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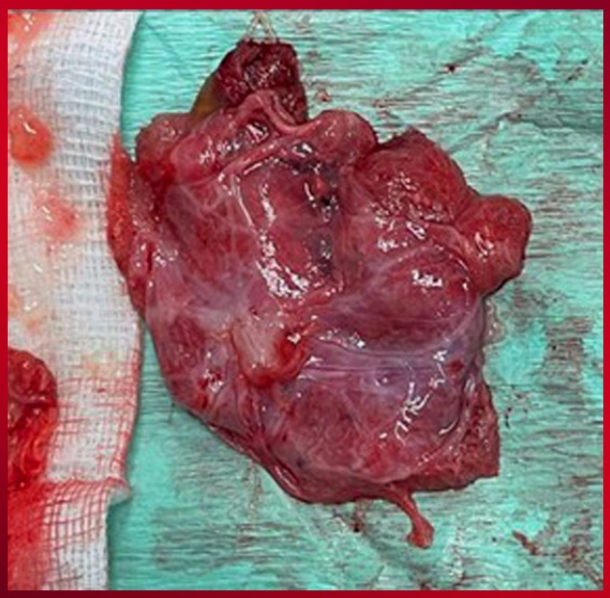

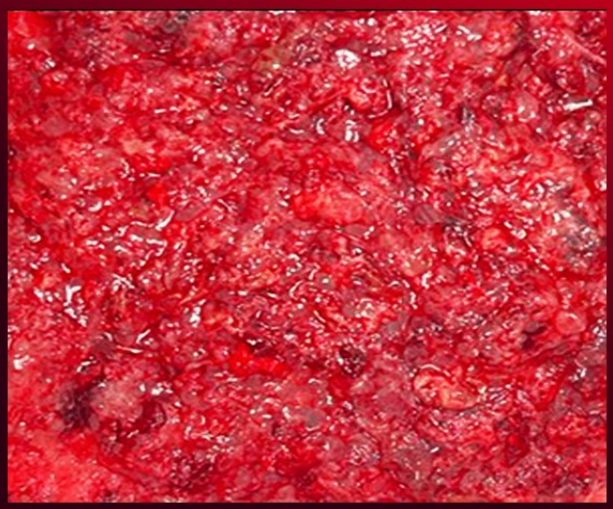

REVIEW ARTICLE

ORIGINAL ARTICLE

CASE REPORT

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TABLE OF CONTENTS

IMJM
IIUM MEDICAL JOURNAL MALAYSIA
Volume 25, Issue 3, July 2026
https://doi.org/10.31436/imjm.v25i03

ORIGINAL ARTICLES

CASE REPORT

EDITORIAL

Volume 25 Number 3, July 2026

Trends in Treatment of Obesity: Is it a "déjà vu" Moment for Surgeons?

The World Health Organization (WHO) classifies obesity as a chronic, relapsing disease.[1] It results from complex interactions between genetics, neurobiology, eating behaviours, diet availability, market forces, and the environment.[1] This global public health crisis affects over a billion people and is increasing in nearly every country. Since 1990, adult obesity rates have more than doubled, and adolescent rates have quadrupled. In Malaysia, 54.4% of adults are overweight or obese, increasing to 70.1% with Asian BMI criteria.[2] Among children and adolescents, rates rose from 8% in 1990 to 20% in 2022.[1] This trend threatens worker productivity, healthy aging, and health system resilience.

Malaysia is undergoing a nationwide obesogenic transition driven by biological, behavioral, and environmental factors, including unbalanced diets, sedentary lifestyles, and demographic changes. Authorities have implemented several measures, including affordable farmers' markets, nutritious school meal programs, healthy cafeteria guidelines, regulations on unhealthy food marketing, and higher taxes on sugary drinks. The latest Clinical Practice Guidelines (CPGs) recommend comprehensive lifestyle modifications, along with medical nutrition therapy and physical activity. The guidelines also recommend pharmacotherapy to further enhance these measures.[2] If these measures fail despite patient compliance, surgery should be considered.

The main benefits of surgery-induced weight loss include remission of metabolic effects and improved quality of life. Common procedures performed by surgeons are the Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG). At one year, mean weight loss is 31.2% for RYGB and 25.2% for SG; at five years, RYGB achieves 25.5% and SG 18.8%.3 Both the Finnish (SLEEVEPASS) and Swiss (SM-BOSS) trials consistently showed that RYGB is more effective than SG for percent excess weight loss.[3]

Malaysia has the highest obesity rates in Southeast Asia, leading to more bariatric surgeries. These procedures involve resection or bypass of the upper gastrointestinal tract and carry adverse effects, especially in younger patients. Skilful marketing often overshadows the adverse scientific evidence on metabolic surgery. Thus, surgeons must emphasize the need for a strict postoperative diet and exercise regimen. Weight regain occurs in 20–25% of patients after initial loss. Unlike other surgeries for benign conditions, surgeons must commit to long-term follow-up with these patients.[3]

Obesity management globally is shifting toward primarily non-surgical modalities. This trend is driven by new medications that can now achieve 15–25% weight loss, comparable to results from previous bariatric surgery.[3] Injectable Tirzepatide, Semaglutide, and Liraglutide deliver significant weight loss and reduce cardiovascular risk. New agents such as Retatrutide and oral elecoglipron, by targeting multiple pathways, also provide favorable results.

These developments have renewed interest in medical therapy in Malaysia, partly because many patients are reluctant to undergo surgery. Ideally, patients need comprehensive support and realistic expectations for lasting weight loss with medical therapy. In practice, weight loss averages 8–12%, whereas clinical trials report 12–20%.[4]

Major challenges remain. For example, high costs and lack of insurance limit access to obesity medications. Clinicians often prescribe these drugs for their metabolic benefits or other approved uses to address these issues. Managing obesity requires advanced monitoring and personalized treatment plans, as it is a chronic disease that requires long-term effort.

This evolving modality raises an important question: Is obesity treatment approaching a 'peptic ulcer moment'? In the 1970s, radical surgeries for peptic ulcers, including Truncal Vagotomy and Antrectomy, were common. Cimetidine, the first H_2-receptor antagonist, was introduced in 1977 and transformed treatment. In 1982, after Drs. Barry Marshall and Robin Warren discovered *Helicobacter pylori,* whose eradication drastically reduced the need for surgery. The launch of PPI in 1988 further shifted treatment from surgery to medicine. This transition marked a major change for surgeons. Have we reached the same point in obesity care? To answer this vexed question, be mindful of the key differences from ulcers. Obesity has no single cause. It results from complex interactions among areas such as genetics, neurobiology, eating behaviours, diet availability, market forces, and environment. In contrast, identification of the pathophysiology of peptic ulcers enabled targeted medical treatment. Management of obesity requires a multidisciplinary team to address all related issues, much as in oncology.

Although medication has advanced, major challenges persist. GLP-1 drugs are highly effective but are not a cure, unlike eradicating *H. pylori* to treat ulcers. GLP-1 drugs target neurobiology, not eating habits. Surgery remains the most durable option for severe obesity and metabolic disease, with higher long-term diabetes remission and sustained weight loss rates. Until behavioral change is achievable, surgery will remain the dominant approach to alleviating obesity. Medical options now supplement, not replace, surgery for obesity.

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EXPERT OPINION

Breaking the Rule of Stone: Expanding Urolithiasis Analysis to the Microbiome and Metabolome

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INTRODUCTION

Urolithiasis is the most prevalent urological disorders and continues to rise in parallel with obesity, diabetes, westernized diets, sedentary lifestyles, and climate-related dehydration.[1,5,7] Technological progress has transformed intervention; flexible ureteroscopy, laser lithotripsy, and ambulatory pathways have made stone treatment safer and more effective than ever before.[6,12] Yet, recurrence remains common, with many patients returning with new stone events despite successful surgical clearance.[4,8] Despite advances in minimally invasive surgery, recurrence remains a major challenge, emphasizing the need to move beyond procedural success toward personalized preventive strategies.[3,4] A urinary stone is frequently the final manifestation of an ongoing metabolic or environmental process rather than an isolated disease entity.[10]

Recent global epidemiological analyses demonstrate a paradoxical trend in urolithiasis burden: while the absolute number of cases continues to rise substantially, the age-standardized incidence rate has modestly declined. In 2021, an estimated 106 million new cases of urolithiasis were reported worldwide, representing a marked increase from 1990 and reflecting the effects of population growth and demographic aging. However, the global age-standardized incidence rate showed a gradual reduction over the same period, with an annual average percentage change (AAPC) of 0.81% between 1990 and 2021.[5] These findings suggest that the increasing healthcare burden of stone disease is driven primarily by demographic changes rather than an intrinsic rise in individual disease risk. Consequently, healthcare systems are likely to face escalating demands for stone-related care despite improvements in prevention and risk reduction strategies. This trend highlights the importance of implementing effective preventive measures, optimizing resource allocation, and developing precision medicine approaches to mitigate the growing socioeconomic impact of urolithiasis in aging populations.[5]

Thus, clinical experience dictates a strategic shift in our approach. For too long, the field has been restricted to a mechanical and surgical mindset, prioritizing stone removal while ignoring the biological drivers that guarantee the recurrence. We must recognize urolithiasis for what it is: a complex metabolic disorder rooted in the "gut-kidney axis." Understanding the microbiome's role in systemic oxalate regulation is no longer an optional academic pursuit; it is a strategic imperative. The gut-kidney axis serves as the primary physiological interface where intestinal health dictates renal burden.

Current State of Urolithiasis Management

According to the European Association of Urology (EAU) Guidelines, all patients presenting with urolithiasis should undergo standardized clinical evaluation including imaging confirmation, serum biochemistry, urinalysis, and stone analysis whenever material is available.[3] Patients should subsequently be stratified into low- and high-risk groups for recurrence.[3] High-risk stone formers require comprehensive metabolic evaluation, including 24-hour urine analysis and targeted laboratory investigations to facilitate individualized preventive strategies.[3,4] Subsequently intervention required to remove the stone and the stone fragment will sent for analysis.

The analysis of urinary stone composition has evolved substantially over the past century, progressing from simple macroscopic examination to advanced analytical techniques such as X-ray diffraction (XRD) and Fourier-

transform infrared spectroscopy (FTIR).[2] FTIR is currently regarded as the reference standard for stone analysis because of its high accuracy and ability to identify both crystalline and amorphous components[2]. More recently, advanced technologies including scanning electron microscopy, Raman spectroscopy, laser-induced breakdown spectroscopy, metabolomics, and proteomics have expanded our understanding of stone mineralogy and pathogenesis.[2,10]

Identification of stone composition enables tailored preventive interventions. For example, uric acid stones can be managed through urine alkalinization and metabolic syndrome control, whereas infection stones require eradication of urease-producing organisms and complete stone clearance.[3,8,11] Detail specific preventive therapy base on specific stone type shown in Table 1.

