. Sixteen different psychotherapy modalities were administered. Among adolescents with MDD and GAD, supportive therapy was the most common intervention (n=34, 20.2%), followed by cognitive behavioural therapy (CBT; 17.3%) (Figure 2).

There were (n= 23; 39.7%) patients who received a single agent of selective serotonin reuptake inhibitors (SSRIs) followed by mirtazapine (3.4%), quetiapine (1.7%), lorazepam (3.4%), and methylphenidate (1.7%). Twelve MDD patients received SSRIs with benzodiazepines or non-benzodiazepines, and two patients received a combination of olanzapine and benzodiazepines. Among 11 adolescents diagnosed with GAD, only one received SSRIs. Other than that, (3.4%, n= 2) were prescribed benzodiazepines and SSRIs. Eight patients were diagnosed with MDD and GAD, and four of them received SSRIs. Two patients received benzodiazepines together with SSRIs and one patient received methylphenidate and escitalopram (Table 4).

A Pearson's Chi-square test was conducted to analyse the association between the improvement of the symptoms and the type of therapy prescribed to the patients. The results are shown in Table 5. There was a statistically significant association between the improvement of patients' symptoms and the type of therapy ($p = 0.005$).

Discussion

This study examines the intricate relationship between psychosocial factors and treatment outcomes in adolescents diagnosed with MDD and GAD. Dysfunctional family dynamics emerged as a critical determinant, consistent with global findings on adolescent mental health [10]. Growing up in a dysfunctional family environment can hinder the development of healthy coping mechanisms, often leading to maladaptive strategies such as avoidance, self-blame, and externalizing blame onto others [11]. Family stability is crucial in maintaining a sense of security and system homeostasis. Parental conflicts or chronic familial discord can disrupt this balance, leaving adolescents vulnerable to emotional distress. Adolescents who perceive instability in their family system may exhibit problematic behaviours, such as withdrawal, defiance, or difficulties in forming healthy peer relationships. These challenges further exacerbate their risk of developing MDD and GAD by creating a cycle of insecurity, interpersonal conflicts, and impaired emotional regulation. Addressing these family dynamics through targeted psychosocial interventions is essential to improving treatment outcomes in this vulnerable group.

Next, low self-esteem has been associated with an increased risk of depression through mechanisms such as inflammation, interaction effects, or cognitive biases [12]. Self-perceptions of worthlessness and uselessness have been linked to mental health issues [13]. It was found that poor self-esteem is associated with higher levels of anxiety, sadness, and suicidal thoughts. It can also result in substance abuse, early sexual engagement, and eating disorders in young individuals [14].

Our study found that adolescents with disabilities were nearly 25 times more likely to develop MDD and/or GAD, which is substantially higher than the threefold increased risk reported in studies focusing on individuals with physical disabilities in the general population [15]. This discrepancy may be attributed to differences in study populations, as our research included a broader range of disabilities, including intellectual and developmental disorders such as autism spectrum disorder (ASD) and attention deficit/hyperactivity disorder (ADHD), which may elevate the risk further. The relatively small sample size in our study may have also influenced the observed effect size. Individuals with intellectual development disorders (PWDID) are more prone to anxiety and stress-related illnesses and are commonly misdiagnosed, particularly those with more severe disabilities [16].

Adolescents facing significant life stressors or dysfunctional family environments were more likely to be prescribed combination therapy. This approach reflects the need to address both emotional and biological aspects of mental health conditions. For instance, supportive therapy, which accounted for 20.2% of prescribed treatments, was often utilised in adolescents with family-related stressors to provide a stable and empathetic therapeutic environment. The practice of prescribing supportive therapy is recommended by clinical practice guidelines (CPG) as supportive therapy is indicated to be applied to patients who are tolerating high levels of anxiety and experiencing subsyndromal symptoms [17].

Similarly, CBT was prescribed to 17.3% of patients and was particularly effective in adolescents with academic pressures or peer-related issues, helping them develop coping strategies and restructure maladaptive thought patterns. Several randomised controlled trials have shown that CBT is effective for a variety of mental and behavioural problems [18].

The success of these treatments was significantly associated with the type of therapy, as revealed by the Chi-square analysis ($p = 0.005$). The finding that monotherapy appears more effective than combination therapy contradicts the existing literature, which often supports the superiority of combination therapy in treating MDD and GAD. The discrepancy, where monotherapy appeared

more effective, may be attributed to various factors. The limited sample size and possible selection bias could have influenced the results, as patients undergoing monotherapy may have experienced milder symptoms or encountered fewer psychosocial stressors. Furthermore, combination therapy is frequently recommended for more severe or treatment-resistant cases [19], which may inherently result in less favourable outcomes. Variations in treatment adherence, especially regarding psychotherapy sessions, may have reduced the effectiveness of combination therapy. Moreover, the type, frequency, and quality of psychotherapy, along with the therapist's expertise, may have impacted patient outcomes. Ultimately, the treatment duration and follow-up period may not have been adequate to fully assess the advantages of combination therapy, which typically necessitates a longer timeframe (6 months to 24 months) to show substantial improvements [20, 21].

Adolescents with disabilities, who are at an elevated risk for severe symptoms, demonstrated greater benefits from integrated care approaches that addressed the complex challenges they encounter. This is consistent with a meta-analysis indicating that the combination of psychotherapy and medication is more effective than monotherapy for individuals with anxiety disorders [22].

Some psychosocial factors were not explicitly associated with specific treatment choices, which raises questions regarding individualised care plans. This issue illustrates the necessity for clinicians to integrate a thorough psychosocial assessment into treatment planning. Tailoring interventions to the specific needs of each adolescent can enhance outcomes.

Conclusion

In conclusion, this study highlights the significant role of psychosocial factors in the development and treatment outcomes of MDD and GAD in adolescents. Low self-esteem, dysfunctional family dynamics, and the presence of disabilities emerged as critical determinants. The findings emphasise the potential of integrating psychotherapy and pharmacotherapy in addressing complex cases, particularly for adolescents facing severe psychosocial stressors or disabilities. Although monotherapy appeared more effective in this study, the discrepancy with existing literature signals the need for further exploration of the factors influencing treatment outcomes, such as severity of symptoms, treatment adherence, and duration of therapy. This information not only contribute to the growing evidence supporting integrated care models but also highlight the importance of culturally sensitive, individualised treatment plans. Future research should focus on longitudinal studies to assess the long-term efficacy of combination therapy, thereby informing clinical guidelines and health policies for adolescent mental health.

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Conflict of interests

The author declares no conflict of interest regarding the publication of this manuscript.

Authors' contributions

NARMR: Conceptualisation of the research, supervision of the study, editing the manuscript and final approval of the manuscript for submission.

NQAL: Data collection, results analysis and drafting the manuscript.

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Table 1. Demographic characteristics of adolescents who are diagnosed with MDD and/or GAD.

Characteristics	Frequency (N=80)	Percentage (%)	Range	Mean (SD)	Skewness (Kurtosis)
Age			11-18	16.29 (1.836)	-0.865 (-0.303)
Gender					
Male	15	18.8			
Female	65	81.3			
Ethnicity					
Malay	77	96.3			
Chinese	3	3.8			
Parental education					
Middle	28	35			
High	52	65			
Household income					
RM3000-RM8000	32	40			
RM8000 above	48	60			
Living arrangements					
With both parents	57	71.3			
With father only	2	2.5			
With mother only	13	16.3			
With father and stepmother	2	2.5			
With mother and stepfather	3	3.8			
With adopted family	3	3.8			

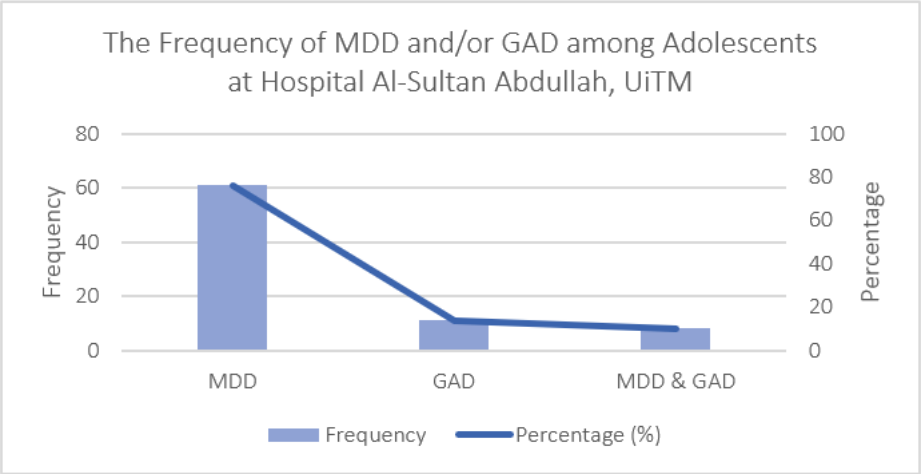

Figure 1. The frequency of MDD and/or GAD among adolescents at HAS

Table 2. Psychosocial determinants of MDD and/or GAD among adolescents in Hospital Al-Sultan Abdullah, UiTM

Psychosocial determinants	**Frequency (N=80)**	**Percentage (%)**
Only one contributing psychosocial determinant	3	3.8
More than one contributing psychosocial determinants	77	96.3
	Frequency (n=260)	**Percentage (%)**
Domestic violence	1	0.4
Dysfunctional family dynamics	40	15.4
Family of history mental health problems	21	8.1
Isolation	20	7.7
Peer rejection	14	5.4
Misuse social media	1	0.4
Bullying	19	7.3
Excessive workload	10	3.8
Adjustment (new school environment)	17	6.5
Academic pressures	31	11.9
Traumatic events	13	5
Disability	4	1.5
Substance abuse	12	4.6
History of mental health problems	14	5.4
Low self-esteem	43	16.5

Table 3. Logistic regression analysis of psychosocial determinants associated with Major Depressive Disorder and Generalized Anxiety Disorder among adolescents at HASA

Variables in the Equation						
Predictor variable	**B**	**S.E.**	**Wald**	**df**	**p-value***	**Exp (B)**
Dysfunctional family dynamics	0.534	0.923	0.334	1	0.563	1.705
Isolation	-2.869	1.902	2.276	1	0.131	0.057
Disability	3.213	1.571	4.183	1	0.041	24.853
Substance abuse	-19.423	10549.336	0.000	1	0.999	0.000
Low self-esteem	-0.183	0.985	.035	1	0.852	0.833
History of mental health problems	0.846	1.314	0.414	1	0.520	2.329
Traumatic events	1.726	1.047	2.721	1	0.099	5.620
Family history of mental health problems	-0.703	1.098	0.410	1	0.522	0.495
Adjustment to new school environment	-1.073	1.479	0.526	1	0.468	0.342
Academic pressures	1.080	0.910	1.409	1	0.235	2.944
Excessive workload	1.225	1.209	1.027	1	0.311	3.405
Peer rejection	1.207	1.447	0.696	1	0.404	3.345
Bullying	0.787	1.005	0.612	1	0.434	2.196
Misuse of social media	0.804	41554.342	0.000	1	1.000	2.234

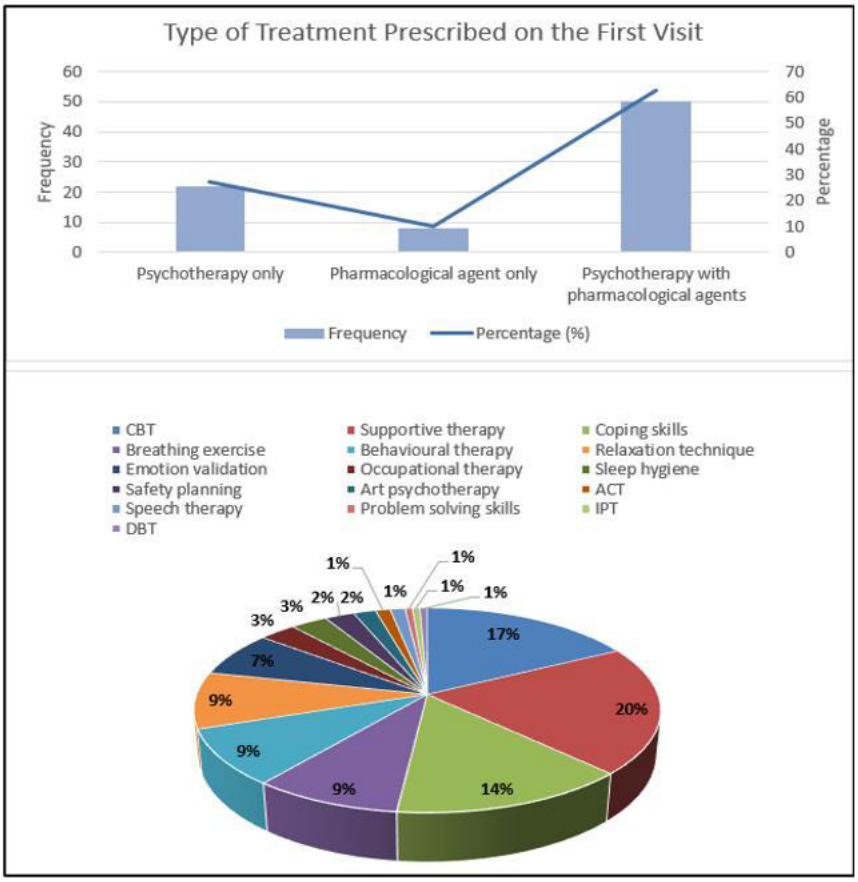

Figure 2. Type of treatment prescribed on the first visit

Table 4. Pharmacological agents received by MDD and/or GAD adolescents

Diagnosis	Pharmacological agent	Frequency (n=58)	Percentage (%)
MDD	**Single-agent**		
	SSRI		
	Sertraline	7	12.1
	Escitalopram	13	22.4
	Fluoxetine	3	5.2
	TCAs		
	Mirtazapine	2	3.4
	Atypical antipsychotic		
	Quetiapine	1	1.7
	Benzodiazepines		
	Lorazepam	2	3.4
	CNS stimulants		
	Methylphenidate	1	1.7
	Double agents		
	Escitalopram + Lorazepam	5	8.6
	Sertraline + Alprazolam	2	3.4
	Sertraline + Lorazepam	2	3.4
	Fluoxetine + Olanzapine	1	1.7
	Olanzapine + Lorazepam	2	3.4
	Sertraline + Risperidone	1	1.7
	Escitalopram + Zolpidem	1	1.7
	Triple agents		
	Quetiapine + Mirtazapine + Alprazolam	1	1.7
	Quetiapine + Venlafaxine + Lorazepam	1	1.7
	Sertraline + Alprazolam + Risperidone	1	1.7

	Escitalopram + Quetiapine + Alprazolam	1	1.7
GAD	**Single agent**		
	SSRI		
	Escitalopram	1	1.7
	CNS stimulants		
	Methylphenidate	1	1.7
	Double agents		
	Escitalopram + Lorazepam	1	1.7
	Sertraline + Alprazolam	1	1.7
MDD and GAD	**Single agent**		
	SSRI		
	Sertraline	2	3.4
	Escitalopram	1	1.7
	Fluoxetine	1	1.7
	Double agents		
	Sertraline + Lorazepam	1	1.7
	Escitalopram + Alprazolam	1	1.7
	Escitalopram + Methylphenidate	1	1.7

Table 5. Association between improvement of symptoms and type of therapy prescribed

Type of therapy	**Response**		**X^2 statistic (df)**	**p-value***
	Symptoms not improved	**Symptoms improved**		
Monotherapy	0	30		
Combination therapy	11	39	1[a]	0.005

[a]Pearson's Chi-square test

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ORIGINAL ARTICLE

The Effect of Visceral Manipulation on Abdominal Pain and Quality of Life in Adult Patients with Functional Dyspepsia: A Pilot Study.

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Abstract
Background: A pilot study was conducted to determine the effect size of visceral manipulation (VM) sessions on abdominal pain and quality of life in adult individuals with functional dyspepsia (FD).
Methods: Twenty-nine subjects diagnosed with FD participated in a pre-post-study design. The participants were subjected to a two-week treatment regime involving VM intervention sessions. Each session lasted for 30 minutes and was conducted five times a week. Data were collected using the Abdominal Pain Index (API) and Short-Form Nepean Dyspepsia Index (SF-NDI) instruments. The Friedman test was used for analysis. with a significance level set at $p < 0.05$. This study was approval by the Health Research Ethics Committee of the Health Polytechnic, Ministry of Health, East Kalimantan, Indonesia (Ethics No. DP.04.03/7.1/12146/2023).
Results: Among FD patients, there was a significant reduction in abdominal pain, pain time, duration, and intensity before and after the VM intervention (all $p < 0.05$). The quality of life also improved in the following domains: anxiety, activity limitation, eating and drinking, knowledge, and work/study (all $p < 0.05$)**.**
Conclusion: After 2 weeks of VM intervention in FD patients, we found a significant reduction in abdominal pain and improved in quality of life. Although the small sample size limits the generalizability of the findings, the observed improvement in abdominal pain and quality of life may hold clinical relevance for this population.

Keywords: *Abdominal pain, functional dyspepsia, pilot study, quality of life, visceral manipulation.*

Introduction

Functional dyspepsia (FD) is a most common chronic upper gastroduodenal disease without obvious organic causes or metabolic disturbances [1,2]. FD is characterized by symptoms such as upper abdominal discomfort or pain, early satiety, postprandial fullness, bloating, and nausea, which can significantly affect the quality of life of patients. FD is classified as chronic if it has lasted for the last 3 months, with the incidence of symptoms having been felt for at least 6 months prior to diagnosis. Globally, the prevalence of FD varies, with women having a slightly higher prevalence than men, at 25.3% vs 21.9% [3]. The pathophysiology of FD involves abnormalities in gastric motility, gastric neuromuscular function, and visceral hypersensitivity [4,5].

Dyspepsia accounts for one of the top 10 diseases in Indonesia, with a prevalence of 40–50% [6]. Additionally, the prevalence of FD among individuals aged 26 to 35 years is estimated to be as high as 50% [7]. Moreover, it has been reported that FD cases constitute nearly 30% of general practice and up to 60% of gastroenterology practice [8]. Despite the availability of various treatment options, the management of FD remains challenging due to the heterogeneity of symptoms and the limited efficacy of existing therapies in some patients.

The gastroduodenal region, comprising the stomach and duodenum, exhibits remarkable physiological mobility and motility, essential for normal functioning. Impairment of this motility can have significant implications, leading to functional disturbances in the organ itself and its surrounding structures [9]. Such limitations in organ motion may result in various pathological effects, including irritation, visceral spasm, dysmotility, increased tension, inflammation, visceral hypersensitivity, and emotional distress [10]. These motility disturbances often manifest as FD, a condition characterized by chronic or recurrent upper abdominal pain or discomfort, often accompanied by bloating, early satiety, or nausea [1,2].

Pharmacological interventions have been a primary focus in the management of FD, but their efficacy has been variable. Studies have shown that many pharmacological interventions provide only temporary relief and are not consistently superior to placebo [3]. Furthermore, not all treatments are effective in all cases of functional dyspepsia, highlighting the need for alternative approaches [11]. In this context, nonpharmacological therapies have gained attention as potential interventions for FD. Conservative interventions, such as dietary modifications, psychological interventions, exercise, and complementary therapies, have shown promise in reducing the symptoms of patients with FD [12,13,14,15].

The ineffectiveness of drug therapy alone in managing FD has prompted a shift towards a more comprehensive and holistic approach to patient care. Nonpharmacological therapies offer the advantage of addressing the multifactorial nature of FD, targeting not only the physical symptoms but also the psychological and social aspects of the condition [16]. Abdominal manipulation therapy, including visceral manipulation (VM), has been suggested as a potential treatment for FD. Lee and Maeng noted the potential effectiveness of VM for FD patients but emphasized the need for further studies to establish its efficacy [17].

The theoretical basis of VM posits that adhesions or limitations in the visceral tissues may alter neurophysiological processes and biomechanics potentially leading to pain and discomfort. VM is a manual therapy technique aimed at improving the mobility and function of abdominal soft tissues and organs through specific, gentle manoeuvres [18,19]. In recent years, non-pharmacological approaches, such as VM, have gained increasing recognition as viable treatments options for visceral disorders, including FD. While existing evidence supports the use of VM for certain gastrointestinal disorders, such as functional constipation, its efficacy in treating FD remains insufficiently established [20].

A pilot study was conducted to examine the effects of VM interventions on abdominal pain and the quality of life in individuals with FD. The

study aimed to quantify the short-term effects of VM sessions incorporating three specific techniques: lesser omentum stretching, stomach mobilization, and duodenum mobilization. We hypothesize that the combined effects of these interventions would have the capacity to have immediate changes in pain and quality of life.

Methods

Study participants

Twenty-nine FD patients participated in this nonrandomized pre-post pilot study. Participants were recruited from Wiyata Husasa Physiotherapy Clinic. Inclusion criteria were: (1) referral to outpatient physiotherapy with an FD diagnosis; (2) FD without gastritis for at least 3 months; (3) ability to read and write the Indonesian language; and (4) age 20 - 60 years. Exclusion criteria included: (1) gastritis; (2) diabetes/pancreatitis; (3) liver and biliary tract disease; (4) gastrointestinal tumour or malignancies; (5) Helicobacter pylori infection; and (6) use of analgesic medications. All participants provided written informed consent before enrollment into the study. The study received ethical approval from two institutions: the Faculty Ethics Review Committee (FERC) of UiTM Puncak Alam Campus (Approval ID: 500-FSK (PT.23/4)) and the Health Research Ethics Committee of the Health Polytechnic, Ministry of Health, East Kalimantan, Indonesia (Ethics No. DP.04.03/7.1/12146/2023).

To monitor the study, participants were carefully screened for any ongoing treatments, including medications and supplements, before enrolling in the study. Those who were taking any such treatments (medications and supplements) that could potentially interfere with the outcomes of VM were excluded from the study. This information was used to ensure that there were no significant differences between the experimental groups at the start of the study. And, Throughout the study, participants were regularly monitored and asked to report any new treatments or changes to their existing treatments.

Outcome measures

The primary outcomes were adherence rate, adverse events, and recruitment feasibility. Adherence rate was measured as the percentage of completed VM sessions of a maximum of 10 sessions (5 times per week for 2 weeks). Every session began and ended with questions. Participants were asked about adverse effects during the session, including a ticklish sensation, pain, light-headedness, and nausea. A non-serious adverse event was defined as an event that results in minor discomfort and does not require session or study termination. The number of participants who gave their consent and signed up each month served as a gauge of recruitment feasibility.

The secondary outcome was abdominal pain and quality of life among individuals with FD. Abdominal pain was measured using the Abdominal Pain Index (API), which includes pain frequency, pain time, pain duration, and pain intensity [21]. It consists of a questionnaire that asks patients to rate the severity of their abdominal pain on a scale from 0 to 10. The API may also include questions about the location and type of pain, as well as any associated symptoms. Furthermore, the frequency of pain is evaluated on a six-point scale that ranges from never to persistent pain throughout the day. The API demonstrated good construct validity for children and adolescents with chronic pain [19,22].

The Short-Form Nepean Dyspepsia Index (SF-NDI) was used to evaluate the quality of life. The SF-NDI is a valid instrument that can measure the disease-specific impact of FD on quality of life, which included anxiety, daily activity limitation, eating/drinking, knowledge/control, and work/study [23]. The questionnaire consists of 10 items, and each item is measured by a 5-point Likert scale ranging from 0 (not at all or not applicable), 1 (a little), 2 (moderately), 3 (quite a lot), and 4 (extremely). Individual items in each subscale are accumulated to obtain a quality-of-life score ranging from 0 to 100. Patients with scores above 15 on the SF-NDI indicate a significant reduction in quality of life.

Study protocol

Three licensed physiotherapists with 5-20years of clinical experience participated in this study. All therapists had received advanced training in VM and maintained clinical caseloads consisting of 80-85% visceral disorder cases, with approximately 85% of these being FD referrals from internal medicine doctors. Trained assessors conducted baseline and post-treatment measurements after completing standardized training to ensure measurement consistency and reliability. Participants were recruited through the outpatient physiotherapy clinic following referral for FD symptoms. The assigned physiotherapist evaluated each patient for study eligibility. Eligible patients who provided informed consent were enrolled in the study.

Participants received ten 30-minute VM sessions over two weeks (5 sessions/week). The decision to measure the effects of VM over a two weeks was based on the following considerations: (1) Previous studies by Silva et al [23] and Eguaras et al [24] had demonstrated VM effectiveness within two weeks; (2) Two weeks was deemed optimal to maintain participant engagement and minimize dropout rates, and ensuring the integrity of the data collected; (3) Conducting a longer-term study requires more resources, including time, funding, and personnels. Given these constraints, two weeks were a practical and feasible choice for this pilot investigation.

To minimize the risk of overreporting bias in our study, we implemented several strategies: (1) We used well-established and validated questionnaires that are designed to reduce bias and increase the reliability of self-reported data (such as the API and SF-NDI questionnaires). These instruments have been widely used in similar studies and have demonstrated robust psychometric properties; (2) Participants were blinded to the specific hypotheses of the study to reduce the likelihood of response bias. They were informed that the study aimed to assess the general effects of VM without disclosing the expected outcomes; (3) Participants were asked to complete their self-reports at regular intervals throughout the study rather than relying on a single point of data collection. This approach helped in capturing consistent and reliable data over time, reducing the risk of any single instance of overreporting significantly impacting the overall results; (4) We emphasized the anonymity and confidentiality of participant responses, encouraging honest and accurate reporting. Participants were reassured that their responses would be anonymized and used solely for research purposes, and; (5) In our data analysis, we applied statistical techniques to identify and control for potential outliers and overreporting to ensure that the results were not unduly influenced by biased reporting.

The VM intervention consisted of a standardized treatment protocol incorporating gastric and duodenal mobilization techniques along with lesser omentum stretching.

(1) Stretching the lesser omentum: The participant lies supine with both limbs bent. The practitioner stands on the left side of the patient. Both hands of the practitioner are placed on the left and right sides of the median line below the xiphoid process, with the fingers just above the stomach wall. With both hands, the practitioner slowly applies posterior pressure to the inside of the abdomen and performs stretching of the lesser omentum.
(2) Oscillations on the stomach: The participant lies supine with both limbs bent. The practitioner stands on the left side of the patient. The practitioner places the fingers of both hands on the abdomen in the gastric region and applies pressure posteriorly until the hands fully reach the gastric wall. Oscillatory movements are applied to the stomach.
(3) Frontal plane stomach mobilization: The participant lies on his right side. The practitioner stands behind the patient and places both hands on the left lateral costal margin (ribs 6-7) below the diaphragm. With both hands, he performs caudomedial mobilization of the stomach, followed by

counter-directional mobilization of the stomach craniolaterally.

(4) Transverse plane stomach mobilization: Patient lies right lateral decubitus, and the practitioner stands behind him. Using costal contact, the practitioner rotates the stomach medially to the right. Then, the practitioner performs the reverse movement with lateral rotation of the stomach to the left.
(5) Sagittal plane stomach mobilization: The stomach mobilization technique in the sagittal plane follows the same procedure as the frontal and transverse plane mobilizations. The practitioner's left hand is placed on the anterior part of the left costal margin at the level of 6^{th}-7^{th} ribs. The right hand is positioned on the posterior part of the left shoulder. With both hands, the practitioner mobilizes the stomach via the ribs in the sagittal plane by pressing the stomach in the anteroposterior direction and the right hand in the posteroinferior direction.
(6) Duodenum mobilization: Participant lies in a side-lying position, facing to the right, and both limbs slightly bent. The practitioner places both hands on the medial part of the abdomen, lateral to the ascending colon, then apply pressure to the inside of the posteromedial abdomen and stretches medially and craniocaudally. The practitioner maintains this position briefly until tissue relaxation is achieved.

Statistical analysis

The SPSS 16.0 program was used for statistical analysis of the obtained e measurement data. Since the data did not meet the assumption of normal distribution, Friedman's non-parametric test was applied. Descriptive statistics (mean age, gender, occupation, education, and marital status) were calculated for the study participants. Cohen's effect size was computed to assess baseline and post-intervention effect sizes for the aforementioned variables.

Results

Demographic characteristics of the study participants

A total of 33 subjects were screened for eligibility in this study. Of these, 29 met the inclusion criteria and completed the VM intervention, while 4 were excluded. The demographic characteristics of the participants are summarized in Table 1.

Primary outcomes: adherence and feasibility

The 29 participants who met the inclusion criteria completed the intervention with a 100% retention rate. Throughout the 2-week VM intervention, all participants tolerated the treatment well, with no significant or serious side effects reported. Seven participants experienced a ticklish sensation during the first VM intervention. Three participants felt a slightly uncomfortable sensation during the first abdominal VM mobilization but showed no resistance reaction or other signs of side effects. The remaining participants reported a comfortable sensation during the abdominal VM intervention. Notably, no dropouts occurred during the 2-week intervention period, and all participants provided positive feedback on the pilot study. Twenty-three participants reported improvements within the first week, including easier breathing, better sleep patterns, and increased abdominal comfort. The remaining 6 participants reported similar benefits after the second week of treatment. All participants noted a significant positive impact and expressed a desire for a long-term continuation of the therapy.

Secondary outcomes: Effect of visceral manipulation on abdominal pain and quality of life in FD patients

Table 2 presents the results of Friedman tests assessing abdominal pain changes in FD subjects across three time points (baseline, 1-week treatment, and 2-week treatment). The analysis revealed statistically significant differences in four pain-related parameters: (1) pain frequency

at baseline (mean difference = 3.52±0.57, p=0.001), after 1-week treatment (mean difference = 2.31±0.54, p=0.001), and after 2-week treatment (mean difference = 0.59±0.50, p=0.001); (2) pain time at baseline (mean difference = 1.48±0. 1, p=0.001), after 1-week treatment (mean difference = 1.17±0.38, p=0.001), and after 2-week treatment (mean difference = 0.59±0.50, p=0.001); (3) Pain duration at baseline (mean difference = 2.66±0.48, p=0.001), after 1-week treatment (mean difference = 1.52±0.51, p=0.001), and after 2-week treatment (mean difference = 0.59±0.50, p=0.001); and (4) Pain intensity at baseline (mean difference = 3.52±0.51, p=0.001), after 1-week treatment (mean difference = 2.10±0.67, p=0.001), and after 2-week treatment (mean difference = 0.59±0.50, p=0.001).

Table 3 shows significant changes in FD subjects' quality of life as indicated by Friedman test results: (1) anxiety of at baseline (mean difference = 3.14±0.58, p=0.001), after 1-week treatment (mean difference = 1.93±0.75, p=0.001), and after 2-week treatment (mean difference = 1.31±0.47, p=0.001); (2) limitation of daily activities at baseline (mean difference = 3.31±0.47, p=0.001), after 1-week treatment (2.07±0.46, p=0.001), and after 2-week treatment (mean difference = 1.03±0.19, p=0.001); (3) Eating and drinking at baseline (mean difference = 3.45±0.51, p=0.001), after 1-week treatment (mean difference = 2.03±0.42, p=0.001), and after 2-week treatment (mean difference = 1.03±0.19, p=0.001); (4) Knowledge and control at baseline (mean difference = 3.17±0.71, p=0.001), after 1-week treatment (mean difference = 1.34±0.48, p=0.001), and after 2-week treatment (mean difference = 1.00±0.00, p=0.001); and (5) Work and study at bseline (mean difference=3.14±0.58, p=0.001), after 1-week treatment (mean difference = 2.00±0.38, p=0.001), and after 2-week treatment (mean difference = 1.07±0.26, p=0.001). These results demonstrate a statistically significant improvement in the quality of life from baseline to 1-week treatment and 2-week treatment.

Discussion

The pilot study aimed to determine the effect size of VM sessions on abdominal pain and quality of life in adult individuals with functional dyspepsia (FD). The results demonstrated high levels of adherence, positive feedback, and satisfaction, indicating that VM intervention was well-received. These findings suggest that VM may be a promising alternative for those with FD.

Participant feedback highlighted several reasons for the favourable reception of VM, including perceived comfort, relaxation, reduced abdominal pain, and improved quality of life. The aforementioned positive outcomes served to reinforce the participants' acceptance of VM. Furthermore, no significant adverse effects were observed, supporting the safety of VM. Finally, the findings of this study demonstrated that VM intervention can significantly reduce abdominal pain and improve the quality of life of FD patients during the two-week treatment period. These results align with concurrent findings from studies by Maeng and Lee (2015) and Silva et al. (2018), which support the notion that visceral manipulation therapy holds promise as a therapeutic modality for individuals grappling with functional dyspepsia [17,19].

A multitude of mechanisms have been identified to explain the effects of VM, as supported by various studies. Mechanical effects- arising from physical forces such as compression, stretching, mobilization, and oscillations of body tissues and organs- have been shown to enhance proprioceptive communication through mechanical interactions within the body. This, in turn, may reduce pain threshold, structural abnormalities, and faulty posture [26]. From a neurological perspective, VM is believed to stimulate the parasympathetic nervous system, promoting relaxation and reducing anxiety [27]. The combined effects of these mechanisms can enhance visceral mobility and function, as well as

improving emotional well-being, thereby contributing to a better quality of life [20].

Given the encouraging results of this preliminary study, clinicians should consider incorporating visceral manipulation as a therapeutic approach for patients with functional dyspepsia [24]. The study's strengths lie in its focus on the potential clinical benefits of visceral manipulation, particularly in alleviating abdominal pain and improving patients' quality of life. These findings offer preliminary evidence that could facilitate the development of more effective treatment strategies for managing functional dyspepsia.

Nevertheless, this study has several limitations. First, the small sample size and lack of a control group may limit the generalizability of the findings. Second, standardizing manual therapy interventions is challenging due to the variability in pressure and sensitivity among practitioners. Finally, the study design did not assess the long-term sustainability of symptom reduction.

Future research should prioritize large scale randomized controlled trials to further examine the efficacy and safety of VM in patients with FD.

Conclusion

The results of this pilot study suggest that VM may benefit adult patients with FD, as evidenced by reduced abdominal pain and improved quality of life. The findings indicate that this manual therapy approach could serve as a promising adjunctive treatment option for individuals with FD, a condition with limited treatment options.

Given its non-invasive and relatively safe nature, VM presents an appealing therapeutic option for individuals seeking complementary or alternative treatments. This study lays the groundwork for further research into VM's role in managing abdominal pain and enhancing the quality of life in FD patients.

Ethics approval and consent to participate:

The research had been approval by the Faculty Ethics Review Committee (FERC) of the Faculty of Health Sciences, UiTM Puncak Alam Campus (Approval ID: 500-FSK (PT.23/4)) and received ethical approval from the Health Research Ethics Committee of the Health Polytechnic, Ministry of Health, East Kalimantan, Indonesia (Ethics No. DP.04.03/7.1/12146/2023). During the research, the researcher pays attention to the ethical principles of information to consent, respect for human rights, beneficence and non-maleficence.

Patient consent for publication

Written informed consent was obtained for anonymized patient information to be published in this article.

Authors' Contributions

AA: Conceptualization, Data Curation, Formal Analysis, Methodology, Validation, Visualization, Writing – Original Draft, Review & Editing; HM: Supervision, Visualization, Writing – Review & Editing

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Conflict of interest

The authors declare no conflict of interest.

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Table 1. Demographic data of the participants characteristics

	Frequency	Percentage
Demographics	**n = 29**	
Gender		
Male	12	41.4
Female	17	58.6
Age groups		
20-35	6	20.7
36-45	9	31.0
>46	14	48.3
Marital status		
Single	0	0.0
Married not at home	0	0.0
Married at home	27	93.1
Divorced/Widower	2	6.9
Educational level		
Junior high school	0	0.0
High school	0	0.0
Bachelor's degree	29	100
Employment status		
Civil servant	4	13.8
Private employee	1	3.4
Self-employed	8	27.6
Retired	5	17.2
Not working	11	37.9

Table 2. Results of VM Effect on FD patients' abdominal pain.

	Baseline	1 weeks	2 weeks	Significance
Outcome measure	(Mean±SD)	(Mean±SD)	(Mean±SD)	***p-value***
Pain frequency	3.52±0.57	2.31±0.54	0.59±0.50	0.001*
Pain time	1.48±0.51	1.17±0.38	0.59±0.50	0.001*
Pain duration	2.66±0.48	1.52±0.51	0.59±0.50	0.001*
Pain intensity	3.52±0.51	2.10±0.67	0.59±0.50	0.001*

SD: standard deviation; * $p<0.05$

Table 3. Results of VM Effect on quality of life in FD patients.

Outcome measure	Baseline Mean±SD	1 weeks Mean±SD	2 weeks Mean±SD	Significance
Anxiety	3.14±0.58	1.93±0.75	1.31±0.47	0.001*
Daily activity limitation	3.31±0.47	2.07±0.46	1.03±0.19	0.001*
Eating/drinking	3.45±0.51	2.03±0.42	1.03±0.19	0.001*
Knowledge/control	3.17±0.71	1.34±0.48	1.00±0.00	0.001*
Work/study	3.14±0.58	2.00±0.38	1.07±0.26	0.001*

SD: standard deviation; * $p<0.05$

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ORIGINAL ARTICLE

Assessment of 90-day Return to Hospital among COVID-19 Patients: A Single Centre Study.

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Abstract

Introduction: Readmissions among COVID-19 patients increase healthcare burdens and resource utilization. Identifying risk factors can help mitigate this issue**.** This study aimed to determine the proportion and predictors of hospital returns among COVID-19 patients.

Materials and methods: A single-centre retrospective cohort study was conducted involving adult COVID-19 patients admitted between December 2020 and May 2021. Patients who died during hospitalization or were transferred to another hospital were excluded. Demographic and clinical characteristics from index hospitalisation were collected. Subsequent emergency department visits or readmission for acute illness within 90 days post-discharge were recorded, including dates and reasons for return, and readmission outcome. Multivariable logistic regression was used to identify the independent predictors for return to hospital.

Results: A total of 1000 COVID-19 patients were included, and 86 patients [8.6% (95% CI: 7.0–10.5] returned to the hospital within 90 days post-discharge. Most returns (n = 52, (60.5%), occurred within two weeks of discharge. Multivariable analysis identified chronic kidney disease (AOR=3.11, 95% CI: 1.40-4.90) and complication with organizing pneumonia (AOR=3.17, 95% CI: 1.36-7.40) as independent predictors for return to hospital. Additionally, the combination of underlying cardiac disease and concomitant bacterial infection significantly increased the risk (AOR=5.47, 95% CI: 2.57-11.24).

Conclusions: Several factors, including underlying medical conditions and complications during admission, were independent predictors of hospital returns. These factors should be carefully addressed prior to discharge to reduce readmission risk.

Keywords: *Coronavirus, COVID-19, readmission, SARS-CoV-2.*

Introduction

Coronavirus disease (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to significant global morbidity and mortality since its emergence[1]. The dramatic widespread progression of COVID-19 into a pandemic has placed a substantial burden on healthcare systems worldwide, with its broad clinical presentations ranging from mild respiratory symptoms to severe multi-organ dysfunction [2].

The management of COVID-19 remains a challenge for healthcare providers and public health authorities due to the evolving nature of the virus, the emergence of new variants, and the long-term consequences of infection. While acute care has been the primary focus, post-discharge outcomes, including hospital readmission, have gained increasing attention. Returns to hospital, whether through emergency department (ED) visits or readmissions, contribute to healthcare strain by increasing patient load, resource utilization, and overall economic costs [3]. Several international studies have reported the proportion of readmission or return to hospital among COVID-19 patients and their associated factors; however, data within Malaysia remain scarce. This study aims to address this knowledge gap. Understanding the local burden and determinants of hospital returns is crucial for optimizing post-discharge care strategies, improving patient outcomes, and reducing unnecessary healthcare utilization.

Therefore, we aimed to determine the proportion of hospital returns among hospitalised COVID-19 patients and identify independent predictors for such returns. These findings have important implications for discharge management, potentially reducing readmission-associated morbidity and mortality. By identifying the risk factors for hospital returns this study will guide healthcare providers in optimizing care for high-risk patients and preventing readmissions.

Materials and methods

Study design and participants

This retrospective cohort study involved COVID-19 patients admitted to the adult medical ward of Hospital Raja Perempuan Zainab (HRPZII) between December 2020 to May 2021. HRPZll served as the primary referral centre for COVID-19 in Kelantan, Malaysia during the study period.

Inclusion criteria comprised of adult patients (≥ 18 years), with laboratory-confirmed diagnosis of COVID-19 by reverse transcriptase–polymerase chain reaction (RT-PCR) assay, Antigen Rapid Test kit (RTK-Ag), or GeneXpert performed on nasopharyngeal swab specimens. We excluded those who were transferred to other facilities for step-down care or expired during the index hospitalisation.

Index hospitalisation is defined as the patient's first COVID-19-related admission during the study period. Return to hospital is defined as the first subsequent visit to the emergency department or readmission for acute problems within 90 days post-discharge (excluding elective procedures, deliveries, and trauma cases).

Sample size was calculated using an online calculator based on the single proportion formula [4]. Using an expected proportion of 9% derived from previous study [5], with 2% precision at a 95% confidence level, the minimum required sample size was 962 after accounting for a 10% dropout rate. No sampling method was applied in this study because all available samples within the sampling period were screened for eligibility. This approach was adopted to maximise the number of samples and minimise the risk of bias.

Ethical approval

This study adhered to the Declaration of Helsinki and Malaysian Good Clinical Practice Guideline. It was registered in the National Medical Research Registry (NMRR-21-1410-60651), and approved by the Medical Research & Ethics

Committee (MREC), Ministry of Health Malaysia (KKM/NIH/ P21-1365 (4)).

Data collection

Facility approval was obtained from the head of medical department and the hospital director prior to data collection. Patients' data was extracted from the electronic medical system using keyword search technique based on the discharge diagnosis of COVID-19. Collected data included demographics, comorbidities, highest C-reactive protein (CRP) value, chest X-ray results, steroid duration, ICU admission, complications, and length of stay during their index hospitalisation. Hospital returns within 90 days post-discharge were traced using electronic medical records, with patients who were lost to follow-up categorized as 'no return'. The primary reason for return to hospital was also identified based on the documented diagnosis at the emergency department. Readmitted patients, ICU admissions and outcome upon discharge were collected. All data were extracted from both electronic and physical clinical records using a standardised data collection form.

Statistical analysis

Demographic and clinical characteristic variables were analysed using descriptive statistics. Categorical variables were presented as frequencies and percentages, while continuous variables were presented as mean ± standard deviation (SD) or median and interquartile range (IQR) depending on the normality of distribution. The proportion of return to hospital was reported as a percentage with 95% confidence interval (CI).

Univariable analyses were performed using chi-square or Fisher's Exact test for categorical variables and independent t-test or Mann-Whitney for continuous variables. Multiple logistic regression analysis was used to identify the significant predictors for return to the hospital. Variables with $p < 0.25$ from univariable analyses were included for the multivariable model. Both forward and backward LR method were applied for variable selection. Multicollinearity was assessed with the variance inflation factor (VIF), and the model assumptions were examined using classification table and the Hosmer-Lemeshow test. Two-way interaction terms were further stratified for interpretation. Adjusted odds ratios (AORs) with 95% CIs were reported for the final model.

The statistical analyses were performed using IBM's SPSS software version 23 and RStudio version 1.4.1103. A p value of less than 0.05 was considered statistically significant.

Results

Study population and baseline characteristics

A total of 1,000 patients who fulfilled the study criteria were included in the analysis. The mean age was 52.76 ± 17.18 years old, with a male predominance (54.5%, n = 545) and a predominantly Malay race (98.3%). The most common comorbidities were hypertension (48.1%), diabetic mellitus (40%), cardiac disease (10.8%), chronic kidney disease (CKD) (8.4%), and chronic lung disease (6.8%). Demographic and clinical characteristics for index hospitalisation are presented in Table 1.

Hospital Return Outcomes

The proportion of patients returning to hospital within 90 days post-discharge was 8.6% (95% CI: 7.0 – 10.5). Among those who returned, 64 patients (74.4%) required readmission. The interval [median (IQR)] from discharge to return was 12 (29) days, and most of the returns (60.5%) were within two weeks post-discharge. The most common reasons for return were sepsis (31.3%, n = 27) followed by pneumonia (22.1%, n = 19) and long COVID syndrome (20.9%, n = 18). On readmission, 6 (7%) patients required ICU care, and 4 patients (4.7%) had inpatient mortality (Table 2).

Predictors of Hospital Return

The final multiple logistic regression model consisted of four independent predictors. This model significantly improved the prediction of return to hospital among hospitalised COVID-19 patients compared to a null model, $\chi^2(5)=35.603$, $p<0.001$. The model also explained 7.9% (Nagelkerke R^2) of the variance for the study outcome, and the correct prediction rate was 91.4% of cases. The Hosmer-Lemeshow test showed that the overall model fit well ($p = 0.934$). The model indicated that underlying CKD (AOR = 3.11, 95% CI: 1.40-4.90, $p = 0.004$) and complications with organising pneumonia (AOR = 3.17, 95% CI: 1.36-7.40, $p = 0.009$) were significant predictors for return to the hospital. There was significant interaction between underlying cardiac disease and complications with bacterial infection. Further subgroup analysis revealed that among those without underlying cardiac disease, concomitant bacterial infection had 1.68 higher odds of return ($p = 0.043$). Meanwhile, the presence of both cardiac disease and bacterial infection resulted in 5.47 times higher odds of return ($p < 0.001$). The result of multiple logistic regression is summarised in Table 3.

Discussion

This study describes the demographic and clinical characteristics of COVID-19 patients admitted to a tertiary hospital on the east coast of Malaysia and identifies risk factors for hospital return. The cohort primarily comprised middle-aged and elderly patients with pre-existing comorbidities, including hypertension, type 2 diabetes mellitus, cardiac disease, and chronic kidney disease (CKD). These results are related to the reported incidence of COVID-19 in Malaysia, which was highest among the 55-to-64-year age group, and most cases involved chronic comorbidities such as diabetes, hypertension, and heart disease [6]. This pattern is consistent with data reported from China and New York [7, 8].

In this study, 8.6% of patients returned to the hospital, and 6.4% required readmission within 90 days post-discharge from index hospitalisation. A direct comparison with previous studies is difficult due to variations in follow-up duration, as most studies focus solely on readmission. A study in New York reported a lower proportion of return at 3.6% albeit a shorter follow-up period of 14 days [3]. The overall 30-day readmission rate ranges between 4.3% to 7.6% [9-11]. Another study in Spain, with a longer six-month follow-up, reported a much lower readmission rate at 4.3% [12]. Meanwhile, a large-scale cohort study in the United States found a 9% readmission rate within two months of discharge [5]. Most returns were due to infection which is related to the predictors identified in our analysis.

Examining factors associated with return to hospital, our study found that underlying CKD is a significant predictor in multivariable analysis. CKD has also been shown to predict readmission in a few published studies [5, 9, 11]. This is expected because patients with CKD or kidney failure are already at high risk of recurrent hospitalisations even without a COVID-19 infection [13]. Those with CKD are generally older and often have some degree of functional impairment, along with renal and cardiovascular complications that may contribute to readmission [14]. Kidney disease is also associated with secondary immunodeficiency, which increases susceptibility to infection [15]. Thus, special care must be taken for this group of patients before discharge.

In terms of acute complications, patients with organising pneumonia (OP) had a higher risk of returning to the hospital. This can be explained by the fact that the primary site of COVID-19 infection is the lungs, and OP may occur as a pulmonary reaction to the infection. Acute inflammatory process triggered by viral-induced damage to the alveoli is the key mechanism for the development of OP [16]. Patients may experience ongoing respiratory symptoms such as exertional dyspnoea and fatigue post-discharge. Worsening symptoms and recurrent infection are common and often lead to return to the hospital. While most patients recover from OP within a

year, some may require specific treatment [16]. Outpatient follow-up is therefore essential to monitor patients'
progress.

Our results showed that cardiac disease alone does not predict a return to the hospital, contrary to several previous studies [5, 10, 11]. However, the co-occurrence of cardiac disease and bacterial infection significantly increases risk of return. Bacterial infection was defined as the initiation of antibiotics based on clinical diagnosis by the treating clinicians regardless of culture results. This approach may overestimate true bacterial infections, given the the excessive use of antibiotics in COVID-19 patients [17]. According to a cohort study in Italy, bacterial infection may reflect disease severity in COVID-19 patients but is not associated with increased mortality [18]. More severe disease inevitably contributes to a longer recovery period and consequently increases the risk of return. COVID-19 is also known to exacerbate pre-existing cardiac disease, leading to a severe clinical course and adverse outcomes [19]. The interplay between bacterial infection and underlying cardiac disease during COVID-19 infection further aggravates the outcome. To our knowledge, none of the previous studies reported a synergistic interaction between cardiac disease and bacterial infection leading to return or readmission to the hospital. This result merits further investigation. Nevertheless, it should be interpreted with caution given the non-standard definition of bacterial infection used in this study.

This study has several limitations. First, its retrospective design means that data quality relies on documentation in clinical records and cannot capture real-time disease progression. Second, the return rate may have been underestimated because visits to other healthcare facilities were not captured during the follow-up. Other potential factors that may influence hospital readmission that include COVID-19 variants, patients' adherence to outpatient follow-up, and medications compliance, were not considered. Additionally, the generalisability of the results may be limited due to the relatively small sample size. Another limitation is the 90-day follow-up period, which does not allow assessment of longer-term outcomes. Lastly, this study was conducted prior to the completion of the mass vaccination program in Malaysia. Follow-up studies might be required to compare these findings with current patient profiles.

Conclusions

Our study found that the proportion of return to hospital was 8.6%, and the predictors of return were chronic kidney disease, organising pneumonia, cardiac disease, and concomitant bacterial infection. Return to hospital and readmission among COVID-19 patients will continue to impose additional burdens on the healthcare system. Although COVID-19 has now entered the endemic phase, continuous monitoring and evaluation of best practices crucial for managing future outbreaks. Vulnerable patient groups with these risk factors require comprehensive assessment and proper predischarge plan to reduce the risk of return or readmission. The use of stratification with a validated scoring method is warranted to facilitate healthcare providers in strategizing discharge plans for COVID-19 patients.

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Conflict of interest

The authors declare they have no conflict of interest.

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Authors' Contributions

YY & NA - concept, design, literature search, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing. MM, FCH & GAR – concept, data acquisition, manuscript review.

Table 1**.** Demographic and clinical characteristics for index hospitalisation

Characteristics	Total n (%)	No return n (%)	Return n (%)	*P* value
		914 (91.4)	86 (8.6)	
Age group, year				
<40	267 (26.7)	250 (27.3)	17 (19.8)	0.307
40-60	349 (34.9)	317 (34.7)	32 (37.2)	
>60	384 (38.4)	347 (38.0)	37 (43.0)	
Gender				
Male	455 (45.5)	410 (44.9)	45 (52.3)	0.184
Female	545 (54.5)	504 (55.1)	41 (47.7)	
Race				
Malay	983 (98.3)	899 (98.4)	84 (97.7)	0.652*
Non-Malay	17 (1.7)	15 (1.6)	2 (2.3)	
Comorbidities				
Hypertension	481 (48.1)	434 (47.5)	47 (54.7)	0.203
Diabetes Mellitus	400 (40.0)	352 (38.5)	48 (55.8)	0.002
Cardiac disease	108 (10.8)	91 (10.0)	17 (19.8)	0.005
CKD/ESRF	84 (8.4)	68 (7.4)	16 (18.6)	0.001
Chronic lung disease	68 (6.8)	59 (6.5)	9 (10.5)	0.158
Length of stay, median (IQR), days	7 (5)	7 (5)	9 (10)	0.007†
ICU admission, yes	148 (14.8)	131 (14.3)	17 (19.8)	0.175
CRP, median (IQR), mg/L	25.3 (72.8)	23.5 (68.7)	48 (100.8)	0.004†
Steroid use	619 (61.9)	553 (60.5)	66 (76.7)	0.003
Complications	555 (55.5)	493 (53.9)	62 (72.1)	0.001
Sepsis	404 (40.4)	353 (38.6)	51 (59.3)	<0.001
Acute kidney injury	74 (7.4)	66 (7.2)	8 (9.3)	0.481
Organising pneumonia	34 (3.4)	25 (2.7)	8 (9.3)	0.005*
Transaminitis	99 (9.9)	93 (10.2)	6 (7.0)	0.342
Pulmonary embolism	21 (2.1)	19 (2.1)	2 (2.3)	0.7*
ACS	10 (1.0)	7 (0.8)	3 (3.5)	0.047*

* Fisher's exact, † Mann-Whitney

Notes: CKD = chronic kidney disease; ESRF = end stage renal disease; ICU = intensive care unit; CRP = C-reactive protein; ACS = acute coronary syndrome

Table 2. Characteristics and outcomes of COVID-19 patients who returned to hospital.