Table 1: Targeted preventive therapy for specific type of stone

Stone Type	Primary Metabolic Drivers / Associations	Targeted Preventive Interventions
Calcium Oxalate	Hypercalciuria, hyperoxaluria, hypocitraturia, high sodium/ protein intake	High fluid intake, sodium restriction, normal dietary calcium, citrate supplementation
Uric Acid	Acidic urine, obesity, insulin resistance, metabolic syndrome	Urine alkalinization, weight reduction, glycemic control, purine moderation
Struvite	Urease-producing infections.	Complete stone clearance, infection eradication, surveillance for regrowth
Cystine	Genetic (High-risk, recurrent, often in younger patients).	Aggressive hydration, urine alkalinization, sodium restriction, thiol-binding drugs
Brushite / Rare	Matrix stones, drug-induced compositions, or treatment-resistant systemic factors.	Specialized metabolic review, medication adjustment, and intensive surveillance.

Microbiome Depletion as a Pathophysiology of Oxalate Stone Formation

Recent evidence suggests that metabolic risk factors for urolithiasis may vary substantially across geographic regions, challenging the applicability of traditional Western metabolic profiles to non-Western populations. In industrialized Western countries, hypercalciuria has historically been regarded as the predominant urinary abnormality associated with calcium stone formation. However, studies from Peninsular Malaysia demonstrate a markedly different pattern, with hyperoxaluria (61.4%) emerging as the most prevalent metabolic abnormality, followed by hypomagnesuria (59.3%) and hypocitraturia (57.2%).[1] These findings indicate that regional dietary habits, environmental exposures, genetic factors, and lifestyle characteristics may significantly influence urinary biochemical profiles and stone pathogenesis. Consequently, precision management of urolithiasis requires the development of population-specific metabolic reference data rather than reliance on foreign models, as the adoption of non-representative metabolic profiles may result in suboptimal risk stratification, inappropriate preventive strategies, and less effective therapeutic interventions.[1]

Similarly, the recent study found regulation of *Oxalobacter formigenes*, a specialized anaerobic bacterium that regulates oxalate homeostasis by degrading dietary oxalate in the gut, thereby limiting its systemic absorption and subsequent renal excretion. When this gatekeeper is lost, the resulting "oxalate leak" into the bloodstream places an unsustainable burden on the kidneys, leading to crystallization[10] Such observations highlight the importance of localized epidemiological and metabolic studies to support precision stone medicine and optimize recurrence prevention in diverse populations. Thus, in population with high oxaluria possible predictive model for stone formation can be elaborated as shows in Figure 1.

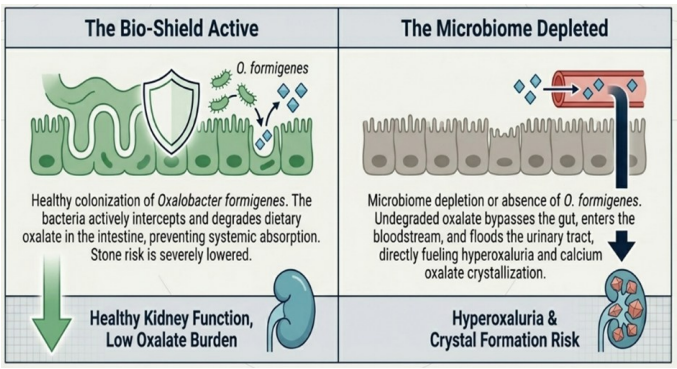

Figure 1: Microbiome dysbiosis causing hyperoxaluria

Development of new model to predict stone type

Traditionally, stone analysis has relied on postoperative physical and chemical laboratory examinations of retrieved calculi. In contrast, precision stone medicine integrates multi-omics technologies, artificial intelligence (AI), advanced imaging modalities such as spectral and dual-energy computed tomography, and comprehensive patient profiling to decipher the underlying biological mechanisms of stone formation.[1,2,13] Crucially, this approach shifts the focus from a single specimen to a

holistic biological ecosystem. By leveraging the combinatory power of the gut microbiome and host metabolome, we can now map how systemic microbial communities interact with biochemical metabolites to drive biomineralization. Rather than viewing these data streams in isolation, AI serves as the core predictive engine, synthesizing these complex multi-omic datasets alongside clinical variables to forecast stone characteristics.

Consequently, emerging predictive models combine these clinical, biochemical, metabolomic, and microbial profiles within advanced scoring systems capable of estimating stone composition and recurrence risk even before stone retrieval. Such integrative frameworks have the potential to bypass traditional, stone-dependent analyses, enabling earlier diagnosis, personalized preventive strategies, targeted therapeutic interventions, and more effective long-term recurrence prevention. As these technologies mature, precision stone medicine is expected to transform urolithiasis management from episodic treatment to proactive risk prediction and individualized disease prevention. To this end, we propose that the conceptual framework outlined above (Figure 2) be further developed and trained on AI architectures to optimize pre-operative stone type prediction.

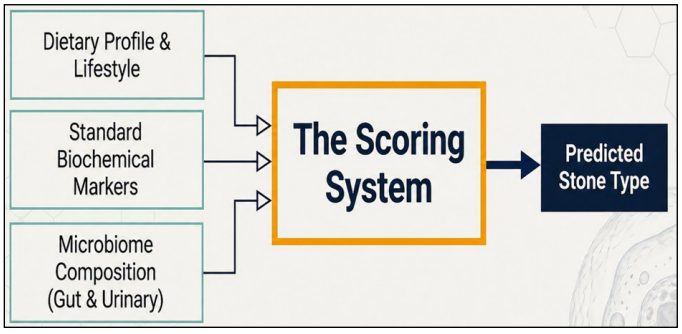

Figure 2: The pre-operative prediction stone type model

CONCLUSION

Stone analysis remains a simple, practical, and clinically meaningful tool for recurrence prevention. The high prevalence of calcium oxalate stones in Asian populations and the predominance of hyperoxaluria in Malaysian cohorts underscore the limitations of adopting non-local metabolic models and highlight the importance of precision medicine approaches tailored to regional characteristics. Future advances integrating artificial intelligence, metabolomics, microbiome science, and individualized risk assessment are expected to transform urolithiasis management from reactive treatment to proactive prevention.

FUNDING

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REVIEW ARTICLE

Synthesis of Evidence on the Combination of High-Intensity Laser Therapy and Rehabilitation Exercise for Knee Osteoarthritis: An Umbrella Review of Systematic Reviews

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ABSTRACT

High-intensity laser therapy (HILT) is a promising adjunctive treatment for knee osteoarthritis (KOA) due to its deep tissue penetration and anti-inflammatory effects. However, inconsistent findings hinder clinical interpretation. This umbrella review synthesised current evidence on the effects, safety, and clinical applicability of HILT in KOA management. A systematic search of five electronic databases was conducted in accordance with PRISMA guidelines, covering studies up to December 2024. Eligible systematic reviews included adult populations with KOA receiving HILT, assessing outcomes such as pain, stiffness, physical function, and safety. Methodological quality was evaluated using AMSTAR-2 and PRISMA checklists. The Corrected Covered Area (CCA) was calculated to assess overlap among primary studies. Seven systematic reviews published between 2017 and 2024 were included, comprising 50 unique primary studies involving adults aged 40–70 years. The CCA score of 0.047 indicated minor overlap. Most studies applied HILT in combination with rehabilitation exercise rather than as a standalone therapy. HILT significantly reduced pain and improved physical function, often exceeding minimal clinically important differences. Treatment parameters ranged from 808–1064 nm and 0.51–120 J/cm², administered over 4–8 weeks. Compared to low-level laser therapy, HILT demonstrated greater effects in pain relief and functional outcomes, with a favourable safety profile. While HILT can be used independently, combining it with exercise is the most commonly applied and effective approach for KOA. Despite promising results, variability in protocols and limited long-term data highlight the need for standardised treatment guidelines and further research.

Keywords:
High-Intensity Laser Therapy, Knee Osteoarthritis, Systematic Reviews, Pain Management, Rehabilitation Therapy

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INTRODUCTION

Knee osteoarthritis (KOA) is a chronic degenerative joint disease characterized by progressive cartilage loss, pain, stiffness, and reduced physical function.[1] It is a leading cause of disability, particularly among adults aged 40 years and older, with its global prevalence rising due to aging populations, sedentary lifestyles, and increasing obesity rates.[1,2] KOA significantly impacts individuals' quality of life by limiting mobility, reducing independence in daily activities, and contributing to substantial social and economic burdens.[3-7] Current management strategies for KOA include pharmacological therapies, rehabilitation exercise,[8,9] self-management and education[7] and, in severe cases, surgical intervention.[10,11] However, the most commonly prescribed pharmacological agents, specifically nonsteroidal anti-inflammatory drugs (NSAIDs), are associated with adverse effects, especially when used for extended periods,[11] highlighting the need for safer, non-pharmaceutical, non-invasive alternatives.[12,13]

Among non-pharmacological approaches, photobiomodulation therapy using high-intensity laser therapy (HILT) has gained significant attention due to its deep tissue

penetration, ability to stimulate biological processes, and promising effects on pain reduction and functional recovery.[14-16] HILT operates at wavelengths ranging from 808–1064 nm, with higher power outputs compared to low-level laser therapy (LLLT).[12,17] It can penetrate deeper tissues, stimulate cellular activity, promote ATP production, and reduce inflammation through photochemical and photothermal effects, making it a promising option for managing KOA symptoms. When combined with rehabilitation exercise, HILT may enhance the impact of rehabilitation by reducing pain, decreasing inflammation, and promoting tissue repair. Together, HILT and rehabilitation exercise can improve joint function, accelerate recovery, increase adherence to physiotherapy, and make progressive exercise more tolerable and effective.[16-18]

Despite emerging evidence supporting the efficacy of HILT in KOA, inconsistencies in study protocols, such as variations in laser parameters (e.g., wavelength, energy density, frequency, and duration of treatment), pose challenges in translating research findings into clinical practice.[3,14] Furthermore, the growing number of systematic reviews and meta-analyses investigating the effectiveness of HILT has led to potential duplication and overlap of evidence, making it increasingly difficult for clinicians and researchers to interpret and integrate findings into practice. These factors highlight the need for a higher-level synthesis of the available evidence.

In this umbrella review, we aim to systematically synthesize evidence from published systematic reviews, with or without meta-analyses, evaluating the effectiveness, safety, and clinical application of HILT in the management of KOA. By examining the scope, quality, and consistency of existing evidence, this review seeks to provide clinicians, researchers, and policymakers with a comprehensive understanding of HILT's role in KOA management and identify areas for future research.