Characteristics	n (%)
Interval, weeks (from discharge to return)	
<2w	52 (60.5)
2-4w	11 (12.8)
4-8w	16 (18.6)
>8w	7 (8.1)
Required admission	
Yes	64 (74.4)
No	22 (25.6)
Reason for return	
Sepsis	27 (31.3)
Pneumonia	19 (22.1)
Long covid syndrome	18 (20.9)
Acute kidney injury	5 (5.8)
Acute coronary syndrome	4 (4.7)
Gastrointestinal bleed	2 (2.3)
Stroke	1 (1.2)
Heart failure	1 (1.2)
Acute respiratory distress syndrome	1 (1.2)
Others	22 (25.6)
ICU admission	
Yes	6 (7.0)
No	86 (93.0)
Outcome	
Discharge home	81 (94.2)
In-patient mortality	4 (4.7)
Step down care	1 (1.2)

Table 3. Multiple logistic regression analysis to determine predictors for return to hospital among COVID-19 patients

Predictors	X^2 stat (df)*	Adjusted OR (95% CI)	*P*
Chronic kidney disease	5.06 (1)	3.11 (1.40, 4.90)	0.004
Organising pneumonia	6.84 (1)	3.17 (1.36, 7.40)	0.009
Cardiac disease and bacterial infection	20.45 (1)		
Yes, Yes	4.55†	5.47 (2.57, 11.24)	<0.001
No, Yes	2.03†	1.68 (1.02, 2.77)	0.043
Yes, No	-0.55†	0.71 (0.17, 2.10)	0.582
No, No (reference)		1	

* Likelihood Ratio (LR) test, † Z test.

Notes: OR = odd ratio; CKD = chronic kidney disease.

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ORIGINAL ARTICLE

Investigating Menopausal Symptoms and Healthcare-Seeking Practices Among Midlife Women in Malaysia.

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Abstract
Background: Menopause is a natural biological process marked by the cessation of menstruation and a decline in oestrogen levels, often accompanied by various physical and psychological symptoms. The experience of menopause can differ across populations due to cultural and dietary factors. However, effective management of menopausal symptoms is crucial for improving quality of life. **Objective:** This study aims to assess the prevalence and severity of menopausal symptoms among midlife Malaysian women and to explore their healthcare-seeking practices.
Research Method: A cross-sectional, survey-based study was conducted among 300 Malaysian women aged 40-60, residing in Ipoh, Perak. A non-probability sampling method using combination of purposive and snowball sampling was used to recruit the study participants. A structured online questionnaire was used to assess demographic information, severity of menopausal symptoms, and the management approaches adopted. Data were analysed using descriptive statistics via SPSS software. **Results:** In this study, most respondents (39.0%) reported that their menopausal symptoms caused mild problems, while 35.7% experienced moderate problems, and 13.0% experienced severe to complete problems. The most common symptoms included joint pain (74%), mood swings (72.3%), and forgetfulness (70%). Only 12.7% of respondents reported using any treatment for menopause, with Hormone Replacement Therapy (HRT) being the most common (20 out of 39 respondents). Approximately 34.7% of respondents sought medical consultation for their symptoms. **Conclusion:** The study highlights that a significant number of Malaysian women experience mild to moderate menopausal symptoms, with physical and psychosocial issues being the most common. Despite the prevalence of symptoms, only a small proportion of women sought treatment. These findings emphasize the need for increased awareness and healthcare support to improve the quality of life for menopausal women. Future research should investigate cultural and societal factors influencing treatment-seeking behaviour.

Keywords: *Malaysian women, Menopausal symptoms, Menopause.*

Introduction

Menopause is a significant transitional phase in a woman's life, characterised by the cessation of menstrual periods and a decrease in reproductive hormones, notably oestrogen. This natural biological process, which commonly occurs between the ages of 45 and 55, is frequently accompanied by a range of physical, emotional, and psychological symptoms that might vary in severity, intensity and impact on daily living [1,2]. Inadequate management of common symptoms such as hot flashes, mood swings, vaginal dryness, nocturnal sweats, and joint pain, can significantly affect woman's quality of life [3].

In Malaysia, the menopausal experience is influenced by a distinct interaction of cultural, dietary, and healthcare traditions. According to some studies, menopausal symptoms among Malaysian women are less intense in comparison to those in Western countries. Specifically, there is a higher occurrence of musculoskeletal complaints rather than vasomotor symptoms such as hot flashes [4,5]. However, there was a tendency for the women to have more of the atypical symptoms such as tiredness and reduced concentration level [6].

Effective management of menopausal symptoms is crucial for improving quality of life throughout these physiological changes, with treatment options ranging from lifestyle modification to medicinal treatments. Mild symptoms can typically be alleviated by adopting lifestyle modifications such as practicing a well-balanced diet, engaging in regular physical activity, managing stress, and using complementary therapies like herbal supplements, including phytoestrogens found in soy products. However, the effectiveness of these strategies requires more investigation [7]. For moderate to severe vasomotor symptoms, more targeted treatments such as Hormone Replacement Therapy (HRT) are often required. HRT, which includes the administration of oestrogen or a combination of oestrogen and progesterone, is highly efficient in alleviating severe symptoms such as hot flashes and night sweats. Additionally, it provides advantages such as the prevention of osteoporosis and the maintenance of cardiovascular health [8,9].

In Malaysia, the management of menopausal symptoms is often impacted by cultural perceptions and healthcare resources. A significant number of women opt to address their symptoms using traditional or herbal therapies instead of seeking medical intervention [10,11]. The objectives of this study are to explore the variety and severity of menopausal symptoms experienced reported by midlife Malaysian women, as well as the factors influencing their treatment-seeking behaviour. This study will provide insights into improving menopausal women's' quality of life by better understanding their symptomatology and management options.

Methods

Study location and study design

This survey-based study targeted respondents residing in Ipoh, the capital city of Perak, a state located in the northern region of Peninsular Malaysia. The study utilized a cross-sectional design for data collection, with participants completing an online questionnaire.

Study Participants and Sample size calculation

Malaysian women aged 40-60 years, from various ethnicities (Malay, Indian, Chinese, indigenous, and others), were invited to participate in the study. The inclusion criteria encompassed women with menopause status, while women with a history of surgical, chemical, or other menopause-inducing conditions, as well as those who had experienced premature menopause, were excluded. The minimum sample size was calculated using a 95% confidence level, a population proportion of 20.5% (the percentage of women aged 40-64 years in Malaysia)[12], and a 5% margin of error, yielding a requirement of 242 participants. However, we successfully recruited 300 participants for this study.

Data collection method

A non-probability sampling method that combines purposive and snowball sampling was used to recruit the study participants. A structured questionnaires was provided in Google Forms and distributed online. Respondents were invited to participate through a link to the questionnaire posted on various social media platforms such as Facebook, Twitter, WhatsApp for 4 months. The form included a cover letter and informed consent. No incentives were offered to responders. The data were used for scientific purposes, and their confidentiality was guaranteed.

Questionnaire

This study used self-administered questionnaire, which consists of three parts:

1. Socio-demographic details of respondents: This section collects the socio-demographic information of the participants.
2. Menopausal symptoms: This section contains 29 statements designed to assess the severity of menopause symptoms experienced by the respondents. The total score ranges from 0 to 87, with responses graded on a Likert scale, 0 (not at all), 1 (quite a bit), 2 (a little bit) and 3 (extremely). The severity of symptoms is categorised as follows: 'no problem' (≤4), 'mild problems' (4-22), 'moderate problems' (23-43), 'severe problems' (44-82), and 'complete problems' (≥82).
3. Management of menopause: This section addresses the approaches used by respondents to manage menopause symptoms. The responses were analysed using descriptive statistics.

To ensure the validity of the questionnaire, a validity test and pilot study were conducted. Two expert teams reviewed and critiqued the questionnaire for content validation. The Content Validity Index (CVI) was calculated, with all questions achieving a score greater than 0.80/1.00, thereby meeting the required standard. Additionally, a pilot study for the questionnaire reliability test was conducted with 30 participants. The Cronbach's Alpha values was 0.916, indicating good reliability.

Ethical consideration

Prior to participation, all participants provided informed consent for the study. The researchers adhere to the principles of the Declaration of Helsinki (the Helsinki Declaration of 1975), which emphasise the principles of justice, beneficence, and respect for persons are used to ensure that all processes are kept confidential and private. Personal details remain confidential and accessible only to authorized study personnel.

Data Analysis

The data was analysed using the Statistical Package for Social Science (SPSS) version 20.0 (SPSS Inc, Chicago, IL). Descriptive analyses were used to illustrate demographic characteristics and analyse the study parameters. All variables were categorised as categorical and were provided as absolute numbers with percentage values.

Results

Respondents' characteristics

A total of 300 responses collected via Google Forms that met the inclusion criteria were included in the data analysis. Table 1 summaries the socio-demographic characteristics of the respondents. The majority were Malay, accounting for 73.3% of the total sample. Approximately 69% of respondents had attained a higher level of education, with 73.3% having no educational background in health sciences, medicine, or non-health sciences. Additionally, most respondents belonged to the M40 income group (RM 4,360 – RM 9,619), and 45.3% resided in urban areas.

Menopausal symptoms

Menopausal symptoms were assessed using 29 questions, as detailed in Table 2. These questions aimed to evaluate the severity of menopausal symptoms experienced by midlife women. The total score from the questionnaire ranged from 0 to 87, with 0 representing the absence of symptoms and 87 indicating the most severe symptoms. Scores below 4 were categorized as indicating no significant problems, scores from 4 to 20 were considered to reflect mild problems, scores from 21 to 42 were classified as moderate problems, scores from 43 to 82 were regarded as severe problems, and scores exceeding 82 were categorized as complete problems [13].

As shown in Table 3, the majority of respondents reported mild menopausal problems with menopausal symptoms (39.0%), followed by moderate problems (35.7%), severe problems (12.3%), no problems (12.3%), and only 1.0% of respondents reported complete problems. These findings suggest a relatively low incidence of severe menopausal symptoms among Malaysian women.

The most commonly reported menopausal symptoms among respondents included pain or stiffness in joints and muscles (74%), mood swings (72.3%), forgetfulness (70%), difficulties concentrating (62.3%), easy weight gain (69%), easily feeling tired/fatigue (68.7%), frequent headaches (64.3%), increased irritability (64.3%), and hot flashes (61.7%). The severity of these symptoms ranged from mild to extremely significant.

Additionally, over half of the participants reported symptoms such as breast pain (56.7%), vaginal dryness (56.4%), heart discomfort (55.0%), and symptoms related to sleep disturbances, including night sweats (59.0%), difficulty falling asleep and staying asleep (54.0% and 57.7%), and waking up early (55%). Psychological symptoms, such as being more depressed and anxious, were also reported by 59.3% of the respondents. Urinary incontinence was reported by 59.3% of respondents. Other urinary symptoms, reported by less than half of the respondents, included pain when urinating (39.3%), burning during urination (38.3%), and difficulty urinating (41.3%).

Menopause management

The management of menopause assessed in this study is outlined in Table 4. We specifically focused on the management of menopausal symptoms using interventions such as Hormone Replacement Therapy (HRT) and the consumption of supplements, vitamins, or herbs. A total of 120 respondents (40.3%) reported not using any treatment to manage their menopausal symptoms, while 39 respondents (12.7%) reported using some form of treatment. Of these 39 respondents, 20 had taken HRT, while 9 had used supplements, vitamins, herbs, or traditional medications. Additionally, 104 respondents (34.7%) consulted a physician during menopause, while 55 (18.3%) did not seek medical consultation. Meanwhile, 141 respondents (47.0%) reported not experiencing any menopausal symptoms.

Discussion

Menopausal symptoms

A study involving midlife women attending a primary health clinic in Malaysia found that, women usually experience at least one menopause symptom with joint pain, menstrual changes, and hot flushes being the most frequent symptoms [14]. In our study, the five most commonly reported menopausal symptoms (69-74%) were mood swings, forgetfulness, joint or muscle pain or stiffness, fatigue, and weight gain, highlighting the physical and psychological burden of menopause. These findings are consistent with other studies conducted in Malaysia, which also identified joint and muscle discomfort, followed by fatigue, as the most prevalent menopausal symptoms [15,16]. Similarly, a systematic review in Malaysia

confirmed that although there is a wide variation in the reported prevalence of menopausal symptoms, physical symptoms are the most common, followed by psychological, vasomotor, and sexual symptoms [10].

Notably, sleep disturbances, including night sweats (59%) and difficulty falling or staying asleep (54%–57.7%), were prevalent, indicating the significant impact of menopause on overall well-being. Psychological symptoms, such as increased anxiety (59.3%) and depression, highlight the mental health dimension of menopause, which often remains under-addressed. A holistic approach combining medical, psychological, and lifestyle interventions is recommended, especially for managing psychological and sleep-related symptoms.

Low oestrogen levels in menopausal women were found to contribute to vaginal issues among our respondents, including vaginal dryness (56.4%), vaginal itchiness (47.7%), and vaginal infections (32.7%). These findings are consistent with another study among Malaysian women, where 40.3% of women reported vaginal dryness and 34.1% reported sexual issues [15]. However, this study did not include questions related to sexual issues, as they are considered a sensitive issue in Asian culture. Additionally, this study did not measure participants' lipid profiles, even though menopause may impact lipid metabolism. Lipid abnormalities are highly prevalent among menopausal women, with the late menopause group exhibiting the highest incidence of elevated serum triglyceride levels [17].

While vasomotor symptoms such as hot flushes, sweating, and vaginal dryness were observed in this study, their prevalence was slightly lower compared to physical and psychosocial problems. Similarly, a study conducted at a menopause clinic in Kuala Lumpur found that vasomotor symptoms, particularly hot flushes (characterized by intense heat in the face, neck, and chest), were common among Malaysian menopausal women [17]. It is also consistent with several studies which reported that Asian women tend to experience more musculoskeletal symptoms, while Western women report higher rates of vasomotor symptoms [18,19]. It has been suggested that the higher consumption of soy-based foods among Asian women, compared to Caucasian women, may explain the lower incidence of vasomotor symptoms, although this hypothesis has not been conclusively proven [4,5].

Women experiencing hot flushes during menopause often report a significant reduction in quality of life, which is paradoxically associated with decreased productivity [17]. A study in Malaysia reported that 52% of women indicated that menopausal symptoms impacted their quality of life, though only 2.7% being severely affected [15]. In our study, only 12% of study participant has no problems with menopausal symptoms while the other have mild problems (39.0 %), moderate (35.7%), severe (12.0%) and complete problems (1.0%). It can be concluded menopause had an impact on the quality of life for around half of the study participants. These findings underscore the multifaceted nature of menopausal symptoms, affecting physical, emotional, and psychological health.

Menopause management

The findings revealed that menopausal symptoms varied in severity, with the majority of respondents experiencing mild to moderate symptoms. These results suggest that while most women encounter menopausal symptoms, the severity remains relatively manageable for the majority. a portion of respondents reported no menopausal symptoms, which could be due to differences in perception, reporting bias, or variations in the menopausal transition.

Several treatments are available to alleviate menopausal symptoms, including hormone replacement therapy (HRT), vaginal oestrogen, low-dose antidepressants, gabapentin, clonidine, and medications for preventing osteoporosis.

Complementary and alternative therapies are also available to relieve bothersome menopausal symptoms [20,21, 22]. According to the Asian Menopause Survey, the most common reasons for women seeking treatment were sleeplessness, followed by hot flushes, headaches/migraines, and mood changes [23]. Manoharan et al. (2023) found that in Malaysia, women preferred doctors at public and private clinics over medical specialists. The most commonly prescribed treatments were vitamins, massage, and traditional medicine, with HRT being the least prescribed [24].

Previous research has shown that using complementary and preventive therapies, along with effective management strategies, can improve the quality of life for menopausal women. Effective management of menopausal symptoms may also contribute to the prevention of chronic conditions [25]. In many Asian cultures, postmenopausal symptoms are often overlooked or treated with herbal or natural remedies due to the perception of menopause as a natural process. This perception is compounded by a general lack of knowledge about treatment options, HRT, and the associated health risks [23].

Despite the significant prevalence of menopausal symptoms, this study highlights a gap in treatment uptake. Many respondents reported not using any treatment, while only a small group utilised management strategies, including HRT and supplements, vitamins, or herbs. Although menopausal symptoms are commonly experienced, only a small percentage of women are severely affected. Nevertheless, many women hesitate to seek treatment for their symptoms [26]. Some women sought medical consultations, but others avoided professional help professional guidance, possibly due to stigma, lack of awareness, or fear of side effects. These findings suggest the need to address barriers to treatments to ensure better care and symptom management.

In this study, 24.5% of respondents (39 women) with severe menopausal symptoms reported using medication to manage their symptoms. This figure is lower than that found in another study, which revealed that 59% of Asian women did not seek treatment for postmenopausal symptoms [23]. Only a small proportion of our respondents (12.7%) reported using treatment, either through HRT or alternative methods such as supplements, vitamins, or complementary Chinese medicine. This may be due to the fact that most respondents experienced only mild to moderate symptoms.

Another study conducted in Malaysia yielded similar results, with the majority of women (75.2%) not seeking treatment for their symptoms. Of the 24.8% who did seek treatment, only 20.3% used HRT. They found no significant association between treatment-seeking behaviour and factors such as ethnicity, age, parity, marital status, or occupational status. Women who believed that their quality of life was impacted by menopausal symptoms were more likely to seek treatment [15]. However, this study did not assess the association between treatment-seeking behaviour and patient characteristics. Future research should explore the factors influencing treatment-seeking behaviour and the long-term health implications of untreated menopausal symptoms.

Our findings suggest that menopause awareness programs should address both physical and mental health aspects. Healthcare providers must discuss menopause during consultations to improve symptom recognition and treatment uptake, while educational campaigns can reduce stigma around treatments like HRT. Integrating menopause care into primary healthcare is crucial, including routine symptom screening, counseling services, and peer support groups. Training healthcare professionals to manage menopausal symptoms effectively is also essential.

Study limitations

Some limitations of this study include the exclusion of specific subgroups and the lack of objective clinical assessment. Women with surgical, chemical, or premature menopause were excluded, limiting insights into these groups' experiences and healthcare practices. Additionally, the study relied solely on self-administered questionnaires, which provided only subjective assessments of symptom severity. Moreover, we did not include questions related to the duration of menopausal symptoms, which may have introduced recall bias, as individuals often struggle to accurately remember past events. Furthermore, potential confounding factors, such as mental health conditions, comorbidities, and family support systems, were not thoroughly assessed.

Conclusion

This study provides valuable insights into the prevalence and severity of menopausal symptoms among Malaysian middle-aged women. The majority of respondents (39.0%) reported mild to moderate symptoms, with only a small percentage suffering from severe (12.3%) or complete problems (1.0%). Physical and psychosocial symptoms were more common than vasomotor symptoms like hot flushes.

The management of menopausal symptoms remains an area of concern, as only a minority of respondents reported seeking treatment, either through HRT or alternative methods such as supplements and herbal remedies. These findings emphasise the importance of healthcare support and education for women experiencing menopausal symptoms to improve their quality of life and prevent potential long-term health issues. Overall, recommended initiatives include educational campaigns for women to raise awareness about menopause symptoms and available treatment options, as well as better access to menopause-related healthcare services. Healthcare professionals also play a key role in providing guidance, early intervention, and tailored management strategies for menopausal symptoms.

Future study should include diverse menopausal subgroups, incorporate objective clinical assessments, and consider potential confounding factors to provide a more comprehensive understanding of menopausal symptoms and healthcare-seeking behaviour. Additionally, research should focus on exploring the underlying cultural and societal factors that influence treatment-seeking behaviour, with the objective of developing more effective interventions and support systems for menopausal women in diverse populations.

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Authors' contribution

RMP was responsible for the concept, design, and intellectual content, while AMZ was responsible for data collection. RMP and AMZ contributed to questionnaire development, data analysis and interpretation, and writing the manuscript. ZMN was responsible for reviewing, editing and finalizing the manuscript.

Conflicts of interest

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

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This study did not receive funding from any institutions.

Table 1. Respondents' Characteristic

Questionnaire item	∑N=300	%
Age		
40-44	62	20.7
45-49	81	27.0
50-54	75	25.0
55-60	82	27.3
Marital status		
Unmarried	17	5.7
Married	256	85.3
Widowed	17	5.7
Divorced	10	3.3
Highest level of education		
No formal education	7	2.3
Primary education	8	2.7
Secondary education	78	26.0
Higher education	207	69.0
Educational background		
Related to health science/medical	23	7.7
Non-health science	57	19.0
Not applicable	220	73.3
Occupation		
Working (full time)	209	69.7
Working (part-time)	15	5.0
Housewife	50	16.7
Retired	26	8.7
Family income		
B40 (less than RM 4,360)	81	27.0
M40 (RM 4,360 – RM 9,619)	154	51.3
T20 (More than RM 9,619)	65	21.7
Ethnicity		
Malay	284	94.7
Chinese	9	3.0
Indian	7	2.3
Residence		
Urban	136	45.3
Suburban	114	38.0
Rural	50	16.7
Social status		
Heavy smoker	5	1.7
Occasionally smoker	6	2.0
Heavy alcohol intake	4	1.3
Occasionally alcohol intake	2	0.7
Not applicable	283	94.3

Table 2. Menopausal Symptoms

	Questionnaire item	Not at all n (%)	A little bit n (%)	Quite a bit n (%)	Extremely n (%)
Vasomotor	Hot flashes in upper body (face, neck or chest)	115 (38.3)	119 (39.7)	47 (15.7)	19 (6.3)
	Excessive sweats	110 (36.7)	114 (38.0)	60 (20.0)	16 (5.3)
	Night sweats	123 (41.0)	111 (37.0)	49 (16.3)	17 (5.7)
Physical	Breast pain	130 (43.3)	115 (38.3)	49 (16.3)	6 (2.0)
	Gain weight easily	93 (31.0)	132 (44.0)	67 (22.3)	8 (2.7)
	Easily feeling tired/ fatigue	94 (31.3)	110 (36.7)	77 (25.7)	19 (6.3)
	Pain or stiffness in joints and muscle	78 (26.0)	132 (44.0)	74 (24.7)	16 (5.3)
	Having headache frequently	107 (35.7)	117 (39.0)	63 (21.0)	13 (4.3)
	Constipation	151 (50.3)	94 (31.3)	46 (15.3)	9 (3.0)
	Diarrhoea	176 (58.7)	82 (27.3)	37 (12.3)	5 (1.7)
	Indigestion	158 (52.7)	95 (31.7)	42 (14.0)	5 (1.7)
Genitourinary problems	Vaginal dryness	131 (43.6)	101 (33.7)	56 (18.7)	12 (4.0)
	Abnormal vaginal discharge (changes in colour)	154 (51.3)	102 (34.0)	36 (12.0)	8 (2.7)
	Vaginal infection	202 (67.3)	62 (21.0)	29 (9.7)	6 (2.0)
	Vaginal itchy	157 (52.3)	95 (31.7)	38 (12.7)	10 (3.3)
	Feeling pain when urinating	182 (60.7)	78 (26.0)	35 (11.7)	5 (1.7)
	Feeling burning when urinating	185 (61.7)	74 (24.7)	37 (12.3)	4 (1.3)
	Feeling difficult to urinate	176 (58.7)	83 (27.7)	37 (12.3)	4 (1.3)
	Urinary incontinence	122 (40.7)	107 (35.7)	62 (20.7)	9 (3.0)

Sleep problems	Difficulty in falling asleep	138 (46.0)	96 (32.0)	54 (18.0)	12 (4.0)
	Difficulty staying asleep	127 (42.3)	106 (35.3)	51 (17.0)	16 (5.3)
	Waking up early	135 (45.0)	96 (32.0)	53 (17.7)	16 (5.3)
	Heart discomfort	135 (45.0)	106 (35.3)	53 (17.7)	6 (2.0)
Psychosocial	More depressed	122 (40.7)	109 (36.3)	62 (20.7)	7 (2.3)
	More irritable	107 (35.7)	111 (37.0)	70 (23.3)	12 (4.0)
	More anxious	122 (40.7)	110 (3.6)	57 (19.0)	11 (3.7)
	Having mood swing	83 (27.7)	146 (48.7)	59 (19.7)	12 (4.0)
	Difficult or unable to concentrate	113 (37.7)	124 (41.3)	55 (18.3)	8 (2.7)
	Become forgetful	90 (30.0)	125 (41.7)	68 (22.7)	17 (5.7)

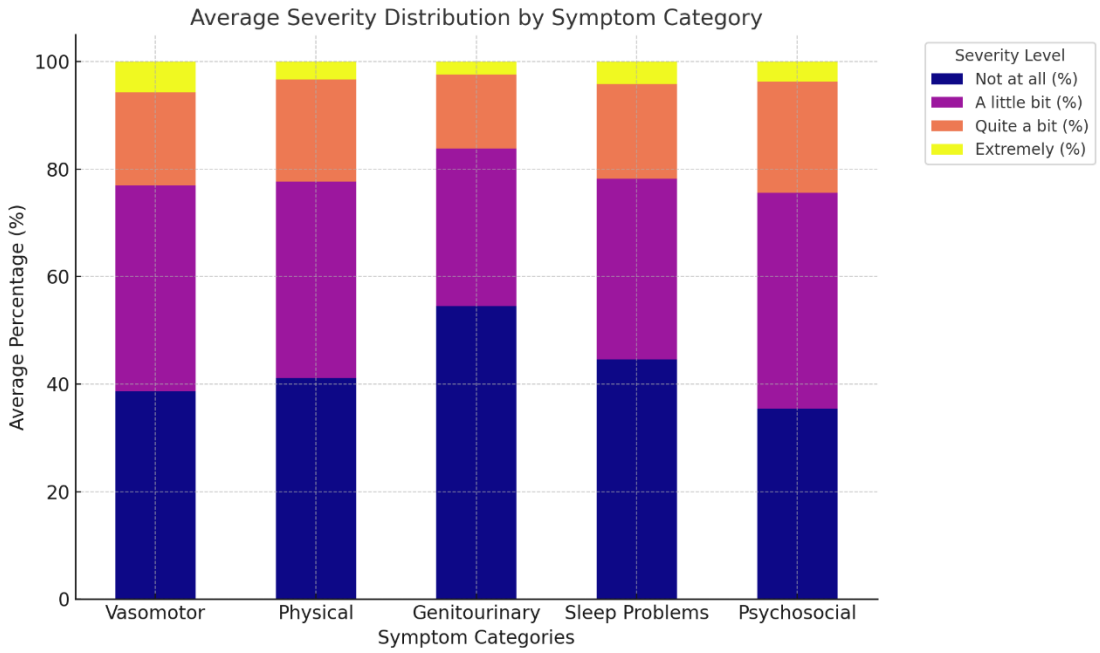

Figure 1. The summary of menopause symptoms distribution across the five symptom categories

Table 3. Level of Symptoms

Level of Symptom	∑N=300	%
No problem	37	12.3
Mild problems	117	39.0
Moderate problems	107	35.7
Severe problems	36	12.0
Complete problems	3	1.0

Table 4. Management of Menopause

No	Question	Options	n (%)
1	Is there any treatment do/did you currently use to manage the symptoms related to menopause?	Yes	39 (12.7)
		No	120 (40.3)
		I do not experience with any symptoms	141 (47.0)
2	What treatment do/did you take to manage the symptoms related to menopause? (you can choose more than one)	HRT (Hormone Replacement Therapy)	20 (6.7)
		Others (Supplements, Vitamin and Herbs/traditional medication	19 (6.3)
		Not applicable	261 (87.0)
3	Do/did you consult to a doctor during menopause or when having symptoms related to menopause?	Yes	104 (34.7)
		No	55 (18.3)
		I do not experience with any symptoms	141 (47.0)
4	Do/did you take HRT to manage your menopausal symptoms?	Yes, I am currently on HRT	11 (3.7)
		Yes, I have taken HRT but not currently	12 (4.0)
		No, I do not and have never taken HRT	227 (92.3)

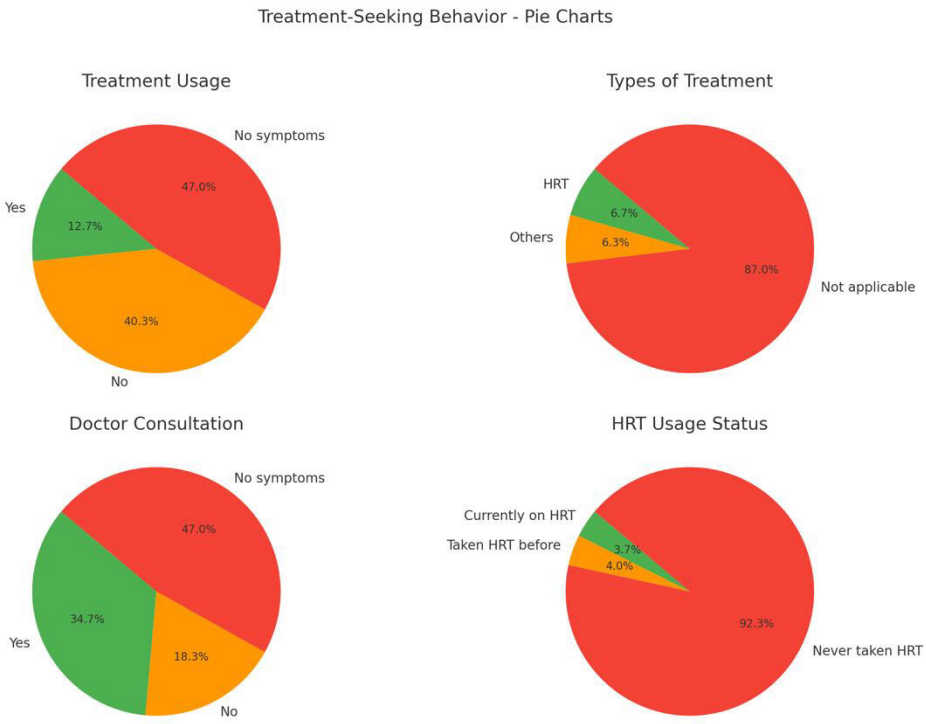

Figure 2. Summary of menopause treatment seeking behaviors

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ORIGINAL ARTICLE

Medical Professionalism and its Association among Clinical Medical Students.

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Abstract
Medical professionalism is a crucial competency, defined as the behaviours and attitudes that embody core values such as trust, accountability, and patient-centered care. It is a dynamic trait that evolves primarily during medical education and residency. However, the relationship between contributing factors and professionalism remains unclear, as previous studies have reported mixed results. This study aims to explore the level of medical professionalism among clinical students at a local university and its associated factors. A cross-sectional study was conducted among all 302 clinical medical students at the university, recruited via universal sampling. The validated Learner's Attitude of Medical Professionalism Scale (LAMPS) was used as the assessment tool. Sociodemographic data, including educational background, parental occupations, and prior exposure to medical professionalism training, were collected. Significant associated factors were analyzed using chi-square tests and multiple logistic regression. The results showed that only 58.3% of students achieved a good medical professionalism score. Significant contributing factors included willingness to pursue a career in medicine (OR 4.5, CI: 2.37–8.49) and a previous attendance at an Islamic medical school (OR 1.7, CI: 1.05–2.76). In conclusion, fostering medical professionalism should begin early, before students enroll in medical school. The Islamic curriculum plays an important role in shaping students' professionalism. Additionally, screening prospective students for their willingness to pursue medicine is crucial in producing medical doctors with integrity.

Keywords: *Clinical students, factors, medical professionalism.*

Introduction

Professionalism, as defined by Merriam-Webster, encompasses 'the conduct, aims, or qualities that characterize a profession or a professional person,' with a profession being 'a calling requiring specialized knowledge and often long and intensive academic preparation.' In the medical context, professionalism embodies the values, conduct, and obligations that prioritize trust, accountability, and patient-centered care [1]. It is primarily imparted during medical education through lectures and role modeling in clinical settings, emphasizing the importance of an educational community for professional growth [2]. Professionalism is critical for maintaining high-quality care and trust in the healthcare system while fostering collaboration among healthcare teams [3].

A cross-sectional study conducted in Tehran, Iran, assessed medical professionalism knowledge among students and physicians using a questionnaire. Among 149 participants (mean age: 30.81 years; 61.64% male), 44.29% had heard of the term 'medical professionalism,' with no significant differences in knowledge based on age or degree [4]. Similarly, in Malaysia, a study at Universiti Sultan Zainal Abidin (UniSZA) found no significant differences in professionalism scores among medical students across different years of study (P=0.996). A Brazilian study using the 50-item Professional Attitudes Scale for Medical Students (PASMS-50) found that professionalism scores varied significantly only at the extremes of the age range (<20 and ≥26 years), likely due to differences in curriculum phases [5].

Gender differences in professionalism have yielded mixed results. Studies in Slovenia and Turkey reported higher professionalism scores among female students, attributed to traits such as empathy and communication skills [6,7]. Conversely, studies in Malaysia and Saudi Arabia found no significant association between gender and overall professionalism scores, though males scored higher in the 'duty or accountability' component [8,9]. Socioeconomic factors and educational background also appear to have minimal influence on professionalism. In Brazil, no significant correlation was observed between family income and professionalism scores [5]. Similarly, secondary school type (public vs. private) did not impact attitudes toward professionalism [5]. While matriculation programs prepare students academically, their relationship with professionalism remains unclear. However, some studies suggest associations between professionalism and academic performance in specific clinical courses [10,11].

The absence of formal professionalism curricula in some institutions underscores the importance of structured teaching and assessment strategies. Institutions such as King's College London have implemented professionalism policies to guide and monitor student behavior, highlighting the role of leadership in fostering these values [12,13]. However, studies indicate a decline in professionalism scores during clinical years, as students shift their focus toward technical knowledge [5]. These findings emphasize the need for targeted interventions to support the development of medical professionalism across demographics, curriculum phases, and educational backgrounds.

Materials and methods

This cross-sectional study was conducted at the medical faculty of a local university, involving 302 clinical medical students. The study aimed to describe the sociodemographic profile of clinical medical students at the university, measure their level of medical professionalism, and identify factors associated with professionalism scores.

The inclusion criteria include actively enrolled clinical medical students at IIUM. Students on long study leave were excluded. The minimum required sample size, based on a 90% confidence interval and a precision of 0.05, considering the prevalence of good medical professionalism among medical students, was 302 students [14]. After accounting for a 10% dropout rate, the final minimum sample size required was 324 students. The study employed universal sampling,

recruiting all medical students from Years 3 to 5 (clinical-phase). Participants were approached in a lecture hall, followed by distribution of the questionnaire via Google Forms. Of the 330 medical students approached, 302 agreed to participate, yielding a response rate of 92%.

The assessment tool used was the validated Learner's Attitude of Medical Professionalism Scale (LAMPS) [15]. This questionnaire was validated in 2021 by Al-Eraky et al., with a Cronbach's alpha of 0.79, confirming acceptable reliability [15]. It consists of 28 items across five significant domains, with details provided in Appendix 1. Approval for its use was obtained from the developer via email.

Sociodemographic data, including previous educational background, parental occupations, and history of attending medical professionalism classes, were recorded. Professionalism scores were collected as continuous data, with a good score defined as exceeding 112 marks, based on the minimum total desired scores for all 28 items. Significant associated factors were analyzed using chi-square and multiple logistic regression. This study received ethical approval from the Kulliyyah of Medicine Research Committee (IIUM/305/20/4/1/7) on April 18, 2024.

Results

Demographic data of the respondents

Table 1 summarizes the sociodemographic characteristics of 302 respondents. The mean age was 22.6 years, with a predominantly female population (74.8%). The largest group consisted of third year students (55.3%). Most participants had attended boarding schools (62.3%), with Islamic schools representing the most common educational background (45.5%). Nearly all respondents completed their matriculation outside of Centre for Foundation Studies (CFS) IIUM (96%). Additionally, 88.7% reported having attended medical professionalism classes. Regarding parents' occupations, most came from non-medical backgrounds (85.8%).

Level of medical professionalism

Table 2 shows the descriptive statistics for medical professionalism scores of the medical students. They had scores ranging from a minimum of 83.00 to a maximum of 138.00. The mean score for medical professionalism is 113.0 (SD = 8.00), which falls within a good level of medical professionalism score.

Associated factors for the level of medical professionalism

Table 3 (univariate analysis) and table 4 show the significant variables associated with good medical professionalism score. They are the willingness to do medicine (OR 4.5, CI: 2.37 – 8.49) and previous history of attending Islamic secondary school (OR 1.7, CI: 1.05 – 2.76). Other variables were not statistically significant, as all p-values exceeded the threshold of 0.05.

Discussion

Professionalism has become a core competency for medical students, as inappropriate professional attitudes can adversely affect patient welfare, health outcomes, and physician morale [6]. In our study, 88.7% of students reported attending a medical professionalism class, highlighting their strong commitment to professionalism in education. This reflects a holistic approach by curriculum policymakers in integrating professionalism training to ensure that future physicians are compassionate, competent, and ethical. The overall attitude of respondents towards professionalism was positive, consistent with findings from prior studies [7,9]. A previous study among non-clinical medical students also showed similar positive attitudes toward professionalism [16]. In our study, the range for good professionalism scores was between 112 and 140, with a mean score of 113, indicating a solid understanding of professionalism and ethical principles among the participants.

Although female respondents outnumbered males, no significant differences in professionalism scores were observed between genders. These

findings align with previous research, which also reported no gender-based differences in professionalism levels [8,9,17]. The collaborative nature of the medical field may help mitigate gender disparities in professionalism. However, contradictory findings exist; for instance, a Turkish study found higher professionalism scores among females [7]. Such discrepancies suggest that cultural and societal factors influence how professionalism is perceived and practiced. Professional behavior is influenced by individual values, experiences, and the cultural context of medical training [18].

No significant differences in professionalism scores were observed between students across different years of study. Previous research also suggests a lack of association between the year of study and professionalism levels [5,8]. Although Santos et al. noted a decline in certain professional attitudes during clinical years, overall professionalism remained consistent. This finding underscores the need for sustained professionalism training throughout medical education.

Parental occupation did not significantly influence professionalism scores. This finding aligns with a Brazilian study, which reported no correlation between family income and professionalism levels among medical students [5]. These results suggest that socioeconomic factors, such as parental occupation or income, have minimal impact on the development of professionalism. Our study found no significant relationship between the history of attending professionalism classes and professionalism scores. This aligns with the findings by Jahan et al. (2016), which highlighted the absence of formal professionalism training in some curricula [19]. Instead, professionalism is commonly assessed through clinical evaluations and Objective Structured Clinical Examinations (OSCEs). Shakour et al. (2015) similarly noted the lack of reliable instruments for selecting medical students with strong professional qualifications [20]. The variability in content and teaching approaches in professionalism classes may account for their limited impact on students' professional behaviour.

The most significant factors associated with higher professionalism scores were students' willingness to pursue medicine and a history of attending Islamic schools. Intrinsic motivation, such as a passion for helping others or an interest in science, often aligns with the values underlying medical professionalism. Students who voluntarily choose medicine tend to demonstrate greater professionalism, including altruism, empathy, and ethical behavior [21,22]. Conversely, external pressures—such as family expectations—may reduce adherence to professional values.

Islamic education emphasizes ethical principles such as Amanah (trust) and Ihsan (excellence), which resonate with the values of medical professionalism. Students from Islamic schools often exhibit heightened responsibility, accountability, and respect for human dignity, as these values are integral to Islamic teachings [23,24]. The Islamic curriculum focuses on moral development and integrity through the internalization of ethical principles, preparing students for service-oriented professions like medicine [25]. This may explain the association between Islamic education and enhanced professionalism observed in our study.

The medical professionalism curriculum in medical schools is developed through several platforms. These include: (1) the formal curriculum, which incorporates medical ethics and professionalism courses; (2) experiential learning, gained through clinical clerkships and mentorship by senior doctors; (3) the informal curriculum, shaped by institutional culture and environment; (4) formal assessments, such as Objective Structured Clinical Examinations (OSCEs) and reflective writing; and (5) student-led initiatives and extracurricular activities [6,7,9]. It is expected that students from an Islamic curriculum in secondary school have a greater potential to adapt to these five platforms of the medical professionalism curriculum. This is because Islamic education aligns with the unity of

knowledge and compassionate education, as emphasized in Tawhidic epistemology [23-25]. This alignment may explain the higher odds of achieving a strong professionalism score among students with an Islamic educational background.

Limitation

Our study has some limitations, including being conducted at a single institution, which may limit the generalizability of the findings, and a relatively small sample size, which may affect the robustness of the results. Furthermore, other variables were not included but could serve as significant cofactors, such as academic performance and involvement in extracurricular activities. While we used a validated instrument (LAMPS) to ensure measurement reliability, the self-reported nature of data collection introduces the possibility of response bias. Participants may have provided socially desirable responses rather than accurate self-assessments of their professional behaviours.

Conclusion and recommendations

In conclusion, fostering medical professionalism should begin early, before students enroll in medical school. The Islamic curriculum plays an important role in shaping students' professionalism. Integrating professionalism training with cultural and individual considerations may further enhance its effectiveness. Future research should focus on refining professionalism curricula and exploring the long-term impact of intrinsic motivation and religious education on professional behaviour. The implementation of medical ethics based on Islamic teachings should be incorporated into the curriculum from the first year of medical school. Additionally, screening prospective students for their willingness to pursue medicine is crucial to producing medical doctors with integrity.

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Authors' Contributions

MSES was responsible for conceptualization, finalizing data analysis, supervising the research, and finalizing the manuscript. AFMF, ASTA, and AAA conducted the research, collected data, and drafted the manuscript.

Conflicts of interest

None

Table 1. Demographic Data of The Respondents

Characteristics	N	%
Age(years) (mean, SD)	22.6	1.2
Gender		
Male	76	25.2
Female	226	74.8
Academic Year		
Year 3	167	55.3
Year 4	84	27.8
Year 5	69	16.9
Secondary school		
Boarding	188	62.3
Non-boarding	144	37.7
Curriculum of secondary school		
Islamic school	145	48.0
Ordinary school	157	52.0
Matriculation		
IIUM matriculation	290	96.0
Others	12	4.0
Parents' Job		
Medical Professionalism	43	14.2
Non-medical Professionalism	259	85.8
Willingness to do Medicine		
Yes	224	74.2
No	78	24.8
Attending medical professionalism workshop		
Yes	268	88.7
No	34	11.3

Table 2. Medical Professionalism Score

Medical Professionalism Score	
Good n (%)	176 (58.3)
Poor n (%)	126 (41.7)
Mean (SD)	113 (±8)
Minimum	83
Maximum	138

n = number, % = percentage

Table 3. Association between sociodemographic and medical professionalism score (n=302)

Characteristic	Medical Professionalism Score		**χ2**	**Df**	**p value**
	Good n (%)	Poor n (%)			
Willingness for Medicine					
Yes	111 (63.4)	113 (88.9)	25.073	1	< 0.001
No	64 (36.6)	14 (11.1)			
Secondary School's Curriculum					
Islamic	95 (54.3)	50 (39.4)	6.567	1	0.010
Ordinary	80 (45.7)	77 (60.6)			

n = number, % = percentage, χ2 = Chi square , Df = degree of freedom

Table 4. Multiple logistic regression analysis of factors associated with good medical professionalism score.

	B	S.E.	Wald	df	Sig.	Exp(B)	95% confidence interval Lower	Upper
Islamic secondary school	0.532	0.246	4.658	1	0.031	1.702	1.050	2.760
Willing Medicine	1.500	0.326	21.182	1	<.001	4.481	2.366	8.487
Constant	-3.806	0.711	28.681	1	<.001	0.022		

Variable(s) entered: Islamic secondary school (curriculum), Willingness to do Medicine.
Exp (B) = Odd ratio, SE = standard error, B = estimated coefficient

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Appendix 1

Questionnaire Items of LAMPS [15].

Behavioral item within domains ‘‘Do you agree when the doctor...?’’

Duty/Accountability
1. Admits wrong diagnosis before a patient
2. Leaves before handing over patients to the next colleague on duty
3. Actively participates in orientation for new residents
4. Encourages patients to contribute to decision making
5. Discusses patients' cases with colleagues in a crowded elevator
6. Calls insurance company to follow up a valid patient claim
7. Declines an invitation to an infection control committee meeting

Excellence/Autonomy
1. Reflects on clinical cases to discover his/her unmet learning needs
2. Attends patient’s questions to explain their illness in a busy clinic
3. Searches for the best evidence available in patient care
4. Collaborates with colleagues to draft new hospital guidelines
5. Invests part of his/her income on attending medical conferences
6. Makes a deal with a pharma company to sponsor his/her conference

Honor/Integrity
1. Gives wrong information to a patient to protect a colleague
2. Issues a false sick leave for a kid of a friend to study home
3. Changes actual data in his/her research based on supervisor’s advice
4. Hides information about fatal diagnosis to avoid patient disturbance
5. Introduces medical students as doctors to patients

Altruism
1. Declines sport club to respond to an emergency call
2. Frequently skips clinical teaching to prepare for a conference
3. Cancels a family appointment for an urgent patient’s need
4. Does not witness against employer hospital in favor of a patient before the court
5. Turns down a home visit to a disable patient due to busy clinic

Respect
1. Respects the roles of all members of the healthcare team in the department
2. Considers patient background when explaining their clinical illness
3. Keeps patients waiting in his/her clinic without apology
4. Gives priority to some patients based on social status or nationality
5. Criticizes a prescription written by a colleague in front of patients

ORIGINAL ARTICLE

The Role of Biochemical Parameters, Body Fat, and Comorbidities in Health-Related Quality of Life among Haemodialysis Patients.

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Abstract
Introduction: Health-related quality of life (HRQOL) is often compromised in patients with end-stage renal disease (ESRD), despite the life-saving benefits of haemodialysis (HD). Although poor nutritional status is prevalent among HD patients, the association between HRQOL and specific factors, such as biochemical parameters, body fat, and comorbidities, remains insufficiently explored. This study aimed to examine the correlations between these factors and HRQOL in HD patients. **Methods:** A cross-sectional study involving 97 ESRD patients from two HD centres in an urban area of Selangor was conducted to ascertain the correlation between HRQOL and nutritional status. Data on socio-demographic characteristics, anthropometric measurements, biochemical parameters, and medical history were collected. HRQOL was evaluated using the Kidney Disease Quality of Life Short Form (KDQOL-SF^{TM} version 1.3). **Results:** The mean KDQOL-SF™ scores ranged from 30.41 ± 29.37 to 85.91 ± 16.38. The mean scores for physical composite summary (PCS) and mental composite summary (MCS) were 40.89 ± 9.77 and 47.17 ± 9.84, respectively. Significant differences in HRQOL were observed across socio-demographic characteristics with the exception of gender and money allowance. Positive correlations with HRQOL were found for serum phosphorus, sodium, creatinine, albumin, HDL-cholesterol, and duration of ESRD diagnosis. Meanwhile, serum chloride, total iron-binding capacity (TIBC), transferrin, body fat, and the number of comorbidities were inversely correlated with HRQOL. **Conclusion:** This study highlights the role of biochemical parameters, body fat, and comorbidities on HRQOL in haemodialysis patients, emphasizing the need for regular monitoring and targeted interventions to enhance HRQOL and overall patient outcomes.

Keywords: *Biochemical parameters, body fat, haemodialysis, HRQOL.*

Introduction

End-stage renal disease (ESRD) is on the rise throughout the world. Over the past two decades, the global prevalence of ESRD has increased from 165 per million population (pmp) in 1990 to 284 pmp in 2010 [1]. The increment of 1.7% was due to the increasing ageing population, the prevalence of diabetes, and hypertension [2-4]. In 2010, 2.6 million people received renal replacement therapy (RRT) worldwide, and expected to increase by 5.4 million people in 2030, with the most growth in Asia [5].

In Malaysia, the prevalence of ESRD has also been on an upward trend for the past 10 years. According to the 26th Report of the Malaysian Dialysis and Transplant Registry, 44,136 patients underwent dialysis therapy in 2018, with 39,593 on haemodialysis (HD) (86.2%) and 4,543 on peritoneal dialysis (PD) (9.9%), with only 1,801 on renal transplantation (3.9%) [6]. In 2008, 4,606 new ESRD patients were treated with dialysis, but by 2018, the number had risen dramatically to 8,431. The prevalence of patients with ESRD on dialysis also increased by 1,363 pmp in 2018 compared to 706 pmp in 2008, whereas the new cases and the prevalence of renal transplantation remained stable for the past 10 years [6].

RRT is lifesaving for ESRD patients, yet, compared to renal transplantation, dialysis therapy itself is time-consuming, costly, and requires a restriction of fluid and dietary intake [7]. Besides that, dialysis is a lifelong therapy that causes physiological discomfort as well as limitation of physical activities [8]. Apart from that, adverse effects of the medication and therapy such as pain, sleep disorder, the weakening of fluctuations in blood pressure, and stomach ache exacerbate the difficulties faced by dialysis patients, leading to poor health-related quality of life (HRQOL) [9]. HRQOL usually declines as chronic kidney disease progresses, and HD patients reported the lowest HRQOL when compared to PD patients [10].

Other than HRQOL, dialysis patients also face nutritional issues, with HD patients having a poorer nutritional status than PD patients [11]. Multiple factors contribute to malnutrition in dialysis patients, including loss of nutrients due to dialysis, inflammation, inadequate dialysis, as well as insufficient protein and calorie intake due to loss of appetite, taste alteration, insulin resistance and low diet quality [12]. Nutritional status in ESRD patients was found to be correlated with HRQOL and poor HRQOL was closely related to mortality [13].

Malnutrition and diminished HRQOL are significant risk factors for mortality among patients with ESRD, underscoring the necessity for systematic monitoring of nutritional status and HRQOL[14]. Early intervention has demonstrated efficacy in improving HRQOL and reducing mortality rates in malnourished individuals. However, research examining these factors in the Malaysian population remains limited. This study aims to investigate the influence of biochemical parameters, body composition, and comorbidities on HRQOL in HD patients. The nutritional parameters selected for analysis—serum phosphorus, sodium, creatinine, albumin, and body fat—are recognized for their robust associations with nutritional status and health outcomes in HD patients, thereby enabling a thorough evaluation of overall health in ESRD.

Materials and methods

Study design and subjects

A cross-sectional study was conducted among 101 ESRD patients from two HD centres located in an urban area of Selangor, Malaysia. Inclusion criteria included Malaysian nationality, age above 18 years, a confirmed diagnosis of ESRD, and undergoing HD therapy at least three times a week for more than three months. Exclusion criteria encompassed individuals with acute kidney injury, Hepatitis A or B, recent kidney transplants, non-adherence to dialysis treatment

and communication barriers such as hearing deficits or mental health conditions that could impair participation.