MATERIALS AND METHODS

Review design

The review adhered to the PRISMA guidelines to ensure comprehensive and transparent reporting.[19] The protocol for this umbrella review was registered prospectively with the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD42025628674.

Keywords and data sources

A comprehensive search strategy was implemented using five electronic databases: PubMed, Embase, Medline, Web of Science, and Scopus, covering all records from their inception to December 2024. The search strategy combined keywords and MeSH terms related to HILT, KOA, and systematic reviews. Specific search terms included combinations such as "high-intensity laser therapy," "laser," "photobiomodulation," "knee osteoarthritis," "knee arthr*," "gonarthrosis," and "review." Boolean operators (AND, OR) were used to refine the search. Reference lists were manually searched to identify additional studies. Two authors independently searched to reduce bias. Any discrepancies in the search process or inclusion decisions were resolved through discussion to reach a consensus.

Eligibility criteria

Systematic reviews, with or without meta-analyses, were eligible for inclusion. Primary studies within the systematic reviews had to involve: (i) adults aged 18 years or older diagnosed with KOA; (ii) HILT combined with the rehabilitation exercise as the primary intervention; (iii) control groups receiving placebo, sham laser therapy, conventional rehabilitation exercises, or no intervention; and (iv) outcomes such as pain reduction, physical function, disability, or quality of life. Narrative reviews, scoping reviews, primary research studies, protocols, conference abstracts, and non-English articles were excluded. Where systematic reviews included multiple conditions or intervention types, only data pertaining to KOA participants treated with HILT in combination with rehabilitation exercise were extracted for synthesis.

Quality assessment

Review quality was assessed using the A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR 2), which covers 16 key domains of systematic reviews, including protocol registration, adequacy of literature

searches, risk of bias assessment, and appropriateness of meta-analytical methods.[20] Reviews will be categorized into four quality levels: high, moderate, low, or critically low quality, based on the presence and severity of flaws in critical domains.[21] Additionally, adherence to methodological standards was assessed using the PRISMA checklist, with scores of 24 and above indicating high compliance with reporting standards.[19]

Data extraction and synthesis

Two reviewers independently extracted data using a predefined form, capturing study characteristics, intervention details (e.g. wavelength, energy density, session frequency, irradiation site, mode) and outcomes (e.g. pain, function, disability, quality of life, adverse events). Discrepancies were resolved through discussion or third-party input. A third reviewer verified the data for accuracy. Findings were synthesised narratively with supporting tables and statistics. Overlap across reviews was assessed using the Corrected Covered Area (CCA) method as overlap can inflate the perceived body of evidence and introduce potential bias in conclusions.[22-24] The formula for CCA is:

$$CCA = \frac{N - r}{r(c - 1)}$$

where N represents the total number of primary study occurrences across the systematic reviews, r is the number of unique primary studies, and c is the number of systematic reviews.[22] The CCA score ranges from 0 to 1, where 0 indicates no overlap and 1 indicates complete overlap.[22]

RESULTS

Data screening, selection, and extraction process

A comprehensive search across five databases yielded 392 articles. After removing duplicates (N=245), 147 unique articles were screened based on their titles and abstracts, of which 107 were excluded for reasons such as (i) irrelevant study designs (e.g., primary research studies, narrative reviews, scoping reviews, conference abstracts or protocols), (ii) non-relevant populations (e.g., animal studies or conditions other than KOA), (iii) non-relevant interventions (e.g., LLLT or pharmacological treatments), and (iv) non-English publications. The remaining 40 articles underwent full-text screening, and 33 were excluded for various reasons, including non-systematic reviews (N=11), non-relevant to HILT (N=5), insufficient reporting of outcomes (e.g., pain, physical function, or safety measures) (N=9), and non-KOA populations (e.g., reviews that included other musculoskeletal conditions without separate data for KOA) (N=8). Finally, 7 systematic reviews met the eligibility criteria and were included in the final analysis. The study selection process is summarized in the PRISMA flowchart (Figure 1).

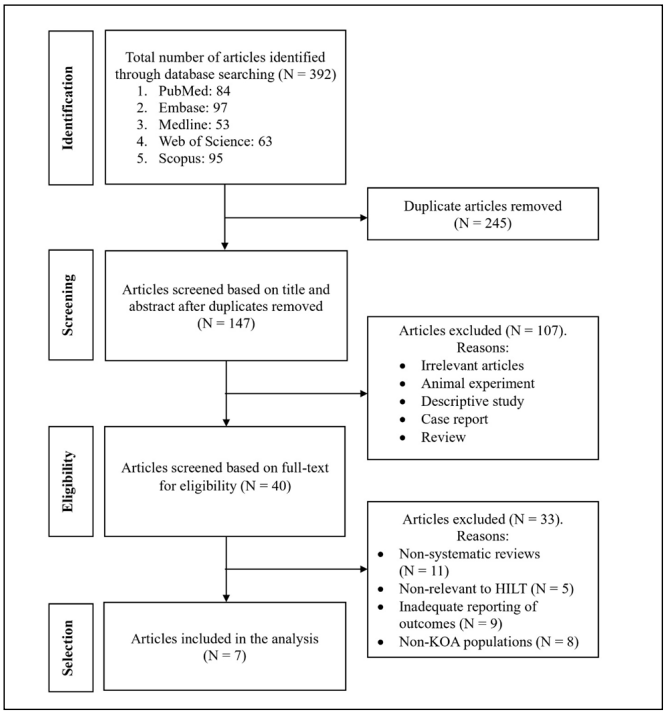

Figure 1. PRISMA flowchart depicting the study selection process.

Characteristics of included reviews

The seven systematic reviews included in this umbrella review were published between 2017 and 2024, reflecting growing research interest in the use of HILT for KOA management. The corresponding authors represented institutions from the United States, the United Kingdom, China, Iran, Poland, and Malaysia, highlighting the global relevance of the topic. All included reviews were verified to ensure that extracted data represented KOA populations. For reviews with broader musculoskeletal scopes, only KOA-specific outcomes were retained for analysis. The reviews used rigorous search strategies, screening between three[13,15] and six[14] electronic

databases, most commonly PubMed, Embase, Web of Science, and the Cochrane Library. The number of primary studies included in each review ranged from six[3] to nine,[4] with cumulative sample sizes varying from approximately 30[25] to over 700[15] participants. Interventions assessed across these reviews focused on HILT, with treatment parameters including wavelengths between 808 nm and 1064 nm, energy densities ranging from 0.51 to 120 J/cm², and session frequencies of two to three times per week over a treatment duration of four to eight weeks. Comparators included sham laser therapy,[12] LLLT,[14] and conventional physical therapy.[4] A summary of the included reviews is presented in Table I.

Table I. Summary of included systematic reviews on high-intensity laser therapy for knee osteoarthritis (N = 7).

Author & Year; Type; PRISMA score	Databases; Number of studies; Year of publication; Quality assessment; Inclusion criteria; Intervention; Outcomes	HILT intervention details: Sessions and frequency; Laser parameters	Exercise intervention details	Significant findings on pain, physical function, and/or disability: Yes/ No
Ahmad et al. (2022); Systematic review and meta-analysis; PRISMA score 25/27	PubMed, PEDro, CINAHL, SPORTDiscus, Web of Science; n=10; 2003–2019; PEDro score average 7.3; KOA-specific; RCTs included KOA patients; Intervention: HILT combined with exercise; Outcomes: pain intensity, WOMAC, functional tests	2–3 sessions/week, 4–6 weeks; Energy density: 0.51–120 J/ cm²; Wavelength: 808–1064 nm; Total energy delivered: 1250–3000 J/session	Knee ROM exercises, quadriceps strengthening, and functional training	Pain: Yes Stiffness: Yes Physical Function: Yes Disability/QOL: N/A
Cai et al. (2023); Systematic review and meta-analysis; PRISMA score 26/27	CENTRAL, MEDLINE, CINAHL, EMBASE, Web of Science, PEDro; n=9; 2005–2022; Cochrane Risk of Bias; KOA-specific; Inclusion of RCTs comparing HILT to placebo combined with conventional therapies or exercise for pain reduction; Outcomes: Pain intensity and functional tests	2–3 sessions/week, 4–8 weeks; Wavelength: 1064 nm; Energy density: 10–120 J/cm²	Lower limb stretching and mobility exercises	Pain: Yes Stiffness: N/A Physical Function: Yes Disability/QOL: Yes
Khalilizad et al. (2024); Systematic review and network meta-analysis; PRISMA score 27/27	PubMed, Embase, Scopus; n=11; 1990–2023; AMSTAR-2 High Quality; KOA-specific; RCTs focusing on KOA patients receiving HILT or LLLT with exercise; Outcomes: pain intensity, WOMAC, functional tests	3 sessions/week, 4–8 weeks; Wavelength: 808–1064 nm; Total energy delivered: 3000 J/ session; Combination with exercise therapy	Stretching, strengthening, aerobic, and balance exercises	Pain: Yes Stiffness: No Physical Function: Yes Disability/QOL: Yes
Saleh et al. (2024); Systematic review and meta-analysis; PRISMA score 25/27	Cochrane Library, PubMed, Scopus; n=12; 2000–2022; PEDro score average 6.8; Comparison of HILT to LLLT in musculoskeletal disorders with or without exercise (KOA subset data extracted only); Outcomes: Pain intensity and quality of life (KOA-specific)	2 sessions/week, 6 weeks; Wavelength: 808 nm; Energy density: 5–100 J/cm²	Not specified; rehabilitation exercises	Pain: No Physical Function: N/A Disability/QOL: Yes
Song et al. (2020); Systematic review and meta-analysis; PRISMA score 24/27	MEDLINE, EMBASE, Cochrane CENTRAL, Web of Science; n=6; 2008–2020; Cochrane Risk of Bias; KOA-specific; Inclusion of RCTs of HILT intervention with or without exercise; Outcomes: pain intensity, WOMAC, functional tests	2–3 sessions/week, 4–6 weeks; Wavelength: 1064 nm; Energy density: 20–80 J/cm²	Knee ROM and strengthening exercises	Pain: Yes Stiffness: Yes Physical Function: N/A Disability/QOL: N/A
Wu et al. (2022); Systematic review and network meta-analysis; PRISMA score 27/27	PubMed, Embase, Cochrane Library, Web of Science, PEDro; n=10; 2000–2022; AMSTAR-2 High Quality; KOA-specific; HILT with exercise compared to other physical therapy modalities; Outcomes: pain intensity, WOMAC, functional tests	3 sessions/week, 4–8 weeks; SUCRA value: 98.9% for WOMAC; Energy density: 25–100 J/cm²	Mobility, strengthening and balance exercises	Pain: Yes Stiffness: No Physical Function: Yes Disability/QOL: N/A
Wyszynska & Bal-Bochenska 2018; Systematic review; PRISMA score 24/27	PubMed, EBSCO, Web of Science; n=6; 2005–2017; CONSORT Risk of Bias; RCTs focusing on KOA and HILT intervention exclusively or with exercise (only HILT + exercise arm data included); Outcomes: pain intensity, WOMAC, functional tests	2–3 sessions/week, 4–6 weeks; Wavelength: 1064 nm; Energy density: 0.51–120 J/cm²	Knee ROM and strengthening exercises	Pain: Yes Stiffness: Yes Physical Function: Yes Disability/QOL: N/A

Note: When reviews included mixed musculoskeletal conditions or multiple intervention arms, only data for KOA participants receiving HILT combined with rehabilitation exercise were extracted for synthesis.

Abbreviation: AMSTAR-2: A Measurement Tool to Assess Systematic Reviews 2; CINAHL: Cumulative Index to Nursing and Allied Health Literature; CENTRAL: Cochrane Central Register of Controlled Trials; HILT: High-Intensity Laser Therapy; KOA: Knee Osteoarthritis; LLLT: Low-Level Laser Therapy; PEDro: Physiotherapy Evidence Database; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT: Randomized Controlled Trial; ROM: Range of Motion; SUCRA: Surface Under the Cumulative Ranking; VAS: Visual Analogue Scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

Participant characteristics

The included reviews primarily examined adults aged 40–70 years, both male and female, with body mass index values between 25 and 35 kg/m², reflecting overweight to obese populations.[12,15] KOA diagnosis was based on clinical and radiographic criteria, most commonly using the Kellgren-Lawrence grading system. Studies predominantly focused on mild to moderate KOA (Grades 1-3),[4,14] though some reviews also included cases of advanced disease (Grade 4).[4] Symptom duration ranged from 1 to 5 years, representing both early and chronic KOA.[3,15] Baseline pain, typically assessed using the Visual Analogue Scale (VAS), ranged from 5 to 8, indicating moderate to severe intensity.

Study quality and assessment of overlap

The PRISMA scores ranged from 24 [12] to 27,[14] reflecting high reporting quality across reviews. The AMSTAR-2 assessments rated three reviews as high quality,[4,14,25] with rigorous methods and comprehensive bias assessments. The remaining four were rated moderate due to limitations in protocol registration, publication bias assessment, or bias evaluation methods. No reviews were rated critically low, indicating overall reliable evidence. Overlap among primary studies was assessed using the CCA method. The calculated values were N=64 (total occurrences of primary studies), r=50 (unique primary studies), and c=7 (systematic reviews included), resulting in a CCA score of 0.047, indicating minor overlap.[22]

Characteristics of rehabilitation exercise

The systematic reviews described a range of rehabilitation exercise approaches delivered in conjunction with HILT. One review provided detailed synthesis, reporting that adjunctive rehabilitation exercise commonly included quadriceps strengthening, knee range of motion exercises, stretching, balance, and functional lower limb training.[12] These programmes were delivered through both supervised sessions and home based exercise, with supervised sessions typically prescribed two to three times per week for 45 to 50 minutes, and home based programmes performed daily.[12] Another meta-analysis highlighted progressive strengthening, stretching, aerobic, and balance exercises as core elements of multimodal programmes.[25] Similarly, one network meta-analysis reported mobility, strengthening, and balance training as part of conventional physiotherapy,[4] while another review described strengthening and range of motion exercises as the most common components.[3] In contrast, some reviews[14,15] referred more generally to "rehabilitation exercise" or "conventional physiotherapy" without providing specific details. One earlier review also noted the frequent inclusion of range of motion and strengthening activities.[13]

Across reviews, the most consistently reported elements included aerobic conditioning, stretching, quadriceps and hamstring strengthening, mobility training, balance work, and functional task practice. Nonetheless, the intensity, frequency, and delivery of exercise varied considerably. While some reviews[3,25] included trials where HILT was delivered with or without exercise, none conducted subgroup analyses directly comparing HILT alone to HILT combined with exercise. As such, although the combined approach reflects common clinical practice, this variability limits the ability to attribute observed benefits solely to exercise as an adjunct.

Characteristics of HILT intervention

The systematic reviews collectively analysed laser parameters, reporting wavelengths ranging from 808 nm to 1064 nm and energy densities between 0.51 and 120 J/cm² per session.[12] The total energy delivered per session ranged from 1250 [4] to 3000 J,[14] depending on the specific treatment protocols synthesized across the reviews. The systematic reviews reported that treatment protocols generally involved 2–3 sessions per week for 4–8 weeks, with session durations varying between 10[3] and 20 [15] minutes, depending on the targeted knee region. The included reviews documented that HILT was applied to key anatomical regions of the knee, such as the anterior, medial, and lateral compartments, with a focus on pain reduction and stiffness alleviation.[12]

To optimize therapeutic outcomes, the beam spot size ranged from 1 to 5 cm²,[4,14] ensuring precise targeting of affected tissues, as consistently noted across the systematic reviews. The reviews also highlighted variation

in the mode of application, with studies employing both continuous and pulsed laser modes.[25] The pulsed mode was particularly emphasized for minimizing thermal effects while enhancing photobiostimulation, contributing to tissue repair and inflammation modulation.[12] All systematic reviews that assessed safety protocols consistently reported the use of protective goggles for both practitioners and patients, treatment curtains, and adherence to established laser safety guidelines.[12] Furthermore, HILT was reported to be well-tolerated, with only mild and transient adverse effects such as localized warmth or temporary discomfort, reinforcing its favourable safety profile across multiple reviews.[3,4,12,13]

Several systematic reviews also synthesized findings on HILT combined with adjunctive therapies, such as conventional exercise therapy, to enhance clinical outcomes.[12,14,25] The evidence from these reviews supports the notion that multimodal approaches incorporating HILT yield superior benefits in pain relief, physical function, and quality of life, further endorsing its integration into comprehensive KOA rehabilitation strategies.[12,14,25]

Synthesis of findings

Pain reduction

The included systematic reviews consistently indicate that HILT combined with exercise is effective in reducing pain among individuals with KOA (Figure 2), with improvements often exceeding the Minimal Clinically Important Difference (MCID) for pain relief.[4,12,14] One systematic review with meta-analysis reported a mean difference (MD) of -2.04 (95% CI: -2.12 to -1.96) in VAS scores, demonstrating a significant analgesic effect compared to placebo or conventional therapies.[14] Additionally, a network meta-analysis found that HILT combined with rehabilitation exercise resulted in significantly greater pain reduction (MD= -1.41; 95% CI–1.90 to –0.92) than LLLT combined with rehabilitation exercise, highlighting the superior analgesic properties of HILT.[25] Another systematic review further supported these findings, reporting an MD of -1.18 (95% CI: -1.68 to -0.69) compared to placebo, reinforcing the effectiveness of HILT in pain management.[3]

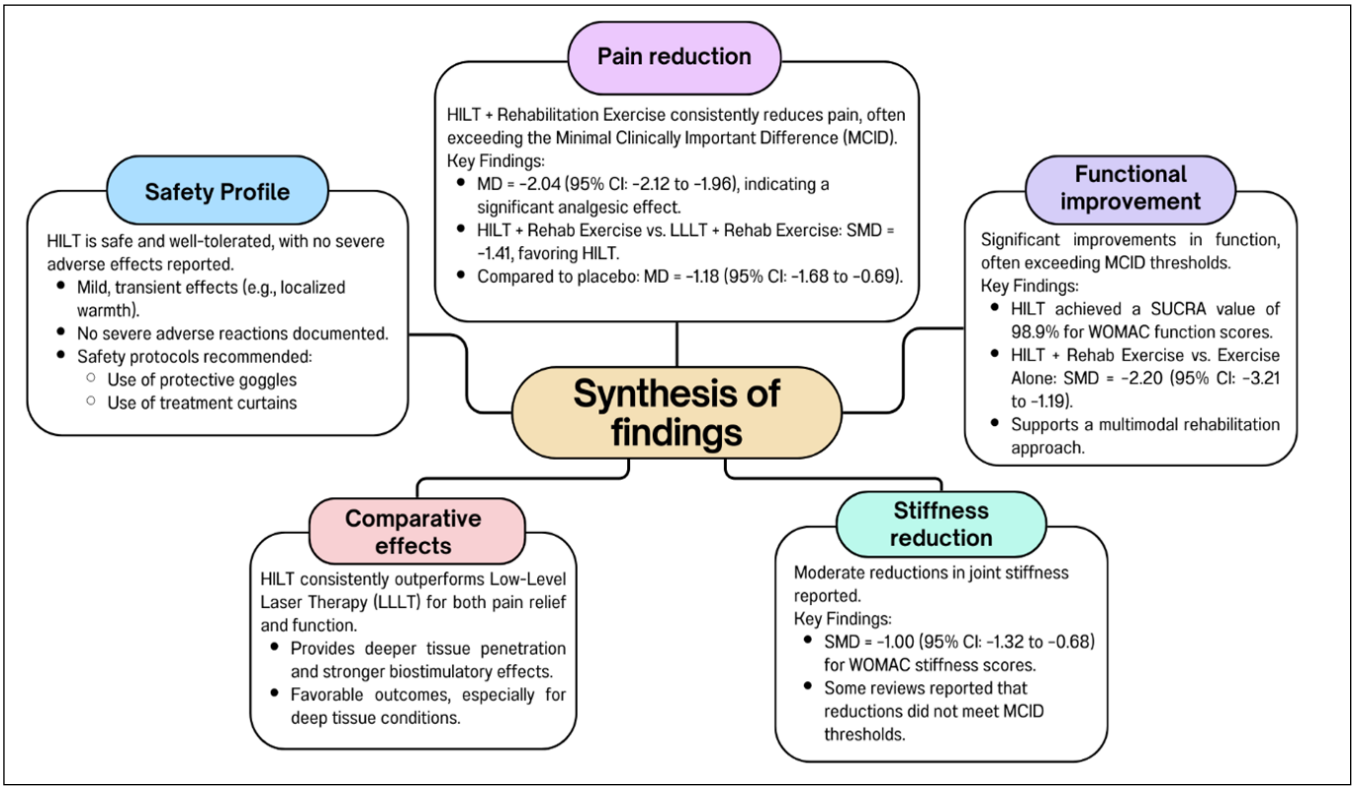

Figure 2. Summary of key findings from systematic reviews on the effectiveness of HILT combined with rehabilitation exercise in the management of KOA.