Sample size and recruitment

The sample size was determined using G*Power version 3.1. The statistical test employed was the "Correlation: Bivariate normal model" within the "exact" test family. A two-tailed test was selected, with an alpha error probability of 0.1 and a desired power of 0.9. A medium effect size resulted in a calculated sample size of 92. A 10% increase was added to the calculated sample size to account for potential non-responses or recording errors during data collection. Thus, the total sample size was determined to be 101 patients. A face-to-face interview was conducted for each recruited patient. Patients were approached for participation, and a self-administered questionnaire was used to assess patients' HRQOL, while anthropometric and biochemical parameters were retrieved from the medical records.

Socio-demographic characteristics

Socio-demographic characteristics such as age, ethnicity, gender, marital status, and education level were collected using a self-administered questionnaire. Information on employment and financial status was also collected.

Body fat

Total body fat mass and body fat percentage were measured using OMRON body fat analyser HBF-356 (Omron Matsusaka Co. Ltd, Matsusaka, Japan).

Biochemical parameters and medical history

Biochemical parameters included serum creatinine, calcium, phosphorus, albumin, sodium, chloride, potassium, total protein, alkaline phosphatase, triglyceride, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), haemoglobin, total iron-binding capacity (TIBC) and transferrin were obtained from the medical report of the patients. Medical history, such as duration of diagnosis with kidney failure, having HD, number of co-morbidities, primary cause of ESRD, and previous treatment options were obtained via face-to-face interview.

HRQOL

Kidney Disease Quality of Life-Short Form (KDQOL-SF^{TM}) version 1.3 is a validated, self-administered questionnaire designed to measure HRQOL in patients with kidney disease undergoing dialysis [15]. This questionnaire is available in English and was translated into Mandarin Chinese and Malay (Singapore version) by the KDQOL-SF^{TM} group and RAND [16]. This instrument comprises two scales: generic and kidney-specific, with 80 items and 19 subscales. Kidney-specific scale focuses on health-related concerns of individuals with kidney disease (43 kidney disease-targeted items and 11 subscales): symptoms/problems, effects of kidney disease, burden of kidney disease, work status, cognitive function, quality of social interaction, sexual function, sleep, social support, dialysis staff encouragement and patient satisfaction. The generic scale is the SF-36 health survey, which has 36 items and eight subscales: physical functioning, role-physical, pain, general health, emotional well-being, role emotional, social function, and energy. The final item, the overall health rate item, asks the patients to rate their health on a scale of 0 to 10. The generic scale results are further summarised in the physical composite summary (PCS) and mental composite summary (MCS), with PCS aggregating subscales from physical functioning, role physical, pain, and general health, and MCS aggregating subscales from emotional well-being, role emotional, social function, and general health. Scores of the different subscales were calculated according to the KDQOL-SF™ scoring program, with a range of 0 to 100, higher scores reflecting better HRQOL [15].

Ethical approval and permission

This study was approved by the Institutional Review Board of [JKEUPM Ethics Committee for Research Involving Human Subjects], approval number [MJKEtikaPer/F01(UPM)(U)Nov(11)]. All participants provided informed consent before participation.

Statistical analysis

The data collected were analysed using the IBM SPSS Statistics for Windows, version 22.0. Armonk, NY. Descriptive data were presented as frequency, percentage, mean, and standard deviation. The difference in mean KDQOL-SF™ across group was analysed by independent-samples t-test and one-way analysis of variance (ANOVA) test. Pearson correlation test was used to measure the associations between continuous variables with KDQOL-SF™ score. The level of significance of the *P*-value was set at 0.05 or below for all statistical tests.

Results

A total of 101 patients agreed to take part in this study, but four patients did not complete the questionnaires. Hence, they were excluded from the analysis, resulting in a final sample size of 97 patients. Table 1 shows the socio-demographic characteristics, anthropometric measurements, biochemical parameters, and medical history of the patients in this study. The mean age of the patients was 59.38 ± 11.28 years. The majority were Chinese (n = 76, 78.4%), female (n = 50, 51.5%), married (n = 67, 69.1%), and had secondary level education (n = 44, 45.3%). Although most patients were unemployed (n = 84, 86.6%) and had a household income of less than or MYR3000 per month (n = 67, 72.0%), only 25.8% (n = 25) of them received a monthly allowance for their HD treatment. The mean body mass index (BMI) of the patients was 24.17 ± 4.52 kg/$m^{2,}$ with almost half of them (n= 40, 41.3%) classified as obese. The mean values for inter-dialytic weight gain (IDWG), mid-upper arm circumference (MUAC), total body fat, and percentage of body fat were 1.59 ± 0.09 kg, 27.01 ± 3.43 cm, 16.77 ± 8.08 kg, 26.18 ± 9.69%, respectively. For biochemical parameters, majority of the patients had a higher level of creatinine (n = 60, 61.9%) and haemoglobin (n= 73, 75.3%), whereas 85.6% (n = 83) of them had undesirable level of HDL-cholesterol. Furthermore, 68.0% (n = 66) of the patients had low albumin levels, while the others had desirable or optimal levels of total cholesterol (n = 81, 83.5%) and LDL-cholesterol (n = 45, 46.4%). The mean duration since kidney failure diagnosis and HD therapy initiation was 8.82 ± 6.00 and 6.42 ± 3.99 years, respectively. The majority of the patients presented with co-morbidities (n = 77, 79.4%), with a mean of 1.33 ± 0.89 per patient. The primary cause of ESRD in this study was diabetes mellitus (n = 32, 33.0%), followed by hypertension (n = 30, 30.9%), others (n = 22, 22.7%), and unknown causes (n = 13, 3.4%).

The mean score of KDQOL-SF™ is presented in Table 2. The mean score for each subscale ranged from 30.41 ± 29.37 to 85.91 ± 16.38. For kidney-specific scale, patient satisfaction (85.91 ± 16.30) had the highest score, while work status (30.41±29.37) had the lowest score. The mean score for PCS and MCS were 40.89 ± 9.77 and 47.17 ± 9.84, respectively. The highest score for PCS and MCS were pain (78.17 ± 28.32) and social function (72.94 ± 24.78), while the lowest score were role-physical (42.27 ± 40.08) and energy/fatigue (52.58 ± 23.90), respectively.

Table 3-1 and Table 3-2 show the mean score of KDQOL-SF™ by socio-demographic characteristics. Significantly lower KDQOL-SF™ scores were observed in older patients, especially in the domains of cognitive function, PCS, physical functioning, social function, energy/fatigue, and overall health. As for working status, unemployed patients had a significantly lower scores in work status, physical functioning, and energy/fatigue compared to employed patients. For ethnicity, significant differences were observed between groups in terms of

symptom/problem list, burden of kidney disease and pain. Marital status showed significant differences in social support scores. Additionally, patients with no formal education scored significantly lower in physical functioning than those with primary or secondary education.

The correlations between anthropometric measurements, biochemical parameters, and medical history and KDQOL-SF™ are presented in Table 4-1 and Table 4-2. Among anthropometric measurements, only body fat percentage showed a significant correlation with KDQOL-SF™, specifically demonstrating a negative correlation with physical functioning. Regarding biochemical parameters, serum phosphorus, sodium, creatinine, albumin, and HDL-cholesterol levels showed positive correlations with several subscales of KDQOL-SF™. Conversely, serum chloride, TIBC, and transferrin exhibited negative correlations with KDQOL-SF™ scores. Furthermore, duration since kidney failure diagnosis was positively correlated with PCS, role-physical and social function scores. In contrast, in the number of comorbidities showed inverse correlations with several subscales of KDQOL-SF™, including effects of kidney disease, PCS, physical functioning, and social function.

Discussion

This study was conducted to determine the HRQOL and its correlation with nutritional status among HD patients in Malaysia. The findings revealed significant relationships between HRQOL and age, ethnicity, education level, marital and working status. Among anthropometric measurements, only body fat percentage significantly influenced HRQOL. In biochemical parameters, serum phosphorus, sodium, creatinine, albumin, HDL-cholesterol, chloride, TIBC, and transferrin were significantly correlated with HRQOL. Additionally, duration kidney failure diagnosis and number of co-morbidities significantly affected HRQOL outcomes.

The present study demonstrated that older patients exhibited lower HRQOL across all domains compared to their younger counterparts. This contrasts with previous studies reporting better scores among older patients on kidney-specific scales and the MCS, but did not show comparable improvements in the PCS scores [17-19]. This discrepancy may imply thatolder patients developed better adaptation to chronic illness, particularly regarding mental health aspects.

Consistent with prior research, married and Malay patients were less affected by kidney disease and its treatemnt [17, 20, 21]. This might be because married and Malay patients received more support from their surroundings, as illustrated by the results of the social support subscales in this study. Furthermore, it has been emphasized in previous studies that affectionate social support did impact HRQOL, which demonstrated the importance of family support in HD patients [22].

The findings of better HRQOL in a group with higher education level were consistent with previous studies [17-19]. As in the previous study, employed patients had higher HRQOL than unemployed patients [17]. These findings collectively suggest that better socioeconomic status and education level significantly influenced HRQOL in HD patients. This is probably due to a better understanding of the disease and available financial resources that facilitate adaptation to renal disease and reduce their life stress [23].

Analysis indicated that BMI was unrelated to HRQOL in HD patients. This outcome was consistent with earlier research conducted in Singapore [19]. However, a new finding was discovered in this study, where body fat percentage had an impact on HRQOL. This may be related to reduced physical functioning in this population of patients.

In terms of biochemical parameters, this study showed that serum phosphate, chloride, TIBC and transferrin were related to HRQOL, which had not been demonstrated in other studies [24, 25]. Meanwhile, similar to previous studies, lower serum creatinine, sodium, and albumin were found to be related to poor HRQOL [17-19, 24-26]. Low serum creatinine is a predictor of skeletal muscle mass loss, whereas low levels of sodium and albumin have always been associated with malnutrition, mortality, and morbidity [27-29]. Thus, it is plausible to expect an association between low creatinine, sodium, or albumin levels and poor HRQOL. Another interesting finding is that HDL-cholesterol level was also correlated with HRQOL, and this might be explained by physical activity level in HD patients [30].

A previous study highlighted that the duration of therapy was related to HRQOL in HD patients, however, the result was in contrast to this study. Similarly, a significant correlation between duration of kidney failure diagnosis and HRQOL was observed in this study [19]. The most likely explanation is better disease adaptation among long-term patients [19]. In this study, as the number of co-morbidities increased, HRQOL worsened. This finding was in line with a previous study that emphasized that presence of multiple co-morbidities impacts HRQOL [19]. It has been well established that ESRD patients typically have lower HRQOL, thus, presenting with other co-morbidities will worsen their current condition, and as the number of co-morbidities increases, the condition becomes more severe [31]. Notably, malnutrition has also been identified as the most significant predictor of impaired KDQOL-SF scores, reinforcing the importance of nutritional status in influencing quality of life in this population[14].

Limitations

Several limitations in this study need to be addressed. First, this is a cross-sectional design, which restricts the establishment of causal relationships among the variables. The cultural and dietary practices of the population may not represent other ethnic groups, limiting the generalizability of the findings. Furthermore, factors such as co-morbidities, socio-economic status, and access to healthcare may not have been sufficiently controlled, potentially confounding the observed relationships.

Conclusion

In conclusion, this study highlights the role of biochemical parameters, body fat, and comorbidities in determining HRQOL among haemodialysis patients. We identified positive correlations between HRQOL and serum phosphorus, sodium, creatinine, albumin, and HDL-cholesterol levels, while inverse association were observed with serum chloride, TIBC, transferrin, body fat, and comorbidities. These findings underscore the critical need for regular nutritional status assessment and biochemical markers monitoring in clinical practice, which could facilitate personalized interventions to improve HRQOL and optimize treatment outcomes for haemodialysis patients.

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Conflicts of interest

The authors have no conflicts of interest to declare.

Authors' Contributions

LPJ conceptualized and designed the study, led data collection, and analysis, and interpreted findings. As Principal Investigator, ZI supervised all aspects of the research including data analysis and interpretation, prepared the initial manuscript draft, and critically reviewed the final manuscript.

Table 1. Socio-demographic characteristics, anthropometric measurements, biochemical parameters, and medical history of the patients (n = 97)

Variables	*n (%) / Mean±SD*
Socio-demographic characteristics	
Age	59.38±11.28
18-60	50 (51.5)
≥ 60	47 (48.5)
Ethnicity	
Chinese	76 (78.4)
Malay	14 (14.4)
Indian	6 (6.2)
Others	1 (1.0)
Gender	
Male	47 (48.5)
Female	50 (51.5)
Marital status	
Single	19 (19.6)
Divorced	1 (1.0)
Married	67 (69.1)
Widowed	10 (10.3)
Level of education	
Primary	36 (37.1)
Secondary	44 (45.3)
Tertiary	4 (4.2)
No formal education	13 (13.4)
Working status	
Yes	13 (13.4)
No	84 (86.6)
Household income*	
No income	5 (5.4)
≤ MYR3000	67 (72.0)
> MYR3001	21 (22.6)
Money allowances	
Yes	25 (25.8)
No	72 (74.2)
Anthropometric measurements	
BMI (kg/m^2)	24.17±4.52
Underweight	7 (7.2)
Normal	33 (34.0)
Overweight	17 (17.5)
Obesity	40 (41.3)
IDWG (kg)	1.59±0.09
MUAC (cm)	27.01±3.43
Total body fat (kg)	16.77±8.08
Percentage of body fat (%)	26.18±9.69
Biochemical parameters	
Serum creatinine (mg/dL)	10.57±2.26
Normal (< 10)	37 (38.1)
Higher (≥ 10)	60 (61.9)
Serum calcium (mmol/L)	2.34±0.22
Serum phosphorus (mmol/L)	1.86±0.56
Serum albumin (g/L)	38.19±3.68
Low (< 40)	66 (68.0)
Normal (≥ 40)	31 (32.0)
Total protein (g/dL)	68.35±3.91
Alkaline phosphatase (g/dL)	129.71±99.67
Serum sodium (mmol/L)	135.71±13.17
Serum chloride (mmol/L)	96.04±6.29
Serum potassium (mmol/L)	4.87±0.73
Triglyceride (mmol/L)	2.19±1.40

Total cholesterol (mmol/L)	4.85±4.20
Desirable (< 5.2)	81 (83.5)
Borderline high (5.2 – 6.2)	12 (12.4)
High (> 6.2)	4 (4.1)
HDL-cholesterol (mmol/L)	0.84±0.37
Undesirable (<1.0)	83 (85.6)
Acceptable (1.0 – 1.6)	11 (11.3)
High desirable(> 1.56)	3 (3.1)
LDL-cholesterol (mmol/L)	2.60±0.84
Optimal (< 2.6)	45 (46.4)
Near optimal (2.6 – 3.3)	38 (39.2)
Borderline high (3.3 – 4.1)	7 (7.2)
High (4.1 – 4.9)	6 (6.2)
Very high (> 4.9)	1 (1.0)
Haemoglobin (g/dL)	11.19±1.60
Normal (< 10)	24 (24.7)
Higher (≥ 10)	73 (75.3)
TIBC	35.55±7.70
Transferrin	1.59±0.35
Medical history	
Years of diagnosed kidney failure	8.82±6.00
Primary cause of ESRD	
Diabetes mellitus	32 (33.0)
Hypertension	30 (30.9)
Unknown causes	13 (13.4)
Others	22 (22.7)
Years having HD	6.42±3.99
Previous treatment options	
Peritoneal dialysis	11 (11.0)
Acupuncture	1 (1.0)
Chinese herbal remedies	4 (4.0)
No other treatment	81 (84.0)
Co-morbidities	1.33±0.89
Not present with co-morbidities	20 (20.6)
Present with co-morbidities	77 (79.4)

*n=93, missing data, as patients refuse to answer

Values are n (%), mean ± standard deviation (SD)

MYR: Malaysian Ringgit, BMI: Body mass index, CVD: Cardiovascular disease, ESRD: End stage renal disease, HD: haemodialysis, IDWG: Inter-dialytic weight gain, MUAC: Mid upper arm circumference, TIBC: Total iron-binding capability

Table 2. Mean score of KDQOL-SF™ for the patients (n = 97)

Scale	*Mean±SD*
Kidney-specific scale	
Symptoms/problem list	83.23±12.86
Effects of kidney disease	72.31±17.50
Burden of kidney disease	46.01±28.90
Work status	30.41±29.37
Cognitive function	81.44±20.17
Quality of social interaction	81.37±18.18
Sexual function	67.05±27.43
Sleep	67.35±20.97
Social support	79.90±22.94
Dialysis staff encouragement	67.14±29.61
Patient satisfaction	85.91±16.38
Overall health	66.80±16.62
Generic scale	
PCS	40.89±9.77
Physical functioning	52.89±31.34
Role-physical	42.27±40.08
Pain	78.17±28.32
General health	56.96±22.20
MCS	47.17±9.84
Emotional well-being	70.06±19.61
Role-emotional	68.39±41.49
Social function	72.94±24.78
Energy/fatigue	52.58±23.90

Values are mean ± standard deviation (SD)
MCS: Mental component summary, PCS: Physical component summary

Table 3-1. Mean score of KDQOL-SF™ by socio-demographic characteristics among patients (n = 97)

Variables	*Kidney-specific scale*												*t test / ANOVA F value*	*P value*
	Symptom /Problem	*Effects of kidney disease*	*Burden of kidney disease*	*Work status*	*Cognitive function*	*Quality of social interact-tion*	*Sexual function*	*Sleep*	*Social support*	*Dialysis staff encourage-ment*	*Patient satisfac-tion*	*Overall health*		
Age:														
18-60	85.02± 12.35	73.82± 16.14	50.40± 30.93	30.85± 28.65	**86.67± 14.11**†	79.58± 18.46	72.50± 26.81	71.33± 21.88	77.31± 26.10	68.35± 29.36	84.04± 17.01	**70.85± 15.30**†	-2.518	0.012
≥ 60	81.54± 13.23	70.88± 18.74	41.88± 26.49	30.00± 30.30	**76.53± 23.65**	83.07± 17.93	55.36± 26.86	63.60± 19.56	82.33± 19.46	66.00± 30.10	87.67± 15.72	**60.00± 17.06**	-2.381	0.019
Ethnicity:														
Chinese	**83.94± 12.18**‡	72.26± 17.78	**44.41± 27.11**‡	30.26± 30.64	80.35± 21.19	81.84± 17.47	66.18± 26.80	68.09± 19.64	78.29± 23.57	66.61± 31.12	85.75± 15.80	66.45± 16.71	F=3.847	0.012
Malay	**93.40± 7.39**	82.30± 18.92	**77.08± 25.21**	16.67± 25.82	90.00± 18.74	87.78± 12.94	-	74.17± 31.57	86.11± 26.70	89.58± 20.03	-	76.67± 22.51	F=2.767	0.046
Indian	**74.55± 14.51**	68.53± 15.43	**42.86± 34.31**	35.71± 23.44	82.38± 14.47	75.24± 23.30	62.50± 32.27	62.32± 22.99	84.52± 17.86	58.93± 19.87	79.76± 19.80	65.00± 13.45	-	-
Gender:														
Male	84.57± 11.62	70.15± 16.98	46.94± 26.99	32.98± 33.42	83.69± 20.04	81.28± 20.36	61.61± 31.19	67.82± 23.70	80.50± 23.91	67.29± 28.62	85.46± 14.99	65.22± 17.18	-1.002	0.319
Female	81.96± 13.93	74.33± 17.91	45.13± 30.83	28.00± 25.07	79.33± 20.26	81.47± 16.07	76.56± 16.95	66.90± 18.26	79.33± 22.22	67.00± 30.80	86.33± 17.72	60.40± 16.00	1.179	0.241
Marital status:														
Single	84.43± 12.72	73.08± 18.89	49.34± 31.45	34.21± 23.88	81.05± 19.91	76.14± 17.68	-	67.50± 18.10	**62.28± 33.26**‡	63.16± 31.59	85.96± 17.80	66.32± 17.39	F=5.530	0.002
Married	83.46± 12.66	71.04± 17.23	46.08± 27.93	29.10± 31.56	81.89± 20.92	83.08± 18.65	65.48± 27.07	67.28± 22.77	**84.33± 17.38**	71.27± 27.27	84.33± 16.64	66.87± 17.16	-	-
Widowed	79.17± 15.60	80.63± 16.32	38.13± 33.26	30.00± 25.82	79.33± 18.18	82.67± 13.41	-	67.25± 15.25	**81.67± 18.34**	51.25± 35.58	95.00± 8.05	68.00± 13.17	-	-
Level of education:														
Primary	81.02± 13.33	69.88± 20.14	41.32± 28.48	29.17± 27.71	78.89± 21.29	84.26± 14.27	60.00± 37.91	66.39± 18.81	80.56± 22.36	70.14± 31.52	86.57± 15.85	65.28± 17.15	F=0.419	0.74
Secondary	84.87± 12.14	72.71± 16.01	46.20± 29.45	29.35± 32.62	81.01± 20.94	80.73± 21.19	67.19± 24.10	69.84± 20.87	78.99± 25.20	68.75± 26.05	84.78± 16.79	68.48± 14.90	-	-
Tertiary	75.00± 26.52	65.63± 13.26	56.25± 8.84	50.00± 0.00	96.67± 4.72	73.34± 9.43	-	52.50± 56.57	-	87.50± 17.68	75.00± 11.78	55.00± 7.07	-	-
No formal education	84.77± 12.42	78.61± 14.92	56.73± 29.14	34.62± 24.02	87.69± 13.57	76.92± 17.35	-	63.46± 22.51	-	50.00± 33.46	89.74± 17.40	66.92± 21.75	-	-
Working status:														

*Values are mean ± standard deviation (SD;†P<0.05, independent t-test; ‡P<0.05, oneway ANOVA; CVD: Cardiovascular disease

Table 3-2. Mean score of KDQOL-SF^{TM} by socio-demographic characteristics among patients (n = 97) (cont.)

Variables	*Generic scale*										*t test / ANOVA F value*	*P value*
	PCS	*Physical functioning*	*Role-physical*	*Pain*	*General health*	*MCS*	*Emotional well-being*	*Role-emotional*	*Social function*	*Energy/ fatigue*		
Age												
18-60	**44.29± 8.39**†	**67.87± 25.66**†	46.28± 39.69	81.06± 26.73	48.73± 8.56	48.73± 8.56	73.96± 20.03	74.47± 37.57	**78.46± 23.56**†	**57.66± 24.38**†	-5.134	0.001
≥ 60	**37.69± 9.97**	**38.80± 29.80**	38.50± 40.47	75.45± 29.75	45.70± 10.78	45.70± 10.78	66.40± 18.66	62.67± 44.49	**67.75± 25.01**	**47.80± 22.66**	-2.167	0.033
Ethnicity												
Chinese	41.26± 10.27	52.43± 32.03	41.45± 40.94	**83.45± 25.85**‡	47.52± 9.95	47.52± 9.95	70.58± 18.94	70.18± 39.84	72.53± 24.83	53.68± 23.33	F=6.359	0.001
Malay	43.03± 8.43	69.17± 39.04	69.17± 39.04	**70.42± 26.48**	50.66± 13.86	50.66± 13.86	74.00± 34.57	66.67± 51.64	85.42± 20.03	70.00± 28.11	-	-
Indian	37.90± 7.47	46.43± 22.91	46.43± 22.91	**51.25± 28.11**	44.15± 7.09	44.15± 7.09	67.14± 15.94	57.14± 47.91	70.54± 27.12	39.29± 20.93	-	-
Gender												
Male	41.53± 8.94	56.91± 30.06	43.09± 39.60	82.77± 27.33	47.40± 9.62	47.40± 9.62	69.28± 19.97	73.76± 39.28	75.00± 24.73	55.53± 22.89	-1.561	0.122
Female	40.29± 10.54	49.10± 32.34	41.50± 40.91	73.85± 28.83	46.95± 10.13	46.95± 10.13	70.80± 19.43	63.33± 43.25	71.00± 24.93	49.80± 24.72	-1.24	0.218
Marital status												
Single	41.22± 9.79	56.58± 29.49	39.47± 35.66	76.32± 33.09	46.29± 9.12	46.29± 9.12	69.47± 22.60	71.94± 37.29	67.76± 32.09	51.05± 24.36	F=2.235	0.089
Married	41.38± 9.71	55.07± 31.53	44.40± 40.78	79.96± 27.55	47.46± 10.21	47.46± 10.21	70.63± 19.98	70.15± 41.09	74.81± 23.49	52.99± 23.57	-	-
Widowed	37.02± 10.76	29.50± 27.23	37.50± 46.02	72.00± 25.81	47.93± 9.22	47.93± 9.22	68.40± 11.54	56.67± 49.81	71.25± 18.68	55.50± 27.13	-	-
Level of education												
Primary	39.64± 11.26	**44.58± 32.04**§	45.83± 44.92	76.32± 30.92	46.63± 10.89	46.63± 10.89	69.56± 20.93	67.59± 43.27	69.79± 25.24	50.69± 23.91	F=7.777	0.001
Secondary	43.17± 8.60	**65.98± 27.38**§	38.59± 36.40	80.05± 26.96	47.26± 9.68	47.26± 9.68	70.43± 20.85	68.84± 39.38	76.63± 25.77	55.65± 23.44	-	-
Tertiary	44.58± 3.90	**65.00± 35.36**§	62.50± 53.03	72.50± 38.89	50.04± 1.82	50.04± 1.82	78.00± 19.80	-	81.25± 26.52	50.00± 28.28	-	-
No formal education	35.71± 7.65	**27.69± 19.32**§	42.31± 40.03	77.50± 27.31	47.89± 8.58	47.89± 8.58	68.92± 10.97	64.10± 48.04	67.31± 19.46	47.31± 26.43	-	-
Working status												
Yes	44.77± 7.16	**80.77± 14.56**†	40.38± 34.67	84.42± 29.65	48.96± 6.43	48.96± 6.43	74.77± 16.92	76.92± 34.39	82.69± 18.78	**65.77± 16.31**†	-6.109	0.001
No	40.29± 10.01	**48.57± 31.06**	42.56± 41.03	77.20± 28.17	46.89± 10.26	46.89± 10.26	69.33± 19.98	67.06± 42.51	71.43± 25.34	**50.54± 24.31**	2.180	0.032
Money allowances												
Yes	42.88± 7.91	59.60± 30.34	48.00± 40.77	80.70± 27.45	46.57± 9.05	46.57± 9.05	71.04± 20.27	61.33± 41.59	77.50± 23.94	55.80± 21.92	1.187	0.238
No	40.20± 10.29	50.56± 31.55	40.28± 39.93	77.29± 28.75	47.37± 10.15	47.37± 10.15	69.72± 19.50	70.83± 41.47	71.35± 25.04	51.46± 24.60	1.247	0.216

*Values are mean ± standard deviation (SD); $^{\dagger}p<0.05$, independent t-test; $^{\ddagger}p<0.05$, oneway ANOVA; $^{\S}p<0.05$, oneway ANOVA, significant difference within the group using post hoc test; CVD: Cardiovascular disease; MCS: Mental component summary; PCS: Physical component summary

Table 4-1. Correlation between anthropometric measurements, biochemical parameters, and medical history with KDQOL-SF™

Variables	*Kidney-specific scale*												*P value*
	Symptom /Problem	*Effects of kidney disease*	*Burden of kidney disease*	*Work status*	*Cognitive function*	*Quality of social interact-tion*	*Sexual function*	*Sleep*	*Social support*	*Dialysis staff encourage-ment*	*Patient satisfac-tion*	*Overall health*	
	r	*r*	*r*	*r*	*r*	*r*	*r*	*r*	*r*	*r*	*r*	*r*	
Anthropometric measurements													
BMI (kg/m^2)	-0.950	-0.135	0.510	0.048	0.072	0.084	0.024	-0.036	0.019	0.060	0.094	0.073	0.187
IDWG (kg)	-0.168	-1.530	-0.088	-0.180	-0.030	-0.187	-0.188	-0.145	-0.094	0.106	-0.011	-0.008	0.067
MUAC (cm)	0.006	-0.062	0.156	-0.004	0.162	0.111	0.121	0.002	0.116	0.018	0.050	0.033	0.114
Total body fat (kg)	-0.130	-0.009	0.091	0.034	0.047	0.016	0.113	0.036	0.009	0.071	0.148	0.025	0.151
Body fat (%)	-0.127	0.069	0.099	-0.030	0.050	-0.075	0.179	0.001	-0.044	0.064	0.112	0.052	0.219
Biochemical parameters													
Serum creatinine (mg/dL)	0.155	-0.039	0.092	-0.057	0.103	0.022	0.241	0.020	0.190	0.032	0.003	0.163	0.063
Serum calcium (mmol/L)	-0.018	0.082	0.030	0.125	-0.164	0.008	-0.110	0.061	0.039	-0.034	0.060	-0.031	0.111
Serum phosphorus (mmol/L)	0.131	0.147	**0.203***	0.070	**0.205***	0.008	0.414	-0.054	0.069	0.094	0.097	0.106	0.048
Serum albumin (g/L)	0.105	-0.052	-0.019	-0.033	-0.06	0.077	0.223	0.032	0.117	-0.094	0.087	0.126	0.221
Total protein (g/dL)	0.001	0.068	-0.073	0.119	0.06	-0.009	0.276	-0.018	-0.035	0.099	0.067	0.017	0.214
Alkaline phosphatase (g/dL)	0.003	0.085	-0.116	-0.143	0.031	-0.100	-0.286	-0.006	-0.005	-0.069	0.058	-0.051	0.161
Serum sodium (mmol/L)	**0.281***	0.080	0.108	0.145	**0.307***	0.008	-0.406	0.172	**0.235***	-0.061	0.087	0.128	0.005
Serum chloride (mmol/L)	-0.060	-0.023	-0.175	-0.007	-0.139	-0.073	**-0.511***	0.199	0.097	-0.009	-0.138	0.002	0.015
Serum potassium (mmol/L)	0.035	-0.030	0.034	-0.157	0.055	0.022	0.136	0.081	-0.069	0.019	0.162	0.173	0.089
Triglyceride (mmol/L)	-0.009	-0.111	-0.003	-0.076	0.065	0.194	0.202	-0.016	0.097	0.172	0.180	0.167	0.056
Total cholesterol (mmol/L)	0.092	0.073	-0.044	0.192	-0.049	0.121	-0.231	-0.069	0.006	0.080	0.087	0.046	0.059
HDL-cholesterol (mmol/L)	0.104	0.017	-0.167	0.018	-0.133	-0.034	-0.043	-0.093	-0.153	-0.015	0.057	0.115	0.102
LDL-cholesterol (mmol/L)	-0.063	0.151	0.057	-0.156	-0.026	-0.023	-0.188	0.081	-0.026	-0.034	-0.133	-0.057	0.141
Haemoglobin (g/dL)	-0.003	-0.066	0.008	0.008	-0.129	0.028	-0.374	0.028	0.081	0.003	0.190	0.096	0.062
TIBC	-0.189	**-0.257***	-0.186	0.141	-0.186	**-0.248***	-0.041	-0.189	-0.045	-0.040	0.079	-0.016	0.011
Transferrin	-0.200	**-0.250***	-0.174	0.156	-0.167	**-0.243***	-0.035	-0.186	-0.046	-0.047	0.074	0.025	0.014
Medical history													
Years of diagnosed kidney failure	0.006	0.101	0.011	0.104	0.028	0.023	-0.060	0.118	0.184	-0.057	0.074	0.034	0.072
Years having HD	-0.027	0.063	-0.007	-0.040	-0.087	-0.095	0.115	0.052	0.166	-0.129	0.172	0.072	0.093
Number of co-morbidities	-0.149	**-0.243***	-0.113	-0.109	-0.093	0.006	-0.316	-0.181	-0.072	-0.009	0.001	-0.090	0.017

Values are *r:* Pearson correlation coefficient; BMI: Body mass index; HD: Haemodialysis; IDWG: Inter-dialytic weight gain; MUAC: Mid upper arm circumference; TIBC: Total iron-binding capability; *Bold number indicate significant for correlation (*P<0.05), Pearson correlation

Table 4-2. Correlation between anthropometric measurements, biochemical parameters, and medical history with KDQOL-SF^{TM} (cont.)

Variables	*Generic scale*										*P value*
	PCS	*Physical functioning*	*Role-physical*	*Pain*	*General health*	*MCS*	*Emotional well-being*	*Role-emotional*	*Social function*	*Energy/ fatigue*	
	r	*r*	*r*	*r*	*r*	*r*	*r*	*r*	*r*	*r*	
Anthropometric measurements											
BMI (kg/m^2)	-0.105	-0.090	-0.046	-0.007	-0.055	0.019	0.008	0.038	-0.017	0.018	0.307
IDWG (kg)	0.001	0.106	-0.103	0.004	-0.109	-0.043	-0.066	-0.005	-0.061	-0.048	0.289
MUAC (cm)	-0.019	0.042	0.012	-0.002	0.011	0.054	0.014	0.033	0.060	0.064	0.534
Total body fat (kg)	-0.082	-0.132	0.006	0.027	0.043	0.009	0.088	-0.108	-0.031	-0.074	0.201
Body fat (%)	-0.146	**-0.235***	-0.065	-0.006	0.081	0.015	0.052	-0.121	-0.075	-0.084	0.021
Biochemical parameters											
Serum creatinine (mg/dL)	**0.240***	**0.440****	0.078	-0.019	0.168	0.083	0.032	0.121	0.154	0.168	0.001
Serum calcium (mmol/L)	0.142	0.057	0.149	-0.015	0.126	-0.082	-0.030	-0.034	0.020	-0.079	0.147
Serum phosphorus (mmol/L)	0.062	**0.247***	0.077	-0.044	0.106	**0.255***	0.180	**0.249***	-0.017	0.129	0.013
Serum albumin (g/L)	**0.306***	**0.272***	**0.274***	0.101	**0.253***	0.027	0.086	0.134	0.058	**0.281***	0.007
Total protein (g/dL)	0.167	0.125	0.198	0.003	0.056	-0.091	-0.019	-0.014	0.009	0.011	0.051
Alkaline phosphatase (g/dL)	-0.183	-0.110	-0.089	-0.131	-0.163	-0.045	-0.034	-0.116	0.030	-0.136	0.073
Serum sodium (mmol/L)	0.195	**0.217***	0.114	**0.206***	**0.236***	0.114	**0.216***	0.001	**0.235***	**0.207***	0.021
Serum chloride (mmol/L)	0.064	0.141	-0.088	0.021	0.027	0.012	0.021	-0.056	0.191	0.057	0.061
Serum potassium (mmol/L)	0.136	0.097	0.148	-0.040	0.139	0.029	0.068	0.100	0.009	0.193	0.058
Triglyceride (mmol/L)	0.056	-0.031	-0.103	0.123	0.009	-0.127	-0.114	-0.075	0.121	0.101	0.217
Total cholesterol (mmol/L)	0.085	0.067	0.156	0.067	0.073	0.114	0.137	0.088	0.132	-0.003	0.126
HDL-cholesterol (mmol/L)	0.174	0.117	**0.217***	0.099	0.145	0.148	0.142	0.165	0.074	0.077	0.032
LDL-cholesterol (mmol/L)	-0.140	-0.041	0.022	-0.121	0.008	0.121	0.039	0.095	0.022	-0.037	0.173
Haemoglobin (g/dL)	0.070	-0.020	0.128	-0.055	0.195	-0.038	-0.036	-0.052	0.032	0.138	0.055
TIBC	0.114	0.076	0.123	-0.059	-0.044	-0.151	-0.169	-0.023	-0.006	-0.023	0.100
Transferrin	0.101	0.067	0.128	0.089	-0.051	-0.145	-0.169	-0.027	-0.014	-0.020	0.099
Medical history											
Years of diagnosed kidney failure	**0.251***	0.164	**0.204***	0.103	0.161	-0.082	0.050	-0.094	**0.236***	-0.059	0.045
Years having HD	0.060	0.036	0.112	-0.083	0.120	0.034	0.113	-0.141	0.160	-0.070	0.117
Number of co-morbidities	**-0.223***	**-0.308***	-0.118	-0.164	0.004	-0.088	-0.066	-0.072	**-0.253***	-0.063	0.002

Values are *r:* Pearson correlation coefficient; BMI: Body mass index; HD: Haemodialysis; IDWG: Inter-dialytic weight gain; MUAC: Mid upper arm circumference; TIBC: Total iron-binding capability; *Bold number indicate significant for correlation (*P<0.05), Pearson correlation

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ORIGINAL ARTICLE

Knowledge and Attitude of Ipoh Residents towards Using "Time Bank" in Care of the Elderly.

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Abstract

Background: Time banking is a socially based system of transaction that uses time instead of money. Members of a time bank can earn time credits by providing services, which they can later spend these credits by receiving services from others. Time banking is one way where the society can maximize its social capital and lessen the burden of the ageing population. This study aims to identify the level of knowledge and attitude towards the use of time banking in elderly care among residents of Ipoh Perak.

Method: A cross-sectional study with a sample size of 386, calculated using OpenEpi. Data were collected through an online Google Form distributed to various groups on different online platforms, as well as through self-administered questionnaires.

Results: Most of the respondents, 75.7% (n=292) were found to have poor knowledge on time banking in elderly care. However, 55.7% (n=215) of the respondents had a positive attitude towards it. Respondents without health problems had a positive attitude compared to those with health problems.

Conclusions: Overall, most of the Ipoh residents demonstrated poor knowledge on time banking in elderly care.. On the contrary, a positive attitude was observed among them. There was also a significant association between knowledge of time bank in elderly care and attitude. More programmes and campaigns on time banking are recommended to increase the knowledge of the Malaysian population on its role in elderly care.

Keywords: *Attitude, knowledge, Ipoh, sociodemographic features, time banking.*

Introduction

Malaysia is anticipated to become an ageing nation, with 15% of the population expected to be 60 years and above by 2030. The elderly population has been steadily increasing over the past 40 years, rising from 316,858 in 1970 to 1,427,340 in 2017. It was projected to increase by 7.8% in 2020; however, the actual increase was 11.1% [1]. The increase in the elderly population is partly due to rising life expectancy. However, a growing proportion of elderly individuals is also associated with an increased prevalence of poor health as older adults tend to be less healthy than younger individuals due to physical and social changes, as well as diseases commonly associated with ageing. Furthermore, elderly malnutrition is anticipated to become a significant issue, driven by alterations in dietary practices, poor dental health, and the types and quantities of food consumed [2]. According to 2000 Census, approximately 7% (94,000) of older people lived in single-member households. Those who live alone are more likely to require outside support in the event of illnesses or disabilities, are more likely to experience social isolation, and are disproportionately more likely to be poor, particularly older women [3]. Living alone, having distant family members, having fewer ties to their culture of origin, or being unable to actively take part in neighbourhood activities all contribute to the loneliness that many elderly people experience. Demoralization and depression frequently follow when this happens in conjunction with physical impairment [4].

As members of families in modern society, we have realised that we usually rely on one another in many ways, especially when it comes to offering support to our aging family members. When elderly individuals find it difficult to manage daily house chores as easily as they once did, other family members should step in to help out. Caregiving includes everything from helping the care recipient with everyday tasks and giving them direct care to navigating the complicated health care and social services systems which might include assisting in daily household tasks, self – care and mobility [5]. However, Malaysia is known to be one of the most overworked countries in Asia Pacific ranking 4th overall with having an average of 42 hours of working hours per week, thus making it harder for them to be always available at home [6]. An overworked culture is prevalent in many Malaysian companies, leading to employee burnout, depression and disconnection from loved ones, which increases the risk of neglecting elderly parents [7]. Additionally, the high living cost in Malaysia can be one of the factors that force many adults to migrate from rural areas to urban centres for a better pay and more job opportunities [8]. Besides that, the process of ageing might impair the physical and sensory ability of the elderly to do simple chores for themselves without the help of other people [9]. We believe that time banking offers a novel approach to take care of the elderly by utilizing time credit. Hence, we would like to assess the knowledge and attitude of time banking among Ipoh residents which might help in the care of the elderly. The development and growth of time banking have frequently been an effort to address the lack of community-based care for the senior citizen. It offers a potential solution by providing accessible and affordable community-based care for the elderly. In this situation, the elderlies are the primary recipients of care services offered by community volunteers in exchange for time credits. Typically, the majority of time banking beneficiaries are elderly individuls, while service providers are often from younger age groups [10]. With advancing age, the elderly have lost their capability to do the chores and attending their necessities by themselves. Therefore, the establishment of time banking will have a really huge impact and benefit the elderly to live more comfortably with the help of community members. Time banking is a system of exchanging various services for one another based on the labour theory of value, developed by various socialist thinkers. Labor-time units can be credited to a person's time bank account and redeemed for services from other time bank members. Time banking can be thought of as a type of community currency. People receive

labor-time credits in a time-banking environment when they provide a service to another time-bank member (and the member receiving the service is debited an equal amount). Regardless of the service provided, every hour of time is generally valued the same. In theory, any service can be traded for another. However, services traded frequently revolve around simple, low-market-value tasks such as elderly care, social work, and home repair. However, labour-time credits are not accepted outside the time bank's membership, and do not function as a form of money in the broader economic sense . Time banking is part of an international movement aimed at changing the conventional, asymmetrical social service delivery models into social networks where members offer and receive services that are valued equally. There is some proof that time banks improve health, and they have been shown to increase social capital. The concept, originated by Edgar Cahn in 1980, was designed to make social service recipients into "coproducers" of the services they receive, by also providing services that others need [11].

Ipoh City is Malaysia's third largest city in the country with a current population of over 857,00 people. In 2015, 16.7% out of 739,700 people in Ipoh City were more than 60 years of age (World Health Organisation). Nationally, the percentage of Malaysia's population aged 65 and over increased from 7.0% in 2021 to 7.3% in 2022. Malaysia has become an ageing society based on the United Nations definition (Department of Statistics Malaysia). This statistic shows that the population of the older people increases every year. Generally, elderly individuals may have weak physical strength and are often no longer able to perform tasks involving physical strength. Moreover, half of the elderly people in Perak live alone, unaccompanied by family members [12].

Time banking has proven to be useful and beneficial in strengthening the community in terms of social interaction, exchanging physical services, humanity and understanding different cultures [13]. Hence, we would like to assess the knowledge and attitude of time banking among Ipoh residents, as it offers a practical solution elderly care.

Materials and methods

A cross-sectional study was conducted utilizing an online Google Form from 15th May 2023 until 9th June 2023 among the population of Ipoh. According to DOSM, the current population in Ipoh is 923,003. The sample size was calculated using OpenEpi version 3.01 based on one proportion sample. The sample size needed for 95% confidence level was 386. Convenience sampling was used to collect the data from 386 Ipoh residents. The inclusion criteria required participants to be Ipoh residents aged 18 and above who provided consent to participate. The questionnaire was pre-tested on 30 individuals meeting the same inclusion criteria and was found to be clearly understood by all participants during the pretest. The knowledge section of the questionnaire consisted of eight questions, with respondents required to answer either "Yes I know" or No, I do not know". The attitude section also included eight questions, with respondents selecting from "Strongly disagree", "Disagree", "Neutral", "Agree" and "Strongly Agree".

Statistical Package for the Social Sciences (SPSS) build 1.0. 0.1275 was used to analyse the data. All categorical data were expressed as frequencies. In the assessment for knowledge on time banking, score "1" was given for "Yes I know" and score "0" for "No, I do not know". The maximum score for knowledge on time banking was 8 and the minimum was 0. A score of ≤ 2 was considered indicative of poor knowledge, a score between 3 and 5 as moderate knowledge, and a score of 6 and above as good knowledge. For the assessment of attitude towards time banking, a Likert scale was used. "Strongly disagree", "Disagree", "Neutral", "Agree" and "Strongly Agree" were as scored 1, 2, 3, 4, and 5 respectively. The maximum score for attitude was 40 and the minimum was 8. Based on the mean of the total responses, scores between 8 and 18 were classified as poor attitude, scores between 19 and

29 as moderate attitude, and scores between 30-40 as good attitude. Chi-Square test and Fisher's exact test were used to analyse the association between sociodemographic factors (such as age, gender, level of education, ethnicity, household status, employment status, and marital status) and respondents' knowledge and attitude towards time banking. P-values of less than 0.05 were considered statistically significant.

Results

The demographic characteristics of the participants are shown in Table 1. The majority of the participants were adults between 18-44 years old (60.6%), predominantly Malay (70.5%), with slightly more female (56.2%) than male, almost equal single (47.1%) and married participants (48.2%) and the highest percentage of the participants had College/University educational background (79.9%). Regarding the health status of respondents (Table 2), most of the participants (88.8%) did not have chronic health problems requiring constant assistance from others, while only 22% required help with household chores. In terms of knowledge about time banking, the majority (75.7%) had poor knowledge, while 55.7% had a positive attitude toward time banking. We tested for possible association between the participants' knowledge and the attitude toward time banking with selected sociodemographic variables, as well as the health status (Table 3). The results showed that knowledge was significantly associated with the participants' race (p value = 0.007) and chronic health problems (p value < 0.001). Attitude of the participants on time bank was significantly associated with marital status (p value = 0.008), education level (p value < 0.001), and employment status (p value = 0.017). Finally, we tested the association between knowledge and attitudes of the participants on time bank. We found that there was a significant association between them (p value = 0.012) (Table 4)

Discussion

Regarding the level of knowledge about "time banking" in elderly care among Ipoh community, the majority of the respondents demonstrated poor level of knowledge of "time bank". A preliminary study by Normi Sham Awang Abu Bakar et al. (2024) found that 51% of participants were aware of the time banking concept, while 86% expressed willingness to participate in a time banking project [14]. However, their study included non-Malaysian participants, and it was observed that 80% of those aware of time banking were non-Malaysians. Both their research and our study highlight that time banking remains poorly understood or recognized among Malaysian nationals. This underscores that time banking is still not widely known in Malaysia, despite its long-standing development and implementation in other countries. In fact, most respondents in our study had never heard of time banking. Time banking has the potential to shape the future of care services in relation to senior citizens in Malaysia, particularly as the country's population continues to age. Time bank can give more emphasis to the formal and informal care of elderly by providing a comprehensive community-based care. It also promotes thoughts on what it means to age meaningfully and how the current economic climate affects the provision of services for the aged [10]. Thus, it is important to educate the community about the benefits of time banking especially in elderly care and gain their trust so that they will be always willing to participate in this concept.

In terms of attitude towards "time banking" in elderly care among Ipoh residents, more than half of them showed positive attitude towards "time bank" and its role in improving the elderly care. There is a common belief among population that, time bank can contribute to positive value in a community in terms of physical, social and economic aspects [15]. The high number of respondents with positive attitude in this study suggests that time banking could gain significant support and volunteers if implemented in

Malaysia. Similarly, Normi Sham Awang Abu Bakar et al. (2024) demonstrated that 80% of their respondents found that time banking is an appealing concept [14]. This percentage is significantly higher compared to 55.7% of respondents in this study with positive attitude toward time banking. However, more efforts are needed to increase awareness and understanding of the concept. This will help people appreciate its benefits, particularly in the context of elderly care. It would be worth to mention that few of the respondents had neutral and negative attitude towards time banking possibly, due to lack of information. Likewise, lack of information about time bank may affect the level of participation because it is a new form of service exchange that many individuals may not know about it [16]. In addition, cultural beliefs may also be one of the factors that respondents did not agree to implement time banking in Malaysia. Common awareness about the time bank system does not exist in nations where, alternative or complementary economic systems exist and perform traditionally well. People tend to be wary of fraud, associate time banks with a sect, or just fail to see any benefits if the dubiously positive rhetoric about them is included. Breaking prejudices takes a long time [17].

Overall, the Ipoh community exhibits a poor level of knowledge and portrayed good attitude towards "time bank" in elderly care. Further research is needed to explore knowledge and attitude toward time banking across diverse communities in Malaysia. Only then can we assess whether this concept can be successfully implemented and gain the necessary community support to enhance elderly care services in the country.

Limitations

There were few limitations. The first one is time constraint which only six weeks to conduct and complete the research which includes proposal preparation, data collection, data cleaning, data analysis, and report writing. In addition to that, our sample needed a high number of respondents that include different age groups which was young adults, middle-aged and elderly, which took a long time to collect the data especially the elderly because they need to understand and comprehend the questions given in the questionnaire.

We faced challenges to achieve the required number of respondents using only online Google Forms. To overcome this issue, our group went to a few locations, like parks and malls, to conduct the questionnaires face-to-face. Additionally, there are limited journals and studies on time banking in Malaysia, making it difficult to find relevant references for our research topic.

Conclusion

Time banking may serve as one of the methods to maximise social capital within the communities, helping to ease the load posed by the ageing population. The growth of time banking aims to assist lonely and disadvantaged elderly individuals who may lack access to basic care or consistent medical consultations from family and friends. It is clear that people are still lacking on the knowledge regarding time banking, despite that time banking has been implemented 50 years ago in other countries. However, majority of the respondents shows a positive attitude which indicate that most respondents view time banking as a good initiative in helping the elderly. Given these findings, we believe that time banking can be gradually introduced to the community to raise awareness and understanding. This will pave the way for its potential implementation in Malaysia, offering a valuable approach to supporting elderly care and assisting those in need.

Conflict of interest

The authors declared that no conflict of interest may arise from the research publication.

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Ethics
Ethical approval was granted by the UniKL Medical Research Ethics Committee, under reference number UniKLRCMP/MREC/2022-2023/MBBSYR4-SRP-285

Authors' contribution
All the authors contributed to the conceptualization of research, methodology, proposal submission, results analysis, drafting & editing of report, and preparation of the manuscript.

Table 1. Sociodemographic characteristics of the participants

Variables	Frequency (n)	Percentage (%)
Age Group (years old)		
– Young Adults (18-44)	234	60.6
– Middle Adult (45-59)	81	20.9
– Elderly (60 and above)	71	18.5
Gender		
– Male	169	43.78
– Female	217	56.22
Race		
– Malay	272	70.47
– Chinese	54	13.99
– Indian	50	12.95
– Others	10	2.59
Marital status		
– Single	182	47.1
– Married	186	48.2
– Divorced/widowed	18	4.7
Household Status		
– Living Alone	33	8.55
– Living with Family	278	72.02
– Living with Friends	75	19.43
Education Level		
– No Formal Education/Primary	3	0.9
– Secondary School	74	19.2
– College/University	309	79.9
Employment Status		
– Unemployed	227	58.8
– Employed	159	41.2

Table 2. Health Status of respondents / Need for Assistance (N=386)

Variables	Frequency	Percentage
Chronic health problem requiring constant assistance from others		
– Yes	43	11.14
– No	343	88.86
Usually need someone to help you in household chores		
– Yes	85	22.02
– No	301	77.98
Person who usually does household chores in your house		
– Yourself	216	55.96
– Family member	141	36.53
– Paid assistance (e.g. maid)	23	5.96
– Friends	6	1.55

Table 3. Association between Knowledge and Attitude on time bank with few selected sociodemographic characteristics.

	Knowledge					**Attitude**				
	Good	**Moderate**	**Poor**	**X^2**	**p-value**	**Positive**	**Neutral**	**Negative**	**X^2**	**p-value**
Total N=386 (%)	**54 (14.0)**	**40 (10.4)**	**292 (75.7)**			**215 (55.7)**	**154 (39.9)**	**17 (4.4)**		
Race										
Malay	**30**	**30**	**212**	**17.7**	**0.007 Fisher**					
Chinese	**6**	**7**	**41**							
Indian	**14**	**2**	**34**							
Others	**4**	**1**	**5**							
Marital Status										
Single						**118**	**60**	**4**	**17.5**	**0.008 Fisher**
Married						**87**	**86**	**13**		
Divorced /widowed						**10**	**8**	**0**		
Education level										
No formal education/ Primary school						**0**	**3**	**0**	**24.7**	**<0.001 Fisher**
Secondary school						**25**	**46**	**3**		
College/ University						**190**	**105**	**14**		
Employment										
Non Employed						**116**	**100**	**10**	**24.6**	**0.017**
Employed						**99**	**54**	**7**		
Chronic health problems	**14**	**122**	**207**	**27.1**	**<0.001**					
Yes	**3**	**32**	**8**							
No										

Table 4. Association between level of Knowledge on "time bank" in care of the elderly and Attitude.