Functional improvement

HILT has been associated with significant improvements in physical function, with multiple systematic reviews highlighting functional gains that exceed MCID thresholds.[4,12,14] A meta-analysis reported that HILT outperformed other physical therapy modalities in improving Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) function scores, achieving a Surface Under the Cumulative Ranking (SUCRA) value of 98.9%, positioning it as the most effective intervention among those analysed.[4] Evidence also indicates that HILT combined with exercise leads to greater functional improvements compared with exercise alone, reinforcing the value of a multimodal rehabilitation approach.[12,14,25] For example, one systematic review [25] demonstrated significant improvements in WOMAC function scores for HILT combined with rehabilitation exercise (MD = –2.20; 95% CI: –3.21 to –1.19), providing strong support for its role in functional rehabilitation. Similarly, another recent systematic review [14] reported consistent benefits for WOMAC function (SMD = –0.70; 95% CI: –1.10 to –0.30) compared with placebo, further confirming the value of combining HILT with rehabilitation exercise.

Stiffness reduction

Multiple systematic reviews have reported reductions in stiffness following HILT intervention, though the clinical relevance of these findings remains uncertain.[3,4,12] One systematic review and meta-analysis found that HILT combined with exercise produced significant improvements in WOMAC stiffness scores (MD = –0.84; 95% CI: –1.43 to –0.24) compared with exercise alone, indicating a meaningful adjunctive effect.[12] Another meta-analysis also reported significant improvements in stiffness (MD = –1.00; 95% CI: –1.32 to –0.68).[3] However, some evidence suggests that although reductions were statistically significant, they did not consistently exceed MCID thresholds, indicating limited clinical significance in certain patient populations.[4]

Comparative effects: HILT vs LLLT

Several systematic reviews have compared HILT and LLLT, with findings consistently favouring HILT for pain relief and functional improvements.[4,12,14,15] Indirect evidence shows that HILT combined with exercise produced significantly greater improvements in knee pain compared with exercise alone, with a mean difference of –2.06 (95% CI: –3.14 to –0.98; $p < 0.001$) based on four primary trials.[12] In contrast, LLLT combined with exercise also demonstrated significant benefits over exercise alone, but the effect size was smaller, with a mean difference of –0.67 (95% CI: –1.05 to –0.29; $p<0.001$) across seven trials.[12] This difference in magnitude suggests that while both modalities are effective, HILT achieves more clinically meaningful reductions in pain, likely due to its deeper tissue penetration and stronger photobiostimulatory and photothermal effects.

Network meta-analyses further ranked HILT among the most effective physical therapy modalities for functional outcomes, and additional evidence reported superior results when comparing HILT plus exercise with LLLT plus exercise.[4,25] Although both modalities improve KOA symptoms, HILT was consistently associated with more pronounced benefits, particularly in deeper tissues.[4,25] Worth noting, these conclusions are based on indirect comparisons, as no systematic review has provided direct head-to-head analyses between HILT and LLLT.

Safety profile

HILT is consistently reported as safe and well tolerated, with only mild and temporary effects such as localized warmth or discomfort.[3,4,12,13] One review highlighted its non-invasive and painless nature, supporting its suitability for long term use.[13] Another confirmed no serious adverse events across included studies, reinforcing its favourable safety profil.[4] Additionally, the importance of safety measures is emphasized, including the use of protective goggles for both patients and practitioners and treatment curtains to prevent unintended laser exposure.[3,12]

DISCUSSION

This umbrella review synthesizes evidence from seven high-quality systematic reviews on the effects, safety, and clinical use of HILT for KOA. Findings consistently

showed that HILT combined with rehabilitation exercise effectively reduced pain and improved physical function, often surpassing MCID thresholds. It also had a favourable safety profile, with only mild, transient side effects reported, supporting its use as a non-invasive, well -tolerated option. While exercise therapy is widely recognized as a first-line, evidence-based intervention for KOA, emerging evidence suggests that it may not fully address the multifactorial nature of the condition when used in isolation.[26] Factors such as persistent pain, inflammation, and structural joint changes can limit participation and slow functional gains, indicating that exercise therapy alone may not be sufficient to achieve optimal outcomes without adjunctive interventions like HILT, which can enhance pain relief and tissue healing, thereby facilitating more effective rehabilitation. However, variations in treatment protocols and limited long-term data underscore the need for standardized guidelines and further research.

The included systematic reviews consistently report significant pain reduction following the use of HILT as an adjunct with rehabilitation exercise, with meta-analyses demonstrating substantial effect sizes compared to sham or conventional interventions. For instance, one review that analysed nine RCTs reported an MD of -2.04 in VAS scores, indicating a robust analgesic effect.[14] These findings are supported by the photobiological mechanisms of HILT, which include deep tissue penetration, modulation of inflammatory pathways, and stimulation of cellular regeneration.[18] HILT operates at wavelengths ranging from 808 to 1064 nm,[27] allowing it to penetrate deeper into tissues compared to LLLT, targeting key structures such as the synovial membrane, cartilage, and subchondral bone.[28] The photobiomodulation effects are mediated through the absorption of photons by mitochondrial chromophores, leading to increased adenosine triphosphate (ATP) production, enhanced cellular metabolism, and reduced oxidative stress.[29,30] These mechanisms contribute to the anti-inflammatory and analgesic effects observed in KOA, including the reduction of pro-inflammatory cytokines, as well as the modulation of pain pathways and release of endogenous opioids.[29]

In addition to pain relief, HILT significantly improves physical function, as measured using the WOMAC. Some reviews reported SMD as high as -2.20, exceeding MCID thresholds.[4,12] The combination of HILT with rehabilitation exercises yields superior outcomes compared to either intervention alone. For example, one review found that HILT combined with rehabilitation exercise resulted in greater improvements in pain and function compared to exercise alone or LLLT combined with rehabilitation exercise.[12] This synergistic effect is attributed to HILT's ability to reduce pain and inflammation, enabling individuals with KOA to engage more effectively in physical therapy and strengthening exercises.[29] Furthermore, HILT enhances tissue repair by stimulating collagen synthesis and promoting angiogenesis, which are critical for functional recovery in KOA.[29] These biological effects, combined with the mechanical benefits of exercise, create a multimodal approach that addresses both symptoms and underlying pathophysiology.[31]

It is also observed that HILT offers superior therapeutic outcomes compared to LLLT,[15] particularly in pain relief and functional improvement, due to its higher energy densities and deeper tissue penetration.[4,12,31] However, variability in laser parameters, such as wavelength, energy density, and treatment duration, remains a significant limitation, underscoring the need for standardized protocols to optimize treatment efficacy.[12] The safety profile of HILT is consistently favourable, with no serious adverse events reported. The most commonly observed side effects include localized warmth and temporary discomfort, which are mild and transient.[4,13] This reinforces HILT's suitability for long-term clinical use, particularly for individuals who may not tolerate pharmacological treatments well.

Strengths and limitations

This umbrella review provides a comprehensive synthesis of systematic reviews evaluating the effects, safety, and clinical application of HILT in KOA. A key strength is the rigorous methodological appraisal using AMSTAR-2 and PRISMA tools, which ensures high-quality evidence integration. The CCA score of 0.047 further indicates

only minor overlap among primary studies, reducing redundancy and strengthening the robustness of the findings. An important consideration is the diversity of exercise protocols reported across the reviews. Strengthening, stretching, aerobic, and balance training were commonly included, yet the type, intensity, and progression of exercises varied. While this reflects routine physiotherapy practice, it also introduces heterogeneity that may partly explain differences in effect sizes. The frequent inclusion of multimodal programmes aligns with current best practice guidelines for KOA rehabilitation.[2,8] Future trials should provide clearer descriptions of exercise type, progression, and supervision to improve comparability and clarify which exercise modalities yield the greatest benefits when paired with HILT.

Another limitation is the absence of direct comparisons between HILT alone and HILT combined with rehabilitation exercise. Although the combined approach was most commonly applied, none of the included systematic reviews conducted subgroup analyses by intervention type. This reflects the routine integration of exercise in KOA care but limits the ability to determine whether improvements are attributable to HILT itself or to its combination with exercise. Addressing this gap requires well-designed randomised controlled trials that directly compare HILT monotherapy with HILT plus exercise. Finally, heterogeneity in HILT treatment protocols including variations in wavelength, energy density, and session frequency complicates the development of standardised clinical guidelines. In addition, the limited availability of long-term follow-up data restricts conclusions about sustained benefits, highlighting the need for longitudinal studies to support clinical implementation.

CONCLUSION

This umbrella review consolidates evidence from seven systematic reviews, demonstrating that HILT is a safe and effective intervention for managing KOA. HILT with the combination of rehabilitation exercise, significantly reduces pain and improves physical function, often exceeding the MCID. Its greater efficacy compared to LLLT and its favourable safety profile make it a promising non-invasive adjunct for KOA. Clinicians should consider integrating HILT into conventional physiotherapy to optimize outcomes for individuals with KOA.

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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REVIEW ARTICLE

Exercise, GLUT4 and Skeletal Muscle Glucose Uptake: Advances and Emerging Directions

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ABSTRACT

Skeletal muscle is the principal site of postprandial glucose disposal, and its exercise-stimulated glucose uptake is a cornerstone of metabolic health. This process depends on the glucose transporter GLUT4, which is regulated by both insulin- and contraction-stimulated pathways. Understanding exercise-driven GLUT4 dynamics is crucial for combating insulin resistance and type 2 diabetes. Over the past decades, research has progressed from descriptive physiology to a mechanistic framework, identifying key insulin-independent regulators such as AMPK, Rab GTPases, SNAREs, Rac1, and redox mediators. Emerging methodologies, including high-resolution imaging, quantum dot tracking, and proteomics profiling, have provided insight into vesicle docking, fusion, and signalling convergence. Comparative exercise studies reveal modality-specific effects (e.g., HIIT) and that regulation varies by age, sex, and metabolic status, highlighting the need for population-specific approaches. Nevertheless, important questions remain: the kinetics of GLUT4 exocytosis and endocytosis in human muscle remain incompletely defined, and the integration of redox signalling with canonical kinases such as AMPK and CaMKII is poorly understood. Moreover, most mechanistic insights are derived from rodent models or young male subjects, limiting generalisability to elderly, female, or insulin-resistant populations. Addressing these gaps requires translational studies combining advanced imaging, CRISPR reporters, and molecular phenotyping with human exercise interventions. Integrating exercise with pharmacological or nutritional strategies may also unlock synergistic effects on glucose regulation. In conclusion, GLUT4 sits at the nexus of exercise biology and metabolic disease. Elucidating its regulation across diverse populations is pivotal for advancing precision exercise medicine and developing targeted interventions for insulin resistance and type 2 diabetes.

Keywords:
Exercise, skeletal muscle, glucose uptake, GLUT4, insulin resistance.

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INTRODUCTION

The ability of skeletal muscle to increase glucose uptake during exercise has been recognised for nearly a century, with early studies using arteriovenous balance and isotopic tracers establishing muscle contraction as a potent driver of glucose disposal.[1] This foundational work laid the groundwork for later discoveries that muscle glucose uptake can be stimulated independently of insulin, offering key insights into how exercise preserves glycemic control in insulin-resistant states.[2] Central to this process is the glucose transporter type 4 (GLUT4), identified in the late 20th century as the primary mediator of insulin- and contraction-stimulated glucose uptake.[3] GLUT4 accounts for the majority of postprandial glucose disposal in skeletal muscle and is tightly regulated by two complementary pathways: insulin signaling, which mobilizes GLUT4 via phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) cascades and SNARE-mediated vesicle fusion,[4] and contraction-stimulated pathways involving AMP-activated protein kinase (AMPK), calcium-calmodulin signaling, and nitric oxide (NO).[5] In the long term, chronic exercise enhances GLUT4 expression through transcriptional regulators such as myocyte enhancer factor 2 (MEF2), contributing to improved insulin sensitivity and metabolic health.[6]

Rapid advances have refined our understanding of GLUT4 regulation, revealing a complex interplay between energy sensors (AMPK), vesicle trafficking proteins such as Ras-related protein in brain (Rab8a, Rab10), and cytoskeletal elements such as Ras-related C3 botulinum toxin substrate 1 (Rac1) and soluble N-ethylmaleimide–sensitive factor attachment protein receptor (SNAREs).[7] Despite these developments, key gaps remain, particularly regarding the kinetics of GLUT4 trafficking in human tissues, the roles of reactive oxygen species (ROS) and NO, and regulatory differences across sex, age, and metabolic status.[8] This review aims to synthesise recent insights into exercise-regulated GLUT4 dynamics, emphasizing molecular mechanisms, methodological innovations, and translational implications for metabolic disease. Particular focus is given to vesicle trafficking kinetics, redox signaling, and population-specific adaptations, to inform personalised strategies for improving skeletal muscle glucose uptake.[9] The next section outlines the current consensus on exercise-regulated GLUT4 dynamics, setting the stage for recent advances and future directions.

Current Understanding

To understand recent advances in the next section, it is first important to outline current knowledge of how exercise influences skeletal muscle glucose uptake through tightly integrated vascular and metabolic mechanisms. For instance, in moderate to intense exercise, vasodilatory signals such as NO and prostacyclin increase skeletal muscle blood flow, thereby enhancing substrate delivery.[10] This rise in perfusion is accompanied by greater capillary recruitment, expanding the exchange surface for glucose and insulin. Although these adaptations are impaired in obesity and insulin resistance, they can be restored with regular exercise training.[11] At the systemic level, hepatic glucose output also rises as insulin levels fall, ensuring adequate arterial glucose availability to sustain contractile activity.[12] Additionally, redistribution of blood flow toward nutritive microvascular pathways further optimises glucose access at the tissue level.[13]

At the cellular level, these hemodynamic adaptations converge with contraction-induced mobilisation of GLUT4 to the sarcolemma, coupling increased delivery with enhanced transporter availability.[14] Classic studies established that GLUT4 trafficking involves small guanosine triphosphatase (GTPases) and SNARE fusion machinery, with signaling input from both insulin- and contraction-activated pathways.[15] Insulin drives vesicle fusion through endomembrane trafficking routes, whereas contraction engages distinct, parallel signaling processes to achieve GLUT4 translocation.[16] Contraction also recruits mediators such as AMPK, Rac1, and reactive oxygen/nitric oxide species, which operate independently of insulin to ensure glucose uptake[17] (Figure 1).

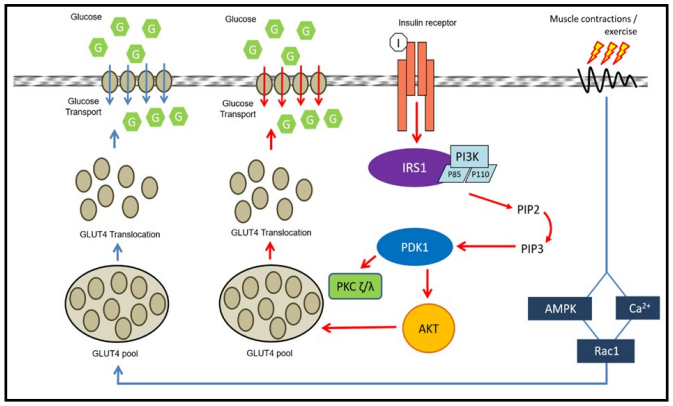

Figure 1: Dual Pathways of GLUT4-Mediated Glucose Uptake in Skeletal Muscle. Glucose uptake in skeletal muscle occurs through two major, complementary mechanisms. Insulin signaling activates the insulin receptor and downstream IRS–PI3K–PDK1–Akt signaling, promoting translocation of GLUT4 vesicles from intracellular pools to the sarcolemma. In parallel, muscle contraction/exercise stimulates insulin-independent pathways involving AMPK, Ca^{2+}-related signaling, and Rac1, which also drive GLUT4 translocation. These converging pathways increase the number of GLUT4 transporters at the cell surface, enhancing glucose entry into muscle cells.

Following GLUT4 translocation, glucose enters the myofiber and is rapidly phosphorylated by hexokinase II (HKII), the rate-limiting enzyme for intracellular glucose metabolism. Exercise enhances HKII expression and activity through AMPK-dependent mechanisms, ensuring efficient trapping of glucose as glucose-6-phosphate (G-6-P).[18] This step is subject to feedback inhibition by G-6-P to avoid excess metabolite accumulation.[19] Muscle glycogen availability also modulates these processes: low glycogen amplifies AMPK activation and GLUT4 translocation, while high glycogen suppresses these responses, reflecting a substrate-sensing mechanism that helps balance energy supply and demand.[20]

Nutritional status further shapes exercise-mediated glucose metabolism. Short-term high-fat feeding, for example, impairs glycogen repletion and alters post-exercise glucose handling, highlighting the importance of diet–exercise interactions in metabolic regulation.[21] These coordinated responses become especially critical at higher exercise intensities, where AMPK activation enhances both GLUT4 translocation and HKII activity to maximize glucose disposal.[22]

Together, this body of work establishes a framework in which vascular adaptations, GLUT4 trafficking, and intracellular metabolism act in concert to facilitate glucose uptake during exercise. Chronic adaptations, such as increased GLUT4 abundance and improved muscle oxidative capacity, further enhance both basal and stimulated glucose uptake, contributing to long-term improvements in insulin sensitivity and metabolic health.[6] Despite these advances, questions remain regarding how contraction-specific signals uniquely regulate GLUT4, the degree of redundancy between insulin- and exercise-activated pathways, and the influence of muscle fiber type on glucose handling.[23]

Recent Advances

Advances in Exercise-Stimulated Signaling Pathways

Over the past decade, substantial progress has been made in understanding how exercise stimulates GLUT4 translocation in skeletal muscle through insulin-independent signaling. A key player in this process is AMPK, particularly the α2 isoform, which becomes activated during muscle contraction and initiates GLUT4 mobilization independently of insulin.[24] One major way AMPK promotes GLUT4 trafficking is by phosphorylating Rab GTPase-activating proteins (RabGAPs), including Tre-2/Bub2/Cdc16 domain family members (TBC1D1 and TBC1D4). This phosphorylation inhibits their suppressive effects on Rab proteins such as Rab8A and Rab10, which in turn coordinate the movement of GLUT4-containing vesicles toward the sarcolemma for membrane fusion and glucose uptake.[7]

Furthermore, phosphorylation of TBC1D4 by both AMPK and AKT also reveals an important signaling convergence point. For instance, AMPK-mediated phosphorylation at specific sites can modulate or enhance subsequent AKT-dependent phosphorylation, forming a molecular basis for the additive effects of exercise and insulin on skeletal muscle glucose uptake.[25] Moreover, beyond Rab GTPase regulation, vesicle docking and fusion at the membrane are coordinated by soluble N-ethylmaleimide–sensitive factor attachment protein receptor (SNARE) complexes. Hence, vesicle-associated membrane protein 2 (VAMP2) and the syntaxin-binding protein Munc18c play key roles in vesicle fusion in insulin -responsive tissues. While the roles of VAMP2 and Munc18c in contraction-stimulated trafficking are less well-defined than in insulin-mediated pathways, the underlying mechanisms have been characterized largely in adipose and cellular model systems and are thought to extend to skeletal muscle, where these proteins are believed to contribute meaningfully to GLUT4 vesicle fusion.[26]

Muscle contraction also engages multiple insulin-independent signaling modules that promote GLUT4 mobilization. These include calcium-sensitive messengers (e.g., nicotinic acid adenine dinucleotide phosphate (NAADP) and cyclic ADP-ribose), Rac1-dependent actin remodeling, and the CaMKII–Kalirin–Rac1 signaling cascade. Together, these pathways bypass classical insulin signaling to support glucose uptake during exercise.[27] Collectively, these findings underscore the robustness of the exercise-activated GLUT4 pathway, driven by redundant and complementary signaling systems that ensure glucose uptake even under insulin-resistant conditions.

Redox Biology in GLUT4 Regulation

Redox signaling, particularly involving ROS and NO, has emerged as a potential modulator of contraction-induced GLUT4 translocation, although its role in humans remains less well established than in experimental models. Much of the mechanistic insight currently derives from rodent studies. In these models, both hydrogen peroxide (H_2O_2) and NO, especially that produced by neuronal nitric oxide synthase (nNOS), enhance skeletal muscle glucose uptake during contraction via pathways that can

operate independently of AMPK. This redox-mediated effect is attenuated by antioxidant treatment such as N-acetylcysteine, particularly during high-intensity exercise, supporting a physiological signaling role for ROS rather than purely oxidative damage.[28] However, glucose uptake is preserved in nNOS-deficient mice, suggesting compensatory mechanisms, possibly involving AMPK or other parallel pathways, can sustain glucose transport in the absence of nNOS.[29]

In humans, evidence for redox involvement is more limited and largely functional rather than mechanistically resolved. Studies indicate that NADPH oxidase 2 (NOX2)-derived ROS contribute to contraction-stimulated glucose uptake, and pharmacological inhibition of NO synthase can reduce exercise-induced skeletal muscle glucose transport.[30] These findings suggest that redox signaling participates in human muscle glucose regulation, but the precise molecular targets and their relationship to canonical GLUT4 trafficking pathways remain unclear. The relative contribution of ROS versus NO also appears to depend on exercise intensity, with ROS-related signaling becoming more prominent at higher workloads.[31]

Overall, while redox modulation of glucose uptake is well supported in rodent muscle, translation of specific molecular mechanisms to humans remains incomplete, and current human data should be interpreted as evidence for involvement rather than definitive pathway mapping. Further research is needed to determine how redox signals integrate with established contraction-mediated pathways and whether mechanisms defined in animal models apply directly to human skeletal muscle physiology.