		Knowledge level			chi square value	p value
		Poor	**Moderate**	**Good**		
Attitude	Negative	11	3	3	12.790	**0.012**
	Neutral	131	10	13		
	Positive	150	27	38		

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ORIGINAL ARTICLE

The Use of Functional Outcome Measures in Stroke Rehabilitation among Physiotherapists in Klang Valley, Malaysia.

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Abstract
The use of functional outcome measures (OMs) in physiotherapy practice is widely recommended for monitoring stroke patients' functional status and is considered an integral component of rehabilitation. The aim of this study is to: (1) determine the utilization rate of functional OMs in stroke rehabilitation; (2) evaluate the relationship between OM usage with work experience, level of education, and facility recommendations; and (3) identify common barriers and facilitators affecting the use of functional OMs among physiotherapists. A cross-sectional online survey was conducted among physiotherapists currently employed in private healthcare settings in Klang Valley. The result showed that 97.7% of participants acknowledged using functional OMs when managing stroke patients. Facility recommendations showed a significant association with OM utilization frequency (p-value = 0.001). However, years of working experience and educational status did not show a significant relationship with the frequency of use. Participants' positive attitudes toward the use of functional OMs, their belief in the value of OMs, and the perception that OM enable ideal clinical assessment were identified as the main facilitators. The main barriers included a lack of familiarity with OMs and a preference for using impairment OM. This study concludes that most physiotherapists in private facilities in Klang Valley use functional OMs in stroke rehabilitation, and facility recommendations serving as a significant driver for OM adoption.

Keywords: *Functional status, outcome measure, physiotherapist, private facility, stroke.*

Introduction

Stroke is an emergency medical condition characterized by an acute compromise of cerebral perfusion or vasculature [1]. The definition of stroke continues to evolve, as the traditional clinical definition does not fully account for advancements in scientific and technological [2]. In many countries, stroke is a leading cause of death and disability. In Malaysia, it is the third leading cause of death, accounting for 8.0% of deaths in 2019 compared to 7.9% in 2018 [3]. An empirical analysis of stroke in Malaysia revealed a concerning rise in stroke incidence among younger Malaysians, with more than 45% increase in cases among those under 65 years old. According to WHO, rehabilitation is defined as a set of interventions designed to optimize functioning and reduce disability in individuals with health conditions in interaction with their environment [4]. Rehabilitation plays a crucial role in improving patients' functional level by maximising their physical capacity, minimising secondary illness progression, optimising their environment, easing psychological adaptation to impairment, and encouraging social integration. Within the constraints of persistent stroke deficits, the fundamental goals of stroke rehabilitation are to prevent deterioration, enhance motor function recovery while achieving the best feasible level of independence [5]. The growing number of stroke cases in Malaysia exhibits a great need for physiotherapists to support with rehabilitation and maximise functional independence in stroke-affected patients. There is a rising demand for health practitioners around the world to be more accountable, including demonstrating that their practice is evidence-based and ensuring reliable metrics are utilised to assess the results of their interventions [6]. The use of outcome measure (OM) in physiotherapy practice has been widely recommended to monitor patients' functional status over time. It is commonly advocated as an integral part of rehabilitation. A comparison of outcome measure (OM) usage between physiotherapists in a developed country (Canada) and a developing country (India) revealed that Indian physiotherapists reported a higher frequency of standardized OM use (96.7%) compared to their Canadian counterparts (89.2%)[7]. In neurological physiotherapy, minor changes in impairment can lead to significant functional improvements, substantially impacting patient's quality of life.

In stroke rehabilitation, external monitoring has traditionally focused on structural aspects of care such as impairment assessment, as these are easier to quantify. Recently, however, there has been a shift toward assessing care processes and functional outcomes, in alignment with the International Classification of Functioning, Disability and Health (ICF) framework [8]. With the use of the ICF concept, the focus has tremendously shifted to patient-centred care as OM selections are based on the ICF framework to measure activity restrictions and quality of life beyond the diagnosis of a patient, therefore treating a patient holistically [9]. WHO has argued that patient improvement goals should consider patient's capacity to function and carry out everyday tasks like sitting, turning, walking, and so forth, in addition to the conventionally evaluated impairment associated with body structure.

The adoption of standardised OM has been partially spurred by the recognition that patient progress must be evaluated based on functional performance, not just conventional impairment measures (e.g., strength, range of motion). Functional outcome data is critical, as improvements in daily activities do not always correlate directly with changes in impairments [10]. While improving disability is important, the main goal of rehabilitation is to maximise functional independence. As mentioned by Veras et al. (2016) [11], evidence-based physiotherapy (EBP) is becoming more popular and standardised OMs are an integral part in neurological rehabilitation [12]. Malaysian physiotherapists have shown a positive attitude toward EBP and a willingness to integrate evidence into clinical practice. Since EBP relies on five core components, including outcome evaluation, standardised measures are vital for

assessing intervention efficacy [13]. Selecting appropriate OMs helps to detect subtle functional changes, fostering continous improvement. This study will focus on evaluating physiotherapists' use of functional OM related to activities of daily living (ADLs), functional status, gait, balance, endurance, and other key domains in stroke rehabilitation.

Materials and methods

Design

This cross-sectional study employed an online survey to assess the current use of functional OM among physiotherapists in Klang Valley. Ethical approval was obtained from the Institutional Research and Ethics Committee of KPJ Healthcare University College.

Sampling

Participants were recruited via convenient sampling and included physiotherapists with experience treating stroke patients. They were drawn from private hospitals and selected physiotherapy centres in Klang Valley that provide stroke rehabilitation. The exclusion criteria were physiotherapists with no experience treating stroke patients in the last 6 months**.** The sample size (S) was calculated using the Krejcie and Morgan table [14], with a population proportion of 0.5. Based on this formula, the target sample size was 210 physiotherapists, including a 20% dropout allowance. All identified physiotherapy departments in private hospitals and centres were contacted via phone numbers obtained through Google searches. Several methods were utilized to collect participants for the quantitative phase. One method was to obtain the contact information for the head of department (HOD) of some of the facilities, and a survey link was sent to them to be distributed to their staff. Besides, using social media and common contacts, participants were approached specifically seeking diversity in years of practice and type of environment (e.g., private hospital and private centre), to solicit their involvement. In addition to word-of-mouth marketing and direct distribution via emails and text messages, the online survey was promoted on many social media platforms via the pages of the Malaysian Physiotherapist and Malaysian Physiotherapy Association. To guarantee that respondents to this survey were Klang Valley workers affiliated with private physiotherapy centres, information was provided on the survey header page.

Data collection tool

The instrument tool used was a modified questionnaire from two previous studies: Agyenkwa et al. (2020) [15] in Ghana and Swinkels et al. (2011) [16] in the Netherlands, which assessed the use of OMs for stroke patients among physiotherapists. Using data from the earlier studies, a 34-item questionnaire was created to assess the practice of functional OMs for stroke patients among physiotherapists in Klang Valley. The questionnaire consisted of three parts: part one consisted of 5 questions that captured information on the demographics of the participants such as age, gender, level of education, years of working experience, and type of facility they are attached to. The second part of the questionnaire consisted of 4 questions assessing the routine details of the use of functional OMs among physiotherapists with stroke patients. The questions included whether participants used functional OM, frequency of usage, types of functional OM used, and if their facility recommended the use of OM. The final section was on barriers and facilitators in the use of functional OM during practice among physiotherapists and it consist of 25 questions based on the Likert scale scoring. Content validation was conducted among six specialists from a pool of academicians and clinicians with more than ten years of expertise in stroke rehabilitation and concluded that the content validity of the modified questionnaire was very acceptable. A pilot survey with a sample size of 21 was carried out to establish the reliability of the developed questionnaire, before full scale distribution.

Data collection procedure

The study was conducted from June to November 2023, with data collection spanning 24 weeks. Following questionnaire validation and pilot testing, an online version was created and distributed via a web URL. One representative from each clinical setting facilitated distribution to their physiotherapy colleagues. The Google Form link was disseminated through multiple channels to maximize participation among Klang Valley practitioners. The survey's homepage included the study objectives, investigators' information and data collection period details. Regular reminders were given to encourage completion. All submitted questionnaires underwent manual verification to ensure complete responses.

Data analysis

Collected data was analysed using the Statistical Package for the Social Sciences (SPSS) version 28.0. Descriptive statistics were employed to analyse the utilisation patterns of functional OMs and reported facilitators and barriers to OM implementation. For inferential analysis, multifactorial ANOVA was conducted to examine relationships between functional OM usage and years of clinical experience and educational qualification level.

Results

The study achieved an 82% response rate, with 172 participants completing the survey out of the target sample size of 210. Table 1 displays the demographic information of participants. There were 124 female (72.1%) and 48 (27.9%) male participants. Exactly 129 (75%) of the participants were degree holders, followed by 22 (12.8%) were qualified with Masters, and 21 participants (12.2%) were diploma holders. In terms of workplace, the number of participants working in the private hospital and centre was almost equally distributed, with 90 of the participants (52.3%) attached to hospitals and the remaining from physiotherapy centres. Most participants (76%) reported 1- 8 years of professional experience.

Level of functional outcome measure use

Table 2 presents the patterns of functional OM use among participating physiotherapists. Key findings include 168 participants (97.7%) reported using functional OM for stroke patients, while only 4 participants (2.3%) indicated non-use. In terms of frequency of use, more than 30% employed functional OM for every five stroke patients they encounter regularly. A mere 2% reported never using functional OM out of the 5 patients seen, which was probably among those who did not utilize the functional OM in their practice. The Berg Balance Scale (BBS) was the most frequently used functional outcome measure (38.4%), followed by the Motor Assessment Scale (MAS) (32%). A significant number of respondents, 168 (97.7%), stated that their facility advocated using outcome measurements in patient care.

Relationship of Work Experience, Level of Education and Facility Recommendation with the Use of Functional OM

Multifactorial ANOVA was performed to determine the effect on the relationship of years of working experience, educational level, and facility recommendation with the frequency of practice functional OM among physiotherapists. Facility recommendation showed a statistically significant influence on OM utilization frequency ($p = 0.001$). However, years of working experience and educational status showed no significant effects on the frequency of OM utilization ($p > 0.05$). The result is summarized in Table 3.

Barriers and Facilitators in using Functional OM

Table 4 lists the factors that encourage physiotherapists to use OM, while Table 5 lists the obstacles to using functional OM as perceived by the participants. It is observed that most participants generally agreed with most of the facilitators listed in the questionnaire, with the

largest proportion of facilitator (85.5%) suggesting having a positive attitude towards employing functional OM. The other two most common facilitators, which were cited by more than 80% of the participants, were the value of functional OM is convincing to the participants, and most of the participants' belief that functional OM enables balanced clinical assessment during stroke rehabilitation. In terms of participants' thoughts on the facilitators, there were minimal disagreement, however, most of the participants disagreed that there was enough OM available in their clinical practice, accounting for the largest percentage of disagreement (9.3%). Primary barriers identified were the knowledge gaps with the majority (79.7%) expressed desire to learn more about functional OM before using it for patient care and therefore limiting their use. Another was that the majority (62.8%) preferred to utilise impairment-based OM rather than functional OM while managing stroke patients. Analysis of the barriers found indicates that the majority of participants do not strongly oppose using OM (73.3%) and do not believe that utilising OM is restricted because of a lack of training (58.7%).

Discussion

This study reveals widespread adoption of functional OMs among experienced physiotherapists in Klang Valley, with 97.7% reported using functional OMs during stroke rehabilitation. This finding, align with a study in Sri Lanka [17], suggesting a regional trend toward evidence-based practice in developing healthcare systems. The adoption rate exceeds figures from Colombia (87%) [18] and Korea (84.1%) [19], but significantly surpasses Ghana's reported 47.6% utilization [15], where facility-level recommendations for OMs were notably absent.

Approximately 80% of participants in this study were under the age of 35, and 75% possessing Bachelor's degrees, suggesting that younger people are more open to utilizing functional OM. Bogahawatta et al. (2022) [17] discovered similar findings with younger participants, which suggested that they were more likely to be familiar with pertinent theories and useful advice regarding the use of OM. These results imply that the foundation of evidence-based practice, which include the use of outcome measurements, are the focus of contemporary physiotherapy education. Nonetheless, a study in Saudi Arabia [20], revealed that physiotherapists with 6 -10 years of experience, were 2.7 times more likely to use OMs. The findings were similar to this study as the majority of participants were of age 26 - 35 years. This study also revealed that younger physiotherapists maintain high implementation rates (75.6% use OMs for ≥3/5 patients), reinforcing Malaysia's EBP-positive culture [13]. However, in Ghana, the frequency of use appears to be lower, with less than 30% of physiotherapists using OM for at least 4 out of their 5 patients [15]. This may reflect the different level of awareness and knowledge of Ghanaian physiotherapists on the importance of OM.

To support excellent clinical practice and service delivery in rehabilitation, continual quality management depends on standardized reporting of functioning data [21] and tracking the functional outcomes of patients. The most reported used functional OM for stroke patients was the BBS (38.4%), followed by MAS (32%), MBI (Modified Barthel Index) (9.9%), and TUG (Timed Up and Go) (8.7%). The BBS is the second most often used functional OM behind the Tinetti Mobility Index and Functional Independence Measure (FIM), according to a similar study done in Columbia [18]. Both the latter options, however, were left off from this study's questionnaire because they are not included in the core set of suggested metrics for stroke therapy [22].

The BBS's psychometric qualities for stroke rehabilitation application is a valuable and simple test to conduct without requiring costly equipment or a lengthy assessment period, also indicating that the test has strong reliability, validity, and responsiveness to change [23]. This

could have had an impact on the high rate of BBS use among physiotherapists and assist in evaluating the balance risk among stroke patients because maintaining a stroke patient's mobility and ability to engage in daily function depends on measuring and tracking their postural balance and fall risk [24]. Besides that, the implementation of the most widely recommended tools (e.g., BBS, MAS, TUG) is feasible due to several factors: these tools are easy to score, free to use, and require no specialized training or equipment [25].

The relationship between physiotherapists' work experience, education level, and facility recommendations regarding the use of functional OM was evaluated to assess how these factors might influence clinical practice. In this analysis, only facility recommendations showed a significant association with the frequency of functional OM use among physiotherapists. This finding aligns with a Ghanaian study [15], which reported higher OM usage in facilities where their use was recommended compared to those without such recommendations. Similarly, a German study [26] identified organizational limitations as a key barrier to OM adoption, while another study [27] highlighted the importance of organisational and peer support in facilitating routine outcome measurement.

In contrast, the frequency of functional OM use did not correlate with years of experience or educational level. This contradicts with previous research, such as a study [28] found that educational level may be a predictor of using EBP. Another study [29] found that physiotherapists with a master's qualification were more likely to use OM, possibly due to greater involvement in research and deeper familiarity with outcome measures. Additionally, a German study [26] reported that university degree holders were more likely to use OMs regularly, with 70% of the study's participants were diploma holders. However, the current study did not replicate this finding, possibly due to the overrepresentation of bachelor's degree holders and underrepresentation of diploma or master's-level qualifications.

During facilitator evaluation , most respondents (85.5%) reported having a favourable attitude towards OM, and 80.2% of them were convinced of the usefulness, which is consistent with prior research [20,30]. Positive attitudes and perceived value of using standardised OMs were also found to be strong facilitators in a Saudi Arabian study [31] on neurophysiotherapists. However, the authors speculate that this might reflect high baseline knowledge, which may not echo the results of this study.

Despite 76.2% reporting familiarity with functional OMs and 70.9% feeling confident in their skills, 79.7% desired further training, suggesting knowledge gaps remain. A Dutch study noted that while physiotherapists had a positive attitude and were persuaded of the benefits of OMs, inexperience in implementation was a major barrier [16]. Additionally, 66.7% of participants preferred impairment-based OM, potentially limiting functional OM adoption. This preference may stem from historical reliance on basic impairment measures (such as range of motion, strength, muscular tone, pain, etc.) in rehabilitation, which poorly correlate with activity/participation outcomes [32]. In Egypt, physiotherapists adopted EBP at a lower rate (8.1%) in the neurology specialty than in musculoskeletal diseases [33]. This is likely due, in part, to the long-standing curricular inclusion and widespread use of impairment measures in rehabilitation syllabuses. Though time restriction has been concluded as one of the main barriers in several studies [19,31,34], Malaysian physiotherapists in this study did not perceived time as a hindrance to their use of OM, likely because the study was conducted in private rather than public settings, with lower patient volumes, allowing adequate time for OM administration.

This is the first study focusing on private practice settings in Malaysia, revealing overwhelmingly positive attitudes towards OMs in stroke rehabilitation despite some barriers. This result corresponds similarly with another Malaysian study [13], in which 57.8% of respondents endorsed EBP as essential to their daily work,

while 60.8% agreed it was necessary for providing higher-quality patient care. This study highlights that while Malaysian physiotherapists broadly support use of functional OMs in stroke rehabilitation, clinical adoption varies by setting. Facility recommendations appear influential, suggesting they could serve as a guideline to promote OM use. Future research should expand to government hospitals and community clinics across Malaysia, involving all physiotherapists treating stroke patients. Such studies would enhance understanding of OM utilization and inform strategies to bridge the gap between evidence and practice.

Conclusion

The results of this study provide insight into the level of functional OM use among physiotherapists specialising in stroke rehabilitation. The majority of private physiotherapists uses functional OM with at least 3 out of 5 patients with stroke. Facility recommendation appears to be the factor most strongly associated with functional OM use.

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Authors' Contributions
RR conceptualised and designed the study, performed data collection and analysis, and drafted and finalised the manuscript. MIMS and SNB contributed to research methodology, data analysis, manuscript editing, and resources for the study. AKK contributed to data analysis and review of the manuscript.

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Conflict of interest: None to declare.

Table 1. Descriptive analysis for demographic data of participants (N = 172)

Parameters		**Frequency (n)**	**Percentage (%)**
Gender			
	Female	124	72.1
	Male	48	27.9
Age			
	Under 25	22	12.8
	26 –35	117	68.0
	36–45	24	14.0
	46–55	7	4.1
	56 and above	2	1.1
Education Status			
	Diploma	21	12.2
	Degree	129	75.0
	Master	22	12.8
Work Place (Private)			
	Hospital	90	52.3
	Physiotherapy centre	82	47.7
Work Experience			
	≤ 8	113	65.7
	9–16	45	26.2
	17–24	6	3.5
	25–32	6	3.5
	≥ 33	2	1.1

Table 2. Routine details on functional outcome measurement use among participants

Parameters		Frequency (n)	Percentage (%)
Total Respondents (N= 172)			
Use of OM			
	Yes	168	97.7
	No	4	2.3
Frequency of OM Use			
	0 out of 5	4	2.3
	1 out of 5	18	10.5
	2 out of 5	20	11.6
	3 out of 5	40	23.3
	4 out of 5	25	14.5
	5 out of 5	65	37.8
Commonly used OM			
	Berg Balance Score (BBS)	66	38.4
	Motor Assessment Scale (MAS)	55	31.9
	Modified Barthel Index (MBI)	17	9.9
	Timed Up and Go	15	8.7
	6-Min Walk Test	10	5.8
	Others	5	3.0
	None	4	2.3
Facility Recommendation			
	Yes	168	97.7

Table 3. Relationship between frequency of use with years of working experience, educational status, and facility recommendation in the practice of functional outcome measure among physiotherapist

	SS (Sum of Square)	df	MS (Mean Square)	F	Sig	Partial Eta Squared
Frequency of Use Functional Outcome Measure						
Years of Working Experience	47.690	34	1.403	0.628	0.942	0.138
Educational Status	7.777	3	2.592	1.161	0.327	0.026
Facility Recommendation	24.099	1	24.099	10.797	0.001	0.075

Using Multifactorial ANOVA for having three independent variable and numerical dependent variables

*Significant at $p < 0.005$

Table 4. Common facilitators towards using functional OM among participants

Factors	Perception, n (%)		
	Strongly Disagree/ Disagree	Neutral	Strongly Agree/ Agree
Facilitators			
Familiarity with functional OM	10 (5.8)	31 (18.0)	131 (76.2)
Sufficient Skills to apply	8 (4.7)	42 (24.4)	122 (70.9)
Positive attitudes towards OM	5 (2.9)	20 (11.6)	147 (85.5)
Patient value use of OM	8 (4.7)	37 (21.5)	127 (73.8)
Co-workers (physiotherapists) support the use of OMs	10 (5.8)	49 (28.5)	113 (65.7)
Supervisors supports the use	7 (4.1)	35 (20.3)	130 (75.6)
The use of OMs fits my way of working in the clinic well	8 (4.7)	38 (22.0)	126 (73.3)
Sufficient availability of OMs in daily clinical practice	16 (9.3)	52 (30.2)	104 (60.5)
OMs allow to make a balanced clinical assessment	3 (1.8)	31 (18.0)	138 (80.2)
Convinced of the usefulness of Oms	3 (1.8)	31 (18.0)	138 (80.2)
Use of OMs is an integral part of treatment	7 (4.1)	36 (20.9)	129 (75.0)
Use of OMs improves the quality of my treatment	7 (4.1)	31 (18.0)	134 (77.9)
Patients want to evaluate treatment results objectively	4 (2.3)	36 (21.0)	132 (76.7)
Referrers want to evaluate treatment results objectively	5 (3.0)	35 (20.3)	132 (76.7)
Using OMs might strengthen negotiations with insurers	7 (4.1)	45 (26.1)	120 (69.8)
I use OMs primarily for evaluative purposes	5 (2.9)	42 (24.4)	125 (72.7)

Table 5. Common barrier towards using functional OM among participants

Factors	Perception n (%)		
	Strongly Disagree/ Disagree	Neutral	Strongly Agree/ Agree
Barriers			
Difficulty in changing routine	58 (33.7)	74 (43.0)	40 (23.3)
Resist using Oms	126 (73.3)	32 (18.6)	14 (8.1)
Patients find use of OM time consuming	73 (42.5)	62 (36.0)	37 (21.5)
Using OMs is a problem because no training	101 (58.7)	44 (25.6)	27 (15.7)
Using OM is problem do not have physical space in practice	93 (53.5)	47 (27.3)	33 (19.2)
To know more about OMs before using	6 (3.4)	29 (16.9)	137 (79.7)
Using OMs requires additional financial compensation	101 (58.7)	50 (29.1)	21 (12.2)
Only primarily use impairment-based OMs	24 (14.0)	40 (23.2)	108 (62.8)
Using OM too time consuming	72 (41.9)	59 (34.3)	41 (23.8)

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ORIGINAL ARTICLE

Formulation of Hydrogel Containing *Oenanthe Javanica* Extract for Topical Use: Extraction, Formulation and Characterization.

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Abstract
Human skin is exposed to aging factors such as sun exposure and environmental pollutants, which cause unwanted stress on the skin, primarily due to the generation of reactive oxygen species (ROS) within the skin. Antioxidants can slow down, prevent or reverse aging by neutralizing the free radicals produced by ROS. *Oenanthe Javanica (O. javanica)* extract carries a potential in the treatment of skin aging due to its high antioxidants content. *O. javanica* extract (0.8%) was incorporated into a hydrogel carrier at different formulation compositions (A1, A2, A3 and A4). Throughout a 30-day stability study, all formulations were found to maintain optimum pH value within the range of 4.5 to 5.5. No significant changes in the physical appearance of the hydrogel containing extract were observed. Sufficient preservative was added to the hydrogel, and no microbial growth was observed on nutrient agar plates after storage under optimal conditions for microbial growth. As for the smoothness evaluation, 9 out of 10 volunteers preferred and were most satisfied with A4 formulation. All formulations were found to be denser than water, ranging between 24.24 and 26.94. Significantly, the percentage of moisture loss was found to be between 89.77 to 90.33%, indicating all the formulated hydrogels contained high amount of water, providing the moisturizing effect. Rheological analysis demonstrated that the hydrogel exhibited pseudoplastic and shear-thinning behaviour. Thus, the novel formulated hydrogels containing *O. javanica* extract could open up new possibilities for the production of cosmeceutical products.

Keywords: *Formulation, Hydrogel, Oenanthe Javanica, Topical, Anti-aging*

Introduction

Human skin is exposed to aging factors such as sun exposure and environmental pollutants, which cause unwanted stress on the skin. According to McDaniel e*t al.* (2017), skin exposed to UV radiation can generate reactive oxygen species (ROS) within the skin [1]. ROS led to the oxidation of DNA, resulting in photodamage and visible tissue aging. Furthermore, Tobin (2017) claimed that ROS can instigate gene expression pathways that lead to increased deterioration of collagen and accumulation of elastin [2]. Excessive quantities of ROS, referred to as oxidative stress, lead to modifications in cell components [3]. Poljšak *et al.* (2011) stated that oxidative stress is the imbalance between the activity of antioxidant defenses and the production of ROS [4].

López-Alarcon and Denicola (2013) reported that antioxidants have the ability to slow down, prevent or reverse aging by neutralizing the free radicals produced by ROS [5]. Although antioxidant do not eliminate all oxidants, they can help maintain the oxygen homeostasis [6]. Antioxidants act as reducing agents that assist in the deactivation of ROS. *Oenanthe javanica (O. javanica)* extract shows potential in the treatment of skin aging due to its high content of antioxidants components. According to Bhaigyabati *et al.* (2017), *O. javanica* contain abundance of phenolic compounds that possess natural antioxidant properties [7]. Phenolic compounds possess antioxidant activity by donating hydrogen atoms to free radicals, which can reduced the oxidative stress [7]. The 2,2-diphenyl-1-picryl- hydrazyl-hydrate (DPPH) free radical scavenging assay showed that *O. javanica* has potent antioxidant properties due to the presence of high levels of phytoconstituents such as phenols and flavonoids [8]. Methanol extraction yields a higher phenolic and flavonoid content than the water extract method [7].

Hydrogel is an organic polymeric gel commonly combined with more complex drug-delivery systems and has a moisturizing effect. Hydrogels are also more stable under changes in temperature and pH compared to emulsion and cream [9]. Hydrogel containing antioxidants can hydrate the skin, restore its elasticity, and promote anti-aging effects. Hydrogel has a low primary irritation index (PII) since it is primarily used in cell culture and biomedical applications that require low irritation index. PII is crucial to assess in cosmetics for skin and eye safety. Cosmetic-based hydrogel products have been shown to help with skin hydration, elasticity restoration, and promote anti-aging effects. According to Silna *et al.* (2016), hydrogels are suitable as topical moisturizers because they have a low irritation index for both eyes and skin [10].

Brady *et al.* (2017) stated that hydroxypropyl methylcellulose (HPMC) is made up partly from O-methylated and O-(2-hydroxypropylated) cellulose ether derivative polymers [11]. HPMC is one of the polymers used in formulating hydrophilic drugs, and is a biodegradable, biocompatible polymer that can be widely used in drug delivery, cosmetics, adhesives, dyes and many other fields [12]. It can also absorb and hold moisture, which is beneficial in cosmetic formulation [13].

Most antioxidants are being administered orally. Oral antioxidant supplements need to undergo first-pass metabolism, which reduces their bioavailability due to rapid metabolism in the liver and intestines. Regular consumption of antioxidant supplements can cause many unwanted side effects. Bhaigyabati *et al.* (2017) noted that prolonged and regular consumption of oral nutritional supplements, such as vitamin E and multivitamins, is associated with a higher risk of prostate and lung cancer [7]. Oral administration of antioxidant supplements such as beta-carotene, vitamin E, C , and A can increase risk of mortality with regular high dose consumptions [14]. Therefore, the formulation of hydrogel containing *O. javanica* extract, which is rich in antioxidant compounds, is believed to be beneficial for the topical application

in addressing skin aging and opens up new possibilities for the production of cosmeceutical products.

Materials and methods

Materials

Oenatha Javanica (*O. javanica*) was purchased from local market in Malaysia. Xanthan gum and phenonip were purchased from Esson Haus Sdn Bhd (Malaysia). Carbopol, HPMC, glycerine, potassium sorbate and sodium benzoate were purchased from Personal Formula Resources (Malaysia) Sdn Bhd.

Extraction of O. javanica plant

Following the method of Akkol *et al.* (2012) with some modifications, a liquid-liquid extraction technique was employed for the extraction of *O. javanica* [15]. Three kilograms of *O. javanica* leaves were collected and dried for 3 days at 40°C temperature. The leaves were then ground and macerated in methanol at ratio weight of 1:10 (*O. javanica*: methanol) and shake for 3 days. The mixture was filtered using a vacuum pump. Then, the solvent was removed from the mixture using rotary evaporator at 40°C under a pressure of 100 mbar. The plant extract was placed in a centrifugal tube and freeze dried for 4 days.

Solubility study

A 0.1% of plant crude extract was dissolved in water medium. The mixture was then stirred and heated (if necessary) to obtain a clear solution. Once the clear transparent solution was obtained, an additional 0.1% of plant crude extract was added into the same mixture. Similar observations were made on the solution's appearance until a cloudy solution was obtained, at which point the cycles were stopped. The maximum amount of plant crude extract that successfully dissolved in the fixed water medium was recorded.

Formulation of hydrogen loaded with O. javanica extract

The hydrogel was formulated by mixing xanthan gum, HPMC, carbopol and 10 mL of distilled water. The mixture was heated and stirred at 60°C until all ingredients were dissolved. Glycerin, potassium sorbate, and sodium benzoate were then added into the mixture. After that, the *O. javanica* extract was added into the vehicle mixture, which was topped up with distilled water until 100 g of hydrogel was achieved. The formulated hydrogel was further homogenized using an overhead homogenizer (Daihan Scientific UR Partner in Laboratory, Korea) at 200 rpm for 1 hour. Drops of phenonip was added to the hydrogel 10 mins before the process completed. Four formulations (A1, A2, A3 and A4) were formulated at different compositions as shown in Table 1 [16].

pH evaluation study

The pH of A1, A2, A3 and A4 were determined using an electrode digital pH meter (Eutech Instruments Pte. Ltd.). pH meter was first calibrated using different pH buffer (pH 4, 7 and 10) to ensure proper functioning. This study was carried out weekly for one month period in triplicate. All data were recorded and analysed [17].

Accelerated stability study

The formulated hydrogels (A1, A2, A3 and A4) were placed in 15 mL centrifugal tubes and subjected to centrifugation at 2,300 rpm for 15 mins. Evaluation on the stability of hydrogels was carried out with respect to their physical appearance, and any noticeable observations were recorded.

Microbial growth study

Nutrient agar was used for the microbial growth study. The hydrogels sample were aseptically transferred onto the sample plates in a cross pattern. The microbial growth was observed daily for 14 days [16].

Smoothness study

Surveys were filled up by 10 volunteers to avoid biased results. All the formulated hydrogels were applied on volunteers' skin and their comments with respect to appearance, smoothness, absorbance ability, oily feeling, itchiness and sign of irritation were recorded using the constructed questionnaire [16].

Relative density study

The weight of empty pycnometers with stopper was measured and recorded. Then, the pycnometer was filled with distilled water until it overflowed and the stopper was placed. The weight of the pycnometer containing distilled water was re-weighed and recorded. The same procedure was repeated for different formulations of hydrogels [16]. Analysis was carried out in triplicate for each sample and the obtained data was analysed using the Equation 1.

$$\text{Relative density of sample w. r. t water} = \frac{\text{Density of sample}}{\text{Density of water}} = \frac{\text{mass of sample}}{\text{mass of water}} \quad \text{(Equation 1)}$$

Moisture content evaluation study

Petri dish weight was first taken and recorded. A 3 g of the formulated hydrogel was placed in the respective petri dish and kept in a desiccator containing anhydrous calcium chloride. After three days, the formulations were re-weighed, and readings were recorded [16]. This study was carried out in triplicate for each sample. The percentage moisture loss was calculated using Equation 2.

$$\text{Percentage moisture loss} = \frac{(\text{Initial weight} - \text{Final weight})}{\text{Initial weight}} \times 100\% \quad \text{(Equation 2)}$$

Rheology study

A Modular Compact Rheometer (Anton Paar, USA) was used to determine the rheological behaviours of the hydrogels (A1, A2, A3 and A4). The shear rate was ranged from 0.01 to 50.00 sec^{-1} at a controlled temperature (25°C). Cone and plate geometry of 4^0/40 mm was used, and the plate gap was set at 0.15 mm. After the sample was placed on the plate, it took 5 mins for the instrument to equilibrate the measurement beforehand. From the 25 data points generated, average viscosity results were recorded in pascal second (Pa·s). The formulated hydrogels were analysed with respect to its behaviour which fit the power law model [18].

Statistical analysis

All analyses were carried out in triplicate and all data are shown as mean ± standard deviation (n=3).

Results and discussion

Extraction of O. javanica

The plant extract of *O. javanica* leaves, obtained through the maceration technique with methanol, resulted in a 22.05% yield of extract. Methanol was chosen because it has been reported to be the best solvent to yield highest amount of phytoconstituents compared to water [19]. Methanol has a methyl group that forms more bonds with the constituents of *O. javanica,* whereas water, with only two hydrogen and one oxygen atom, forms fewer bonds with the extract constituents. Truong et al. (2019) also stated that, methanolic extract produced the most potent extract with the highest radical scavenging activity, indicating higher antioxidant activity [19]. The appearance of the crude extract was dark green and sticky. This is due to the extraction using methanol that can extract sucrose, glucose and other sugars [20]. Quispe-Condori *et al*. (2011) also reported that the sugars do not evaporate during freeze drying and are left as a sticky mass [20]. If the sugar content is very low, powder form can be achieved after freeze drying.

Solubility test of O. javanica extract

Distilled water was observed to successfully solubilized the *O. javanica* extract up to 0.8%

(Table 2). One of the essential criteria for achieving the desired concentration of the drug for pharmacological response is solubility, which involves the dissolution of the solvent to give a homogenous system [21]. Savjani *et al.* (2012) stated that the degree of solubility of a product in a particular solvent is assessed as the concentration of saturation, beyond which no further increase occurs [21]. This statement supports the solubility of *O. javanica* extract in water, as the concentration stop increasing at 0.8%.

pH stability analysis

The average pH reading of the formulated hydrogels (A1, A2, A3 and A4) throughout 1 month storage at 4^0C were recorded (Table 3). All hydrogels were observed to maintain a steady pH throughout the one month observation period, with stable pH values found (Figure 12). Hydrogel of A3 and A4 showed the most stable and consistent pH readings throughout the 1 month storage. Even though A1 and A2 showed a slight increment on the pH values, the changes were not significant, with less than 5% variation. Tracking pH values is vital in determining the stability of hydrogels. Any changes in pH value indicate the presence of chemical reactions which could affect the final product's quality. Some *et al*. (2000) claimed that the most significant components of chemical stability are accelerated testing performance and pH profile kinetics [22]. The pH of human skin generally varies between 4.5 and 6.0. In order to be suitable for industrial application, the pH of a formulation need to be in this range [23].

Hence, it was demonstrated that all the formulated hydrogels possessed a suitable pH range as intended by the industry. Hydrogel A3 exhibited the best property in this analysis, showing stable pH values throughout the 1-month period. It also had the most suitable pH values for human skin application, which can help avoid skin irritation.

Microbial growth analysis

Based on the observation (Table 4), no microbial growth was present on the agar plate for A1, A2, A3 and A4 after storage in an incubator at 38^0C for 14 days. Zhang *et al.* (2017) claimed that the presence of microbial growth, with colony count, is crucial for determining whether the preservative (phenonip) used in this study is effective in inhibiting the growth of microorganisms [24].

Smoothness analysis

The summary of feedback from 10 volunteers by rating on all the formulated hydrogels (A1, A2, A3 and A4) were recorded (Table 5). Majority of volunteers (90%) prefer hydrogel A4 and A1 which provided a comfortable feeling and fast absorption. Fifty-one percent of the volunteers stated that hydrogel A2 and A3 took time to absorb and were a little bit sticky, indicating slower absorption of the product. Eighty percent of the participants strongly agree with the appearance of hydrogel A4, while the least agreement was for hydrogel A1 with only 30% of the participants strongly agreeing. All participants (100%) preferred the smoothness of hydrogel A4, while only 60% preferred hydrogel A2. All participants (100%) strongly agreed that none of the hydrogels irritated the skin. Additionally, 100% of the participants strongly agreed that hydrogels A1, A2 and A4 did not cause any itchiness, while hydrogel A3 had only 90%. One hundred percent of the participants strongly agreed that hydrogel A4 did not have an oily characteristic, while 80% of the participants strongly agreed that hydrogel A2 for the same evaluation.

Hydrogel A2 contains a high amount of HPMC, while hydrogel A3 contains a high amount of xanthan gum . Soni et al. (2018) stated that, high concentration of xanthan gum and HPMC can exhibit an unpleasant sticky feeling on the skin [25]. HPMC has high bioadhesion characteristics, which result in stickiness on the skin and make it more suitable for in vivo formulations [26].

Hydrogel A4 contain carbopol as the main polymer in the formulation, as Soni et al. (2018) stated that carbopol will remain pleasant even at high concentration [25]. Hence, this supports hydrogel A4 to be the most preferred formulation for its transparent appearance and good consistency among the other formulations [27]. Hydrogel A3 contain a high amount of xanthan gum, which Brunchi *et al.* (2016) stated gives the formulation a cloudy appearance and sticky consistency that can create bubbles [28]. Some of the volunteers found that hydrogel A3 tended to be slightly itchy on the skin, which Kovács *et al.* (2020) mentioned as a common effect of xanthan gum on broken skin barrier, causing an itchy sensation [29].

Krongrawa *et al*. (2018) stated that hydrogel is a water-based formulation that should be oil-free, which makes it light and have a watery texture [30]. This is supported by the positive feedback from the volunteers. The participants ranked the formulated hydrogel from the most liked to most disliked hydrogels as follows: A4 > A1 > A2 > A3. This shows hydrogel A4 has the best properties, being preferred by most of the volunteers.

Relative density analysis

The relative density measurements of samples were recorded to be in the range of 24.24 to 26.94 (Table 6). The formulated hydrogels (A1, A2, A3, and A4) were found to be denser than water due to the high concentration of excipients and active ingredients forming hydrogen bonds with water [31]. Hydrogel A2 had the highest relative density of 25.94. The degree of ionization of the polymers HPMC, carbopol and xanthan gum affects the density of ionically crosslinked membranes, making the different polymers to have different densities [32]. Thus, the ingredients in the formulation could influence the relative density of the hydrogels. Hydrogel A2 shows the best property in this analysis, having the highest density among the other hydrogels.

Moisture content analysis

It was found that the percentage of moisture loss in all formulated hydrogels ranged from 89.77 to 90.33% (Table 7). Hydrogel A3 had the highest moisture content at 90.33%, followed by A2 (90.22%), while A1 and A4 had the same moisture content (89.77%). All the hydrogels showed a high percentage of moisture content, indicating a high concentration of water . Goh *et al.* (2019) stated that a high percentage of moisture content produces a good hydrating effect, characterized by a significant increase in skin moisture and smoothness [33]. High moisture content can also repair the skin barrier function and provide moisturization without causing irritation [34]. Hydrogel A3 has the best properties in this analysis, with the highest moisture content, which will increase skin moisture and smoothness. It was also found to repair the skin barrier function and be non-irritating. All hydrogels exhibited a moisture content percentage of more than 80%, which is a good indicator of their effectiveness in moisturizing the skin.

Rheology analysis

The viscosity of the formulated hydrogels was found to range between 78.81 Pa.s and 186.23 Pa.s (Figure 2). Hydrogel A4 exhibited the highest viscosity level of 186.23 Pa.s. Pounikar *et al.* (2012) stated that the higher viscosity provides greater thickness and consistency to the gel [35]. The high viscosity of hydrogel A4 is attributed by its high ratio of carbopol content [35]. All the hydrogels displayed a flow curve with a gradual loss of viscosity as the shear rate increased (Figure 2b), indicating pseudoplastic and shear thinning behaviour [36]. The rheogram curve for pseudoplastic materials results from the shearing action on long-chain molecules, such as linear polymers. As shear stress increases, the disarranged molecules begin to align their long axes in the direction of flow, reducing the size of dispersed molecules and decreasing the apparent viscosity [37].

Figure 2a indicated that all the formulated hydrogels exhibited non-Newtonion behaviour. Non-newtonion behaviour is defined as a change in the viscosity of a fluid when shear is applied. Chhabra (2010) stated that the degree of the curve for shear stress against shear rate may vary due to several factors, such as the nature and concentration of the polymer, the nature of the solvent, and other parameters like particle size, shape, and polymer solutions [36].

Conclusions

Four different hydrogels (A1, A2, A3 and A4) containing 0.8% of *O. javanica* extract with different compositions were successfully formulated and analysed for their physicochemical and rheological characteristics. The pH values of the hydrogels were successfully maintained within the optimal range of 4.5 to 5.5 throughout the stability observation period of one month. Hydrogel A3 showed the best stability based on pH value analysis. No microbial growth was observed on the agar plates after been incubated at 38^0C for 14 days, indicating that all the formulated hydrogels were well-preserved with sufficient preservative content. In a transparency and smoothness study hydrogel A4 was preferred. In the relative density study, all the hydrogels were found to be denser than water, with similar relative density ranging between 24.24 and 26.94. The percentage of moisture loss in the hydrogels were found to be 89.77 to 90.33%, indicating all the hydrogel had a high moisture content with more than 80%, which is expected to provide excellent moisturizing effect. Lastly, rheological analysis confirmed that the hydrogels possessed pseudoplastic, shear-thinning and non-Newtonion behaviour. In near future, these studies should be extended to include prolonged stability analysis, with particular attention to the plant crude extract content throughout the storage. This will further support and validate the potential of the formulated hydrogel containing *O. javanica* extract as an anti-aging skincare product in the cosmeceutical industry.

Conflicts of interest

The authors have declared that no competing interests exist.

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Authors' Contributions

SHM: Conceived the research, conducted the analysis, and drafted the manuscript.
NKHKH: Study the theory, performed the analysis, drafted the results.
CG: Expert in plant extraction and verification.
All authors discussed the results and contributed to the final manuscript.

Table 1. Formulation's composition of A1, A2, A3 and A4.

Ingredients	**Formulation composition (g, w/w)**			
	A1	**A2**	**A3**	**A4**
O. javanica extract	75	75	75	75
Xanthan gum	0.5	0.375	0.75	0.375
HPMC	0.5	0.75	0.375	0.375
Carbopol	0.5	0.375	0.375	0.75
Glycerine	5	5	5	5
Potassium sorbate	0.5	0.5	0.5	0.5
Sodium benzoate	0.5	0.5	0.5	0.5
Distilled water up to	100	100	100	100

Table 2. The limit of *O. javanica* extract solubility in distilled water.

	***O. javanica* extract (%)**								
	0.1	**0.2**	**0.3**	**0.4**	**0.5**	**0.6**	**0.7**	**0.8**	**0.9**
Solubility in distilled water	/	/	/	/	/	/	/	/	X

/ = soluble; X = not soluble

Table 3. The average pH reading for A1, A2, A3 and A4 for 4 weeks storage at 4^0C in triplicate.

Hydrogel formulation	**Storage period (week)**			
	1	**2**	**3**	**4**
A1	4.89±0.036	4.98±0.006	5.03±0.036	5.09±0.015
A2	4.87±0.006	4.98±0.006	5.03±0.036	5.07±0.156
A3	5.02±0.006	5.02±0.006	5.04±0.006	4.98±0.006
A4	4.74±0.025	4.88±0.025	4.87±0.035	4.87±0.035

Table 4. Colony count results for A1, A2, A3 and A4 after incubation at 38^0C for 14 days.

Hydrogel formulation	**Storage period (week)**			
	1	**2**	**3**	**4**
A1	X	X	X	X
A2	X	X	X	X
A3	X	X	X	X
A4	X	X	X	X

X = No colony formation

Table 5. Feedback from 10 volunteers by rating on the formulated hydrogel; (a) A1, (b) A2, (c) A3 and (d) A4.

(a)

Characteristics	**Strength level**				
	1	**2**	**3**	**4**	**5**
*Appearance				7	3
*Smoothness			1	2	7
*Absorbance			1	2	7
**Oily	10				
**Itchiness	10				
**Irritation	10				

*1- Poor, 2- Okay, 3- Moderate, 4- Good, 5- Very good

**1- Not at all, 2- Somewhat, 3- Quite a bit, 4- Very much, 5- Extremely

(b)

Characteristics	**Strength level**				
	1	**2**	**3**	**4**	**5**
*Appearance			2	2	6
*Smoothness				4	6
*Absorbance		1	2	4	3
**Oily	8	2			
**Itchiness	10				
**Irritation	10				

*1- Poor, 2- Okay, 3- Moderate, 4- Good, 5- Very good

**1- Not at all, 2- Somewhat, 3- Quite a bit, 4- Very much, 5- Extremely

(c)

Characteristics	**Strength level**				
	1	**2**	**3**	**4**	**5**
*Appearance		2	1	3	4
*Smoothness			1	2	7
*Absorbance	1	1	1	2	5
**Oily	8	2			
**Itchiness	9	1			
**Irritation	10				

*1- Poor, 2- Okay, 3- Moderate, 4- Good, 5- Very good

**1- Not at all, 2- Somewhat, 3- Quite a bit, 4- Very much, 5- Extremely

(d)

Characteristics	**Strength level**				
	1	**2**	**3**	**4**	**5**
*Appearance				2	8
*Smoothness					10
*Absorbance				1	9
**Oily	9			1	
**Itchiness	10				
**Irritation	10				

*1- Poor, 2- Okay, 3- Moderate, 4- Good, 5- Very good

**1- Not at all, 2- Somewhat, 3- Quite a bit, 4- Very much, 5- Extremely

Table 6. Average weight of hydrogels in 25 mL pycnometer.

Formulation	**Volume of sample (mL)**	**Weight of sample (g)**	**Relative density**
Distilled water	25	25.00±0.00	1.00
A1	25	24.24±0.07	24.24
A2	25	25.94±0.04	25.94
A3	25	24.48±0.02	24.28
A4	25	24.79±0.04	24.79

Table 7. Average weight loss of formulations in desiccator for 3 days.

Hydrogel	**Initial Weight (g)**	**Final Weight (g)**	Moisture content (%)
	3±0.000	0.307±0.006	89.77%
A2	3±0.000	0.293±0.006	90.22%
A3	3±0.000	0.29±0.000	90.33%
A4	3±0.000	0.307±0.006	89.77%

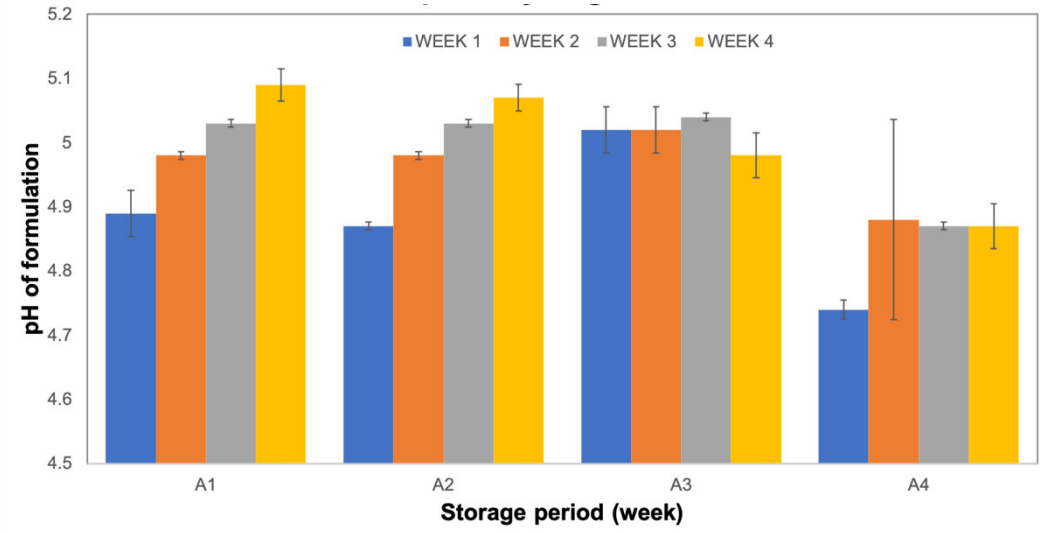

Figure 1. The pH value of A1, A2, A3 and A4 throughout 1 mth storage at 4^0C temperature.

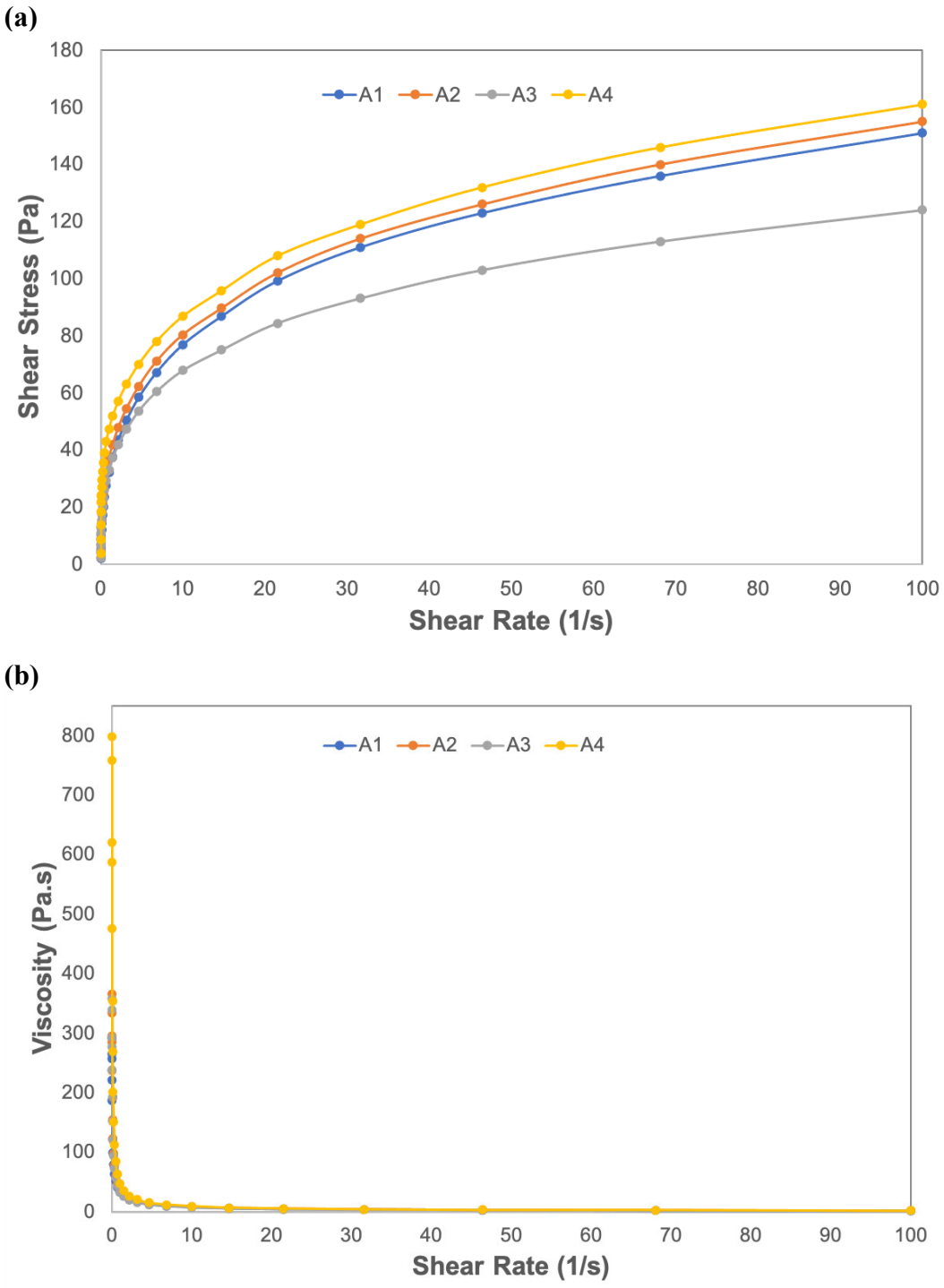

Figure 2. (a) Shear stress against shear rate; (b) Viscosity against shear rate.

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ORIGINAL ARTICLE

Evaluating the Effectiveness of Guest Lecturers in a Malaysian Pharmacy Hospital Clerkship I: A Mixed-Method Study of Student Feedback.

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Abstract

Introduction: The integration of guest lecturers into the RPB40104 Hospital Clerkship I course aims to enhance pharmacy students' learning by bridging theoretical knowledge with practical application. This study evaluates the effectiveness of these guest lecturers based on student feedback, focusing on satisfaction, clarity of instruction, and the relevance of sessions to real-world pharmacy practices.
Methodology: A mixed-method approach was employed, involving an online feedback form distributed to 67 fourth-year Bachelor of Pharmacy (Hons.) students, with a 98.5% response rate. The survey included both quantitative Likert-scale items and qualitative open-ended questions assessing various aspects of the guest lectures.
Results: Quantitative analysis revealed high levels of student satisfaction, with 54.5% reporting satisfaction and 22.7% indicating they were very satisfied. Additionally, 90.9% acknowledged that the sessions enhanced their understanding of pharmacists' roles in hospital settings. Qualitative feedback highlighted the practical application of knowledge and engaging teaching methods as key benefits, while suggestions for improvement included greater clarity in explaining complex topics.
Conclusion: The findings suggest that guest lecturers significantly contribute to enriching pharmacy education by providing valuable insights and fostering student engagement. However, improving the clarity of complex topics could further enhance the educational experience. Continued integration of guest lecturers is recommended to sustain and improve student learning outcomes.

Keywords: *Guest lecturers, pharmacy education, student feedback, practical application.*

Introduction

Guest speakers have become an integral part of teaching at colleges and universities, offering a wealth of knowledge and practical experience that enhances the learning process for students [1]. These speakers often possess expertise in their field, along with relevant industry experience, both of which serve as invaluable assets in helping students grasp concepts that will be beneficial to them in their future careers [2]. Their insights into real-world scenarios, current trends, and practices, as well as case studies, contribute significantly to improving the quality of learning in higher education [3].

Given that guest speakers come from diverse backgrounds and cultures, they bring unique perspectives on various topics, adding an element of diversity to the classroom [4]. Their presence also facilitates networking opportunities, allowing students to interact with professionals in their field and potentially establish connections that may prove valuable as they progress in their careers [1, 5, 6]. As Sage (2013) highlighted, guest speakers create an inclusive and participatory learning environment, encouraging students to engage in active learning. This allows them to ask questions, participate in discussions with peers and instructors, and apply classroom concepts to real-world situations [6].

A study by Zorek et al. (2011) found that the incorporation of guest speakers into a professional development seminar series has been shown to positively influence various aspects of student growth, particularly in enhancing student professionalism, a key learning outcome as the profession evolves from a product-centric to a patient-centred focus [2]. Regular exposure to guest speakers from diverse pharmacy career pathways has also broadened advisees' awareness of career opportunities, enabling them to begin formulating their career plans effectively.

In UniKL RCMP's Bachelor of Phramacy (Hons.) programme, the RPB40104 Hospital Clerkship I course incorporates guest lecturers to bridge the gap between theoretical learning and practical application. These lecturers expose students to real-world challenges and practices in hospital pharmacy settings. This course, designed for Year 4 Semester 1 students, encompasses diverse areas such as Outpatient Pharmacy, Inpatient Pharmacy, Pharmaceutical Store Management, Therapeutic Drug Monitoring (TDM), Parenteral Nutrition, Cytotoxic Drug Reconstitution (CDR), and Drug Information Services (DIS). To provide a holistic learning experience, five guest lecturers were invited to teach six core topics.

The study aims to evaluate the effectiveness of these guest lecturers in meeting the course objectives, with a focus on students' satisfaction, clarity of instruction, and the practical relevance of sessions. By employing a mixed-method approach, this research provides comprehensive insights into the strengths and areas for improvement in utilising guest lecturers within pharmacy education.

Methodology

Study design

The study employed both quantitative and qualitative methods. An online feedback form served as the survey instrument, designed to capture a comprehensive evaluation of the guest lectures over a seven-week period.

Study population

The study population consisted of 67 fourth-year Semester 1 Bachelor of Pharmacy (Hons.) students in UniKL RCMP enrolled in the course, with 66 (98.5%) participants completing the survey.

Data collection

The online feedback form comprised two sections:

1. Quantitative Section:
    - Likert-scale items assessed satisfaction levels, clarity, knowledge transfer, and practical relevance of the guest lecture sessions.

2. Qualitative Section:
    - Open-ended questions explored students' perceptions of the most

beneficial sessions, areas needing improvement, and suggestions for enhancing the sessions.

The feedback form was distributed online via a secure platform, ensuring anonymity and confidentiality of responses. Participation was voluntary, and informed consent was obtained electronically before the survey began. Students were provided with detailed information about the study's purpose and could seek clarification before consenting to participate.

Study instrument

The survey instrument was developed by the authors to align with the specific objectives of this study, as no existing validated tools adequately addressed the context of hospital pharmacy clerkships. To ensure clarity and relevance, the questionnaire was piloted with 10 third-year pharmacy students who were not part of the study cohort. Feedback from the pilot phase was used to refine ambiguous wording and improve the structure of the questions. The survey instrument was a self-administered online questionnaire. Each participant would receive the questionnaire via Microsoft Forms and answer it anonymously. Before starting to answer the questions, informed consent was obtained where participants were given an explanation regarding the study and clicked "I agree" after confirming that they had read and fully understood the information given for the study and that they decided to participate. Should they have any questions, they would have the opportunity to ask the investigators.

The 10-item questionnaire is divided into four sections, each serving a specific purpose. Section A includes the informed consent and demographic profile of the participants. Section B consists of three questions designed to gather students' feedback on the guest lecturers. Section C contains two open-ended questions and one closed-ended question aimed at obtaining specific feedback on the sessions. Lastly, Section D focuses on suggestions for improvement with two targeted questions.

The questions are as follows:

Section B:

1. Overall, how satisfied were you with the sessions conducted by the guest lecturers?
2. Did the guest lecturers encourage interaction and address student questions effectively?
3. How would you rate the following aspects of the guest lecturers' sessions?
    a. The guest lecturers explained the topics clearly and effectively.
    b. The guest lecturers were knowledgeable and provided real-world insights.
    c. The sessions met my learning expectations for the course.

Section C:

4. Which session or topic did you find the most beneficial? Why?
5. Were there any topics that you think require further clarification or improvement? If yes, please specify.
6. Did you feel the sessions helped you better understand the practical roles of pharmacists in a hospital setting?

Section D:

7. What suggestions do you have to improve future sessions with guest lecturers?
8. Would you recommend continuing the practice of inviting guest lecturers for this course?

Data analysis

All statistical analyses for the quantitative study were performed using a statistical package for social sciences (SPSS), version 25.0 (SPSS, inc., Chicago, IL). The categorical variables were summarised in frequency (n) and percentage (%). A descriptive analysis was used to assess the level of satisfaction.

The qualitative data was collected through open-ended questions in a survey. Participants responded to questions about the most beneficial session or topic (Section C, Question 4), topics

requiring further clarification or improvement (Section C, Question 5), and suggestions for improving future sessions with guest lecturers (Section D, Question 7). The data was systematically coded, and labels were assigned to segments of the text that represent a particular concept, idea, or meaning. For instance, feedback related to clarity and practical relevance was coded under labels such as "Clarity" and "Practical Relevance." Similar codes were then grouped to identify broader themes that capture patterns or commonalities across the data.

The identified themes were reviewed and refined to ensure they accurately reflected the content and captured the essence of participants' experiences. Consistency and coherence were checked within and across themes. Each theme was defined and thematically labelled to precisely convey its core concept. The results of the qualitative analysis were expressed in the form of a thematic analysis, incorporating quotations or excerpts from the data to illustrate each theme.

Results

Quantitative study

The results indicated a high level of overall satisfaction among students regarding the sessions conducted by the guest lecturers (Table 2). Notably, 75.8% of respondents reported being "Satisfied," while 13.6% expressed that they were "Very Satisfied." A smaller segment, comprising 9.1%, remained neutral in their assessment, and only one student (1.5%) indicated dissatisfaction. This feedback suggests that the guest lecturers generally met or exceeded student expectations.

In terms of interaction and engagement during the sessions, an impressive 81.8% of students agreed that the guest lecturers encouraged interaction and effectively addressed student questions. This points to a positive learning environment fostered by the guest lecturers, which is essential for enhancing student engagement and understanding. Students also rated the clarity of the lectures highly, with 86.4% agreeing that the topics were explained clearly and effectively. Furthermore, an overwhelming 90.9% felt that the lecturers were knowledgeable and provided valuable real-world insights, reinforcing their credibility and effectiveness in teaching complex subjects.

The sessions were deemed to meet learning expectations effectively, with 84.8% of students agreeing that their expectations for the course were fulfilled. This highlights the overall success of the guest lectures in delivering relevant content that aligns with educational objectives.

Additionally, a significant majority of respondents (90.9%) reported that the sessions helped them better understand the practical roles of pharmacists within a hospital setting, which is crucial for their professional development as future practitioners.

When asked about the continuation of inviting guest lecturers for this course, an overwhelming 95.5% responded positively, indicating strong support for this educational approach.

In conclusion, the analysis of student feedback indicates that the guest lecturer sessions were highly effective and well-received by students. The high levels of satisfaction, combined with positive assessments of lecturer interaction, clarity, knowledge, and relevance to practical roles in pharmacy, suggest that incorporating guest lecturers into the curriculum is an effective strategy for enhancing student learning experiences in pharmacy education. These findings support ongoing efforts to integrate such innovative teaching methods into academic programmes to enrich student engagement and understanding in their respective fields.

Qualitative Study

Themes for the Reasons Behind the Session or Topic that Students Found Most Beneficial (Question 4):

1. Practical Application of Knowledge: Students appreciated the connection between theoretical knowledge and real-world application.
    - *"The guest lectures helped me understand how concepts like Cytotoxic Drug Reconstitution and*

TDM are applied in real hospital settings." – Student A
    - *"I found it enlightening to learn how pharmacists manage challenging cases, especially during the Diabetes Medication Therapy Adherence Clinic (DMTAC) session."* – Student B
2. Engagement and Interest: The sessions sparked interest and sustained motivation among students.
    - *"I was genuinely engaged during the discussions, as the guest lecturers used real-life cases to explain concepts."* – Student C
    - *"The interactive teaching style of the DMTAC session kept me focused and interested throughout."* – Student D
3. Relevance to Future Roles: Students valued the insights into the pharmacist's role in hospital settings.
    - *"Learning directly from practising pharmacists gave me a clearer picture of what to expect in my future career."* – Student E
    - *"The lectures showed us how to handle practical challenges, which I found extremely relevant."* – Student F

Themes for Challenges Encountered During the Guest Lectures (Question 6):

1. Clarity and Depth of Explanation: Some students noted that the complexity of certain topics, particularly TDM, required further clarification.
    - *"The TDM session was too technical, and I struggled to follow the calculations and interpretations."* – Student G
    - *"I would have appreciated more examples and practical demonstrations during the TDM lecture."* – Student H
2. Time Constraints: The limited time for each session was a challenge, leaving little room for deeper exploration of topics.
    - *"The lectures felt rushed at times, especially during the Parenteral Nutrition session."* – Student I
    - *"I wish there had been more time for Q&A or case discussions."* – Student J
3. Resource Availability: Some participants highlighted the lack of additional materials to support their learning.
    - *"Supplementary notes or handouts would have been helpful to revisit the topics after the sessions."* – Student K

Themes for Suggestions to Improve Future Guest Lectures (Question 7):

1. Interactive Learning Methods: Students recommended incorporating more interactive components to enhance engagement and understanding.
    - *"Including case-based discussions or role-playing exercises would make the sessions more engaging."* – Student L
    - *"Real-world problem-solving activities could help us better understand the practical applications."* – Student M
2. Enhanced Clarity for Complex Topics: Specific suggestions were made to improve the delivery of challenging concepts like TDM.
    - *"Simplifying the TDM lecture with visual aids and step-by-step explanations would be beneficial."* – Student N
    - *"Interactive examples or small group discussions on TDM could make it easier to follow."* – Student O
3. Additional Support Materials: Students expressed a preference for supplementary learning resources.
    - *"Providing lecture slides or videos after the sessions would allow us to*

review the content at our own pace."
– Student P

Discussion

Our study findings indicate that incorporating guest lecturers in the hospital pharmacy clerkship course is highly effective, as evidenced by high levels of student satisfaction, engagement, and perceived relevance to real-world pharmacy practice. These findings align with previous research that highlights the benefits of guest lecturers as an effective teaching strategy across various educational fields [5, 7, 8]Click or tap here to enter text.. Inviting industry experts to share their work experiences was particularly valuable, as reflected in both survey results and qualitative feedback. Students appreciated the guest lecturers' use of case studies, hands-on demonstrations, and discussions on practical challenges in pharmacy practice, which allowed them to engage with the subject matter beyond theoretical concepts taught in traditional classrooms. This aligns with findings by Merle & Craig (2017) who reported pharmacy learning is enhanced when the lecturers are professional industrial experts [9]. Furthermore, collaborative teaching with guest lecturers from the field not only enriches practice-oriented knowledge but also plays a crucial role in shaping pharmacy students' professional development and career readiness [10] Click or tap here to enter text.. Our study observed similar trends, with students expressing a strong preference for continuing this approach in the future to better prepare them for their professional roles.

In pharmacy education, guest speakers can help students better understand real-life healthcare situations, which may lead to better health outcomes in their future practice [11]. Phan et al. (2024) concluded that when guest speakers are carefully chosen and supported with well-planned preparation and follow-up activities, they can significantly enhance students' learning experiences [12]. Additionally, a qualitative survey by Jablon-Roberts & McCracken was given to 114 students to explore their past experiences and expectations regarding industry guest speakers [5]. Among those who had attended a class with a guest speaker, 86.1% reported enjoying the experience, particularly when the speaker worked in a related field, spoke with enthusiasm and honesty, and actively answered questions [13].

While Zorek et al. (2011) [2] demonstrated the benefits of guest lecturers in enhancing student professionalism within a general seminar series, our study uniquely focuses on hospital pharmacy clerkships and specialised topics such as TDM and CDR. This context-specific approach provides deeper insights into how guest lecturers bridge theoretical knowledge with hands-on clinical practices, which is critical for pharmacy students transitioning into hospital roles.

Despite the overall positive feedback, students identified several areas for improvement, particularly regarding instructional methods, engagement strategies, and resource availability. One of the primary concerns was the complexity of certain topics, such as CDR and TDM, which some students found difficult to follow, especially in terms of calculations and data interpretation. Given that these concepts are critical for patient safety and pharmaceutical care, structured instructional approaches are necessary to facilitate better understanding. Research highlights that effective teaching relies on a lecturer's ability to deliver clear, well-organised instruction [14] while also incorporating interactive teaching methods to enhance student comprehension and satisfaction [15].

In response to these challenges, students suggested the inclusion of teaching aids, such as visual materials and step-by-step demonstrations, to simplify complex concepts. Additionally, they emphasised the need for more active learning strategies, including role-playing, simulation exercises, and case-based discussions. Studies have shown that these methodologies significantly improve student engagement, knowledge retention, and practical application

skills in pharmaceutical education [16, 17]. Student feedback indicated that the DMTAC session was engaging and effectively maintained their focus, as the guest lecturer used real-life cases to explain key concepts. This approach aligns with previous research highlighting the benefits of instructor-led modelling, role-playing, and small-group case discussions in building students' confidence, satisfaction, and perceived usefulness of the session for real-world practice [18, 19]. Click or tap here to enter text.Students also noted that the interactive delivery of the DMTAC session made it more interesting and helped sustain their attention throughout. However, it is essential to align these teaching strategies with course learning outcomes to ensure their effectiveness [17].

Another major concern was time constraints, particularly given the six-week duration of the Hospital Clerkship I attachment. Many students felt that the limited time available restricted their ability to fully grasp complex topics. To address this, a revised course structure could integrate focused instructional strategies that maximise learning within the available timeframe. Providing pre-lecture materials, such as reading assignments or recorded lectures, may also help students prepare in advance and reinforce their understanding post-session [20]. Furthermore, students recommended incorporating small-group discussions to enhance engagement and allow for more personalised learning experiences. Research suggests that shifting from a speaker-centred to a student-centred guest lecturing model can improve student participation and comprehension [21]. Specifically, for TDM, a study by Bowers & Asbill (2022) mentioned that case-based activities in small discussion groups hone pharmacy students' skills and prepare them for their experiential rotations [22]. Despite that, Li et al (2015) also highlighted that this approach requires careful planning, as it may strain available resources and increase the workload for guest lecturers [21]. A possible solution is to distribute teaching responsibilities among multiple lecturers or increase the number of tutors to facilitate more interactive sessions.

While challenges such as topic complexity, time limitations, and resource constraints were identified, they can be addressed through improved instructional strategies, active learning methodologies, and additional learning resources. By implementing these enhancements, guest lectures can continue to serve as a valuable addition to hospital pharmacy education by bridging the gap between theoretical knowledge and real-world practice. Future studies may explore the long-term impact of guest lectures on student knowledge retention and skills competency to further validate their contribution in Hospital Clerkship I course.

Conclusion

Guest lecturers play an integral role in providing specialised knowledge and practical insights in the RPB40104 Hospital Clerkship I course. While the sessions were highly effective overall, targeted improvements particularly in the clarity of complex topics like TDM are necessary. Adopting more interactive and student-centred approaches will further enhance the educational experience, better preparing students for their future roles in hospital pharmacy.

Limitations of study

This study relied on anonymous, voluntary student feedback collected as part of routine course evaluations. Although formal ethics approval was not sought, all procedures complied with institutional guidelines for educational quality improvement. Additionally, the findings are specific to a single cohort and course, limiting generalisability to other settings or programmes. Future research could incorporate longitudinal designs to evaluate the long-term impact of guest lectures on professional competency.

Conflicts of interest

The authors declare no conflict of interest.

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Authors' Contributions
AAAJ was responsible for the conceptualisation of the research, study design, data collection, formal analysis, interpretation of results, and drafting the manuscript. NSMH is responsible for the discussion and critical revision of the manuscript.

Source of financial / funding: None

Table 1. Descriptive analysis of the demographic characteristics of respondents (n=66)

Data	Number of Students	Percentage (%)
Gender		
Male	17	25.8
Female	49	74.2
Race		
Malay	65	98.5
Indian	1	1.5

Table 2. Student satisfaction levels with guest lecturer sessions (n=66)

Satisfaction Level	Number of Students	Percentage (%)
Very Satisfied	9	13.6
Satisfied	50	75.8
Neutral	6	9.1
Dissatisfied	1	1.5

Figure 1. Students' Perceptions and Evaluations of Guest Lecturers' Teaching Effectiveness (n=66)

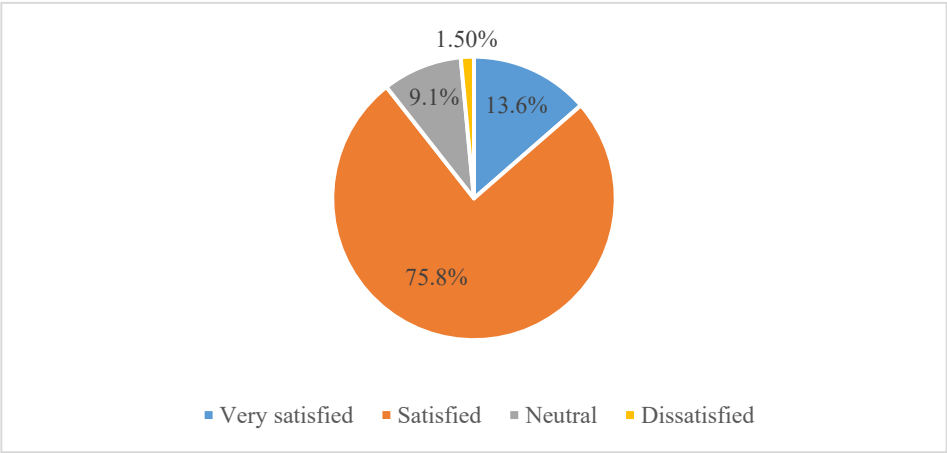

Figure 1a. Overall Experience with the Sessions Conducted by the Guest Lecturers

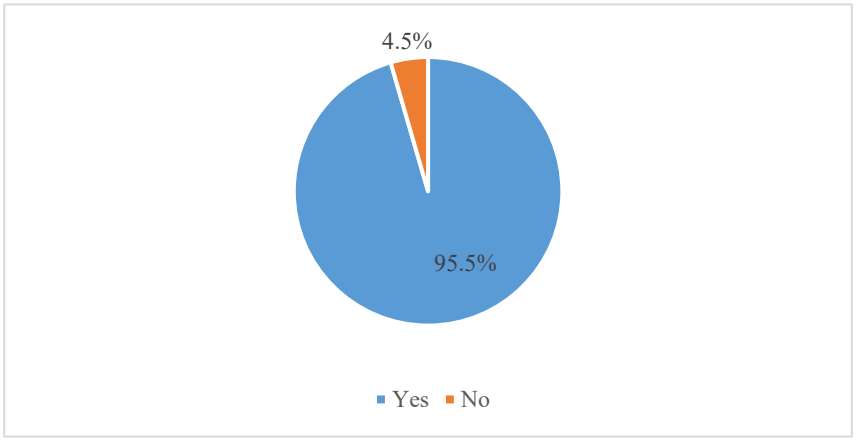

Figure 1b. Guest Lecturers' Encouragement of Interaction and Effectiveness in Addressing Questions

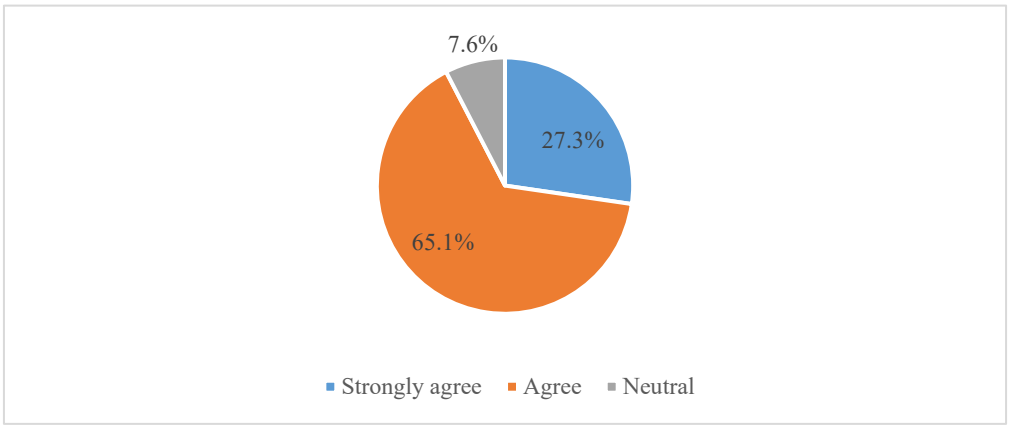

Figure 1c. Student Evaluation of the Clarity and Effectiveness of Topic Explanation by Guest Lecturers

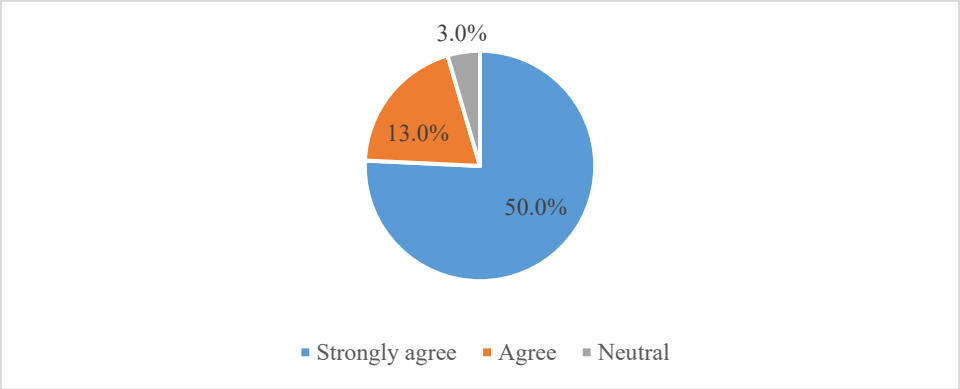

Figure 1d. Knowledge and Real-World Insights Provided by Guest Lecturers

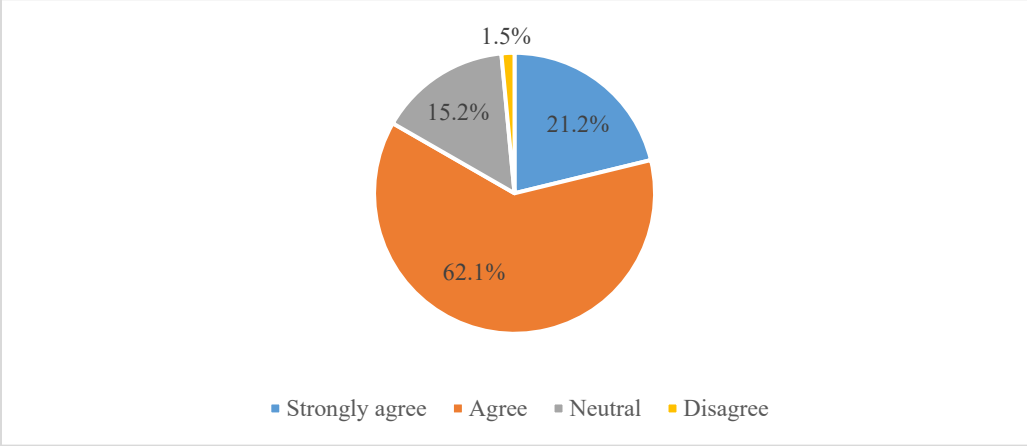

Figure 1e. Alignment of Sessions with Learning Expectations for the Course

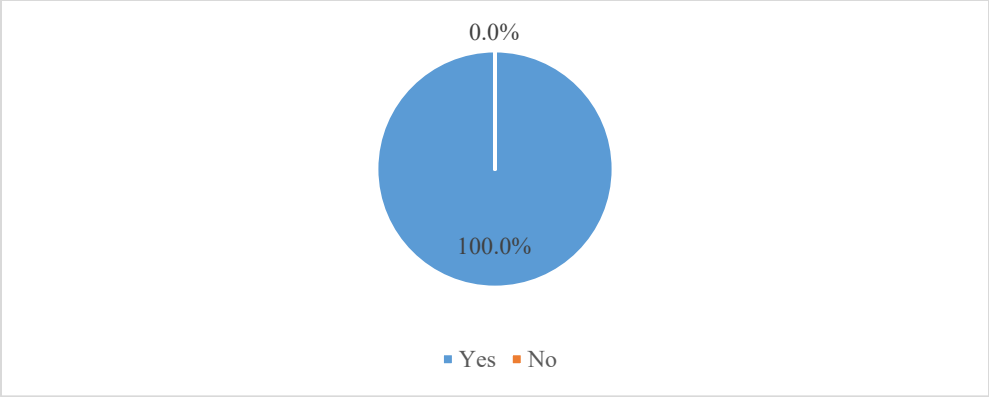

Figure 1f. Effectiveness of Sessions in Enhancing Understanding of the Practical Roles of Pharmacists in a Hospital Setting

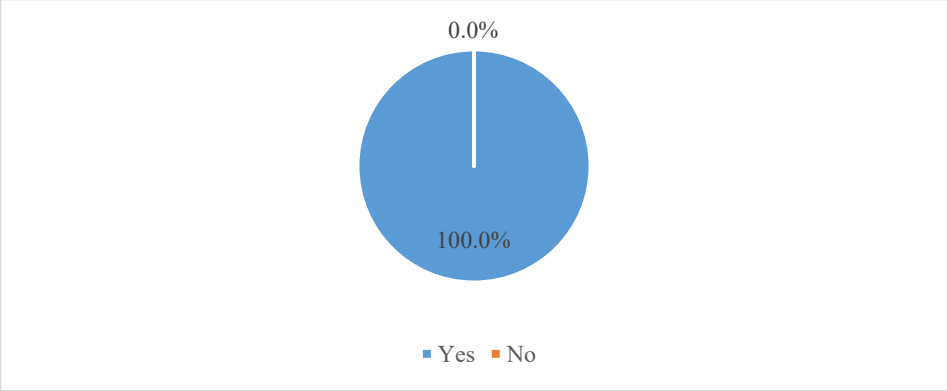

Figure 1g. Student Willingness to Recommend the Continuation of Inviting Guest Lecturers for Future Courses

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ORIGINAL ARTICLE

Phytochemical Screening and Antioxidant Properties of Essential Oil from Grapefruit (*Citrus paradisi*) Peel.

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Abstract

Grapefruit (*Citrus paradisi*), a hybrid fruit from the Rutaceae family formed by crossing sweet orange (*Citrus sinensis*) and pomelo (*Citrus maxima),* is known for its antioxidant properties that help combat oxidative stress caused by free radicals. This study aimed to extract essential oil from grapefruit peel powder via hydro-distillation, analyze its proximate composition, perform phytochemical screening, and evaluate its antioxidant activity using the DPPH assay. The essential oil was extracted using a Clevenger apparatus at 100 °C for 3 hours, yielding a colourless oil with a sweet fragrance. Proximate analysis of the peel powder revealed 10% total ash, 5% acid-insoluble ash, 28% moisture loss, and 44% water extractives, reflecting its physicochemical quality and stability. Qualitative phytochemical screening revealed the presence of terpenoids, while alkaloids, flavonoids, glycosides, and phenols were not detected. However, quantitative analysis showed a total phenolic content (TPC) of 6.57 mg GAE/g and a total flavonoid content (TFC) of 179.10 mg QE/g, indicating the presence of antioxidant-related compounds. The DPPH radical scavenging assay showed a concentration-dependent increase in antioxidant capacity, with grapefruit peel essential oil achieving a maximum RSA of 22.21% at 200 mg/mL and an IC_{50} value of 450.25 mg/mL, indicating moderate antioxidant potential compared to ascorbic acid. In conclusion, grapefruit peel essential oil contains bioactive compounds, particularly terpenoids, phenolics, and flavonoids, contributing to its antioxidant properties. Although its efficacy is lower than synthetic antioxidants like ascorbic acid, it represents a natural, safe alternative with potential applications in food preservation, cosmetics, and pharmaceutical formulations. Further research should explore strategies to enhance its antioxidant efficacy, such as synergistic combinations with other natural antioxidants.

Keywords: DPPH assay, e*ssential oil, grapefruit (Citrus paradisi), hydro-distillation, phytochemical screening.*

Introduction

Grapefruit (*Citrus paradisi*) is a hybrid citrus fruit resulting from the crossbreeding of sweet orange (*Citrus sinensis*) and pomelo (*Citrus maxima*) [1]. Belonging to the Rutaceae family, grapefruit is widely cultivated in tropical and subtropical regions due to its nutritional, medicinal, and industrial applications [2-4]. It is recognized for its distinct aroma, vibrant skin colour variations (white, yellow, orange, and red), and rich phytochemical composition, which contribute to its culinary, therapeutic, and commercial value [1].

The peel of grapefruit, often treated as an agricultural by-product, is a rich source of bioactive compounds such as essential oils (EOs), flavonoids, phenolic acids, and glycosides. These compounds have been linked to antioxidant, antimicrobial, and anti-inflammatory properties [2,3,5]. EO extracted from grapefruit peel (GP) is particularly abundant in monoterpenes like limonene and other volatile and non-volatile phytochemicals with promising therapeutic and industrial potential [6].

Due to its natural antioxidant activity, grapefruit peel essential oil (GP-EO) has garnered interest in mitigating oxidative stress, a key contributor to the pathogenesis of chronic conditions such as cancer, cardiovascular disorders, and neurodegenerative conditions [7,8]. Oxidative stress results from an imbalance between reactive oxygen species (ROS) and the body's antioxidant defense mechanism, leading to cellular damage and disease progression [9]. Natural antioxidants in GP can help neutralize free radicals, protect biomolecules from oxidative degradation, and promote overall health. In contrast to synthetic antioxidants, which may pose health risks due to their potential toxicity and carcinogenicity, natural sources of antioxidants are increasingly favoured for their safety, efficacy, and biodegradability [10,11].

This study aims to extract and analyze the EO from GP using hydro-distillation and evaluate its phytochemical composition and antioxidant properties. The specific objectives include: 1) Extraction of EO from GP powder using the Clevenger apparatus; 2) Conducting proximate analysis to determine total ash, acid-insoluble ash, moisture content (loss on drying), and water extractive values of GP powder; 3) Performing phytochemical screening, including qualitative tests for terpenoids, alkaloids, flavonoids, glycosides, and phenols, as well as quantitative determination of total phenolic content (TPC) and total flavonoid content (TFC); 4) Evaluating the antioxidant activity of GP-EO using the DPPH radical scavenging assay.

By analyzing the phytochemical profile and antioxidant capacity of GP-EO, this study aims to provide scientific evidence supporting its potential applications in pharmaceuticals, cosmetics, food preservation, and natural health products.

Materials and methods

Plant collection

Fresh grapefruit (*Citrus paradisi*) fruits were collected from a local wet market in Ipoh, Malaysia. Although no formal botanical authentication or herbarium specimen deposition was performed, the fruits were identified based on distinct morphological characteristics and cross-verified using established botanical references.

Plant extraction

The collected fruits were thoroughly washed under running water to remove visible dirt, pesticide residues, and other contaminants. The peels were manually separated using a sterilized stainless-steel knife, focusing on the outer zest layer while minimizing inclusion of the bitter white pith. This step was crucial to ensure maximum retention of EO-rich components.

The peels were then uniformly cut into strips approximately 1 cm wide to ensure consistent drying. Drying was carried out in a temperature-controlled oven at 40-50 °C for 24-48 hours, ensuring that moisture content was sufficiently reduced while minimizing the risks of thermal degradation of heat-sensitive volatile compounds.

Once fully dried, the GP peels were ground using a mechanical grinder into a fine, homogeneous powder to enhance extraction efficiency. The powdered material was stored in airtight, amber glass containers at room temperature to prevent oxidation, photodegradation, and moisture absorption before EO extraction.

Proximate analysis

Proximate grapefruit (*Citrus paradisi*) peel powder analysis was conducted to evaluate its physicochemical properties, including total ash content, acid-insoluble ash, moisture content (loss on drying), and water-soluble extractive value. The methods followed the standard procedures outlined by the Association of Official Analytical Chemists [12]. These parameters are essential for assessing the composition, purity, and quality of the plant material for further phytochemical and functional analysis.

A. Total ash content

Approximately 2 g of GP powder was placed in a clean, pre-weighed silica crucible and incinerated in a muffle furnace at 450 °C for 3 hours, or until complete combustion of organic matter was achieved. The resulting white or grey ash (representing inorganic mineral content) was cooled in a desiccator, weighed, and recorded as a percentage of the initial sample weight.

B. Acid insoluble ash

The total ash obtained above was treated with 15 mL of 0.1N hydrochloric acid (HCl) and boiled for 10 minutes. The mixture was filtered through ashless filter paper, and the residue was washed with hot distilled water to remove acid-soluble matter. The residue was dried at 50 °C for 90 minutes, cooled, and weighed. The acid-insoluble ash content was calculated as a percentage of the original sample weight.

C. Moisture content (loss on drying)

To assess moisture content, 2 g of GP powder was heated in a hot air oven at 105 °C for 3 hours. The sample was periodically weighed at 1-hour intervals until a constant weight was achieved. The weight loss percentage was recorded as the moisture content, indicating the sample's drying efficiency and potential stability.

D. Water extraction values

A 4 g of GP powder was mixed with 100 mL of distilled water in a conical flask. The mixture was agitated on an orbital shaker at 200 rpm for 6 hours, then allowed to stand undisturbed for 18 hours at room temperature. The solution was filtered, and the filtrate was evaporated to dryness on a hot plate. The remaining dried extract was further heated in an oven at 105 °C for 1 hour, cooled, and weighed. The water extractive value was expressed as a percentage of the dried extract relative to the original sample weight.

Extraction of essential oil

EO from grapefruit (*Citrus paradisi*) peel was extracted using hydro-distillation with a Clevenger-type apparatus, a widely accepted technique for isolating volatile bioactive compounds from plant material [13]. 100 g of dried, finely ground GP powder was weighed and transferred into a round-bottom flask containing 500 mL of distilled water, maintaining a 1:5 ratio to optimize extraction efficiency [14].

The hydro-distillation process was carried out by heating the mixture to approximately 100 °C, allowing steam to volatilize the EO components. These vapours passed through a condenser unit for collection. The distillation process was maintained for 3 hours to ensure maximum yield of EO.

After the distillation, the EO was carefully separated from the aqueous layer through simple decantation. The extracted EO was dried using anhydrous sodium sulfate (Na_2SO_4) to eliminate residual moisture, which effectively absorbs any remaining water. The purified EO was then filtered and stored in an amber glass bottle to protect it from light exposure and oxidative degradation. For long-term stability and preservation of its bioactive compounds, the final EO product was refrigerated at 4 °C [14]. This hydro-distillation technique provides a high-quality EO, ensuring the retention of its aromatic,

antioxidant, and therapeutic properties for further phytochemical screening and antioxidant analysis.

Phytochemical screening

The phytochemical screening of GP-EO was conducted to identify the presence of bioactive constituents through both qualitative and quantitative analyses. Standard phytochemical testing methods were employed as described by Harborne (1998) and Trease & Evans (2002) for qualitative tests [15,16]. For quantitative assessments, the total phenolic content (TPC) was measured using the Folin-Ciocalteu method (Singleton et al., 1999), and total flavonoid content (TFC) was determined using the aluminum chloride colorimetric method (Chang et al., 2002) [17,18]. This analysis provided essential insights into the bioactive composition of GP-EO, supporting its potential use as a natural antioxidant in pharmaceutical and nutraceutical applications.

A. Test for Terpenoids

Approximately 0.1 mL of EO was mixed with 1 mL of chloroform and 1 mL of concentrated sulfuric acid (H_2SO_4) in a microcentrifuge tube. The appearance of a reddish-brown colour at the interface indicated the presence of terpenoids.

B. Test for Alkaloids

Adding 0.1 mL of EO, 0.2 mL of 0.1N HCl, 1 mL of Mayer's reagent, and potassium mercury iodide, followed by vortex mixing. A yellow-coloured solution would indicate the presence of alkaloids.

C. Test for Flavonoids

Five drops of concentrated HCl were added to 0.1 mL of EO in a microcentrifuge tube. The formation of a red color was indicative of flavonoid presence.

D. Test for Glycosides

Mixing 0.1 mL of EO with 1 mL of distilled water and three drops of sodium hydroxide (NaOH). A yellow color would indicate the presence of glycosides.

E. Test for Phenols

0.1 mL of EO was combined with 1 mL of distilled water, and three drops of iron(III) chloride ($FeCl_3$) solution were added. The development of a blue, green, red, or purple colour would confirm the presence of phenols.

F. Determination of the Total Phenolic Compound

The TPC was determined using the Folin-Ciocalteu (FC) colorimetric method. A 200 µL aliquot of EO was pipetted into a test tube, followed by 1.5 mL of FC reagent solution. After incubating in the dark for 5 minutes, 1.5 mL of sodium carbonate (Na_2CO_3) was added, and the mixture was incubated in the dark for 90 minutes at room temperature. The absorbance was measured at 725 nm using a UV-Vis spectrophotometer. TPC values were expressed as mg of gallic acid equivalents per gram of EO (mg GAE/g).

G. Determination of Total Flavonoid Compounds

The TFC was determined using the aluminum chloride ($AlCl_3$) colorimetric method. 1 mL of EO was pipetted into a test tube, followed by the addition of 300 µL of 5% sodium nitrate ($NaNO_2$), 500 µL of 10% $AlCl_3$ solution, and 500 µL of 4% NaOH solution. The mixture was vortexed and allowed to react at room temperature. Absorbance was recorded at 510 nm using a UV-Vis spectrophotometer, and results were expressed in mg of quercetin equivalents per gram of EO (mg QE/g).

Screening of antioxidant properties

The antioxidant potential of of GP-EO was evaluated using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay (RSA), a widely used method for assessing the free radical scavenging ability of natural compounds [19]. This assay measures the capacity of antioxidant compounds to donate hydrogen atoms or electrons to neutralize DPPH, a stable free radical, resulting in a measurable color change.

To determine the dose-response relationship, GP-EO was tested at six specific concentrations: 6.25, 12.5, 25, 50, 100, and 200 mg/mL. These

concentrations were prepared via serial dilution in a 1:1 mixture of methanol (CH_3OH) and dimethyl sulfoxide (DMSO), using 15 mL centrifuge tubes. Each concentration was tested in triplicate to ensure reproducibility and reliability of the results. For each test, 2.7 mL of 0.06 mM DPPH solution in CH_3OH was added to 0.3 mL of the EO solution, mixed gently, and incubated in the dark at room temperature for 1 hour to prevent light-induced degradation of the DPPH radical. A control solution consisting of DPPH without the EO and a blank solution containing only the solvent mixture were also prepared.

After incubation, the absorbance of each mixture was measured at 517 nm using a UV-Vis spectrophotometer. A decrease in absorbance indicated an increase in antioxidant activity. The percentage of radical scavenging activity (RSA%) was calculated using the following formula:

$$\text{DPPH radical scavenging activity (\%)} = A_0 - A_1/A_0 \; x \; 100$$

where A_0 represents the absorbance of the control (DPPH solution without EO), and A_1 represents the absorbance of the EO-treated sample. The RSA% values were plotted against the corresponding EO concentrations to generate a dose-response curve. The IC_{50} value, defined as the concentration of EO required to inhibit 50% of the DPPH radicals, was calculated from the curve using linear regression analysis.

This method provided quantitative insights into the free radical neutralizing ability of GP-EO, supporting its potential application in cosmetic, food, preservation and pharmaceutical industries as a natural antioxidant.

Results and discussion

Proximate analysis

The proximate analysis of GP powder was conducted to evaluate its physicochemical composition, including total ash content, acid-insoluble ash, moisture loss (loss on drying), and water extractive values (Table 1). These parameters are essential for determining the plant material's purity, stability, and potential bioactivity, which are essential for determining its suitability for pharmaceutical and nutraceutical applications.

The moisture content measured at 28% is considerably higher than the standard acceptable limit for dried plant materials, generally ranging from 8% to 14% [12]. Excessive moisture can lead to microbial growth and degradation of sensitive phytochemicals, thereby affecting the stability, safety, and shelf life of the product. This finding highlights the need for more rigorous or prolonged drying methods to reduce moisture levels before storage or extraction.

The total % ash content of 10% falls within the typical range for crude plant drugs (commonly 5 - 15%), indicating acceptable levels of total mineral content and general cleanliness. However, the acid-insoluble ash value was 5%, slightly above the ideal range of < 2 - 3%, which may indicate the presence of residual silica, sand, or other earthy matter. This suggests the potential for contamination during post-harvest handling or insufficient washing, emphasizing the need for better pre-processing practices.

The water extractive value was 44%, suggesting a substantial presence of water-soluble phytochemicals, such as flavonoids, glycosides, and phenolic acids. This result supports the potential efficacy of the material in aqueous formulations and justifies its traditional and modern use in herbal preparations and water-based extractions.

In conclusion, while GP peel powder demonstrates promising extractable qualities and rich phytochemical content, drying and cleaning protocol improvements could enhance the material's overall quality. These proximate characteristics establish a scientific basis for its use in phytochemical profiling, antioxidant evaluation, and potential incorporation into cosmetic, pharmaceutical, and functional food products.

Phytochemical screening

Phytochemical screening of GP-EO was performed to identify the presence of key bioactive constituents through qualitative and

quantitative analyses. These findings help elucidate the EO's potential therapeutic value, particularly in relation to its antioxidant and antimicrobial properties.

The qualitative analysis confirmed the presence of terpenoids as indicated by the formation of a reddish-brown colour upon reaction with chloroform and concentrated H_2SO_4. This is consistent with the chemical profile of citrus-derived EOs, which are known to be rich in monoterpenes such as limonene. However, tests for alkaloids, flavonoids, glycosides, and phenols yielded negative results, suggesting that these compounds were either absent or present in concentrations below detectable limits using standard qualitative reagents. The dominance of terpenoids in GP-EO aligns with its distinct citrus aroma and bioactivity, reinforcing its potential antimicrobial, antioxidant, and anti-inflammatory properties.

Phenolic and flavonoid compounds are known for their roles in free radical scavenging and biological protection [20-22]. The TPC of GP-EO was measured using the FC colorimetric method, with the absorbance recorded at 725 nm. The TPC was calculated as 6.57 ± 0.32 mg gallic acid equivalents (GAE)/g of EO. The TFC was determined using the $AlCl_3$ colorimetric method, with absorbance measured at 510 nm. The resulting TFC value was 179.10 ± 4.21 mg quercetin equivalent (QE)/g of EO.

These values reflect the presence of moderate quantities of phenolic and flavonoid compounds, which likely contribute synergistically with terpenoids to the antioxidant potential of GP-EO. This phytochemical profile supports the EO's application in food preservation, cosmetic formulations, and pharmaceutical products as a natural source of antioxidants and bioactive compounds.

Screening of Antioxidant Activity - DPPH Free Radical Scavenging Assay

The antioxidant activity of GP-EO was evaluated using the DPPH RSA, a widely recognized method for determining the free radical neutralization potential of natural compounds. This essay measures the ability of the test substance to donate hydrogen atoms or electrons, thereby reducing the deep, purple-coloured DPPH radical into a stable, colorless compound. The extent of this reaction is quantified by a decrease in absorbance at 517 nm.

GP-EO and ascorbic acid (standard antioxidant) were tested at six concentrations: 6.25, 12.5, 25, 50, 100, and 200 mg/mL. The results demonstrated a concentration-dependent increase in RSA% for both samples. At the highest concentration tested (200 mg/mL), GP-EO exhibited a maximum RSA% of 22.21%, while ascorbic acid reached 82.93%. At the lowest concentration (6.25 mg/mL), RSA values were 9.97% for GP-EO and 26.44% for ascorbic acid, clearly demonstrating the superior antioxidant efficacy of the reference standard. The RSA values of GP-EO across the test concentrations are shown in Table 2, and the dose-response is plotted in Figure 1. These results provide visual and quantitative evidence of the comparative antioxidant activity between the EO and ascorbic acid.

Based on Figure 1, the %RSA increased with concentration for both samples. GP-EO exhibited a maximum of 22.21% at 200 mg/mL, while ascorbic acid reached 82.93%. The IC_{50} values were calculated as 450.25 mg/mL for GP-EO and 113 mg/mL for ascorbic acid, confirming moderate antioxidant potential for the EO.

The relatively higher IC_{50} value and lower RSA of GP-EO suggest antioxidant potential when compared to the standard. This may be attributed to and influenced by its high terpenoid content. Though widely known for their biological activities, terpenoids can exhibit variable antioxidant behaviour depending on their structure, concentration, and interactions with other constituents. Some terpenoids may exhibit pro-oxidant effects at higher concentrations, which can counteract the RSA of other compounds within the EO. Additionally, the antioxidant efficiency of terpenoids is generally

lower than that of phenolic compounds, due to the lack of strong hydrogen-donating groups.

Furthermore, the complexity of the EO matrix might lead to antagonistic interactions among its constituents, thereby reducing the overall antioxidant response. The observed IC_{50} thus reflects a cumulative effect of active and less reactive or inhibitory compounds within the oil.

Despite these limitations, the natural origin, safety, and bioactive content of GP-EO support its use as a mild natural antioxidant. It may be particularly beneficial in cosmetic, pharmaceutical, and food preservation applications where a lower level of antioxidant activity is desirable. Future research may explore methods to enhance its antioxidant efficiency, such as purification, fractionation of active compounds, or synergistic combination with other potent antioxidants.

Conclusion

This study successfully extracted EO from grapefruit (*Citrus paradisi*) peel using hydro-distillation. The proximate analysis showed that the GP powder contained 10% total ash, 5% acid-insoluble ash, 28% moisture loss, and 44% water extractives, which helped determine its quality and composition. Phytochemical screening revealed that the EO is rich in terpenoids, while the qualitative analysis did not detect alkaloids, flavonoids, glycosides, or phenols. However, quantitative analysis showed the presence of antioxidant-related compounds, with the TPC of 6.57 mg GAE/g and a TFC of 179.10 mg QE/g. Antioxidant activity, evaluated using the DPPH assay, demonstrated a dose-dependent increase in RSA. The maximum RSA recorded for GP-EO was 22.21% at 200 mg/mL with an IC_{50} value of 450.25 mg/mL, indicating moderate antioxidant activity compared to ascorbic acid, which showed much higher potency. In conclusion, GP-EO contains beneficial bioactive compounds, particularly terpenoids, phenolics, and flavonoids, contributing to its antioxidant potential. While it exhibits lower activity than synthetic antioxidants like ascorbic acid, its natural origin and safety profile support its potential use in food preservation, cosmetics, and pharmaceutical formulations. Future research should focus on enhancing its antioxidant properties, possibly through compound enrichment, formulation optimization, or synergistic blending with other natural antioxidants.

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Authors' Contributions
IFI was responsible for drafting the original manuscript and data curation, while NAK performed the writing, review, and editing of the manuscript. MM contributed to writing, review, editing, data validation, and overall supervision of the research**.**
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Conflicts of interest

The authors declare that they have no conflict of interest.

Table 1. Proximate Analysis of Grapefruit Peel Powder

Experiment	Result
Total Ash	10%
Acid-Insoluble Ash	5%
Loss of Drying	28%
Water Extractive Values	44%

Table 2. Radical scavenging activity (%RSA) of grapefruit peel essential oil (GP-EO) at different concentrations.