Conceptual Integration of Proposed Mechanisms

Current evidence supports several, not mutually exclusive, models for how redox signals influence GLUT4 trafficking during contraction.[28] One model proposes that ROS, particularly H_2O_2 derived from NOX2, act upstream of canonical metabolic kinases, modulating AMPK, CaMKII, or other contraction-sensitive kinases to amplify established GLUT4 trafficking pathways.[27] A second model suggests more direct redox effects on cytoskeletal remodelling and vesicle trafficking proteins, potentially influencing Rac1 activation or SNARE-associated processes involved in GLUT4 vesicle docking and fusion.[27] A third possibility is that NO-related signalling operates through cyclic GMP- and Ca^{2+}-dependent mechanisms that intersect with contraction-stimulated pathways at multiple nodes.[28] Importantly, these mechanisms are not mutually exclusive and may vary with exercise intensity, redox load, and muscle metabolic state.[31]

At present, the strongest mechanistic support for these pathways comes from rodent models, whereas in humans, redox signalling is supported mainly by functional and pharmacological evidence rather than direct molecular mapping.[31]

Methodological Innovations in GLUT4 Trafficking Research

Recent advances in imaging and proteomic technologies have significantly enhanced our ability to study GLUT4 regulation in skeletal muscle at both molecular and cellular resolution. High-resolution fluorescence microscopy and live-cell imaging now allow direct visualization of GLUT4 dynamics in intact human muscle fibers, moving beyond earlier reliance on indirect markers.[32] In addition, quantum dot labeling has further improved temporal resolution by enabling long-term, high-fidelity tracking of individual GLUT4 vesicles during docking and fusion at the plasma membrane.[33]

Proteomic profiling has also yielded new insights, identifying previously unrecognised GLUT4 interactors such as vacuolar protein sorting-associated protein 13A / 13C (VPS13A and VPS13C), which suggest that the regulatory network extends beyond the canonical Rab–SNARE machinery.[34] Proximity labeling combined with mass spectrometry has revealed dynamic phosphorylation sites on TBC1D1 and TBC1D4, providing greater resolution of AMPK- and Akt-dependent signaling mechanisms.[25] Importantly, many of these methods have been applied in both rodent and human systems, increasing the translational relevance of basic discoveries. However, caution is warranted when interpreting findings

from studies that rely on protein overexpression cell lines, as these conditions may not fully capture the behavior of GLUT4 vesicles in native muscle tissue.

Differential Effects of Exercise Modalities

Different types of exercise training exert modality-specific effects on GLUT4 expression, translocation, and glucose uptake capacity in skeletal muscle. Aerobic endurance training consistently enhances insulin sensitivity and GLUT4 translocation, primarily by increasing muscle capillarization and mitochondrial function, which together improve glucose delivery and oxidation efficiency.[35] Resistance training, while less studied in this context, promotes glucose uptake by increasing skeletal muscle mass and total glucose disposal capacity. Some evidence also suggests that resistance exercise may activate distinct intracellular signaling pathways, such as those involving mechanical stress or mechanistic target of rapamycin complex 1 (mTORC1), which could contribute to GLUT4 mobilization. Notably, detraining reduces insulin-stimulated glucose uptake when normalized to muscle mass, underscoring the metabolic importance of maintaining muscle tissue.[36]

High-intensity interval training (HIIT) has emerged as a particularly potent stimulus for GLUT4 upregulation. Remarkably, as few as six HIIT sessions can increase GLUT4 protein expression by up to 369% in individuals with type 2 diabetes, alongside improvements in mitochondrial function and glycolipid metabolism.[37] Clinical trials also show that HIIT enhances skeletal muscle glucose extraction not merely through increased perfusion, but by improving intracellular glucose uptake mechanisms, including both insulin receptor signaling and insulin-independent pathways such as AMPK activation. These adaptations make HIIT a promising intervention for insulin-resistant individuals.[38] While these findings clearly demonstrate the distinct benefits of different exercise modalities, future studies should investigate whether combining aerobic and resistance training produces additive or synergistic effects on GLUT4 regulation, particularly in populations at risk for type 2 diabetes.

GLUT4 Regulation Across Special Populations

Recent studies suggest that GLUT4 regulation is strongly influenced by factors such as age, sex, and metabolic status, although the underlying mechanisms are not yet fully understood. In insulin-resistant and obese individuals, GLUT4 expression is reduced in both skeletal muscle and adipose tissue, contributing to impaired glucose disposal, possibly through chronic inflammation, lipid accumulation, and disruptions in insulin signaling.[39] Importantly, exercise can bypass these signaling defects by activating contraction-induced pathways such as AMPK, thereby restoring GLUT4 translocation and improving glycemic control.[40] Aging is also associated with reduced GLUT4 abundance and diminished insulin sensitivity. However, both endurance and resistance training have been shown to restore GLUT4 function and improve metabolic health in elderly muscle.[40] This finding suggests that exercise remains a viable intervention across the lifespan, even when basal GLUT4 expression is compromised.

Sex differences further contribute to variability in GLUT4 regulation. Women generally exhibit higher GLUT4 expression and greater insulin sensitivity despite higher adiposity, which may be explained by hormonal influences such as estrogen-mediated enhancement of glucose uptake and potential differences in muscle fiber composition.[41] Nevertheless, the evidence is not uniform, with some studies reporting that men display distinct hepatic and peripheral insulin responses.[42] Collectively, these findings underscore the importance of tailoring exercise strategies to specific populations. Future mechanistic studies that account for sex, age, and metabolic phenotype will be critical for optimising exercise-based interventions targeting GLUT4 regulation.

Future Directions

Clarifying GLUT4 Trafficking Kinetics in Human Skeletal Muscle

A major unresolved challenge in the field is the incomplete understanding of GLUT4 trafficking kinetics in human skeletal muscle. Rodent studies using intravital and confocal imaging have demonstrated that GLUT4 vesicles rapidly insert into the membrane during

contraction but are reinternalized more slowly afterward, providing key insights into the temporal sequence of trafficking events.[43] Whether these dynamics accurately represent human physiology, however, remains uncertain.

Although recent imaging platforms have begun to visualize GLUT4 movement in human muscle fibers, most data still come from indirect measures or model systems that may not fully capture endogenous vesicle cycling.[8] The next step is to establish how GLUT4 exocytosis, docking, and reinternalization are quantitatively regulated in intact human tissue during and after exercise.

Future studies should aim to integrate real-time imaging with in situ biochemical assays to resolve how the timing of GLUT4 cycling contributes to both normal glucose tolerance and pathological states such as insulin resistance. Defining these kinetics in humans would provide a critical translational bridge between cellular mechanisms described in animal models and clinical exercise interventions.

Resolving the Role of Redox Signaling in Exercise-Induced Glucose Uptake

ROS and NO are consistently generated during muscle contraction, but their direct contributions to GLUT4 translocation in vivo remain unclear. Rodent studies show that hydrogen peroxide and nNOS-derived NO promote GLUT4 mobilization through AMPK-independent pathways, and antioxidant treatment can blunt this effect.[28] In humans, NOX2-derived ROS has been implicated as a regulatory signal, and pharmacological NOS inhibition has been shown to reduce exercise-stimulated glucose uptake.[30] A major challenge is disentangling redox-dependent effects from canonical signaling cascades such as AMPK, Rac1, and CaMKII, which are often co-activated during exercise. Future progress will require models that enable selective inhibition or knockout of specific redox enzymes, ideally in human muscle or advanced translational systems, to determine whether ROS and NO function as primary effectors, permissive cofactors, or modulatory amplifiers of contraction-mediated GLUT4 trafficking.

Mechanistic Studies in High-Risk Populations

A significant translational knowledge gap exists in understanding GLUT4 regulation in populations at highest metabolic risk, including obese, prediabetic, and elderly individuals. These groups consistently exhibit reduced GLUT4 abundance and defects in vesicle trafficking, yet few studies have pinpointed the precise molecular disruptions or identified the signaling nodes where regulation fails.[9] This lack of mechanistic insight limits the development of targeted therapies. Future research should prioritize in vivo analyses using human muscle biopsies and engineered muscle constructs derived from high-risk individuals. Key questions include whether AMPK and Rac1 signaling remain responsive to contraction, whether SNARE complex assembly is impaired, and whether chronic training can reverse vesicle tethering or membrane fusion defects. Addressing these questions will be essential for translating GLUT4 biology into precision exercise prescriptions and novel pharmacological strategies to combat metabolic diseases.

Integrative Exercise-Pharmacological Strategies

Advances in GLUT4 biology now open the possibility of combining exercise with pharmacological or nutritional agents to amplify glucose uptake. AMPK activators such as 5-Aminoimidazole-4-carboxamide ribonucleotide (AICAR), although limited in clinical applicability, have demonstrated the potential to mimic contraction-induced GLUT4 translocation in both rodents and humans.[44] Emerging evidence also suggests that natural bioactives like tectorigenin can upregulate GLUT4 through AMPK and protein kinase A catalytic subunit alpha (PKACα) signaling, highlighting nutritional compounds as possible adjuncts to exercise.[45] In addition, NO donors may enhance GLUT4-mediated uptake indirectly by improving skeletal muscle perfusion.[46]

Biotechnological approaches such as gene modulation of transcriptional regulators (e.g., MEF2 and GLUT4 enhancer factor) and the development of engineered muscle constructs represent exciting opportunities for precision upregulation of GLUT4.[47] Future studies should systematically evaluate these interventions in combination

with exercise, particularly in insulin-resistant populations, to determine whether they can yield additive or synergistic improvements in glucose regulation.

Personalised Exercise Medicine for GLUT4 Regulation

A key future direction is the personalisation of exercise interventions for GLUT4 regulation, guided by genetic, epigenetic, demographic, and health-related factors. Polymorphisms in metabolic genes, including those influencing GLUT4 expression and signaling efficiency, have been linked to differences in both insulin sensitivity and exercise responsiveness.[48] Age-specific training protocols have already demonstrated improvements in GLUT4 expression and muscle quality in elderly populations [49], while sex-specific differences in GLUT4 regulation and insulin sensitivity suggest that tailored exercise strategies may be needed for women and men.[41]

In addition, patients with comorbidities such as diabetic kidney disease demonstrate variable responses to aerobic, resistance, and HIIT protocols, underscoring the importance of individualised intervention frameworks.[50] Moving forward, integrating genomics, molecular phenotyping, and clinical profiling will be critical to realize precision exercise medicine strategies that optimize GLUT4 regulation and improve metabolic health outcomes.