Concentration (mg/mL)	Grapefruit Peel Essential Oil (%)	Ascorbic Acid (%)
6.25	9.97	26.44
12.5	12.76	42.12
25	16.34	56.78
50	19.85	68.95
100	21.34	76.88
200	22.21	82.93

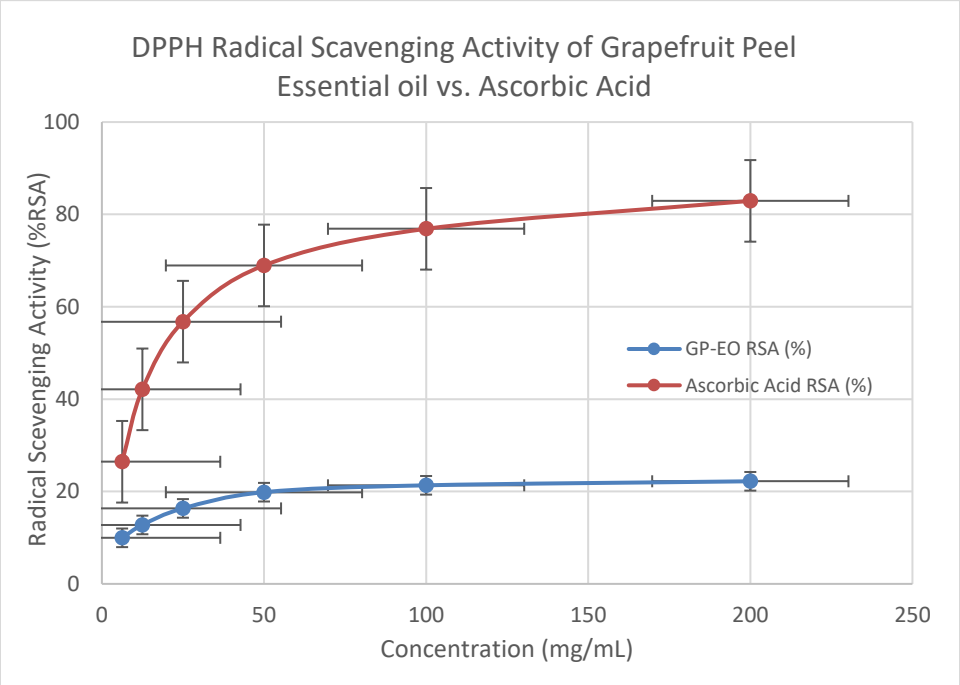

Figure 1. Dose-dependent DPPH radical scavenging activity of *Citrus paradisi* peel essential oil vs. ascorbic acid.

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CASE REPORT

A Rare Case of Porto-Sinusoidal Vascular Disease Associated with Systemic Lupus Erythematosus and Antiphospholipid Syndrome.

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Abstract
Porto-sinusoidal vascular disease is a medical condition characterized by increased blood pressure in the portal vein in the absence of cirrhosis. This condition is considered poorly defined because its exact cause is unknown. It has been reported to be associated with several autoimmune diseases, including systemic lupus erythematosus and antiphospholipid syndrome. We report a case of 49-year-old Indian lady with a background history of systemic lupus erythematosus with secondary antiphospholipid syndrome who was found to have esophageal varices from an esophagogastroduodenoscopy performed for iron deficiency anemia. A follow-up ultrasound and computed tomography of the abdomen confirmed the absence of cirrhosis and excluded portal vein thrombosis as a potential etiology for portal hypertension leading to the diagnosis of porto-sinusoidal vascular disease. She started on propranolol as primary prophylaxis for variceal bleeding. The patient remained well during subsequent follow-ups with the absence of new or bleeding varices during annual esophagogastroduodenoscopy surveillance. This case contributes to the further understanding of PVSD in SLE and secondary antiphospholipid syndrome. Further research is needed to enhance our understanding of its pathophysiology and to help formulate comprehensive guidelines for the effective management of this condition.

Keywords: *Antiphospholipid syndrome, cirrhosis, esophageal varices, porto-sinusoidal vascular disease, systemic lupus erythematosus.*

Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with a wide array of clinical manifestations, including gastrointestinal and hepatobiliary involvement. Porto-sinusoidal vascular disease (PSVD) is a heterogeneous group of liver disorders characterized by signs of portal hypertension in the absence of cirrhosis [1]. The connection between SLE and PSVD underscores the systemic nature of autoimmune diseases, as they can impact different organ systems throughout the body, adding to the complexity of manifestations seen in individuals with SLE. While various causes can contribute to liver dysfunction in systemic lupus erythematosus, PSVD in the context of SLE remains relatively rare [2]. Here we report a case of SLE with secondary antiphospholipid syndrome (APS) who was noted to have PSVD during a diagnostic workup for iron deficiency anemia (IDA).

Case report

This is a 49-year-old lady who was diagnosed with SLE and secondary APS in 2010. She initially presented with oral ulcers, malar rash, joint pain, lupus nephritis, positive antinuclear antibodies (ANA), low complement levels, positive lupus anticoagulant and anticardiolipin antibody on two occasions tested 12 weeks apart. She had a history of four consecutive late fetal losses but had not experienced any thrombotic events prior. Her disease remains well controlled with prednisolone, azathioprine, hydroxychloroquine, and aspirin.

During a clinic review, she was noted to have IDA where her hemoglobin level was 8.9 g/dL with low serum iron and transferrin saturation. She had normal folate and vitamin B12 levels. She underwent esophagogastroduodenoscopy (OGDS) which revealed two columns of grade 1 esophageal varices with no evidence of fundal varices or portal gastropathy. A follow up ultrasound abdomen revealed evidence of hepatomegaly with no evidence of liver cirrhosis, splenomegaly or portal vein thrombosis. In addition, she also tested negative for hepatitis B, hepatitis C, human immunodeficiency virus, and liver autoantibodies.

A computed tomography (CT) of the abdomen revealed a homogenously enhanced liver with smooth margins and a dilated portal vein with no evidence of portal vein thrombosis, confirming the diagnosis of PSVD (Figure 1 and 2). A liver biopsy was not performed as the patient declined. A diagnosis of PSVD was made, and oral propranolol was initiated. She is monitored with annual ultrasounds of the hepatobiliary system and OGDS. Her most recent OGDS revealed one column of grade 1 esophageal varices with no red wale sign. She remains well on propranolol.

Discussion

PSVD is a group of rare, heterogenous liver disorders characterized by intrahepatic portal hypertension in the absence of liver cirrhosis. The exact pathophysiology of PSVD remains unknown, but it has been associated with autoimmune disorders, chronic infections, exposure to medications or toxins, genetic disorders, and prothrombotic conditions [3].

Including our patient, a total of 26 patients with SLE-related PSVD have been reported in the literature [2,4,5]. The most common clinical manifestations of SLE in this cohort include malar rash (75%), arthritis (68.8%), lupus nephritis (56.3%) and hematological involvement (52.2%). Most patients tested positive for ANA (92%) followed by antidouble stranded DNA (anti-dsDNA) (76%) and anti-Sm (24%). Nine (36%) and six patients (24%) tested positive for anticardiolipin antibody and lupus anticoagulant respectively. The most common clinical manifestations of PSVD in this cohort were splenomegaly (76.5%), varices (44.5%), and ascites (29.4%). The most frequently reported liver histology was nodular regenerative hyperplasia (NRH) (61.5%). (Table 1)

A hypercoagulable state and vasculitis caused by deposition of immune complexes in the intrahepatic vessels has been reported to be

possible reasons why PSVD occurs in patients with SLE and APS [6]. Patients can be asymptomatic or present with ascites, variceal bleeding, splenomegaly, and hypersplenism with normal or slightly abnormal liver function tests. Rarely do they develop hepatic encephalopathy, hepatorenal and hepatopulmonary syndrome.

Besides assessing for liver cirrhosis, Dopplar ultrasound of abdomen remains essential to exclude portal vein thrombosis [5]. CT and magnetic resonance (MR) imaging of the abdomen can be useful in assessing vascular abnormalities, cirrhotic changes, and benign hypervascular nodules [7]. Liver biopsy remains the gold standard in the diagnosis of PVSD. Common pathological findings include hepatoportal sclerosis, periportal fibrosis, perisinusoidal fibrosis, and NRH.

Data on the management of PSVD remains scarce due to its rarity and lack of randomized controlled trials. Its management is mainly extrapolated from guidelines in cirrhotic patients with portal hypertension. Primary and secondary prevention of variceal bleeding in PSVD include the use of non-selective beta-blockers and endoscopic variceal ligation [8]. Trans-jugular intrahepatic portosystemic shunting can be a potential salvage therapy for patients who fail to respond to medical and endoscopic therapy. The evidence of corticosteroids is unclear but can potentially be beneficial [2,9]. The use of other immunosuppressants, such as cyclophosphamide or rituximab, should ideally be guided by the involvement of other organ systems in SLE [4]. Splenectomy remains a salvage therapy in refractory cases. Patients who have portal vein thrombosis should be treated with anticoagulation therapy [8].

The overall prognosis of PSVD appears favourable as most patients have preserved hepatic function [8]. Overall survival was reported at 100%, 78% and 56% at 1, 5 and 10 years respectively. The presence of ascites is a poor prognostic factor for these patients [10].

A high index of suspicion of PSVD should be maintained when SLE patients present with unexplained IDA, varices, ascites, thrombocytopenia, and splenomegaly. It is also more common among SLE patients with positive dsDNA and antiphospholipid antibodies. Although usually benign, its early detection remains essential as late complications, such as variceal bleed, hepatic encephalopathy, hepatorenal syndrome and acute liver failure may be potentially fatal.

Conclusion

PSVD is a rare condition, often overlooked both clinically and pathologically, particularly in patients with SLE who exhibit manifestations of portal hypertension in the absence of cirrhosis. Due to the lack of clinical studies, there are presently no evidence-based recommendations for the prevention, treatment, and follow-up of patients with SLE-associated PSVD. This highlights the need for further research to better understand the pathophysiology of SLE-associated PSVD and to establish comprehensive guidelines for managing this condition.

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WCY contributed to the writing of the manuscript while PSO supervised and edited the manuscript.

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Conflicts of Interest
None.

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Table 1. Summary of clinical characteristics, treatment and outcome of patients with SLE-related PSVD

No	Age/ Sex	Interval between SLE and NCPH (yr)	SLE manifestations	Immunological Markers	Clinical Manifestations of NCPH	Hepatic dysfunction	Portal vein thrombosis	Liver histopathology	Treatment of SLE	Treatment of NCPH	Outcome
1 [2]	29/M	3	Malar rash, AIHA, lupus nephritis	ANA, CH50, dsDNA, Sm, RNP, Ro	Splenomegaly, esophageal varices, thrombocytopenia	Yes	No	PF	GCs, Aza	EVL, propranolol, splenectomy	Alive
2 [2]	43/F	N/A	Malar rash, lupus nephritis, fever	ANA, dsDNA, CH50, IgG	Ascites, hepatosplenomegaly	Yes	No	NRH	GCs	N/A	Alive
3 [2]	26/M	6	Malar rash, arthritis	ANA, dsDNA, CH50, aCL	Massive splenomegaly, eosphageal and gastric varices, thrombocytopenia	Yes	No	PF	GCs	GCs	Alive
1 [2]	19/F	8	Malar rash, arthritis, leucopenia, lupus nephritis, pulmonary hypertension	ANA, dsDNA, CH50	Hepatosplenomegaly, ascites, esophageal varices	No	No	PF	GCs, CTX	N/A	Alive
5 [2]	38/M	12	Lupus nephritis, fever	LA, aCL, dsDNA, CH50	Esophageal varices, massive splenomegaly, thrombocytopenia	Yes	No	PF	GCs	EVL, partial splenic embolization, splenectomy and devascularization around stomach	Alive
6 [2]	40/F	14	Malar rash, arthritis, serositis, lupus nephritis	ANA, dsDNA	Esophageal varices	No	No	NRH	GCs	Endoscopic injection sclerotherapy	Dead (Bacterial endocarditis)
7 [2]	39/F	8	Arthritis, malar rash, oral ulcers, lupus nephritis, pericarditis, bicytopenia, PAH	ANA, dsDNA, aCL, low C3/C4	Splenomegaly, esophageal varices, bicytopenia	No	No	NRH	GCs, CTX	N/A	N/A
8 [2]	37/F	3	Arthritis, serositis, PAH	ANA, dsDNA, Sm, RNP, SSA	Hepatosplenomegaly, esophageal varices	Yes	No	NRH	GCs	N/A	Alive
9 [2]	37/F	0	Malar rash, thrombocytopenia	ANA, dsDNA, aCL, SSA, low C3/C4	Hepatosplenomegaly, ascites	Yes	No	NRH	GCs	Propranolol	Alive
10 [2]	54/F	14	Malar rash, arthritis, lupus nephritis	ANA, dsDNA	Splenomegaly, ascities, esophageal	Yes	No	NRH	GCs, Aza	Endoscopic histoacryl injection, EVL	Alive

					varices, pancytopenia						
11 [2]	56/F	18	Malar rash, arthritis, thrombocytopenia	ANA, dsDNA	Esophageal varcies	No	No	NRH	GCs	endoscopic injection sclerotherapy, endoscopic histoacryl injection	Alive
12 [2]	56/F	5	Cutaneous rash, arthritis, pericardial effusion, AIHA	ANA, dsDNA	Splenomegaly, thrombocytopenia, esophageal varices	Yes	No	NRH	GCs, Aza	N/A	Alive
13 [2]	37/F	N/A	N/A	N/A	Esophageal varices, thrombocytopenia, portal hypertensive colopathy.	Yes	No	NRH	GCs, Aza	Banding, betablockers, side-to-side portocaval shunt	Alive
14 [2]	N/A	N/A	N/A	ANA, dsDNA, SSA, IgG	N/A	Yes	No	NRH	MTX	N/A	N/A
15 [2]	N/A	N/A	N/A	ANA, aCL, ASMA	N/A	No	No	NRH	Aza	N/A	N/A
16 [2]	N/A	N/A	N/A	ANA, dsDNA, RNP, IgG	N/A	No	No	NRH	CTX	N/A	N/A
17 [2]	N/A	N/A	ILD	Sm, RNP, IgG	N/A	Yes	No	NRH	CTX	N/A	N/A
18 [2]	N/A	N/A	PAH	ANA, Sm, LKMI	N/A	No	No	NRH	CTX	N/A	N/A
19 [2]	35/F	2	Pancytopenia	ANA	N/A	No	No	NRH, PF	GCs, CsA	N/A	N/A
20 [2]	41/F	6	Pancytopenia	ANA, dsDNA	N/A	No	No	NRH	GCs, MTX	N/A	N/A
21 [2]	25/F	9.5	Pancytopenia	ANA, aCL	N/A	No	No	N/A	GCs, MTX	N/A	N/A
22 [2]	25/F	10	Pancytopenia	ANA, dsDNA, aCL	N/A	Yes	No	N/A	GCs, MTX	N/A	N/A
23 [2]	48/F	2	Arthritis, pancytopenia, lupus nephritis	ANA, Sm, dsDNA, SSA	Splenomegaly, pancytopenia	No	No	N/A	GCs	Metoprolol	Alive
24 [4]	43/F	5	Pancytopenia, alopecia, photosensitivity, retinal vasculitis, lupus panniculitis	ANA, dsDNA, low C3/C4	Splenomegaly, esophageal varices, ascites	No	Yes	Normal	GCs, CTX, diuretics, Belimumab + anticoagulation	N/A	Alive
25 [5]	43/F	22	Discoid lupus, arthritis, lupus nephritis	ANA, dsDNA, RNP, Sm, SSA, SSB, APS -ve	Gastroesophageal varices, splenomegaly	No	No	Normal	GCs, RTX	N/A	Dead (Breast carcinoma)

GCs = Glucocorticoids, CTX = Cyclophosphamide, CsA =. Ciclosporin, MTX = methotrexate, Aza = Azathioprine, ANA = Antinuclear antibody, aCL = anticardiolipin antibody, LA = lupus anticoagulant, ILD = interstitial lung disease, PAH = pulmonary arterial hypertension, AIHA = autoimmune hemolytic

anemia, NRH = Nodular regenerative hyperplasia, PF = Periportal fibrosis, EVL = Endoscopic variceal ligation

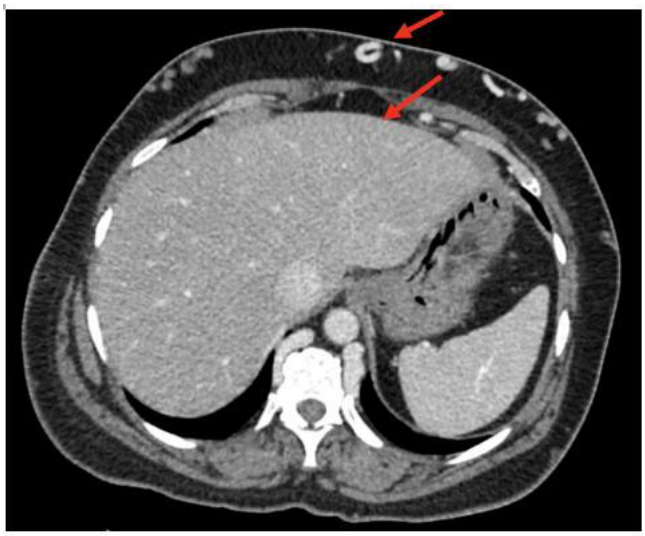

Figure 1. Smooth liver edge and dilated superficial veins (red arrows) with no evidence of liver cirrhosis

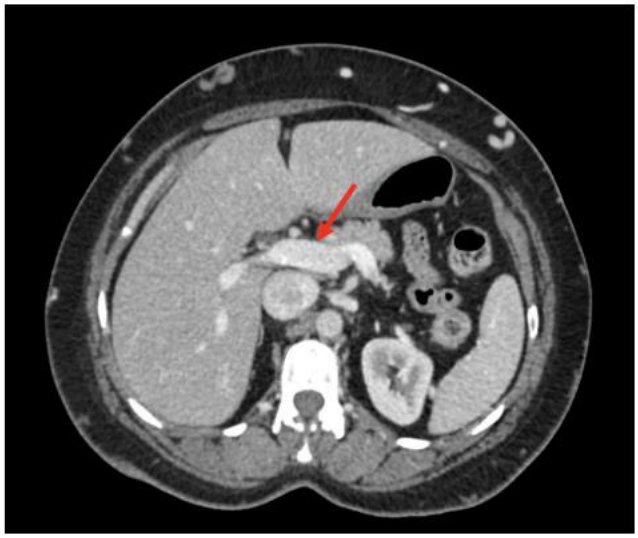

Figure 2. Dilated portal vein (red arrow) with no evidence of portal vein thrombosis

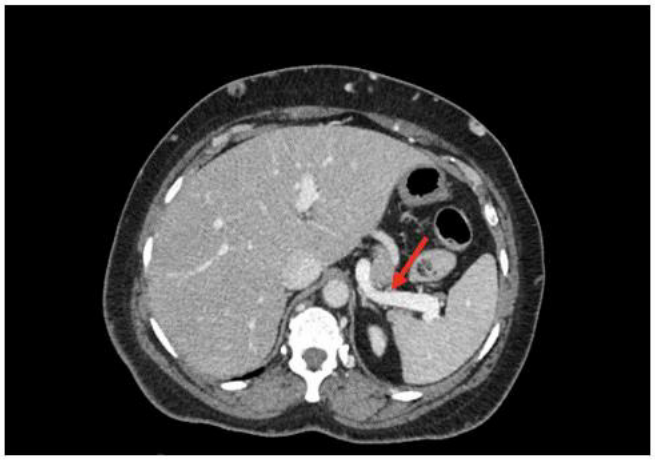

Figure 3. Mildly dilated splenic vein (red arrow) with no splenomegaly

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CASE REPORT

Remitting Seronegative Symmetrical Synovitis with Pitting Oedema (RS3PE) in a Young Patient Mimicking Syphilitic Arthritis: A Case Report.

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Abstract
Remitting seronegative symmetrical synovitis with pitting oedema (RS3PE) is a rare disorder characterized by acute symmetrical synovitis involving both hands and feet, accompanied by pitting oedema. The aetiopathogenesis of RS3PE is still obscured. It commonly occurs in individuals over 50 years of age and has a good prognosis. RS3PE responds well to corticosteroid. We report a case of a young male being treated for sexually transmitted disease (STD) who presented with recurrent episodes of bilateral leg oedema and symmetrical joint pain involving the ankles and hands. He was successfully treated with corticosteroid. Reactive arthritis was excluded in view of the recurrent episodes with no evidence of all phases of syphilis, especially tertiary syphilis.

Keywords: *Corticosteroid, Reactive arthritis, RS3PE, Sexual transmitted disease, Syphilis, Young.*

Introduction

RS3PE is a rare disorder of unknown aetiology and pathogenesis. It was first described in 1985 by McCarty [1]. Nevertheless, it has been suggested that autoimmunity with a possible association with human leukocyte antigen (HLA) haplotypes, plays an important role [2, 3]. RS3PE is characterized by pitting oedema and acute symmetrical synovitis of small joints of the hands, giving a boxing-gloves' appearance. RS3PE has been identified as a distinct entity that predominantly affects elderly male over 50 years of age [1, 4] and has been found to be associated with autoimmune diseases and paraneoplastic syndrome [5]. RS3PE is rare in young individuals, as previously reported [6]. We describe a a case of a young male who had been treated for sexually transmitted disease (STD) and presented with recurrent bilateral lower limbs pitting oedema and joint pain. He was tested negative for rheumatoid factor (RF), anti-citrullinated peptide antibody (ACPA), and other serological markers for autoimmune diseases, but responded well to corticosteroid.

Case report

A 34-year-old Indian man, who had been treated for STD (Venereal Disease Research Laboratory, VDRL 1:16, and positive Treponema Pallidum Hemagglutination Assay, TPHA) in a neighbouring country following unprotected sexual activity, presented with recurrent painless bilateral leg oedema for the past 4 years. He had no other medical illness. He smokes cigarettes and drinks alcohol occasionally but does not take any recreational drugs. He had mild abdominal distension without other gastrointestinal symptoms including melaena, hematemesis, and jaundice. He had no fever, rashes, neurological and cardiorespiratory symptoms. His urinary habit was normal with no cloudiness or frothiness of urine and there was no urethral discharge. He had no history of sore throat. Subsequently, he developed joint pain affecting the ankles and hands. There was no early morning stiffness.

Clinical examination revealed a well-built man, with tattoos on his arms. There were no signs of chronic liver stigmata, oral thrush, or abnormal dentition. Bilateral painless pitting pedal oedema, extending up to the knees and external genitalia, was present. The hands, ankle, and tarsal joints were swollen and tender. There was no deformity present. Peripheral lymph nodes were not palpable. Other systems were unremarkable.

Laboratory investigation revealed reactive VDRL with low titre 1:2, and positive TPHA. Biochemistry profile showed normal serum creatinine, serum albumin, absence of urinary protein, and normal 24-hour urine protein. The pro-B-type natriuretic peptide (BNP) level was normal. Serological markers rheumatoid factor (RF), anti-citrullinated peptide antibody (ACPA), anti-nuclear antibody (ANA), anti-double stranded DNA (anti-dsDNA), and complement levels (C3 and C4), were all negative. Anti-hepatitis C antibody, retroviral study and *Chlamydia* serology were also negative. Ultrasonography of the abdomen showed normal hepatobiliary and genitourinary systems. Computed tomography (CT) scan of the abdomen clarifies the unremarkable findings.

Based on the laboratory and imaging findings, a diagnosis of RS3PE was made and he was given prednisolone 20 mg daily, and spironolactone 25 mg daily. He was asymptomatic after a month of treatment without recurrence of oedema and joint pain. Both steroid and diuretic were then stopped and he remained in complete remission for more than 6 months. However, he is still indulging in sexual activity despite being advised against it.

Discussion

RS3PE is a rare distinct clinical entity of an autoinflammatory condition with an obscured aetiopathogenesis [1]. It has previously been associated with various rheumatic diseases, such as rheumatoid arthritis, systemic sclerosis, and systemic lupus erythematosus. The true

prevalence and incidence of RS3PE is unknown. However, it has been commonly reported among male Caucasians > 50 years of age which is one of the diagnostic criteria defined by Olive et al [7]. Other criteria include the presence of pitting oedema on the dorsum of both hands, sudden onset of polyarthritis, and negativity for RF. The peripheral oedema was not attributed to cardiac, liver, and renal aetiology in this patient.

This patient fulfilled the criteria except for age and achieved remission with a low dose of steroids. RS3PE is rare in young males. Nonetheless, three cases of RS3PE in young adults have been reported by Sattar [8].

Syphilis has been considered a great mimicker of other conditions due to its wide spectrum of clinical manifestations. Reactive arthritis is associated with gastrointestinal and urogenital infections, commonly due to *Chlamydia trachomatis*, *Salmonella, Shigella, Campylobacter*, and *Yersinia.* None of these were found in this patient. Syphilis, caused by the spirochete, *Treponema Pallidum*, does not typically cause reactive arthritis. Arthritis associated with tertiary syphilis was also absent in this patient. Nevertheless, syphilis had been reported to cause arthritis mimicking RA in a few cases [9] and resolved upon treating the syphilis. There were no cases of syphilitic arthritis associated with peripheral oedema or RS3PE specifically reported so far as illustrated by this patient. Neither any signs of all the three stages of syphilis showed in this patient.

Low dose steroids have been shown to be effective in achieving sustained remission in RS3PE patients, in addition to disease-modifying rheumatic drugs (DMARDs) e.g., hydroxychloroquine (HCQ)[1, 10].

Conclusion

RS3PE may occur in young age although more prevalent in elderly. Lack of definitive criteria for this rare and treatable condition may lead to underdiagnosis and delay in treatment. The diagnosis of RS3PE is by exclusion i.e., other differential diagnoses of rheumatological disorders should be thoroughly assessed.

Conflict of interest and financial disclosures
None.

Informed Consent
Written informed consent was obtained from the patient for the publication of this report and the accompanying images.

Acknowledgement
We would like to express our gratitude to all the healthcare providers involved in the care of this patient.

Authors contribution
WS: Ideas, case management, data collection, and manuscript writing; DCL: case management and review of the manuscript.

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CASE REPORT

Focal Segmental Glomerulosclerosis – A Report from Primary Care Perspective.

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Abstract

Nephrotic syndrome is a prevalent condition characterized by heavy proteinuria, hypoalbuminemia, peripheral oedema, and hypercholesterolemia. It primarily affects the lower extremities and can arise from a variety of underlying causes. Focal segmental glomerulosclerosis (FSGS) is a leading cause of primary glomerular disease in adults, accounting for approximately 35% of cases and up to 80% in African American populations. Early diagnosis and appropriate management are essential to mitigate morbidity, mortality, and associated complications. We report the case of a young female presenting with bilateral lower limb swelling and symptoms of fluid overload, ultimately diagnosed with nephrotic syndrome. The diagnosis was confirmed through a simple urinalysis. Despite implementing dietary salt restriction and treatment with diuretic therapy, including daily administration of loop diuretics, the patient did not achieve a therapeutic response. Consequently, she required lifelong renal replacement therapy.

Keywords: *Focal segmental glomerulosclerosis, Primary care, Quality of life.*

Introduction

Nephrotic syndrome is a common condition characterized by heavy proteinuria, hypoalbuminemia, peripheral oedema, and hypercholesterolemia [1]. It has multifactorial etiology for peripheral oedema, including chronic venous insufficiency, pulmonary hypertension, and cardiac, renal, or hepatic disorders [2]. Early diagnosis and timely medical intervention are critical to reducing mortality, morbidity, and complications such as end-stage renal disease (ESRD), which can impose significant emotional, physiological, and financial burdens on patients, caregivers, and healthcare systems.

Focal segmental glomerulosclerosis (FSGS) is a leading cause of primary glomerular disease in adults, accounting for approximately 35% of all cases and up to 80% in African American patients. The diagnosis and evaluation of FSGS are guided by a combination of clinical history, laboratory findings, and renal histopathological analysis [3].

Case report

A 26-year-old woman presented with a two-week history of bilateral lower limb swelling and shortness of breath. The swelling, initially confined to the thighs for the preceding two months, had progressively worsened over the past two weeks, becoming extremely oedematous and extending to the sacral region. No redness or wounds were observed on either lower limb. The patient reported difficulty sleeping at night due to breathlessness, which was alleviated when she assumed a seated position. During the same period, she experienced fatigue, lethargy, and new-onset facial swelling.

Over the past month, her lower limb deterioration led to severe ambulatory limitations, rendering her unable to walk, even for basic tasks such as using the restroom. She required assistance and a wheelchair for mobility and reported significant pruritus over both lower limbs. In the last two weeks, she began wearing diapers to manage her bathroom needs. The patient also reported persistent vomiting over the past two weeks, resulting in poor oral intake and significant weight loss of 3 kg in one week. Her body exhibited noticeable disproportionality, with marked muscle wasting in the upper body contrasting with grossly swollen lower limbs, which she described as resembling "elephant legs." She denied experiencing any lower urinary tract symptoms, such as increased frequency, dysuria, or incontinence. No other significant complaints were noted.

Her symptoms began with bilateral lower limb swelling up to the knees, for which she sought treatment at a private clinic. A diagnosis of cellulitis was made, and she was prescribed antibiotics. Despite completing the course, the swelling worsened, extending up to her thighs. She sought a second opinion at another private clinic and was prescribed diuretics for two weeks, with minimal improvement in the swelling. Subsequently, she sought care at a government healthcare clinic.

On physical examination, the patient was alert but appeared lethargic and pale, with no jaundice. Peripheral examination revealed good pulse volume with a capillary refill time of less than two seconds. Respiratory examination revealed reduced breath sounds bilaterally at the lung bases. There was marked soft pitting oedema in both lower limbs, extending to the sacrum. All other systemic examinations were unremarkable. Urinalysis and blood investigations were performed for further evaluation (Table 1 – 2, Figure 1).

The patient presented with drastically worse blood test results at the time of diagnosis. A complete blood analysis verified normochromic normocytic anemia, indicative of chronic kidney disease (CKD). Due to her pronounced oedema, a renal function assessment was conducted, revealing significant renal dysfunction with elevated creatinine levels (246.8 μmol/L) and raised urea concentrations (11.6 mmol/L). Her eGFR was 14 ml/min/1.73m² (CKD-EPI

equation), categorizing her as Stage 5 CKD (End-Stage Renal Disease) using the KDIGO 2018 guidelines. Liver function tests indicated hypoalbuminemia, consistent with nephrotic syndrome and glomerular disease. Urinalysis showed 4+ proteinuria, confirming nephrotic-range proteinuria (>3g/day). Given the worsening blood investigations and persistent proteinuria, a kidney biopsy was performed, revealing global sclerosis, with 15 glomeruli exhibiting segmental glomerulosclerosis and focal hyalinosis. The tubules displayed widespread early interstitial fibrosis, with 50% of them atrophied, and some tubules contained hyaline casts. Immunofluorescence was negative for IgG, IgA, IgM, C3, C1q, and fibrinogen. She was diagnosed with focal segmental glomerulosclerosis (FSGS) associated with acute tubular necrosis/injury. Had these urine and laboratory tests been conducted earlier, the results might not have been as bad, potentially facilitating an earlier diagnosis and management before the patient progressed to end-stage renal disease.

Discussion

Chronic kidney disease (CKD) has emerged as a global public health challenge due to its rising prevalence, risk of progression to end-stage renal disease (ESRD), and associated morbidity and mortality. In Malaysia, CKD is particularly concerning due to its increasing prevalence and low public awareness. According to the Malaysian National Health and Morbidity Survey (NHMS) 2011, the prevalence of CKD in West Malaysia was 9.07%, which rose to 15.5% by 2018 [1]. A more recent study that included populations from East Malaysia confirmed a similar prevalence of 15.5%, with 6.81% of cases classified as stages 3 to 5 CKD [4]. CKD is often asymptomatic and irreversible, and its progression to ESRD necessitates dialysis, reflecting a significant public health burden [4]. In 2020, over 51,000 individuals in Malaysia required dialysis, with 9,592 new cases reported. The healthcare costs associated with CKD and ESRD in Malaysia are estimated at RM3.2 billion for dialysis and RM1.5 billion for indirect expenses [5]. Chronic kidney disease (CKD) has become a global public health issue due to the rising prevalence of CKD patients, the risk of advancement to end-stage renal disease (ESRD), and increased morbidity and mortality rates.

The management of CKD relies primarily on early detection and intervention to prevent disease progression, as no definitive cure exists. Delayed diagnosis or mismanagement of nephrotic syndrome, a common precursor to CKD, can accelerate the development of chronic kidney failure. Focal segmental glomerulosclerosis (FSGS) and membranous nephropathy are the most frequent primary causes of nephrotic syndrome, contributing to approximately 2% of the 52% of new dialysis cases reported in Malaysia in 2022 [6]. FSGS accounts for 29.8% of primary glomerulonephritis cases in Malaysia, with an estimated 2,320 reported cases. It predominantly affects younger individuals, with a mean age of 35.8 ± 14.9 years, and males (57.2%) are more commonly affected [7].

Nephrotic syndrome typically presents with marked oedema, proteinuria, hypoalbuminemia, and often hyperlipidemia. The most common initial symptom is the sudden onset of oedema, particularly in the lower extremities, which may extend to the proximal lower limbs, abdomen, or genitalia in severe cases [2]. Other symptoms include exertional dyspnea, fatigue, foamy urine, and significant fluid-associated weight gain. Diagnostic criteria include clinical evidence of peripheral edema, heavy proteinuria (spot urine protein-to-creatinine ratio >3.5 g/24 hours or >300 mg/mmol), and hypoalbuminemia [8]. In this case, the patient presented with extensive oedema extending to the sacral region, consistent with nephrotic syndrome.

The 24-hour urine protein collection test remains the gold standard for quantitative protein assessment. However, it is often impractical in

outpatient settings or when patients undergo concurrent laboratory testing. A urine dipstick test, showing proteinuria of 3+ (≥300 mg/dL), provides an accessible screening tool for identifying nephrotic-range proteinuria. Initial laboratory investigations, including a urine dipstick test, played a crucial role in detecting nephrotic syndrome in this patient during her third visit to the government health clinic [1,8].

Primary care serves as the initial point of contact for patients, playing a pivotal role in the early detection and management of nephrotic syndrome. Accurate history-taking, thorough physical examination, and basic laboratory investigations are essential for identifying systemic causes of peripheral edema. In this case, the patient's recurrent complaints of significant lower limb oedema, extending to the sacrum, necessitated renal evaluation through simple yet effective diagnostic tools like urine dipstick tests. These initial findings guided subsequent confirmatory laboratory investigations and timely referral for specialist care [9]. Figure 2 reflects the algorithm of nephrotic syndrome approach in terms of assessment and management [9].

Without early diagnosis and treatment, nephrotic syndrome can progress to ESRD. In this patient, a urine study revealed proteinuria exceeding 3+, consistent with heavy proteinuria. Follow-up tests, including a 24-hour urine protein collection, confirmed the diagnosis. Data from the Malaysian Renal Registry indicate that approximately 15% of nephrotic syndrome patients progress to ESRD within a 72-month follow-up period. The 5 and 10-year survival rates for patients with FSGS are 87.4% and 80.6%, respectively, with hypertension present in 41.3% of cases at diagnosis [7]. In this case, glucocorticoid resistance and high-dose diuretics failed to alleviate the patient's severe edema. She required continuous ambulatory peritoneal dialysis to manage her symptoms and improve her quality of life. Complications such as bacterial infections, including cellulitis, peritonitis, and sepsis, can exacerbate the patient's condition by inducing further edema and thrombosis [1,9].

The patient received her diagnosis of nephrotic syndrome at 26 years old, profoundly affecting her physical, emotional, and social well-being. She required frequent dialysis sessions, which imposed significant emotional and physical burdens on both the patient and her caregiver. This case highlights the critical role of primary care in early diagnosis and the need for comprehensive support systems for young patients facing chronic conditions like ESRD [10].

Conclusion

This case underscores the critical importance of early detection and effective management of nephrotic syndrome, particularly in the context of Focal Segmental Glomerulosclerosis (FSGS). The delayed diagnosis in this patient, despite hallmark symptoms such as severe oedema and proteinuria, highlights the diagnostic challenges often encountered in primary care settings, where FSGS may not be immediately recognized. Timely recognition of nephrotic syndrome, supported by a comprehensive diagnostic evaluation, is essential to prevent progression to end-stage renal disease (ESRD) and the subsequent requirement for renal replacement therapy. This case emphasizes the pivotal role of primary care providers in identifying early clinical signs, initiating appropriate investigations, and ensuring timely referral to specialists. Such proactive approaches are integral to improving patient outcomes and enhancing quality of life. Given the complex and chronic nature of nephrotic syndrome, a multidisciplinary approach to long-term management is imperative. This strategy should focus on optimizing care delivery, preventing complications, and addressing the ongoing physical, emotional, and social needs of patients.

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Authors contribution
KI and MSES contributed to the conceptualization and refinement of the case report, and improving the overall quality of the manuscript.
NHNY contributed to the histopathological examination (HPE) slides and authored the HPE report.

Table 1. Blood parameter in primary care

Test	Result	Reference range
Haemoglobin	7.0	(8.0-17)
White blood cells 10^3	10.3	(3.0-15.0)
Platelet 10^3	247	(150-300)
HCT	24%	(33-42)
MCV(fL)	91	(78-97)
MCH(pG)	29	(27-33)
MCHC (g/dL)	31	(31-35)
Iron (umol/L)	9.1	(5.83-34.80)
UIBC (umol/L)	16	(24-70)
TIBC (umol/L)	25	
TSAT (%)	36	(16-45%)
Serum ferritin (ug/L)	77	(13-68)
Sodium (mmol/L)	141	(129-156)
Potassium (mmol/L)	3.5	(3.0-4.5)
Chloride (mmol/L)	113	(92-115)
Creatinine (umol/L)	246.8	(26-90)
Urea (mmol/L)	11.6	(2.5-7.1)
Albumin (g/L)	21	(35-50)
Calcium (mmol/L)	1.8	(2.0-2.6)
Phosphate (mmol/L)	1.1	(0.8-1.5)

UIBC Unsaturated iron binding capacity, ***TIBC*** Total iron binding, ***TSAT*** transferrin saturation , ***MCH*** Mean corpuscular hemoglobin. ***MCHC*** Mean corpuscular hemoglobin concentration**,** ***MCV*** Mean corpuscular volume

Table 2. Urine analysis in primary care

Test	Result	Reference range
Urine analysis		
Glucose	Negative	
Protein	4+	
Bilirubin	1+	
Urobilinogen	Normal	
pH	6	
Ketone	1+	
Leucocyte	Negative	
Colour	Yellow	
Blood	Trace	
24H Urine Protein	8.93	(g/day)

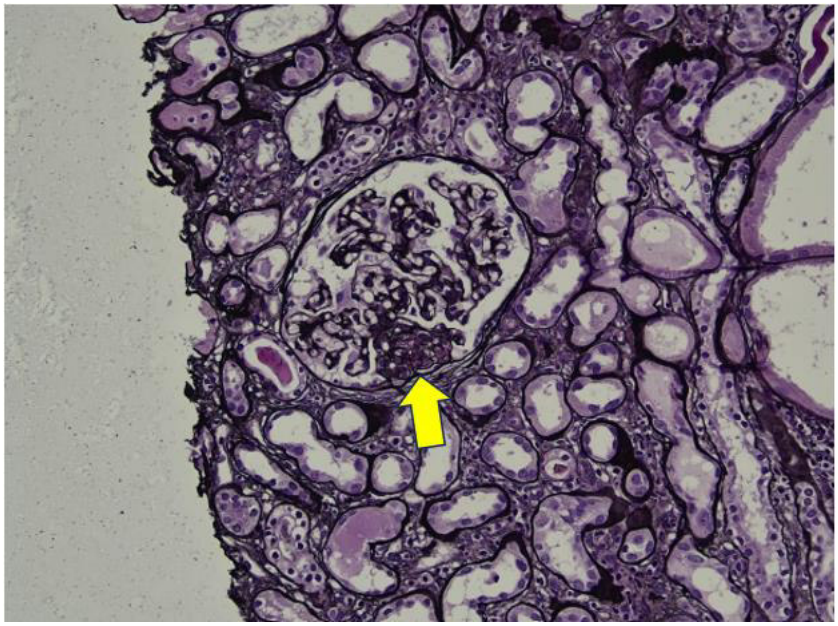

Figure 1. Glomerulus with segmental glomerulosclerosis. Inferior area. There are segments with preserved architecture. (Methenamine silver x200.)

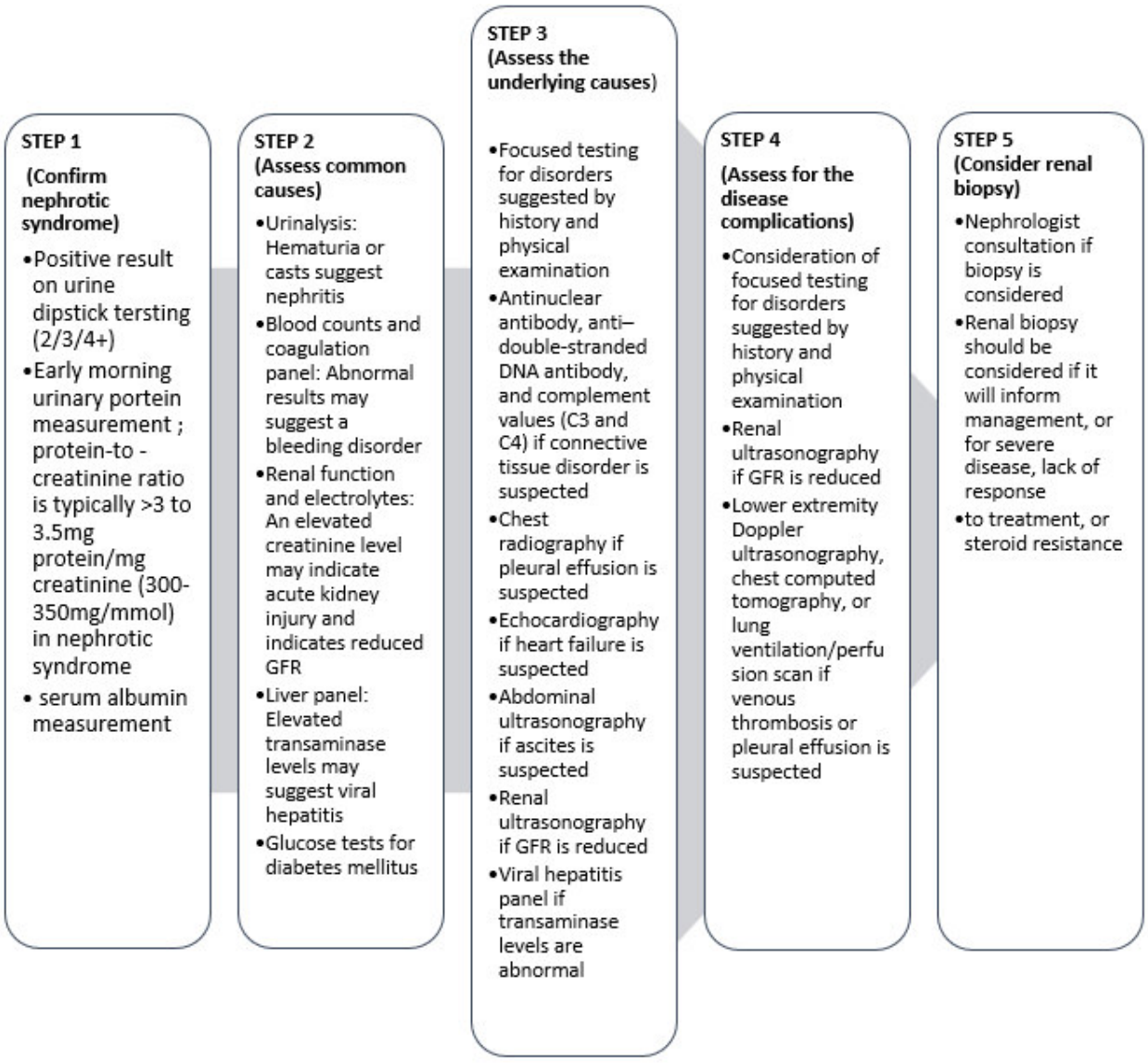

Figure 2. Algorithm for the diagnosis of nephrotic syndrome in adults, adapted from Hull et al, 2008(9)

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CASE REPORT

Refractory Livedoid Vasculopathy: Clinical Response to TNF-α Blocker in a Young Male Patient.

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Abstract

Livedoid vasculopathy is a rare condition characterized by thrombosis of dermal vessels, predominantly affecting the ankles. The patient presented with a painful ulcer, which is usually chronic in nature with relapsing-remitting episodes. It may resemble other vasculitides disorders, such as microscopic polyangiitis and polyarteritis nodosa. Hence, diagnosis is mainly based on clinical and histopathological findings. Livedoid vasculopathy required antiplatelet and anticoagulant therapy, in contrast to vasculitides disorders. We describe a young man who presented with a recent onset of painful ulcers on both ankle regions, consistent with livedoid vasculopathy and supported by histopathological findings. Clinical remission was observed after treatment with subcutaneous adalimumab, after failing to respond to a combination of anticoagulant, corticosteroid, vasodilator, and antiplatelet agents.

Keywords: *Adalimumab, Anticoagulant Antiplatelet, Corticosteroid, Livedoid vasculopathy, Refractory, Thrombosis, Vasculitis, Vasodilator.*

Introduction

Livedoid vasculopathy (LV) is a rare disorder of thrombo-occlusive vasculopathy involving the vessels in the dermis layer [1]. It is characterized by painful, purpuric ulcers on the lower extremities. LV is more common in female than male (ratio of 3:1) with age range between 15 and 50 years [2, 3, 4]. The reported incidence rate is approximately 1 in 100,000 people [5]. The diagnosis is often delayed by about 5 years, according to previous epidemiological studies [6].

Although the term "atrophie blanche" (referring to atrophic ivory or porcelain-white stellate or retiform scars) is descriptive, it is commonly used to refer to one of the features of LV. The condition shares overlapping features with both vasculitis and vasculopathy, such as in granulomatous polyangiitis (GPA) and polyarteritis nodosa (PAN).

We report a case of a young, healthy man who presented with a first onset of typical LV features on both ankles. Remission was achieved with subcutaneous adalimumab after failure to respond to standard treatments, including corticosteroids, anticoagulants, vasodilators, and antiplatelet agents.

Case report

A 22-year-old Chinese man, previously well, developed a sudden onset of painful ulcers and rash on his ankles over the past 4 weeks, with more swelling on the right ankle than the left (Figure 1). He had no other rashes elsewhere and no fever, alopecia, mucosal ulcers, angina, or dyspnoea. He worked as a mechanic and denied any history of trauma. He occasionally smoked vape and drank alcohol. He had no significant contributory family or allergic history.

On physical examination, there were multiple cutaneous telangiectasias and 'atrophie blanche' on both malleoli, which were very tender (Figure 1). The dorsalis pedis and posterior tibialis pulses were present. The patient had tattoos on the dorsum of his right hand, knuckles, and shoulder. Other systems were unremarkable.

Laboratory investigations showed a C-reactive protein (CRP) level of 59 mg/L (normal < 5), an international normalized ratio (INR) of 1.04, and an activated partial thromboplastin time (aPTT) of 36.4 seconds (reference range: 25.6-35.2 seconds). The complete blood count, liver, and renal profiles were normal. Serological tests for HIV, Hepatitis B and C, and the Venereal Disease Research Laboratory (VDRL) test were non-reactive. The antinuclear antibody (ANA), anti-dsDNA, extractable nuclear antigen (ENA), rheumatoid factor (RF), anti-citrullinated peptide antibodies (ACPA), and anti-neutrophil cytoplasmic antibodies (ANCA) screenings were all negative. Lupus anticoagulant was present (first screening) but negative for cardiolipin antibodies (IgM, IgG, and IgA) and β2-glycoprotein 1 antibodies (IgM, IgG, and IgA). Protein S and C levels were normal, as were homocysteine (14.0 umol/L) and lipoprotein A (Lp(a)) levels (<10.2 mg/dL). Other thrombophilia tests, such as anti-thrombin, factor V Leiden, and factor VIII, were not performed. Doppler ultrasound showed no evidence of deep venous thrombosis (DVT) or arterial occlusive disease. Histopathological examination (HPE) of a skin biopsy demonstrated an inflammatory process in the epidermis, with the presence of fibrinoid necrosis, extensive capillary thrombosis, and mild neutrophil infiltration. Fibrosis was also present in the deep dermis, with intraluminal thrombosis noted in the medium-sized vessel. These HPE findings were consistent with LV (Figure 2). The immunofluorescence study was negative.

The patient was initially treated with acetylsalicylic acid (aspirin) 150 mg daily, direct oral anticoagulant (DOAC) dabigatran 150 mg twice daily, and pentoxifylline 400 mg in three divided doses, which led to a gradual resolution of the lesions in the first few weeks. However, he developed new ulcers in the same area despite

treatment. Given the recurrent ulcers, subcutaneous adalimumab 40 mg every 2 weeks was initiated after appropriate counseling and negative screening for latent tuberculosis. All other medications were stopped. The patient received adalimumab for four months, after which the ulcers completely healed without recurrence (Figure 1B).

Discussion

LV is a rare disorder of unclear aetiopathogenesis characterized by painful purpuric ulcers that primarily affect the lower limbs. It is categorized into primary (idiopathic) and secondary forms, which the latter being associated with autoimmune diseases, malignancies or thrombophilia disorders including antiphospholipid antibody syndrome, Factor V Leiden mutation, protein C and S deficiencies, prothrombin mutation, antithrombin III deficiency, hyperhomocysteinemia, and elevated lipoprotein(a) levels [5].

Several hypercoagulable factors, coagulation disorders, fibrinolysis, rheumatological disorders, and endothelial dysfunction have been identified as playing roles in its pathogenesis. Genetic predisposition has also been demonstrated through polymorphisms in genes such as prothrombin G20210A, Factor V Leiden, plasminogen activator inhibitor-1 (PAI-1), and methylenetetrahydrofolate reductase (MTHFR) [7]. However, genetic study was not available for this patient.

The diagnosis of LV requires histopathological confirmation, even when clinical presentation is typical, as it is crucial to exclude other secondary aetiologies. Characteristic histological features include thickening or hyalinized degeneration of the subintimal layer of superficial dermal vessels, endothelial proliferation, intra-luminal fibrin deposits, thrombosis, red blood cell extravasation, and sparse perivascular lymphocytic infiltration, as observed in this patient [5, 8].

To date, there is no specific treatment for LV. The primary aim of treatment is to alleviate the symptoms such as pain, promote ulcer healing, and prevent relapses. Treatment responses vary due to several factors, including availability, accessibility, cost, comorbidities, and compliance. A systematic review by Micieli *et al.* demonstrated that the variability of treatment success depends on these factors [9]. LV is commonly managed with anticoagulants (e.g., rivaroxaban, warfarin, low molecular weight heparin), anabolic steroids (e.g., danazol), antiplatelets (e.g., aspirin, pentoxifylline, dipyramidole), and intravenous immunoglobulins [9]. Other treatment modalities include Psoralen and UV-A (PUVA) therapy and hyperbaric oxygen, either as monotherapy or in combination with other treatments. Unlike vasculitis, treatment of LV primarily focuses on preventing thrombosis or inducing vasodilation [10]. For refractory cases, immunosuppressants and biological agents including tumor necrosis factor α (TNF-α) blocker like adalimumab, have been used with reports of sustained remission [11, 12, 13].

The role of TNF- α blocker in LV is based on the mechanism of inflammation and thrombosis, the latter being associated with endothelial cell damage. TNF- α, a pro-inflammatory cytokine, contributes to pain in LV, which helps explain the therapeutic response to TNF- α blocker.

Conclusion

The diagnosis of livedoid vasculopathy (LV) remains a significant challenge due to its overlapping features with other vasculitides and autoimmune disorders, such as cutaneous polyarteritis nodosa (cPAN), systemic lupus erythematosus (SLE), scleroderma, and other causes of ulcers, including chronic venous ulcers. Histopathological examination (HPE) is crucial to differentiate these conditions. Standard LV treatment focuses on inhibiting thrombus

formation, promoting vasodilation, and stimulating fibrinolytic activity [10]. However, the presence of inflammatory infiltrates suggests a role for inflammatory cytokines, which may explain the observed response to anti-TNF blockers.

This patient's case is exceptionally rare given their young age and the absence of underlying autoimmune conditions or other contributing factors. Despite being refractory to standard treatments, the patient responded to adalimumab, consistent with previous case reports.

Authors' contribution

WS and HFBB were responsible for conceptualizing, collecting clinical data, writing, and finalizing the manuscript, while LBR handled histopathological analysis and report writing.

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Conflict of interest: None

Funding: None

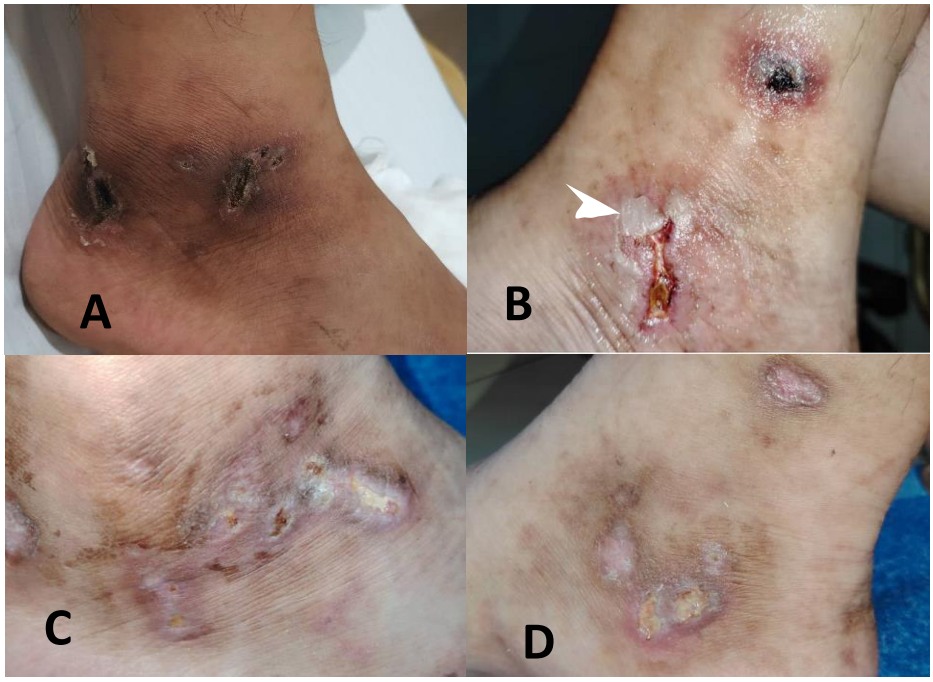

Figure 1. Typical features of livedoid vasculopathy are shown livedo racemosa, ulcers, and 'atrophie blanche' (arrowheads). (A: right foot; B: left foot). Note that the right ankle joint is also swollen. (C and D: healed ulcer after 4 weeks of adalimumab treatment.)

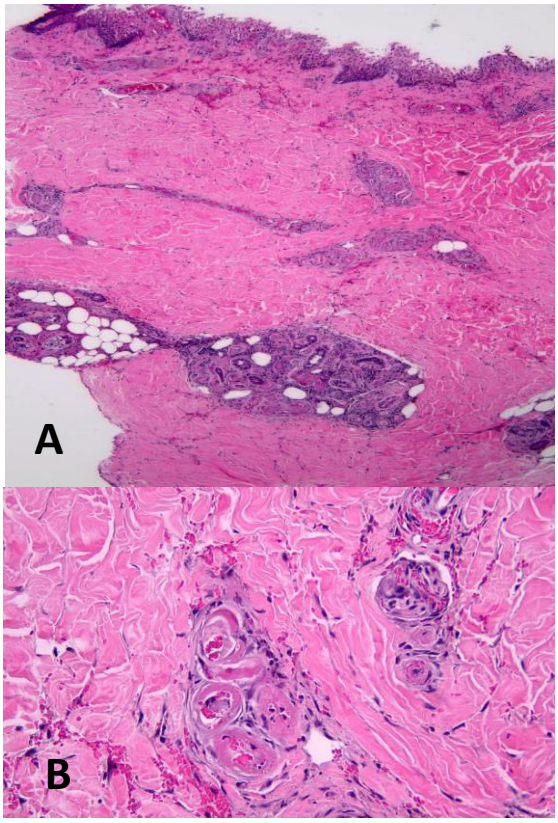

Figure 2. Histopathological examination of a skin biopsy shows the epidermis with spongiosis and neutrophil infiltration, along with acute on chronic inflammation in the underlying granulation tissue. Fibrinoid necrosis and extensive capillary thrombosis with mild neutrophil infiltration are observed (arrow). The deep dermis shows increased fibrosis, while the subcutaneous fat reveals medium-sized vessel thrombosis (arrow).

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CASE REPORT

Ramsay Hunt Syndrome: A Case Report Underlining the Importance of Early Diagnosis to Prevent Complications.

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Abstract

Ramsay Hunt Syndrome (RHS) is a rare neurological disorder and a sequelae of Herpes zoster, resulting from the reactivation of the Varicella zoster virus (VZV) in the geniculate ganglion. Patients usually present with acute unilateral peripheral facial nerve paralysis, often accompanied by vesicular eruptions in the external auditory canal or oral mucosa, a hallmark of herpes zoster oticus. Due to its overlapping clinical features, RHS is frequently misdiagnosed as Bell's palsy, a more common cause of facial paralysis seen in primary care settings. This case report underscores the potential for RHS misdiagnosis, in which can lead to delayed initiation of antiviral and corticosteroid therapy, resulting in suboptimal patient outcome. This case emphasizes the importance of early recognition of the condition, which are critical to improving prognosis, reducing complications, and enhancing the quality of life for affected patients.

Keywords: *Ramsay Hunt, Herpes zoster oticus ,facial nerve palsy.*

Introduction

Herpes zoster oticus, another name for Ramsay Hunt Syndrome (RHS), is a late manifestation of varicella-zoster virus (VSV) infection. It results from inflammation of the geniculate ganglion of the 7th cranial nerve. The initial presentations are ipsilateral facial paralysis, vesicles at the ear, and otalgia [1]. RHS is a clinical diagnosis that requires early treatment to reduce the risk of complications. This case report describes a patient with RHS who developed prolonged facial nerve palsy due to delayed diagnosis.

Case presentation

A 39-year-old man presented with intense left ear pain radiating to the left temporal skull region for one week, associated with a skin lesion on the left pinna. He also reported left-sided facial weakness and an inability to close his left eye. The patient denied headaches, dizziness, tinnitus, hearing impairment, recent trauma, insect bite, or upper respiratory tract infections. Prior to visiting our clinic, the patient sought treatment at another health facility, where he was prescribed a 3-day course of prednisolone. However, he noticed no improvement of his symptoms and decided to seek a second opinion. The patient had a history of varicella zoster during childhood, but no other significant past medical history. He also denied engaging in high- risk behaviours. On examination, the patient exhibited left-sided lower motor neuron nerve palsy, categorized as House-Brackmann grade IV. Examination of the left ear revealed yellow crusting lesions over the concha and desquamation of the skin over the antihelix [Figure 1]. Otoscopic examination identified a few vesicular rashes in the external auditory canal, with bilateral intact tympanic membranes. Routine blood tests showed no abnormalities. Serological test for varicella-zoster virus (VZV) IgG and IgM antibodies was not performed due to unavailability.

Based on the history and clinical findings, a diagnosis of RHS was made. The patient started on oral acyclovir 800 mg five times daily for one week and oral prednisolone 60mg once daily, tapered over two weeks. He was also prescribed analgesics, normal saline eye drops, and advised to use an eye patch over the left eye to prevent corneal irritation. Additionally, he was referred to the physiotherapy department for facial exercises and scheduled a follow-up appointment in two weeks to reassess his symptoms.

One week later, the patient returned to the clinic with worsening otalgia and yellowish, foul-smelling discharge from the left ear in the past three days. Examination revealed minimal dark crusting over the cymbal concha and yellow crusting with slough over the concha cavum, extending to the intertragic notch [Figure 2]. Otoscope examination showed an erythematous external auditory canal with minimal slough, but the tympanic membrane remained intact. The patient was diagnosed with acute otitis externa secondary to herpes oticus and started on ofloxacin ear drops, five drops twice daily.

During the third visit, one week later, the patient reported improvement in otalgia and no new symptoms. By this time, he had completed a 7-day course of acyclovir and was on a tapering dose of prednisolone. Physical examination revealed that the previous lesions had turned black and crusted over the concha area [Figure 3]. Despite the improvement in skin lesions, the facial nerve palsy persisted with no improvement. He was given another follow-up appointment in one month to reassess his symptoms, and physiotherapy was continued. Upon review after one month, the skin lesions over the pinna was healed entirely [Figure 4]. However, the facial nerve palsy remained at grade IV [Figure 5]. The patient was advised to continue follow-up with physiotherapy for facial exercises to improve his facial palsy.

Discussion

RHS is a condition that accounts for approximately 0.3% to 18% of cases of acute non-traumatic facial palsy, making it the second most common cause after Bell's palsy [2]. Once the VZV infects a person, it remains dormant in the spinal and cranial nerve ganglia for life. Reactivation with further replication of the virus can occur during triggering events, leading to the virus spreading into the dermatome associated with the involved ganglion through sensory nerve fibers [3]. All individuals are at risk of getting RHS from early adulthood, regardless of their immune status [4]. Factors that can trigger RHS include stress, infections, malnutrition, cytotoxic drug use, diabetes mellitus, and malignant tumors [4].

RHS is primarily a clinical diagnosis. It is characterized by a vesicular rash involving the auricle, external auditory canal, soft palate, and pharynx. The key clinical features include facial nerve paralysis, otalgia, tinnitus, vertigo, and hearing impairment. In some cases, involvement of additional cranial nerves, such as cranial nerves V, VIII, IX, or X, may also occur [5]. Definitive confirmation of the diagnosis requires serological analysis detecting IgG and IgM antibodies against VZV or polymerase chain reaction (PCR) detection of VZV DNA [4].In this case, the diagnosis was made based on the clinical history and physical examination, as the patient presented with typical features of RHS. The most prominent finding of patients affected by RHS is unilateral hemifacial paralysis. Diagnosing acute facial paralysis demands a high degree of clinical vigilance, as early in its course, it can be challenging to differentiate from Bell's palsy, particularly when facial weakness manifests before the appearance of vesicles [6]. Physicians should perform a thorough facial nerve assessment and grade the severity of facial nerve palsy based on the House-Brackmann grading system. This involves evaluating asymmetry at rest over the face and neck and assessing the major extratemporal branches of the facial nerve. The House-Brackmann grading system helps physicians determine the severity of facial paralysis [1]. Grading of facial nerve palsy, according to House-Brackmann, is further described in Table 1.

Healthcare providers must carefully consider differential diagnoses of facial nerve palsy before initiating treatment for acute facial paralysis to ensure optimal patient outcomes. In this case, the patient was initially treated for Bell's palsy due to symptoms of otalgia and left-side facial nerve palsy without any vesicular rashes , which led to a delay in diagnosis and treatment initiation, eventually worsening the prognosis. It is also essential for healthcare providers to recognize atypical presentations of RHS. In the initial stages of RHS, before the appearance of vesicular rashes and facial palsy, the involvement of multiple cranial nerves can produce diverse early symptoms, increasing the risk of misdiagnosis [4].In the only prospective study on patients with RHS, 14% developed vesicular eruptions after the onset of facial paralysis. The atypical condition known as Zoster Sine Herpete is characterized by peripheral facial paralysis in the absence of ear or oral vesicular rash, with potential involvement of the cervical dermatome [5]. Therefore, a thorough clinical history, physical examination, and recognition of atypical presentation by primary care physicians are essential to avoid misdiagnosis. Another study concluded that the overall possible misdiagnosis of RHS is approximately 41% [7].

Herpes zoster is typically a self-limiting condition, and treatment primarily aims to reduce the risk of long-term complications. High-dose corticosteroids, administered orally or intravenously, should be used in combination with antiviral therapy for optimal management [1]. Oral antiviral treatment is limited to a 7 to 10-day course and should be initiated within 72 hours of rash onset for optimal effectiveness. These medications are well-tolerated at standard doses, such as acyclovir (800 mg five times daily for 7–10 days), famciclovir (500 mg three times daily for 7 days), or valacyclovir (1000 mg three times

daily for 7 days) [8]. The optimal duration of steroid therapy remains uncertain, with recommendations ranging from 4 to 37 days. Treatment should begin with a high dose, typically prednisone at 1 mg/kg/day (up to a maximum of 60 mg) or an equivalent, followed by a gradual tapering schedule [1]. In this case study, the patient was started on oral acyclovir 800mg 5 times daily for one week, oral prednisolone 60 mg once daily, and tapering regimen over two weeks. Symptomatic management is also essential. For pain management, acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), and long-acting opioids can be used. Artificial tears used during the day and ocular lubricant ointment at night can help prevent exposure keratopathy. Healthcare providers must advise patients with lagopthalmos to use an eye patch to avoid corneal abrasion [1]. Treatment for RHS is identical regardless of the timing of diagnosis [9]. However, late diagnosis may cause complications such as postherpetic neuralgia, synkinesis, corneal abrasion, and exposure keratopathy [1].

Conclusion

Healthcare providers must be able to distinguish the typical and non-typical symptoms of RHS and consider differential diagnoses for acute facial nerve palsy. Patients presenting with sudden onset of facial nerve palsy should be thoroughly assessed to establish the correct diagnosis. In this case report, we emphasized the importance of early detection of RHS. Complications arising from late diagnosis have also been highlighted. Permanent facial palsy and other possible sequelae of RHS can significantly impact a patient's social life. Therefore, early diagnosis and treatment are crucial to prevent complications [6].

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Conflict of interest

All authors declare no conflicts of interest.

Ethics: The patient provided consent for the use of images and the publication of his case.

Authors' contributions

AHS contributed to the writing, review, and editing of the manuscript. SR contributed to drafting the manuscript, conducting the literature search, and reviewing and editing the manuscript.

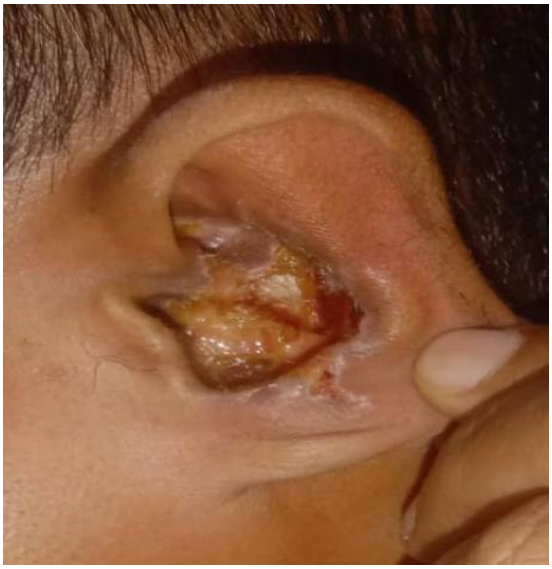

Figure 1. Photograph of the left ear. There was an area of yellow crusting over the concha with desquamation of skin over the antihelix. The pinna was mildly erythematous.

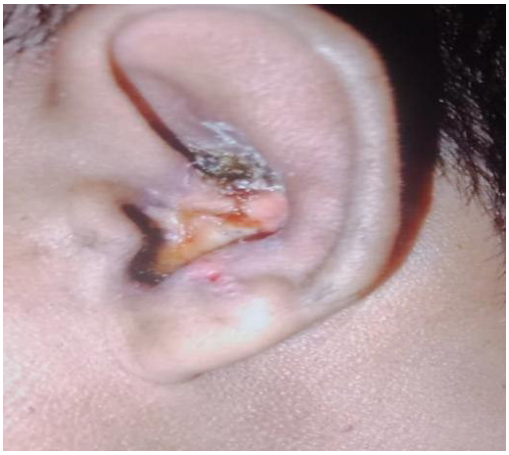

Figure 2. Photograph of the left ear. Minimal dark crusting over the cymba concha. Yellow crusting over the concha cavum extended to the intertragic notch.

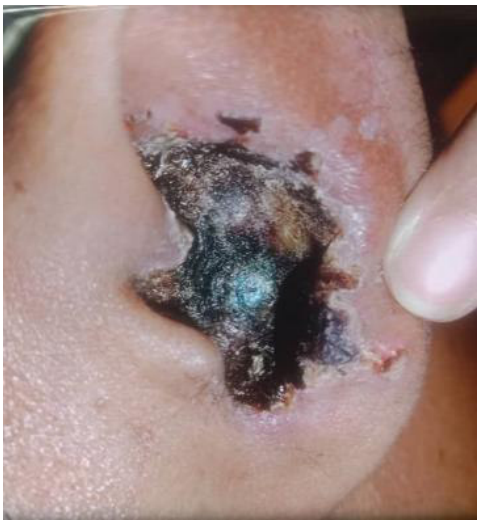

Figure 3. Photograph of the left ear. Noted black crusting over the area of the concha.

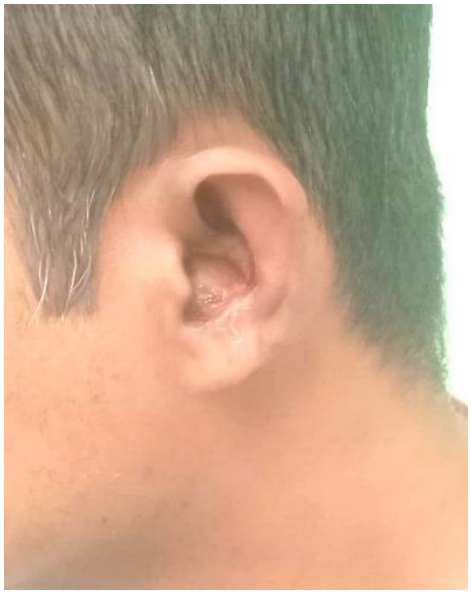

Figure 4. The skin lesion over the left pinna completely healed; no new lesion was seen.

Figure 5. Left facial nerve palsy House-Brackmann grade IV persisted after one month

Table 1. House-Brackmann Classification of Facial Function.[10]

Grade	**Gross**	**Motion**
I. Normal	Normal facial function	Normal facial function
II. Mild dysfunction	On close inspection might notice minimal weakness. Slight synkinesis possible At rest, no facial asymmetry and good tone	Forehead movement sustains from moderate to good Able to close eyes completely Minimal asymmetry of the mouth
III. Moderate dysfunction	Evident of asymmetry but not much difference compare to the other side Synkinesis, contracture, or hemifacial spasm can be seen but not severe At rest, bilateral normal symmetry and tone	Forehead movement light to moderate Able to close eyes completely with effort Slight weakness over the mouth even with maximum effort
IV. Moderately severe dysfunction	Prominent weakness with/without disfiguring asymmetry At rest, bilateral normal symmetry and tone	No forehead movement Incomplete eye closure Mouth appears asymmetrical with maximum effort
V. Severe dysfunction	Slight movement only Evidence of asymmetry at rest	No forehead movement Incomplete eye closure Slight movement of the mouth
VI. Total paralysis	No movement	No movement

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CASE REPORT

Challenges in Antenatal Diagnosis of Conjoined Twins in Primary Care Setting: A Case Report.

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Abstract
Conjoined twins (CT) represent a rare embryologic anomaly with an uncertain aetiology. Although uncommon, this condition is associated with a high perinatal mortality rate. Early detection during the first trimester is therefore crucial to enable timely intervention and referral to a tertiary care centre. First-trimester dating scans in primary care are essential not only for confirming viability and determining gestational age but also for identifying multiple pregnancies. However, anomalies in twin pregnancies-such as conjoined twins-may be overlooked during these early scans due to various challenges. This case report discusses the difficulties in detecting CT and explores factors that may contribute to missed diagnoses.

Keywords: *Conjoined twin, Siamese twin, thoracophagus.*

Introduction

Conjoined twins (CT), also known as 'Siamese twins', are a rare embryologic anomaly of uncertain aetiology. This condition is thought to result from an abnormality during the division of a single zygote, typically occurring between 13- and 15-days post-fertilisation [1]. In such cases, incomplete separation of inner cell mass leads to fusion at various sites during embryonic development.

CTs are classified based on their most prominent point of union for diagnostic and prognostic purposes. The abnormality is described using the suffix -pagus, meaning "fixed", and is divided into ventral and dorsal types, with prevalence rates of 87% and 13%, respectively [1]. Ventral unions may involve the thorax (thoracopagus – 19%), abdomen (omphalopagus – 18%), or pelvis (ischiopagus – 11%). Dorsal unions include the skull (craniopagus – 5%), sacrum (pygopagus – 6%), or spine (rachipagus) [1]. Each type presents unique complications and prognostic challenges, largely dependent on the vital organs involved and the feasibility of future surgical separation.

Early detection of CT is crucial to prevent unnecessary surgical delivery and reduce psychological distress for the expectant parents. Historically, CT was commonly diagnosed in the second trimester. However, with advances in ultrasound imaging, first-trimester detection is now possible. Despite this, diagnosing CT in primary care settings—particularly in Malaysia—remains challenging due to multiple contributing factors. This report presents a case in which an early diagnosis of conjoined twins was missed during a routine first-trimester ultrasound.

Case report

A 25-year-old primigravida at 19 weeks' gestation presented for a post-COVID-19 follow-up. Her symptoms had resolved, and she reported no new complaints. A routine antenatal ultrasound revealed two foetal heads at the same level, within the same plane, and facing each other, along with fused chests and abdomens. Only a single foetal heart was visualized (Figure 1).

An earlier dating scan performed at 9 weeks' gestation had shown a viable singleton pregnancy (Figure 2). During her first antenatal appointment, she was well with a normal BMI. History revealed no family history of twins. This was her first pregnancy, a spontaneous conception with no history of assisted reproductive techniques. Her next routine ultrasound appointment in primary care was scheduled for the 20 weeks' gestation. However, she was reviewed earlier, at 19 weeks, in conjunction with her post-infection assessment. She was subsequently referred to a maternal–foetal medicine (MFM) specialist for further evaluation of suspected thoracopagus conjoined twins.

The diagnosis of conjoined twins was confirmed by the MFM specialist. The parents were counselled regarding the poor prognosis of thoracopagus twins, primarily due to the shared vital organs. As this was her first pregnancy and she was already in the second trimester, the mother initially chose to continue with the pregnancy, influenced by cultural and personal beliefs. However, following further discussion and comprehensive counselling, the parents ultimately agreed to terminate the pregnancy.

Labour was induced with prostaglandin at 21 weeks' gestation. Six days post-induction, a stillborn female thoracopagus conjoined twin pair, weighing 750 grams, was delivered without complications (Figure 3). Lactation suppression and psychological support was provided throughout the postnatal period.

Discussion

Conjoined twins (CT) are an exceedingly rare congenital anomaly, with early detection primarily reliant on ultrasonography (USG). While most cases are identified by the second trimester, first-trimester diagnosis remains challenging, particularly in primary care settings due to various limitations.

There have been reports of CT diagnosed as early as seven weeks of gestation. However, the global prevalence of undiagnosed or missed prenatal CT remains undocumented. Despite technological advances, some cases are not identified until as late as 29 weeks' gestation [3]. In the presented case, CT was diagnosed at 19 weeks, which is considered relatively late, and the pregnancy was terminated—an outcome that may contribute to significant psychological distress for the parents.

CT are classified according to the most prominent point of fusion, which directly influences prognosis and mortality. Thoracopagus twins are the most common type, accounting for up to 19% of cases [1]. This subtype typically involves cardiac and hepatic fusion, leading to a poor prognosis due to limited feasibility of surgical separation. Most thoracopagus twins die *in utero* or shortly after birth. Thus, early diagnosis is vital to facilitate timely counselling and, where appropriate, termination of pregnancy—mitigating emotional and psychological impacts on parents and optimising obstetric outcomes.

Ultrasound plays a central role in diagnosing CT. First-trimester ultrasonography is essential for managing multiple pregnancies, determining chorionicity, and assessing obstetric risks. Studies have shown that the identification of chorionicity based on placental number between 11 -14 weeks' gestation has a sensitivity of 100% and a specificity of 99.8% [4]. In addition, early ultrasound helps establish gestational age and assists in accurate labelling of twins [4].

However, delayed CT diagnosis remains a significant challenge in primary care. Contributing factors to missed early detection include small foetal size, suboptimal foetal positioning, operator inexperience, and limited ultrasound resolution. In this case, the operator's inexperience likely contributed to the missed diagnosis.

Identifying the sonographic features of CT can be difficult for inexperienced primary care clinicians. Features that support a diagnosis include the absence of a dividing membrane between foetuses, visible fusion of body parts, persistent alignment of foetal body planes, fixed positions of the foetuses, and bifid or inseparable appearances despite changes in position [5]. However, in the early first trimester, these features may be subtle or obscured, particularly if foetal positioning is unfavourable, thereby limiting visibility.

Given the stage of foetal development, the risk of missing a CT diagnosis is substantial, especially in resource-limited settings. Research suggests that ultrasounds conducted before 10 weeks of gestation may not reliably detect structural anomalies such as CT, as detection depends on foetal position and image clarity [2].

In this case, the resolution of the ultrasound machine also played a critical role. The initial dating scan at 8 weeks' gestation revealed a single crown–rump length (CRL) with shared cardiac activity, mimicking a singleton pregnancy. Features suggestive of conjoined anatomy, such as fixed foetal positions and shared structures, were overlooked.

To reduce missed or delayed CT diagnoses in primary care, greater emphasis must be placed on foetal anatomic assessment, in addition to viability and gestational age confirmation. If uncertainty exists regarding foetal structure during early scans, follow-up ultrasounds should be scheduled to reassess suspicious findings. Failure to perform follow-up assessments may delay diagnosis until 18-20 weeks' gestation.

In addition, continuous training of primary care practitioners is essential to enhance recognition of atypical features suggestive of CT. Equally crucial is the availability of high-resolution ultrasound equipment with appropriate

magnification in healthcare clinics to improve image quality and diagnostic precision.

In conclusion, this case underscores several key considerations: the importance of adequate training in interpreting first-trimester ultrasounds, the impact of technological advancements on diagnostic capabilities, and the need for clinicians to maintain a high index of suspicion during routine scans. By addressing these elements, the case provides valuable insights into current practice and highlights the importance of vigilance in prenatal screening, especially in primary care settings. Establishing clear referral pathways for suspected foetal anomalies can optimise outcomes by ensuring timely specialist intervention.

Conflict of interest
None

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Authors' contribution:
NFS led the manuscript preparation, data collection, and revisions. NAJ and RH contributed to the manuscript review and final approval.

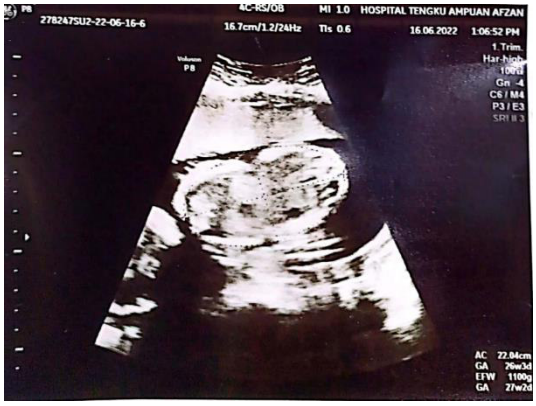

Figure 1. Ultrasound at 19 weeks of gestation

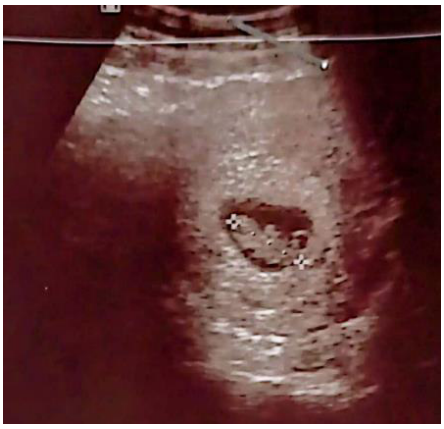

Figure 2. Ultrasound at 9 weeks of gestation

Figure 3. Thoracopagus conjoined twins

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CASE REPORT

Amlodipine-induced Generalised Exfoliative Dermatitis: Not to be Missed!

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Abstract

Amlodipine a calcium channel blocker (CCB), is commonly used in treating hypertension, coronary artery disease, and chronic kidney disease. It is considered a first-line treatment for high blood pressure. Amlodipine acts by selectively inhibiting voltage-gated L-type calcium ion channels, which consequently decreases systemic vascular resistance, total vascular resistance, and muscle contractility. We report a case of amlodipine-induced exfoliative dermatitis, highlighting the importance of recognizing this rare but serious cutaneous reaction to amlodipine, a commonly used drug in primary care. Prompt discontinuation of the offending drug and appropriate management are crucial for improving patient outcomes. Clinicians should maintain a high index of suspicion for drug-induced exfoliative dermatitis in patients presenting with generalized erythema and scaling after initiating new medications.

Keywords: *Amlodipine, calcium channel blocker, exfoliative dermatitis.*

Introduction

Exfoliative dermatitis is an uncommon but serious skin disorder that clinicians must be able to recognize [1]. This skin condition is characterized by widespread erythema (redness of the skin) and exfoliation (shedding of the skin).[1] Drug-induced cases are frequently associated with anticonvulsants, and rare occurrences involving specific antibiotics, antituberculosis drugs, antipsychotics, and calcium channel blockers [2]. Despite the fact that amlodipine is generally well tolerated by most people, certain people may experience adverse effects, as is possible with any medicine.

While cutaneous reactions to calcium channel blockers are uncommon, occurring in approximately 8 per million prescriptions, severe reactions like exfoliative dermatitis are even rarer. [3] Specifically, the incidence of exfoliative dermatitis in patients taking anticonvulsants such as phenytoin and carbamazepine is reported to be 3-5% [3-4]. Other drugs associated with exfoliative dermatitis include salazosulfapyridine, azathioprine, and phenobarbital. Tricyclic antidepressants may also induce this condition, similar to phenothiazines [3-4].

Amlodipine is a dihydropyridine analog of nifedipine and has been used worldwide to treat hypertensive patients for over two decades. Amlodipine's long half-life of 30 to 50 hours allows for once-daily dosing, making it a convenient option for managing hypertension and angina [5]. As a calcium antagonist, it lowers blood pressure by inhibiting Ca2+ influx into cells, leading to peripheral arterial vasodilation. The most common side effects are dose-dependent and related to its mechanism of action as a calcium antogonist, such as vasodilation presenting as leg oedema, flushing, telangiectasia or headache. Potential side effects of amlodipine also include skin-related issues, such as rash or dermatitis [5].

Case presentation

A 71-year-old woman was recently diagnosed with a hypertensive crisis complicated with congestive cardiac failure. During her hospital stay, she was treated with intravenous antihypertensive and diuretic. She was then and stabilized with oral amlodipine, spironolactone, aspirin, atorvastatin, and frusemide and was discharged well. However, one week later, she developed a gradual onset of generalized, diffused, pruritic, erythematous, and scaly skin lesions that initially appeared on both limbs and later spread to the trunk. The was no history of atopy and drug allergies. On examination, she appeared well and was afebrile, with normal vital signs and no signs of angioedema. Examination of her limbs and trunk showed diffuse, dry, scaly skin with generalised erythema. Other systemic examinations were unremarkable. She visited many clinicians for her skin lesions post discharge, and was treated as an eczema flare, yet the lesions were getting worse. She was subsequently referred to the dermatology department and was diagnosed with skin eruption secondary to amlodipine. As a result, amlodipine was abruptly discontinued, and Bisoprolol was initiated. At her follow-up visit to the dermatology clinic one month later, her skin condition had gradually improved.

Discussion

Generalized Exfoliative Dermatitis (GED) is a rare dermatosis characterized by the development of erythema, scaling, and shedding of the skin. This rare condition may occur in a variety of underlying diseases and can be associated with life-threatening events. The clinical presentation of GED is variable, fluctuates throughout the disease, and progresses insidiously [6].

The progression of disease can be described in the following phases:

1. Chronic phase: Mild scaling of the scalp, anogenital region, inner thigh, axillary region, retroauricular area, and other skin folds.
2. Pruritic phase: Itching and scratching involving the upper and lower extremities, back, neck, and malar area.
3. Exfoliative dermatitis: Sharply marginated, elevated, well-defined erythematous plaques on the trunk and extremities that may fissure, bleed, and drain serous fluid.
4. Resolution phase: Improvement and resolution of lesions after weeks to months of treatment [7].

Drug-induced GED is characterized by keratinocyte apoptosis and loss of epidermal integrity. The underlying mechanisms include drug-specific immune activation, which may trigger a cascade of inflammatory events, keratinocyte apoptosis, dysregulation of pro-inflammatory cytokines and chemokines, and disturbed interaction between keratinocytes and infiltrating cells [6,7]. Calcium channel blockers may induce keratinocyte apoptosis by increasing intracellular calcium levels and activating calcineurin and glycogen synthase kinase 3, which lead to the activation of apoptosis-related factors that destabilize mitochondrial membranes, including altered expression of Bcl-2 family proteins and release of cytochrome C [6,7].

Amlodipine is a calcium channel blocker commonly used in treating hypertension, which can result in skin adverse effects. Calcium is crucial for various cellular functions, including the proliferation and differentiation of keratinocytes, transmission of nerve impulses, release of neurotransmitters and hormones, and contraction of smooth and cardiac muscles [8]. It also plays a role in the synthesis of nitric oxide, the secretion of catecholamines, and the release of hormones like insulin. Calcium is essential in maintaining skin barrier function, as calcium levels increase in the skin after birth. In the cornified envelope, free calcium interacts with transglutaminase and involucrin, cross-linking structural proteins. The permeability barrier of normal skin helps maintain hydration, while impairment leads to skin diseases like ichthyosis [8,9]. Oral amlodipine, which acts on L-type voltage-gated calcium channels, significantly inhibits calcium influx in keratinocytes, inducing apoptotic changes. Amlodipine exposure also attenuates epidermal calcium levels and prevents tight junction formation. This inhibitory effect on calcium influx and epidermal calcium levels by oral amlodipine is expected to lead to an impairment of the skin permeability barrier, resulting in transepidermal water loss and the initiation of secondary changes in keratinocytes [2,3,9].

Amlodipine-induced generalized exfoliative dermatitis can lead to severe morbidity and even mortality if not recognized and managed appropriately. At the first step, amlodipine and other possibly offending drugs must be discontinued immediately. Amlodipine-induced generalized exfoliative dermatitis is unlikely to improve until the use of amlodipine is terminated, and alternative treatments are used for hypertension.

Once discontinuation of amlodipine is done, pharmacological agents should be used to manage generalized exfoliative dermatitis. Antihistamines, such as systemic diphenhydramine are the first-line agents to alleviate pruritus. Patients may also find comfort with topical antiseptics and topical steroids. High-potency topical corticosteroids can be effective, with moderate potency steroid creams as symptoms improve. As the skin symptoms improve, lower-potency topical corticosteroids may be substituted. Additionally, are recommended for all patients experiencing dermatitis, crusting, pruritus, or peeling. Emollients, also known as moisturizers, help

restore the skin barrier function by providing hydration and preventing the loss of transepidermal water [9,11]. This is particularly important in exfoliative dermatitis, where the skin barrier is severely compromised. Emollients should be applied once to several times a day to all affected areas. Ointment-based moisturizers can be used as adjunctive therapy [11].

In some cases, dermatologists may evaluate patients for systemic management of generalized exfoliative dermatitis if indicated. Patients may be given systemic steroids as an alternative to immunosuppressive therapies. However, the appropriate use of systemic steroids in generalized exfoliative dermatitis is not clearly defined, and reverse treatment may cause rebound flare-ups of dermatitis.

Systemic therapy is indicated when symptoms are severe and extensive, involving over 30–90% of the skin surface, particularly if accompanied by systemic symptoms such as fever, chills, malaise, or weight loss. It is also necessary in cases associated with underlying conditions, such as psoriasis or cutaneous T-cell lymphoma, where specific systemic treatments or chemotherapy may be required for malignancy-associated erythroderma. Additionally, systemic therapy is crucial in patients at risk of severe complications like dehydration, electrolyte imbalance, secondary infections, or sepsis, stemming from skin barrier disruption, and requires urgent intervention to stabilize the patient and prevent further deterioration.

In severe cases of exfoliative dermatitis, where topical treatments fail to provide desired effects after two weeks, systemic treatments, such as methotrexate, acitretin, cyclosporine, and newer biologic agents could be considered. Methotrexate is the preferred first-line treatment due to its favourable long-term benefit/safety profile and potential for rapid disease control. In patients with poor liver function or hepatic cytotoxicity, acitretin serves as a good alternative in the management of exfoliative dermatitis. In cases resistant to the above systemic treatments, cyclosporine could be considered a successful treatment in some severe cases. However, caution should be exercised due to its potential side effects and monitoring of renal function [4,9,11].

A follow-up plan should be made for patients diagnosed with generalized exfoliative dermatitis. All patients should be educated to seek immediate medical attention for febrile illness, signs of systemic infection, and new-onset, sudden, and severe skin peeling or erythema. Additionally, patients should be advised to avoid taking amlodipine indefinitely, even years after discontinuation.

Conclusion

It is important to recognize that some patients may develop cutaneous adverse reactions, including severe reactions, from CCBs. Amlodipine, which is commonly used to treat hypertensive patients should be considered a potential culprit for exfoliative dermatitis. Risk factors for amlodipine-induced GED such as gender, underlying medical conditions, and concurrent medications remain undetermined [5,8]. However, dermatological complaints were previously documented in patients concomitantly taking amlodipine and statins [12]. Besides these cases, amlodipine has been noted as a probable cross-reactive contact dermatitis agent. Prompt recognition and discontinuation of the offending drug is crucial in managing drug-induced exfoliative dermatitis. However, diagnosis can be challenging, as it may mimic other dermatological conditions and requires a high index of suspicion, especially when multiple medications are involved. Further research and analysis of demographic variables are needed to better understand the risk factors for amlodipine-induced GED.

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Conflict of interest
There is nothing to declare.

Patients' consent for the use of images and content for publication
The patient gave verbal permission for the images and case to be used for publication.

Authors' contribution
MCM, SCA and SA contributed to the case write up, and literature search. NAA drafted the manuscript. All authors participated in review, editing, and approving on the final version of the manuscript.

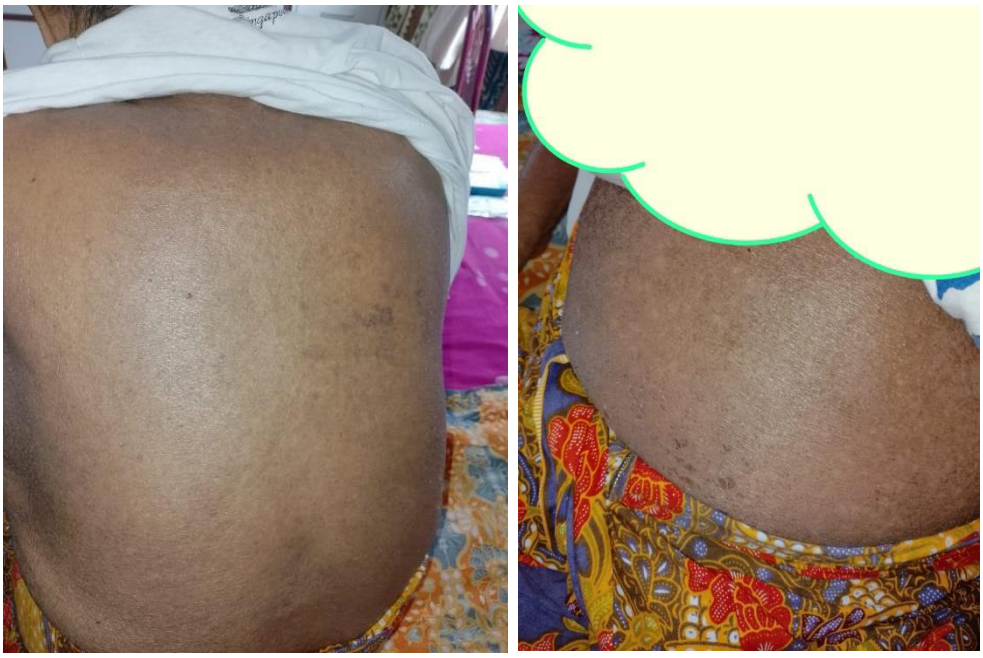

Figure 1. The image shows skin in the area of trunk appears significantly discolored, with darkened patches with texture of the skin is rough and uneven, with prominent scaling and dryness

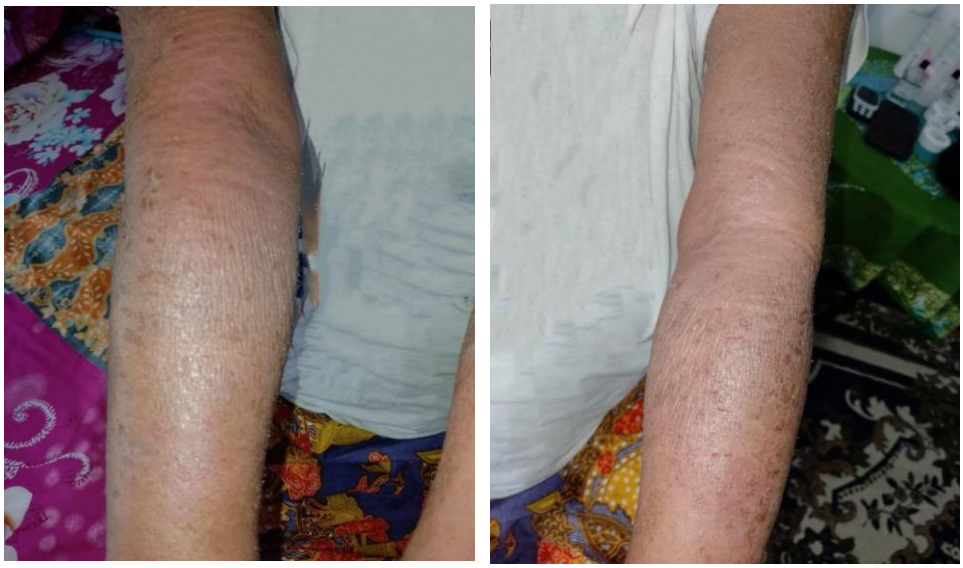

Figure 2. The image shows bilateral hands is dry, with noticeable scaling and a rough texture. There is significant darkening of the skin, indicating hyperpigmentation in the areas affected by the dermatitis.

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CASE REPORT

Anti-synthetase Syndrome with Dermatomyositis Responding to Combination of Mycophenolate mofetil and Cyclosporin: A Case Report.

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Abstract

Anti-synthetase syndrome (ASS) is a rare inflammatory muscle disorder associated with dermatomyositis and polymyositis, characterized by autoantibodies targeting aminoacyl-tRNA synthetases. Clinical manifestations vary but typically include mechanic's hands, interstitial lung disease (ILD), and Raynaud's phenomenon. We report the case of a 42-year-old woman with a positive anti-Jo1 autoantibody, who initially presented with respiratory symptoms that progressed to myositis, along with severe, painful mechanic's hands and feet. Her condition improved with a combination of mycophenolate mofetil (MMF), corticosteroids, and cyclosporine.

Keywords: *Anti-synthetase syndrome, dermatomyositis, polymyositis, anti-aminoacyl-tRNA synthetase, anti-Jo1 antibody, mechanic's hands, interstitial lung disease, corticosteroid, mycophenolate mofetil, cyclosporin.*

Introduction

Anti-synthetase syndrome (ASS) is a rare autoimmune inflammatory myopathy classified under idiopathic inflammatory myopathies (IIM). The exact aetiology and pathogenesis remain unclear. ASS is defined by the presence of autoantibodies against aminoacyl-tRNA synthetases (anti-ARS), occurring in approximately 30% of patients with inflammatory myopathies [1]. Common clinical features include mechanic's hands, ILD, myositis, arthritis, and Raynaud's phenomenon [2].

Anti-Jo1 (histidyl-tRNA synthetase) is the most common anti-ARS antibody, though others, such as anti-PL-12, anti-PL-7, and anti-EJ, have also been reported [3]. ILD affects 70-90% of patients with anti-Jo1 [4, 5] and is more prevalent in ASS than in dermatomyositis and polymyositis [6].

Here, we report the case of a 42-year-old woman with severe mechanic's hands, ILD, arthritis, and myositis, positive for anti-Jo1 antibodies. Interestingly, ASS was not suspected during her initial presentation with respiratory symptoms. Despite severe ILD, her respiratory function was preserved, and she responded well to a combination of MMF, corticosteroids, and cyclosporine.

Case Report

A 42-year-old Indian woman, with no significant medical history, presented with progressive dyspnoea, chest pain, low-grade fever, and a productive cough with yellowish sputum. She was initially diagnosed with pneumonia based on chest radiographs showing bilateral mid-to-lower zone infiltrates. Blood investigations revealed an elevated erythrocyte sedimentation rate (ESR) of 64 mm/hour and C-reactive protein (CRP) of 33 mg/L. Additionally, creatinine kinase (CK) was mildly elevated at 420 U/L, with lactate dehydrogenase (LDH) at 484 U/L and aspartate transaminase (AST) at 92 U/L.

Despite completing antibiotic therapy, her symptoms persisted. A follow-up chest radiograph revealed persistent bilateral consolidations. Over time, she developed painful hyperkeratotic lesions with fissures on both hands and feet. Mild proximal muscle weakness and arthritis also emerged. However, Raynaud's phenomenon, oral ulcers, vasculitis, or lupus-related rashes were absent.

On examination, she exhibited severe mechanic's hands, characterized by dry, scaly, hyperkeratotic lesions on the fingers and toes (Figure 1). Additionally, symmetrical erythematous plaques covered the soles and palms, and stage 2 finger clubbing was noted. Mild proximal myopathy with quadriceps tenderness was present. There were no Gottron's papules, heliotrope rash, or telangiectasia. Fine and coarse crackles were audible in the lower lung fields, although her respiratory function remained stable.

Laboratory tests confirmed positive anti-nuclear antibody (ANA) at a titer of 1:320 (speckled pattern) and strongly positive anti-Jo1 and anti-Ro52 antibodies. High-resolution computed tomography (HRCT) of the thorax revealed bilateral patchy consolidations in the lower lobes (Figure 2A, 2B).

Based on her clinical and serological findings, she was diagnosed with ASS with myositis and ILD. Treatment was initiated with oral methylprednisolone (1 mg/kg/day), MMF (500 mg twice daily), and hydroxychloroquine (200 mg daily), along with topical treatments for her skin lesions.

After one month, her skin condition worsened, and her muscle weakness progressed. CK levels rose to 1437 U/L, CRP to 59 mg/L, LDH to 656 U/L, and AST to 52 U/L. Repeat HRCT revealed the resolution of consolidations but showed ground-glass opacities, subpleural fibrosis, and mild upper-lobe involvement (Figure 2C, 2D).

A skin biopsy demonstrated mild epidermal atrophy, focal hyperkeratosis, and pigment incontinence, along with lymphoplasmacytic infiltration surrounding hair follicles. Mucin accumulation was prominent in the dermis. No vasculitis was detected, and deeper dermis and appendages appeared normal. Immunofluorescence showed granular deposits of IgG and C3 at the dermo-epidermal junction and blood vessels, consistent with dermatomyositis (Figure 3).

Intravenous methylprednisolone (500 mg daily for three days) was administered, and the MMF dose was increased to 1 g twice daily. Cyclosporine (150 mg/day) was added to her regimen. After one month, her skin lesions and muscle strength improved, with CK levels reducing to 405 U/L and normalization of CRP and AST. She remained stable on tapering doses of methylprednisolone, MMF, hydroxychloroquine, cyclosporine, and topical treatments.

Discussion

ASS is a rare autoimmune disorder with diverse clinical manifestations, frequently involving ILD and inflammatory myopathy. This patient fulfilled the diagnostic criteria for ASS, presenting with anti-Jo1 antibodies, myositis, and ILD, as outlined by the Bohan and Peter criteria [6-8]. Anti-Jo1 antibodies are found in approximately 80% of ASS cases and serve as a key diagnostic marker [9].

ILD is a major concern in ASS and significantly influences prognosis. Around 70% of patients with ASS develop ILD, with anti-PL7 and anti-PL12 antibodies associated with more aggressive forms [10, 11]. HRCT findings often reveal patterns consistent with non-specific interstitial pneumonia (NSIP) [12].

In this patient, the presence of both anti-Jo1 and anti-Ro52 antibodies contributed to severe ILD. Anti-Ro52 has been linked to increased ILD severity and recurrence [13-15]. Treatment typically involves corticosteroids, with MMF, azathioprine, or calcineurin inhibitors recommended for ILD management [16].

This patient responded well to corticosteroids, MMF, and cyclosporine, achieving clinical stability despite severe ILD. MMF is known to improve pulmonary function in connective tissue disease-associated ILD, supporting its use in this case [17-19].

Conclusion

ASS is a rare autoimmune disease with significant heterogeneity in presentation, often involving ILD and myositis. Early diagnosis and appropriate treatment are essential to prevent irreversible damage. HRCT is crucial for differentiating ASS-ILD from other ILDs. This case emphasizes the importance of a multidisciplinary approach, involving rheumatologists, dermatologists, and pulmonologists, for optimal management. The patient showed significant improvement with corticosteroids, MMF, and cyclosporine, highlighting the efficacy of this combination.

Conflict of interest and financial disclosures: None.
Informed Consent: Written informed consent was obtained from the patient for the publication of this report and the accompanying images.
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Authors contribution: WS: Case management, data collection, and manuscript writing; HFBB: case management and review of the manuscript; LBR: histopathology interpretation and review of manuscript.

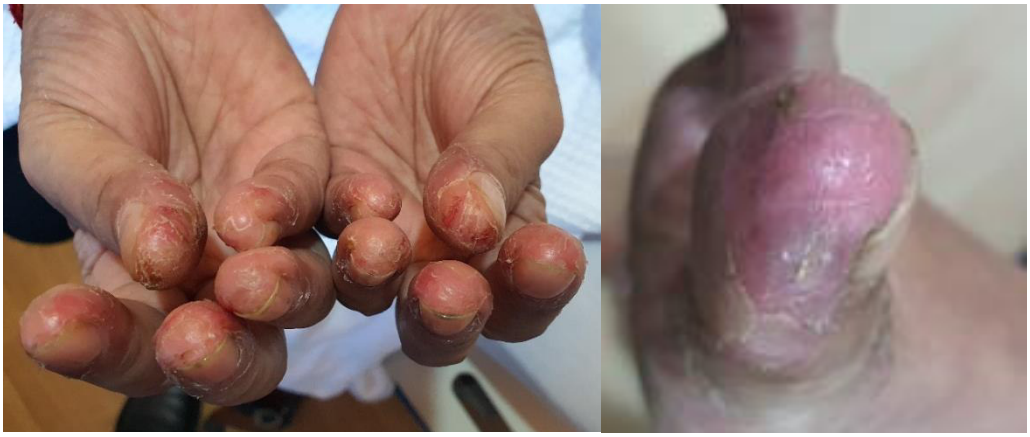

Figure 1. Mechanic's hands: Hyperkeratotic skin with fissures mainly at tips of the fingers and toes.

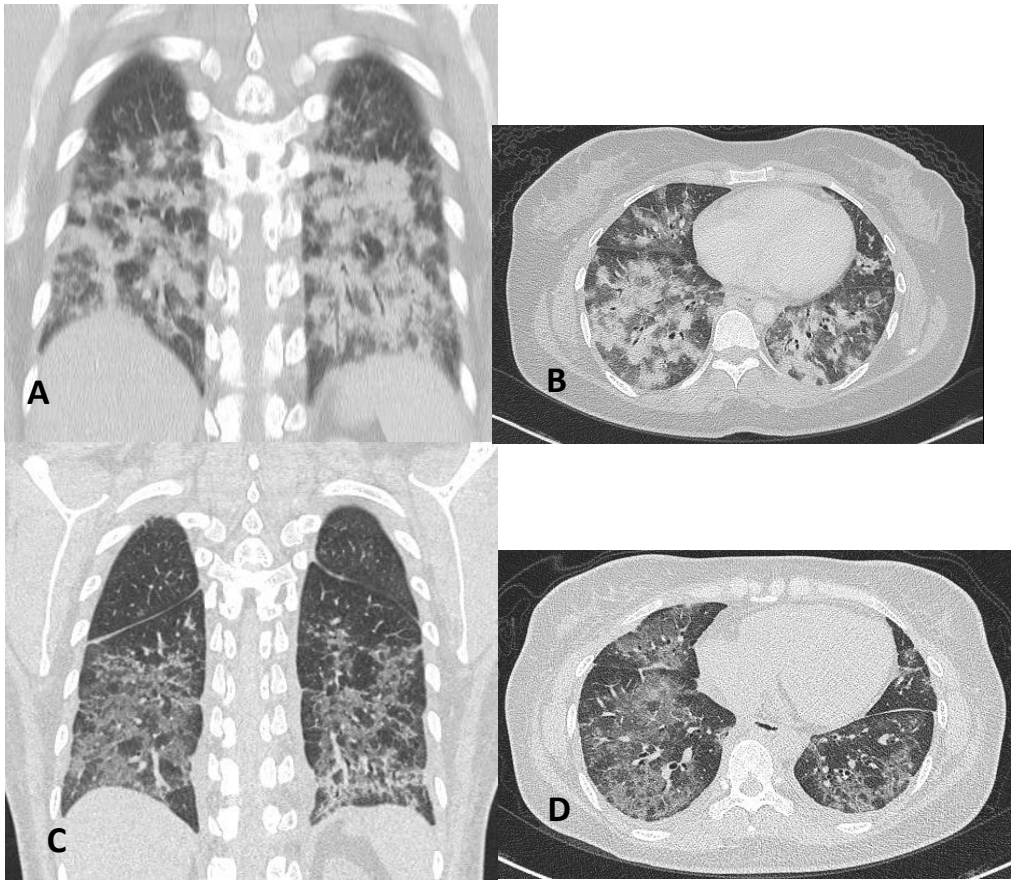

Figure 2. Coronal and transverse section HRCT thorax: A, B: Scattered patches of consolidations in the lower lobes bilaterally. C, D: after 5 months: HRCT thorax showing ground-glass opacities in both lungs are predominantly in both lower lobes with subpleural basal fibrosis.

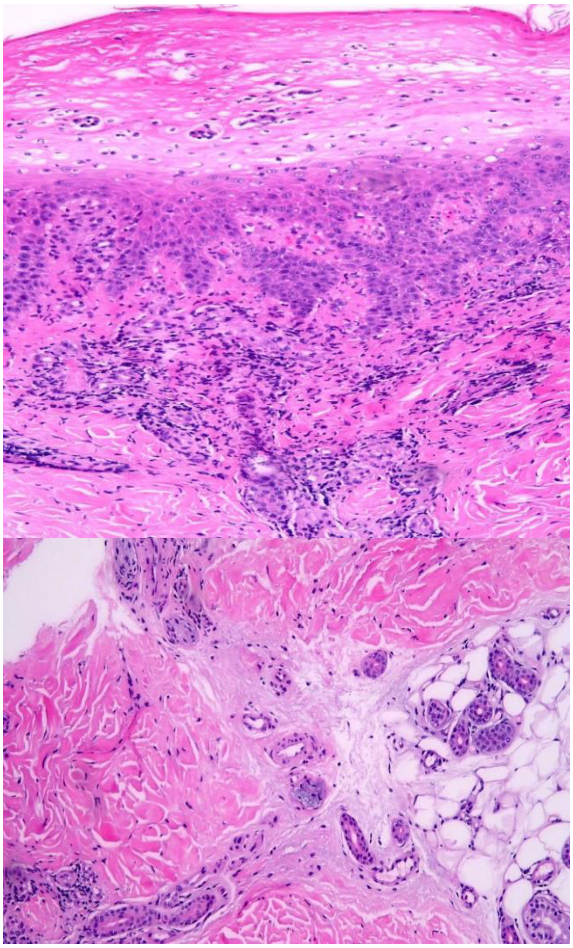

Figure 3. Histopathologic examination from skin biopsy showed lichenoid dermatitis with dermal mucin deposit and immunofluorescence (IF) consistent with dermatomyositis.

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CASE REPORT

Unveiling The Unseen: Apathetic Hyperthyroidism in Primary Care – A Case Report.

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Abstract
Thyrotoxicosis is significantly more challenging to diagnose in elderly patients compared to younger individuals. The thyroid disorder may be masked and overlooked, yet its confounding effects may be devastating. The atypical presentation of the elderly thyrotoxic makes the patient's recognition difficult, and if left untreated, the morbidity may be considerable, but once correctly diagnosed, the condition is readily treatable. We report the case of a 67-year-old man with an unknown medical illness who presented with excessive weight loss for the past 4 months. On examination, he was not tachycardic, and his pulse was in regular rhythm and of normal volume. There was no palpable thyroid nodule. His biochemical investigation revealed hyperthyroidism.

Keywords: *Apathetic Hyperthyroidism, Thyroid Disorder in the Elderly.*

Introduction

In elderly populations, the prevalence of overt hyperthyroidism is 2%, and 10 - 15% of patients are over 60 years of age [1]. Only about 25% of hyperthyroid patients aged 65 years or older present with typical symptoms and signs [2]. Hyperthyroidism in the elderly is not uncommon and often presents in an atypical manner. Signs and symptoms are usually non-specific and may be easily attributed to ageing or diseases in other organ systems, leading to delayed diagnosis and complications [2]. This case report highlights the non-specificity of symptoms of hyperthyroidism in elderly patients, and any delay in recognizing this can cause significant morbidity and mortality.

Case report

A 67-year-old Malay gentleman, an active chronic smoker with no known medical illnesses, presented to the clinic with a complaint of excessive weight loss for the past 4 months. The patient was accompanied by his wife; this was the first time he had sought medical attention since feeling unwell early this year. He had lost almost 20 kg, from 82 to 62 kg, with loss of appetite, accompanied by symptoms of fatigue, lethargy and reduced effort tolerance during routinehousehold chores. Then, 3 weeks ago, his wife noted that he had developed difficulty in sleeping at night. Otherwise, he denied low mood, sadness, anxiety, heat intolerance, palpitations, tremors, or neck swelling.

There was no history of prolonged fever, chronic cough, shortness of breath at rest, night sweats, leg swelling, orthopnea, paroxysmal nocturnal dyspnea, altered bowel habits, or urinary symptoms. He had no family history of malignancy, and was not on any medications.
On examination, he appeared cachexic, but was not pale, jaundiced, or tachypneic. There were no signs of anxiety, exophthalmos, thyroid swelling, or fine tremors. No cervical or supraclavicular lymphadenopathy were detected. Blood pressure was normotensive, pulse rate was not tachycardic, and SpO2 was 99% on room air. Abdominal examination revealed hepatomegaly about 3 fingerbreadths in the right hypochondriac region, with a smooth surface and regular margin. Otherwise, no stigmata of chronic liver disease were noted. Other systemic examinations were unremarkable.

Baseline laboratory investigations were done (Table1), including full blood count, renal and liver profiles, urine analysis, fasting blood sugar, electrocardiogram (ECG) and sputum acid-fast bacilli (AFB) direct smear and viral screening, and all the results were found to be normal.
Chest X-ray was normal, with no evidence of malignancy or infection. Abdominal ultrasound confirmed mild hepatomegaly without other abnormalities (eg, renal stones, renal disease, bladder/prostate masses).
An urgent surgical referral was made for upper and lower gastrointestinal scope to look for any malignancies. However, while waiting for the scope appointment date, the patient developed acute onset of cough, shortness of breath, and fever for two days, prompting hospital admission. On arrival, the patient appeared restless, with extreme lethargy and tachypneic. The patient experienced an episode of desaturation on room air, requiring supplemental oxygen, and was tachycardic (159 beats per minute) and febrile (39ºC). The patient was treated for community-acquired pneumonia with intravenous antibiotics. Further history obtained from his wife revealed that the patient had occasional on-and-off episodes of tremors accompanied by palpitations three years prior. However, these episodes were very infrequent and did not affect his daily activities.

Subsequently, an urgent thyroid function test was sent from the ward, revealing significant thyrotoxicosis with serum-free T4 of 55.63 pmol/L and suppressed serum TSH of < 0.005mIU/L. The calculated Burch-Wartofsky point score (BWPS) was 75, highly suggestive of a thyroid storm. The patient was immediately transferred to the intensive care unit (ICU) and

started on intravenous hydrocortisone, anti-thyroid drugs with Lugol's iodine. However, in the ICU, the patient developed persistent hypotension despite maximal triple inotropic support and eventually progressed to asystole, leading to death. The cause of death was determined to be thyroid storm precipitated by community-acquired pneumonia. Laboratory investigations during admission to the hospital are shown in Table 2.

Discussion

Hyperthyroidism in the elderly is a common yet serious clinical disorder. Peak incidence of hyperthyroidism is in the second and third decades of life, with 10%-15% of hyperthyroid patients are over 60 years of age [3]. Recognition and diagnosis of thyroid diseases among the elderly are challenging due to subtle and non-specific symptoms, and therefore, clinicians need to have a high index of suspicion and a low threshold to investigate for thyroid abnormalities [4].

The clinical features of hyperthyroidism are due to overstimulation of the sympathetic system and the direct effects of thyroxine on end organs [4]. Younger patients tend to exhibit symptoms of sympathetic over-activation, such as anxiety, hyperactivity, and tremors. In older patients, they may be apathetic, rather than hyperactive [4].

Apathetic thyrotoxicosis is a distinct entity first described by Lahey (1931) [5]. The salient features of apathy and depression are associated with profound weight loss, proximal and distal muscle weakness and wasting, ptosis, dry skin, mild tachycardia, and often congestive cardiac failure. Noteworthy is the absence of hyperkinetic motor activity, hand tremors, and ocular signs typical of Graves' disease. This absence of the usual signs and symptoms of thyrotoxicosis may cause the diagnosis to be missed [6].

Older patients have more cardiovascular symptoms, including dyspnoea, increased cardiac output, and atrial fibrillation with unexplained weight loss [4]. Weight loss in thyrotoxicosis results from increased metabolic rate, gut motility, and malabsorption [4]. Our patient, presented with reduced effort tolerance, weight loss, loss of appetite, and fatigue - atypical for hyperthyroidism initially prompting investigation for malignancy or tuberculosis, given his heavy smoking history (≥1 pack/day). Thyroid function tests were overlooked during early assessments.

Additionally, lethargy and reduced effort tolerance in this patient were mistakenly attributed to aging rather than thyroid dysfunction. Insomnia and weight loss raised suspicion for depression, even though the patient denied having any form of persistent low or sad mood. A study by G. R. Sridhar et al (2011) analysed sleep patterns in large sample of thyrotoxicosis patients at an endocrine centre in southern India. They found out that individuals with hyperthyroidism/thyrotoxicosis primarily had difficulty in falling asleep, which was associated with hyperkinetic features [7].

Tachycardia (≥100 beats per minute) is absent in 40% of older hyperthyroid patients, primarily due to coexistent conduction system disease [4]. In this case, the patient had a normal pulse rate of 92 beats per minute, normal blood pressure, absence of thyroid eye signs, and no thyroid swelling. Graves' ophthalmopathy, caused by sympathetic overactivity, possibly mediated by increased alpha-adrenergic receptors, is less common in the elderly [4]. Older patients with Graves' hyperthyroidism are also less likely to have goitre. With aging, the thyroid gland undergoes moderate atrophy and develops non-specific histopathologic changes, such as fibrosis, increased colloid nodules and lymphocytic infiltration. These age-related histological changes make physical thyroid examinations less helpful in diagnosing thyroid disorders. In fact,

the thyroid gland may not be palpable in most elderly patients with thyroid disorders [4].

Despite what was documented in our case, other reported cases of elderly apathetic hyperthyroidism present with cardiac manifestations, such as new onset pulmonary hypertension as well as tricuspid regurgitation [8,9]. Additionally, some reported cases describe elderly patients with apathetic hyperthyroidism who do not exhibit any unintentional weight loss, despite having other features like generalized fatigue and muscle cramps, without typical symptoms such as heat intolerance, palpitations, or diaphoresis [10].

Unfortunately, due to its nonspecific features, hyperthyroidism in this patient was diagnosed at a later stage, after he presented with pneumonia symptoms, which precipitated a thyroid storm. Life-threatening thyrotoxicosis or thyroid storm is a rare disorder characterized by multisystem involvement with mortality rates in the range of 8%–25% in modern case series [11]. A high index of suspicion for thyroid storm should be maintained in patients with thyrotoxicosis associated with any evidence of systemic decompensation. Diagnostic criteria for thyroid storm in severe thyrotoxicosis was first proposed in 1993 and later formalized as the BWPS for thyroid storm. These criteria (Table 3) include hyperpyrexia, tachycardia, arrhythmias, congestive heart failure, agitation, delirium, psychosis, stupor, and coma, as well as nausea, vomiting, diarrhoea, hepatic failure, and the presence of an identified precipitant [12]. Points in the BWPS system are based on the severity of individual manifestations, with a score of > 45 consistent with a thyroid storm, 25–44 suggests impending thyroid storm, and <25 makes thyroid storm unlikely [11]. In this case, the patient scored 75 points due to a precipitating event, restlessness with extreme lethargy, fever (39 degrees Celsius), and tachycardia (159 beats/min), and sinus tachycardia on electrocardiogram (ECG) , absent of symptoms and signs of congestive heart failure as well as no features of gastrointestinal-hepatic dysfunction. Precipitants of thyroid storm in a patient with previously compensated thyrotoxicosis include abrupt cessation of anti-thyroid drugs, thyroidectomy, or nonthyroidal surgery in a patient with unrecognized or inadequately treated thyrotoxicosis, and several acute illnesses unrelated to thyroid disease [11]. Here, community-acquired pneumonia, manifested by days of coughing, was likely to trigger the thyroid storm in this elderly patient .

This case highlights the challenges or dilemmas in diagnosing hyperthyroidism in the elderly primary care patients, who often present with nonspecific symptoms. Given the atypical presentations, a high index of suspicion is important for early diagnosis and management of thyroid disorders to avoid major complications that may result from this as an otherwise easily treatable condition [4]. We recommend that primary healthcare professionals, whenever they encounter elderly patients in their daily practice, always look and ask for symptoms of fatigue or lethargy. If these symptoms are present, proceed with thyroid T3/T4 and TSH levels to screen for possible hyperthyroidism in the elderly population.

Conclusion

This case underscores the significance of sound clinical judgment and heightened suspicion of hyperthyroidism in elderly patients when confronted with atypical symptoms and signs. In the context of an elderly patient, the consideration of apathetic hyperthyroidism becomes crucial when presented with generalized fatigue, lethargy, or reduced effort tolerance. Due to its nonspecific presentation, this condition is being overlooked in primary care settings.

What is new in this case report compared to the previous literature?

- This case highlights the importance of a high index of suspicion of apathetic hyperthyroidism in elderly patients who are presented with unexplained weight loss, reduced effort tolerance, and difficulty falling asleep without thyrotoxicosis features.
- Delayed recognition of apathetic hyperthyroidism will lead to unnecessary management and may cause significant morbidity and mortality. Thus, it should not be missed in clinical settings as it is an easily diagnosed and treatable condition.

What is the implication to patients?

- A delay in establishing the diagnosis of apathetic hyperthyroidism can lead to severe complications for patients due to the progression of the disease and can lead to death.

Acknowledgment

We are profoundly grateful to the patient's wife for granting consent and providing essential insights for this case study. We respectfully acknowledge the deceased patient's contribution to medical learning.

Conflict of interest

None to declare.

Patients' consent for the use of images and content for publication

The patient had provided verbal consent to the case for publication. Following the patient's demise, verbal consent was also obtained from his wife.

Authors' contribution

AZAR: Drafting the manuscript. MCM: Editing and review of manuscript. NHAAH: Editing manuscript.

Table 1. Initial laboratory investigations at the clinic

Parameter	Result	Reference Range
Haemoglobin	10.7	13.0 – 18.0 g/dL
White Blood Cell	7.2	4.0 – 11.0 109/L
Platelets	200	150– 400 109/L
Creatinine	40	71 -115 umol/L
Urea	3.5	2.50 – 6.40 mmol/L
Albumin	32	34 – 50 g/L
Total Protein	67	64 – 85 g/L
Total Bilirubin	13.4	< 22 umol/L
Alanine Transaminase	23	16 – 63 U/L
Aspartate Transaminase	21	< 34 U/L
Fasting Blood Sugar	5.3	3.9 – 6.0 mmol/L
Urine FEME	All negative	
Sputum AFB direct smear	negative	
ECG	Sinus rhythm	
Viral Screening	All negative	

Table 2. Laboratory investigations during hospital admission.

Parameter	Result	Reference Range
FT4	55.63	7.86 – 14.41 pmol/L
TSH	<0.005	0.380 – 5.330 mIU/L
Urea	3.3	2.8 -7.2 mmol/L
Creatinine	47	59 -104 umol/L
Total white cells	14.4	4.08 – 11.37 10^9/L
Platelets	121	142 – 350 10^9/L
Hemoglobin	12.4	11.8 – 16.9 g/L
C-Reactive protein	1.02	< 0.5 mg/dL
Procalcitonin	< 0.1	0.0 – 0.5 ng/mL
Total Bilirubin	18	5 – 21 umol/L
Alkaline phosphatase	178	43 – 115 U/L
Alanine transaminase	24	< 50 U/L
ECG	Sinus tachycardia	

Table 3. Point Scale for the diagnosis of thyroid storm[a]

Criteria	Points	Criteria	Points
Temperature °F (°C)		**Gastrointestinal–hepatic dysfunction**	
99.0–99.9 (37.2 – 37.7)	5	Absent	0
100.0–100.9 (37.8 – 38.2)	10	Moderate (diarrhea, abdominal pain, nausea/vomiting)	10
101.0–101.9 (38.3 – 38.8)	15	Severe (jaundice)	20
102.0–102.9 (38.9 – 39.2)	20		
103.0–103.9 (39.3 – 39.9)	25	**Central nervous system disturbance**	
≥ 104.0 (≥ 40.0)	30	Absent	0
		Mild (agitation)	10
Tachycardia (beats per minute)		Moderate (delirium, psychosis, extreme lethargy)	20
100–109	5	Severe (seizure, coma)	30
110–119	10		
120–129	15	**Precipitating event**	
130–139	20	Yes	10
≥ 140	25	No	0
Atrial Fibrillation		**Congestive Heart Failure**	
Absent	0	Absent	0
Present	10	Mild	5
		Moderate	10
		Severe	20
Total	**> 45**	**Thyroid Storm**	
		Impending Storm	
	<25	**Storm Unlikely**	

[a]Source: Burch and Wartofsky [12].

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CASE REPORT

A Chest Lump in a Toddler – A Report on Approach in Primary Care.

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Abstract
A chest wall lump is an uncommon clinical finding often indicative of underlying pathology, including abscesses, trauma, congenital deformities, or malignancy. Therefore, a systematic approach to evaluation is crucial. One such rare congenital anomaly is a bifid rib, typically asymptomatic but occasionally presenting as a palpable chest wall mass, potentially leading to unnecessary imaging or concern. Additionally, bifid ribs may coexist with syndromic conditions such as Gorlin syndrome, which is linked to an increased risk of skin malignancies. We present a rare case of a 4-year-old girl with a firm, immobile swelling in the right anterior chest wall, raising a diagnostic dilemma regarding the necessity of imaging. Given the clinical characteristics, radiological assessment was pursued, and a plain chest radiograph confirmed the diagnosis of a right bifid rib. This case highlights the importance of careful clinical evaluation and judicious use of imaging to avoid over-investigation while ensuring accurate diagnosis. Furthermore, we propose an evidence-based algorithm for evaluating chest wall lumps in primary care settings to inform clinical decision-making.

Keywords: *Anterior chest wall lump, Approach, Bifid Rib, Gorlin syndrome.*

Introduction

The evaluation of a chest wall lump in primary care requires a systematic approach to differentiate benign from potentially serious conditions. Chest wall masses may arise from a variety of aetiologies, including infectious, traumatic, congenital, or neoplastic causes [1]. While many lumps are benign, such as lipomas, fibromas, or congenital anomalies like bifid ribs, some may indicate malignancies, including soft tissue sarcomas or metastatic lesions [2]. The causes may also include bony growth, either benign causes (such as chondroma, fibrous dysplasia) or malignant (such as Ewing sarcoma or osteosarcoma) [1,2]. A thorough history and physical examination are essential in determining the need for further diagnostic imaging or specialist referral. Key clinical features, such as rapid growth, pain, systemic symptoms, fixation to underlying structures, or concomitant enlarged axillary lymph nodes, may warrant advanced investigations, such as ultrasonography, radiography, or cross-sectional imaging [3]. In primary care, establishing an evidence-based algorithm for assessing chest wall lumps can aid in optimizing diagnostic accuracy, minimizing unnecessary imaging, and ensuring timely intervention when required.

Congenital anomalies of the rib can be categorized into structural or numeric problems. Numeric abnormalities include the presence of an extra or absent rib, while structural abnormalities involve bifurcated, fused, hypoplastic, or forked ribs [4]. A bifid rib is a congenital abnormality of the anterior chest wall where the sternal end of the rib is divided into two. It is a rare congenital rib defect, occurring in approximately 1.2% of the population, and typically involves only a single site on the rib [4-6]. Bifid ribs most commonly affect a single rib and are usually asymptomatic, with the third and fourth ribs being the most frequently involved. In most cases, the diagnosis is made incidentally through an X-ray, although some patients may present with chest wall abnormalities [4,5]. If left uninvestigated, this chest wall swelling might cause confusion or concern for the patient or parents regarding its underlying cause.

The presence of a chest wall lump in a child often raises significant parental concern, as it may be perceived as a sign of a serious underlying condition, particularly malignancy. While most chest wall lumps in paediatric patients are benign, distinguishing them from neoplastic or infectious causes is crucial [7]. Parental anxiety is often heightened when the lump appears firm, immobile, or rapidly enlarges, prompting urgent medical consultations and requests for imaging [8]. Despite the rarity of malignant chest wall tumours such as Ewing sarcoma or rhabdomyosarcoma, healthcare providers must balance the need for thorough evaluation with the avoidance of unnecessary radiation exposure from imaging [9]. Clear communication and reassurance, combined with an evidence-based diagnostic approach, can help alleviate parental worries while ensuring appropriate clinical management.

Case presentation

A 4-year-old girl with no known medical illness was brought to a health clinic with a complaint of a right chest wall lump for almost one year, which had remained unchanged in size. She had no history of trauma, recent infections, or a family history of malignancy. However, the parents were worried due to the persistent nature of the condition, causing them to request further assessment. They have sought multiple opinions from other local clinics but were advised to observe and refer if persistent.

On examination, there were no abnormalities of the face or limbs. The child's anthropometric measurements were within normal ranges. Chest wall examination revealed a swelling over the anterior right chest wall, located medially and below the right nipple, as shown in Figure 1 and 2. The swelling was hard in consistency, approximately 4 cm x 5 cm in size, non-tender, and immobile. No axillary lymph nodes was palpable.

Although our initial clinical assessment suggested a benign condition, we opted for further imaging study due to its hard consistency. The one-year history of the swelling presented as a diagnostic challenge whether it represented a static anomaly or a progressively enlarging mass, such as a tumour. A plain chest radiograph revealed a bifid rib involving the anterior part of the right 5th rib (Figure 3). As the patient was asymptomatic with no other remarkable findings, no treatment was necessary at this time. Regular follow-up was planned to monitor for any future complications. Reconstructive surgery may be considered later if indicated. The parental worries were resolved, and the unnecessary tertiary referral has been avoided. However, we advised the family to return promptly should any new symptoms, changes in the mass, or concerns arise.

Discussion

Chest wall tumours are rare in infants and children; however, a significant proportion up to 50-70% are malignant. They most commonly present as a palpable mass, with pain or respiratory distress occurring less frequently. Therefore, most parents feel worried and request further referral or assessment. Radiographic evaluation should commence with chest radiographs, followed by computed tomography (CT) scan if clinically indicated [10].

Most clinical guidelines and literature propose obtaining an adequate history and performing a physical examination at the primary care level as the initial approach, as illustrate in Figure 3. This includes assessing the onset—whether it has been present since birth or acquired—and determining if it is stable or progressive [1,7,8]. It is important to evaluate other associated symptoms that might indicate infection rather than congenital deformities, such as fever, night sweats, pain, or redness. A history of recent injury or falls may suggest that the lesion could be a hematoma, soft tissue injury, fracture, or even malunion of the bone in cases of long-standing trauma [1,7,8]. A positive family history, meanwhile, may support the presence of congenital anomalies or cancer. Notably, asymptomatic masses may still represent malignancy, particularly if progressive [1,7,8].

In our case, we have a clear-cut history indicating that the mass is asymptomatic. However, its recent onset—within the past year—leaves us in a dilemma as to whether it exhibits benign or alarming features. During further clinical assessment, the patient should undergo a general examination to identify any abnormal vital signs. Anthropometric measurements should focus on signs of failure to thrive or underweight status, which may suggest malignancy or a chronic infection such as tuberculosis. Determining the exact location of the mass, its consistency, and any surrounding abnormalities including presence of palpable lymph node is crucial in assessing whether conservative management is appropriate [1,7,8]. In this patient, the lump was firm in consistency, but no other alarming findings were present. We had a strong clinical suspicion that the mass originated from bone; however, we were unable to confirm its nature. Due to our concerns, along with the parents' worries, we opted for an initial radiograph to further characterize the mass. Furthermore, at this age, there is still possibility of bone tumour such as fibrous dysplasia or chondroma [1,2].

Imaging findings suggestive of malignancy include a moth-eaten or permeative pattern of bone destruction, an adjacent soft-tissue mass, and invasive periosteal reactions such as onion-skin or spiculated patterns [11]. None of these features were present in our case, allowing us to confidently diagnose a benign condition—rib bifurcation, or bifid rib.

A bifid rib is a rare congenital abnormality of the anterior chest wall, typically an incidental finding and usually asymptomatic. It may be associated with a rare autosomal dominant condition known as Gorlin-Goltz basal cell nevus syndrome, which is characterized by multiple naevoid basal cell carcinomas, jaw cysts, and bifid ribs [1,5,6]. Some studies have also reported associations with Job’s syndrome and Kindler syndrome [6]. Under

normal conditions, ribs develop from the costal processes of the thoracic vertebrae. Embryologically, the development of bifid ribs is unclear but is likely caused by incomplete fusion of the cephalic and caudal segments of the sclerotome [4,6]. Bifid ribs most commonly involve the third and fourth ribs and predominantly affect the right side [6].

The diagnosis of bifid ribs can generally be made using a plain chest radiograph. In some cases, patients present with a noticeable anterior chest wall abnormality, as observed in our case. However, patients are often asymptomatic unless they exhibit clinical signs of Gorlin syndrome, which is characterized by a range of developmental abnormalities and a predisposition to basal cell carcinoma (BCC), a form of skin cancer [12]. In our case, the patient exhibited no other characteristics of Gorlin syndrome, and genetic testing was not performed due to logistical issues. However, given that adolescence and early adulthood are the most sensitive periods for diagnosing Gorlin syndrome, there remains a possibility for her to develop signs and symptoms in the future. The median age of onset for basal cell carcinoma (BCC) in Gorlin syndrome is approximately 25 years [12]. As in the algorithm, regular follow-up is essential to ensure early detection and prevention of complications, including missed diagnoses of Gorlin syndrome in this case.

Conclusion

Bifid rib is a rare finding in daily clinical practice, and most patients remain asymptomatic. A thorough history and complete physical examination are essential to distinguish benign from malignant features. Primary care physicians should be familiar with the characteristic imaging findings of this malformation, particularly on plain radiographs. When rib anomalies are identified, comprehensive screening for associated anomalies or syndromic conditions is warranted. Regular follow-up is recommended for all cases to monitor for serious complications, thereby ensuring optimal prognosis and quality of life.

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Authors' contribution:

MSE contributed to the study conceptualization, manuscript editing and finalisation. MYC was responsible for writing the case report and collecting clinical data.

Source of financial/funding Nil

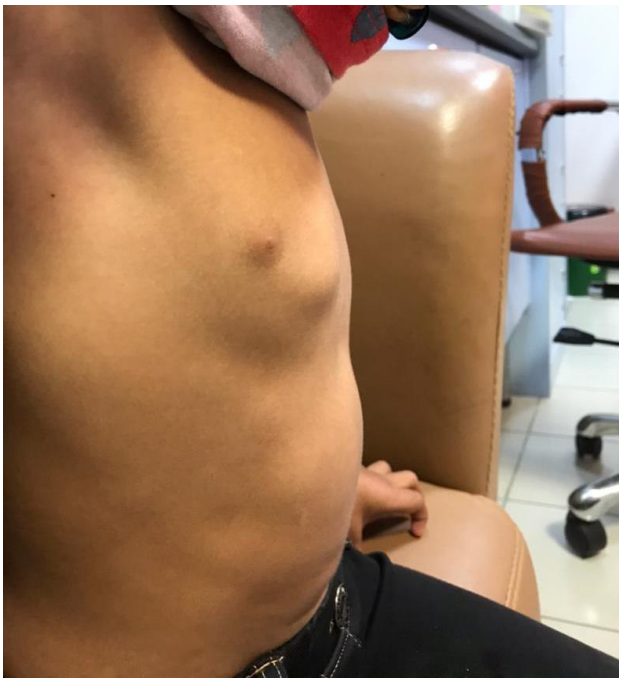

Figure 1. Lateral view of the anterior chest wall reveals the prominent swelling just below the right nipple

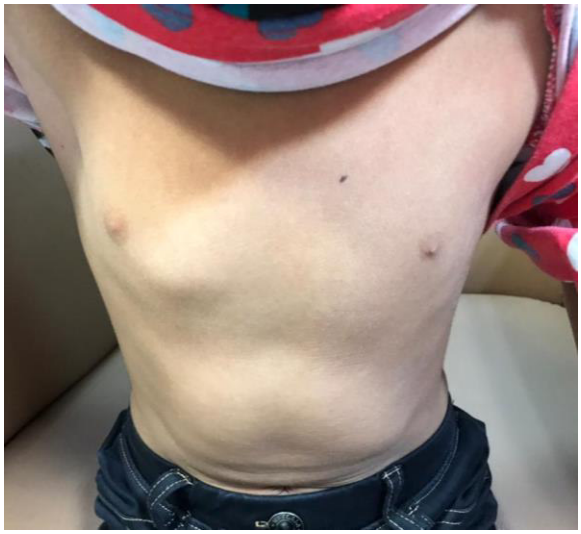

Figure 2. Anterior view of the chest wall

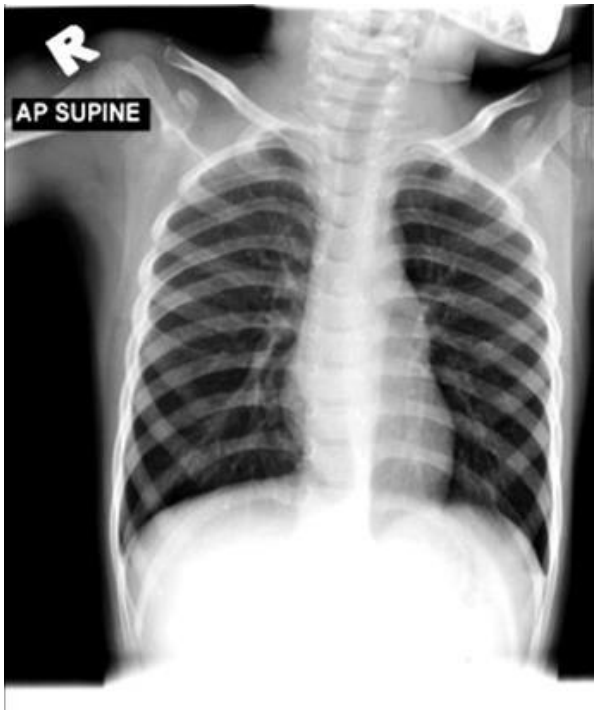

Figure 3. The chest X-ray in anteroposterior view confirmed the presence of the bifid rib of anterior fifth rib.

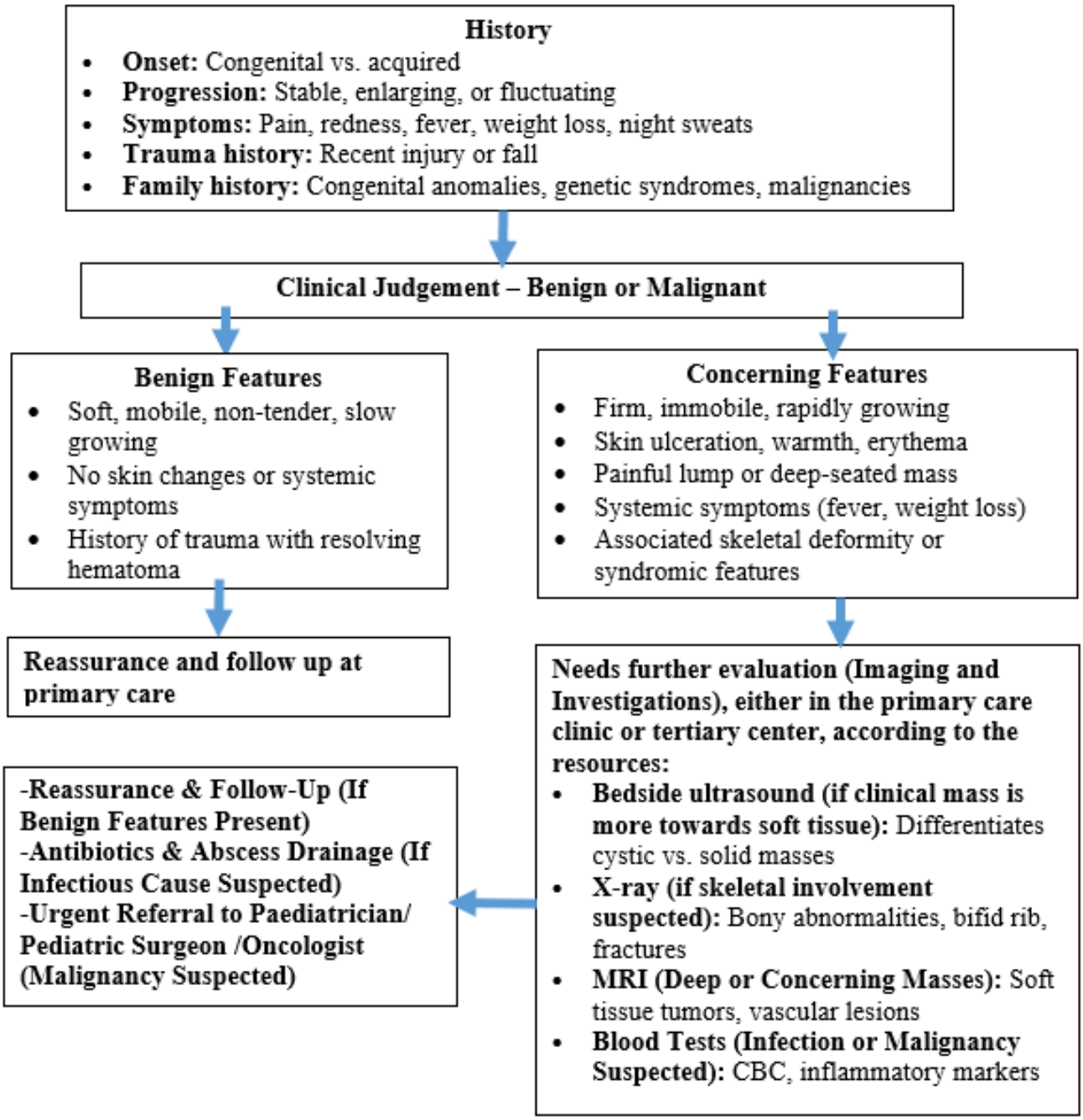

Figure 4. Algorithm of Approach of Chest Wall Lump in Toddler, at Primary Care Level.

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CASE REPORT

Granulomatous with Polyangiitis (GPA) Presenting with Mononeuritis Multiplex: A Case-based Review.

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Abstract
Granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis (WG), is a rare rheumatological disease that can affect individuals of any age. ANCA associated vasculitis (AAV) with granulomatous with polyangiitis proteinase 3 (GPA-PR3) is present in approximately 85-90% of cases. We report a 52-year-old Indian female with positive cytoplasmic-antineutrophil cytoplasmic antibody (c-ANCA) presented with chronic sinusitis, orbital cellulitis, and mononeuritis multiplex of the right foot and possible sensorineural defect hearing impairment.

Keywords: *c-ANCA, Granulomatosis with polyangiitis, Mononeuritis multiplex.*

Introduction

GPA is a type of vasculitis that falls under the category AAV. AAV is characterized by a loss of tolerance to neutrophil primary granule proteins, such as leukocyte proteinase 3 (PR3) or myeloperoxidase (MPO), leading to the production of autoantibodies [1]. These autoantibodies cause severe inflammation in small blood vessels, resulting in endothelial injury and tissue damage. There are three types of AAV classified according to 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides (CHCC): granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis; microscopic polyangiitis (MPA); and eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg-Strauss syndrome [2,3]. A study in Asia found that the mean age for GPA diagnosis among Indians is 40 years, with most cases being PR3-positive, a higher prevalence compared to countries like China, Korea, and Japan [4]. As far as our literature search, we found that this is the first case of GPA with mononeuritis multiplex encountered in Malaysia.

Case report

A 52-year-old Indian female with a history of hypothyroidism (post-total thyroidectomy in 2006), and recurrent chronic sinusitis (underwent Functional Endoscopic Sinus Surgery in 2024 (FESS) and multiple sinus washouts) presented with a one-month history of numbness, paresthesia, and asymmetric distal weakness in her right foot, without any bladder or bowel involvement. She remains ambulatory with the aid of a walking aid, and her upper limbs are unaffected. Additionally, she has experienced a reduced appetite and a five-kilogram weight loss over the past three months, along with recent loose stools for two weeks. She has an intermittent fever without chills or rigor, and a productive cough with yellowish sputum for one week. Otherwise, there are no associated symptoms such as runny nose, sore throat, allergy, asthma, tinnitus, epistaxis, anosmia, hyposmia, foul-smelling nasal discharge, facial pain, hemoptysis, chest pain, palpitations, dyspnea, abdominal pain, rectal bleeding, headache, seizures, dysuria, hematuria, oral ulcers, or malar rash.

The patient has also had a hearing impairment, predominantly on the left side, since January 2024. In February 2024, she developed bilateral eye weakness lasting for one week, accompanied by minimal eye discharge, left facial pain, and headache. A Computer Tomography (CT) scan of the orbit and paranasal sinuses revealed left orbital cellulitis with a subperiosteal abscess secondary to chronic sinusitis. She was treated with intravenous (IV) ceftazidime 1g three times a day for one week and was referred for surgical drainage and a lacrimal gland biopsy. Unfortunately, we were unable to retrieve her biopsy results.

Neurological examination revealed a right-sided foot drop with dorsiflexion and plantar flexion power of 3/5 following the Medical Research Council's scale (MRCS). There was decreased sensation up to knee (L4, L5) to touch, pain, and temperature in the right foot. The left foot had normal power, tone, and sensation. However, other systemic examinations were unremarkable.

Laboratory investigations revealed progressive microcytic hypochromic anemia (Hb range from 7.2 to 7.8 g/dL, MCV 74.5, MCH 13.1), elevated white cell count (17.1 x 10^9/L) with a normal eosinophil count (0.01 x 10^9/L) and normal platelet levels (409 x 10^9/L). Renal and liver function tests were normal, except for low albumin (19 mg/dL). C-reactive protein (CRP) was elevated, 346.9 mg/dL (normal < 5mg/dL). c-ANCA (PR3-ANCA) was strongly positive, 317.4 CU (normal <20 CU), while MPO was negative, 9.1 CU (normal <20 CU). The other serologic tests were negative for antinuclear

antibody (ANA), anti-double stranded DNA (anti-dsDNA), extractable nuclear antigen (ENA) and complement factors. Septic workups were negative except for sputum culture, which yielded *Pseudomonas aeruginosa*. Urine tests showed traces of leukocytes, protein, and blood, with urine red blood cell casts being negative. The electrocardiogram (ECG) and echocardiogram were normal. Plain chest radiograph was normal, and computed tomography (CT) of the abdomen and pelvis showed no significant findings. However, nerve conduction studies were not available.

Based on her clinical presentation and investigations, she was diagnosed with mononeuritis multiplex secondary to positive PR3-ANCA GPA. Due to the element of a concurrent respiratory infection, she was commenced on intravenous tazocin and hydrocortisone 8 hourly for a week. Once the infection was under control, she subsequently underwent induction therapy with intravenous methylprednisolone (MP) 500mg daily for five days and pulse IV cyclophosphamide (CYC) 750 mg/m^2 monthly (planned for 6 months) after completing IV tazosin 4.5g daily for one week. She was also prescribed with oral mecobalamin 500 mg 8 hourly and oral gabapentin 300 mg twice daily. She showed improvement in her right foot drop symptoms after 2 months of IV CYC.

Discussion

Granulomatous with polyangiitis (formerly known as Wegener's granulomatosis) is a rare vasculitis characterized by necrotizing small-to-medium size vessels and classified into three spectrums of AAV phenotypes i.e., GPA, MPA, EGPA [2]. GPA-PR3 positive is present in approximately 85-90% of the cases and typically presents in individuals aged 45-65, with no significant gender difference [5]. GPA primarily affects the upper respiratory tract, pulmonary and renal. It can be classified by granulomatous manifestations (involving the ear, nose, throat, lung, orbital, and pachymeningitis) that tend to relapse, or vasculitic manifestations (granulomatosis, alveolar hemorrhage, scleritis or mononeuritis multiplex), which are associated with higher mortality rates [4]. Table 1 shows types of AAV with a vast spectrum of clinical manifestations reported in Malaysia to date [6-15].

Although in general, neurologic involvement in GPA is uncommon, the peripheral nervous system (sensorimotor polyneuropathy or mononeuritis multiplex) is commonly affected compared to central nervous system [18,19]. Mononeuritis multiplex often involves nerves such as the peroneal, tibial, ulnar, and median nerves, due to inflammation of the vasa nervorum, which leads to ischemia and subsequent axonal degeneration. Mononeuritis multiplex has been reported commonly in EGPA patients, in contrast to our patient with GPA [6,7,9,10,11].

In 90% of cases, patients present with ear, nose, and throat symptoms due to granuloma infiltration from the paranasal sinus. For nasal and paranasal regions, chronic rhinosinusitis occurs in approximately 50% of cases, often accompanied by crust formation, serosanguinous discharge, septal perforation, and saddle nose deformity [17]. This patient had similar symptoms of chronic recurrent sinusitis and underwent FESS and multiple washouts within a year, eventually leading to orbital cellulitis.

Orbital symptoms occur in 45% of GPA patients and typically manifest as episcleritis, orbital cellulitis, and orbital pseudotumor due to granuloma infiltration, though visual loss from nerve compression is rare [18]. Additionally, the lacrimal gland may be affected, often unilaterally, leading to orbital symptoms such as orbital pain, eyelid swelling, proptosis, dacryocystitis, and limited extraocular movement [20]. This patient also presented with orbital pain and minimal eye discharge and was treated for left orbital cellulitis

with a subperiosteal abscess, which was resolved after administration of IV ceftazidime.

Ear involvement occurs in 20-25% of GPA cases and is often secondary to nasal involvement. Patients may present with otitis media, conductive, sensorineural, or mixed hearing loss, as well as vertigo or facial nerve palsy. Conductive hearing loss is more common, typically resulting from granuloma formation that damages the middle ear, whereas sensorineural hearing loss is due to vasculitis [20]. This otologic involvement mirrors our patient's condition, as she has experienced hearing loss on the left side for approximately eight months, though no audiology assessment has been conducted yet.

Throat involvement in GPA is rare compared to ear and nose symptoms, but patients can still present with conditions such as strawberry gingival hyperplasia, ulcerative stomatitis, labial mucosa nodules, or parotid gland enlargement, making the diagnosis challenging [18]. Lung manifestations occur in approximately 90% of cases, with symptoms including cough, dyspnea, and chest pain, and are often seen on chest radiographs as pulmonary nodules or cavitations [18]. Cardiac involvement is also uncommon, occurring in 6-30% of cases, with potential presentations including pericarditis, pericardial effusion, non-infectious endocarditis, myocardial ischemia, and cardiomyopathy [16]. Necrotizing glomerulonephritis is associated with a poor prognosis in GPA patients, presenting with hematuria, proteinuria, edema, decreased urine output, and rapid progressive renal deterioration [16]. However, this patient did not show manifestations in any of the aforementioned systems.

This patient's constitutional symptoms, i.e., loss of appetite, weight loss, and loose stools, may suggest either GPA-related gastrointestinal involvement or another condition. Gastrointestinal manifestations in GPA are typically less specific and can include abdominal pain, diarrhea, and ulceration that mimic inflammatory bowel disease or polyarteritis nodosa (PAN), along with hemorrhage and bowel ischemia secondary to mesenteric vasculitis.[16] These specific symptoms were not observed in this case, although anaemia was noted.

Other non-specific symptoms like fever, anorexia, malaise, weight loss, and muscle pain, which persist for weeks and months, may be mistaken for infections, malignancies, or inflammatory joint diseases if specific organ involvement is not evident. However, if the patient ANCA is positive and involves specific organ systems, GPA should be suspected [19].

Currently, there is no standardized treatment protocol for GPA; however, most institutions utilize immunosuppressive therapies, which have demonstrated a 5-year survival rate of 70-80% [1]. Management of GPA generally involves two phases: the remission induction phase, lasting 3–6 months, typically involves glucocorticoids combined with either cyclophosphamide or rituximab. This is followed by the maintenance phase, which lasts 2–3 years and aims to prevent disease relapse with low-dose glucocorticoids and either rituximab, azathioprine, methotrexate, or mycophenolate mofetil [21,22]. Neuropathic pain management options include tricyclic antidepressants (such as amitriptyline and nortriptyline), serotonin and norepinephrine reuptake inhibitors (SNRIs) like duloxetine and venlafaxine, or antiepileptics (such as gabapentin and pregabalin) [5].

Conclusion

GPA, a subtype of AAV, typically affects the ear, nose, throat, lung, and kidney (ELK) systems and rarely involves neurological manifestations such as mononeuritis multiplex. It should be suspected if these symptoms are present in patients with bronchial asthma and chronic sinusitis with or without other manifestations. The diagnosis of GPA in this patient is probably anticipated earlier

when sinus washout and biopsy were done where histopathological findings may prognosticate the condition. Induction treatment with high dose corticosteroids in combination with pulse CYC may induce remission of GPA followed by maintenance low-dose corticosteroid and longer duration of treatment for 18-24 months may prevent or reduce relapse [23].

Conflict of interest and financial disclosures
None.

Informed Consent
Written informed consent was obtained from the patient for the publication of this report.

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Authors contribution
NAS: data collection, and manuscript writing; WS: Ideas and review of the manuscript.

Table 1. Cases on various types of AAV reported in Malaysia.

Study	Age;sex	Type of AAV	Clinical features	Immune markers and other lab results	Treatment	outcome
Loke *et al*, 1998 [6]	35;F	GPA (WA)	Rt eye uveitis, nasal discharge, LOW, cough, haematuria, dysphagia, hoarseness of voice. (Lt X and XI cranial nerves palsies.) Nasal septum Bx: chronic inflammation with necrotizing vasculitis. Cavitating lung lesion	ANCA – NA	CYC, P	NA
Tan *et al*, 2010 [7]	40;F	EGPA (CSS)	BA, leukocytoclastic vasculitis (skin Bx), Non-healing ulcer Mononeuritis multiplex (NCS)	p-ANCA +ve; Leukocytosis with raised Eos	MP, P, CYC	Residual sensory and motor neuropathy
Tang *et al*, 2010 [8]	39;F	GPA (WA)	multiple non healing ulcers - left face, Rt thigh and both shins and nasal septum; mixed hearing loss, otitis media and chronic sinusitis skin Bx: granuloma with multinucleated giant cells and inflammatory cells	c-ANCA +ve	Declined treatment	Died (pulmonary hemorrhage)
Abdullah *et al*, 2014 [9]	45;M	EGPA	Bronchial asthma; Recurrent Mononeuritis multiplex – both feet and Lt hand (Lt foot drop); Lung: upper zones fibrosis	ANCA -ve; Leukocytosis with predominant Eos.	P, AZA CYC	Remission (with CYC)
Sulaiman *et al*, 2014 [10]	50;M	EGPA	Late onset BA, cough, allergic rhinitis, vasculitis ACS, peripheral neuropathy/mononeuritis multiplex (foot drops) COROS: normal Skin Bx: leukocytoclastic vasculitis with eosinophilic infiltration	ANCA -ve; Raised CKMB and LDH Leukocytosis with raised Eos.	MP, AZA, CYC	Remission
Mohammad *et al*, 2017 [11]	28;F	EGPA	BA, polyarthritis, fever, Mononeuritis multiplex (bilateral wrist drops) NCS: axonal polyneuropathy	p-ANCA+ve, MPO+ve; raised Eos	CYC, P,MTX SABA for BA	Remission
Ang *et al*, 2018 [12]	49;F	GPA	ESRF, epistaxis, hemoptysis, protopsis	p-ANCA +ve	AZA, P CYC (planned)	NA
Anthony *et al*, 2019 [13]	62;F	GPA	Cough, LOW. Lung Bx: necrotizing granulomatous inflammation	c-ANCA+ve, anti-PR3+v3	MTX, P	Remission within 3 months
Sulaiman *et al*, 2019 [14]	15;M	EGPA	Cutaneous vasculitis (skin Bx); no systemic symptoms or signs	ANCA -ve, leukocytosis with raised Eos.; IgE elevated	P, AZA	Remission
Sulaiman *et al,* 2021 [15]	81;F	MPA	Lower limbs weakness; purpuric vesicular lesions on lower limbs; multiple and extensive perforated ischemic bowels. Skin Bx: bullous vasculitis	p-ANCA +ve, MPO+ve, ANA+ve homogenous, anti-dsDNA +ve, low C3,C4	MP, CYC, laparotomy	Died
This case	52;F	MPA	Fever, Chronic sinusitis, mononeuritis multiplex (Rt foot drop), hearing impairment, orbital cellulitis	c-ANCA +ve, MPO +ve	MP, P	Foot drop improving

AAV, ANCA associated vasculitis; F, female; M, male;+ve, positive; -ve, negative; ESRF, end stage renal failure; p-, perinuclear; c-cytoplasmic; GPA, granulomatous polyangiitis; WA, Wegener's granulomatosis; EGPA, eosinophilic granulomatous polyangiitis; CSS, Churg-Strauss syndrome; MPA, microscopic polyangiitis; P, prednisolone; AZA, azathioprine; CYC, cyclophosphamide; MP, methylprednisolone; MTX, methotrexate; BA, bronchial asthma; NCS, nerve conduction study; MPO, myeloperoxidase; SABA, short active bronchodilator agent; ACS, acute coronary syndrome; COROS, coronary angiography; LOW, loss of weight; Bx, biopsy; Eos, eosinophils; Rt, right; Lt, left; NA, not available.

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