CONCLUSION

In summary, exercise-induced regulation of GLUT4 represents one of the most powerful natural mechanisms for maintaining glucose homeostasis. Through converging insulin and contraction pathways, skeletal muscle ensures continuous glucose uptake under both fed and fasting conditions. Advances in molecular and imaging techniques have revealed the complexity of this system, where AMPK, redox mediators, small GTPases, and SNARE proteins operate in an integrated network that sustains glucose transport even in insulin-resistant states.

While significant mechanistic insight has been gained, key challenges remain, particularly in bridging cellular mechanisms with human physiological responses and in addressing underrepresented populations, including women, older adults, and metabolically diverse individuals. Overcoming these gaps will require multidisciplinary and translational approaches that combine molecular profiling with clinical exercise research.

Therefore, understanding and harnessing GLUT4 biology offers a pathway to more precise and equitable strategies for metabolic health. This approach could transform exercise science from general recommendations into targeted, evidence-based interventions for metabolic disease prevention and management.

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REVIEW ARTICLE

The Involvement of Long Non-coding RNAs, MicroRNAs and Circular RNA in the Prediction of Cardiovascular Disease in Hypertensive Disorder of Pregnancy- A Scoping Review

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ABSTRACT

Hypertensive disorders of pregnancy (HDP) is a common condition in pregnant women affecting 5% to 10% of pregnancies worldwide. Women who have had HDP are at a higher risk of developing cardiovascular diseases (CVD) earlier in life compared to those who remained normotensive during pregnancy. HDP is associated with a significant increased risk of early-onset of CVD particularly hypertension and stroke, and this can lead to maternal mortality. Non-coding RNAs (ncRNAs) have been linked to HDP, particularly the long non-coding RNA (lncRNA), microRNA (miRNA), and circular RNA (circRNA). This scoping review identifies the most significant ncRNAs involved in predicting CVD in HDP. The protocol by Arksey and O'Malley was used in this scoping review. The steps were carried out in a systematic manner, including the identification of research questions, identification and selection of relevant studies, data charting and collating, summarizing the data, and reporting the findings. Multiple databases were searched for data collection, including Semantic Scholar, Scopus, PubMed Central, and Science Direct. In all thirty-one relevant studies were explored in this review. This review demonstrates the types, models, methodologies, and descriptions of non-coding RNAs associated with HDP. This review highlights that non-coding RNAs play a key role in predicting heart disease linked to high blood pressure in pregnancy by influencing blood vessels, inflammation, and stress, thus emphasizing their potential as early markers and the need for further study.

Keywords:
long non-coding RNA (lncRNA); microRNA (miRNA); Hypertensive disorders of Pregnancy (HDP); cardiovascular disease (CVD)

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INTRODUCTION

During a normal pregnancy, the mean arterial pressure (MAP) drops in the first trimester due to reduced vascular resistance, then gradually rises as blood volume and cardiac output increases, stabilizing by the third trimester. Hypertensive disorders of pregnancy (HDP) affect 5% to 10% of pregnancies and is rising due to increasing cardiometabolic diseases in younger women. Hypertension is defined as SBP≥130 mmHg or DBP ≥80 mmHg in non-pregnant adults, while in pregnancy, it includes chronic hypertension (BP≥140/90 mmHg before 20 weeks), gestational hypertension (BP≥140/90 mmHg after 20 weeks without proteinuria), and preeclampsia (BP≥140/90 mmHg after 20 weeks with proteinuria or end-organ dysfunction).[1]

HDP results from the failure of the maternal cardiovascular system to adapt to hemodynamic changes in pregnancy, involving the placental, vascular, and systemic factors. Inadequate trophoblast invasion leads to high-resistance, ischemic placental vessels, triggering hypoxia and antiangiogenic factors (sFlt-1, soluble endoglin) that impair endothelial function by reducing VEGF and PlGF. This in turn, causes vasoconstriction, increased vascular permeability, inflammation, and oxidative stress, worsening vascular damage. HDP is also linked to abnormal blood volume regulation, immune dysfunction, and genetic factors, including dysregulated non-coding RNAs.

HDP is strongly associated with an increased risk of maternal cardiovascular disease (CVD) later in life, including chronic hypertension, coronary artery diseases, heart failure, and stroke. Persistent endothelial dysfunction from HDP-induced vascular damage can lead to chronic inflammation, impaired vascular repair, and increased arterial stiffness, all of which elevate long-term cardiovascular risk.[1]

HDP are common pregnancy complications that significantly contribute to maternal morbidity and mortality while increasing the risk of early-onset CVD, particularly hypertension and stroke, within 1 to 10 years postpartum. HDP shares key risk factors with CVD, including obesity, insulin resistance, and dyslipidaemia, and serves as an early marker of these conditions. Women with a history of gestational hypertension or preeclampsia face a higher likelihood of developing chronic hypertension, a major driver of CVD.

Molecular and epigenetic mechanisms, such as the dysregulation of non-coding RNAs (lncRNAs, miRNAs, circRNAs), link HDP to cardiovascular complications by influencing inflammation, oxidative stress, and endothelial dysfunction. These vascular and systemic dysfunctions create a pathophysiological connection between HDP and CVD. Given this association, long-term cardiovascular monitoring and preventive care, including regular screening and lifestyle modifications, are essential for women with a history of HDP.[2]

Further research into the molecular pathways connecting HDP and CVD may lead to novel diagnostic tools and targeted interventions. HDP is not just a pregnancy-related condition but a key predictor of future cardiovascular health, highlighting the need for early recognition and proactive management to reduce long-term complications.[2]

NONCODING RNA IN HYPERTENSIVE DISORDERS OF PREGNANCY

Noncoding RNAs (ncRNAs) does not encode or translate into protein. There are more than 75% of human genome transcripted into noncoding RNAs (ncRNAs) that include microRNA (miRNA), long noncoding RNA (lncRNA) and circular RNA (circRNA).[3] miRNA is a small ncRNA with less than 200 nucleotides and plays important roles in regulating gene expression. lncRNAs are transcripts of more than 200 nucleotides without known protein-coding function and less abundant and far less conserved compared with protein coding genes.

They are implicated in epigenetic processes in the nucleus such as chromatin modification, transcription modulation, alternative splicing regulation and also regulates gene expression by activating or suppressing gene expression and translation.[4] circRNA endogenous ncRNA which have circular structure that function as transcriptional regulator. Numerous previous studies have demonstrated the involvement of noncoding RNAs (ncRNAs) in pathophysiological processes in humans including HDP. Therefore, ncRNAs may contribute as novel biomarkers in the diagnosis of HDP.[3]

METHODOLOGY

A scoping review was conducted following the Arksey and O'Malley's protocol. The review identified key studies on ncRNA involvement in HDP, with stages including research question identification, study selection, data charting, and synthesis. A comprehensive literature search was performed using databases such as Semantic Scholar, Scopus, PubMed Central, and Science Direct, focusing on articles published between 2012 and 2022. The following five stages were used to conduct the review:

Stage 1 Identifying the research question
Stage 2 Identifying relevant studies
Stage 3 Study selection
Stage 4 Charting the data
Stage 5 Collating, summarizing, and reporting the results

Stage 1 : Identifying the research question

Research questions are significant in providing guidelines for the studies conducted. Thus, they are important in preparing strategies for scoping review. The research question was: "What are the noncoding RNA involve in Hypertensive disorders of pregnancy (HDP)?"

Stage 2 : Identifying relevant studies

A comprehensive literature search was performed using databases such as Semantic Scholar, Scopus, PubMed Central, and Science Direct. Keywords were derived from Medical Subject Headings (MeSH), focusing on "Hypertensive Disorders of Pregnancy" and "noncoding RNA," with studies published between 2012 and 2022.

Stage 3 : Study selection

Study selection process involved several steps, as shown in *Figure 1*. Firstly, duplicate studies, conference papers, and review articles were excluded during the initial screening. The remaining studies were then evaluated based on their titles and abstracts according to the inclusion and exclusion criteria specified in *Table 1*. Articles that were incomplete or lacked full text were also excluded from the review.

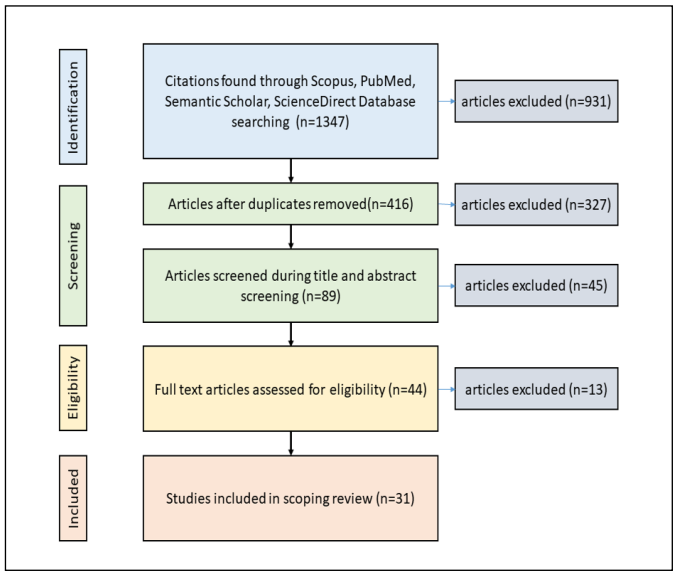

Figure 1 The flow of identification and screening process

Stage 4 : Charting the data

Data extraction involved collecting key information from each study, including the author(s), year of publication, titles of the articles, methodology used, research models, results, and discussions. This data was systematically charted to ensure a comprehensive overview of the relevant studies, allowing for the identification of significant findings related to noncoding RNAs in HDP.

Table I Inclusion and exclusion criteria

Criteria	Inclusion criteria	Exclusion criteria
Types and characteristic of sample	• Pregnancy related human or animal sample which involve in hypertension disease.	• Not hypertension related disease.
Methodology	• *In vivo* studies which produce qualitative and quantitative results.	• In silico studies.
Source of literatures	• Original research article available in English language. • Full text articles published from 2013 to 2023.	• Review articles, conference articles, npublished article which not available in English language. • Articles before stated time frame.

Stage 5 : Collating, summarizing and reporting the results

The remaining selected articles were analyzed to categorize significant noncoding RNAs (ncRNAs) and summarize their involvement in HDP.]

RESULTS

Literature search

Initially, 1347 articles were identified from the four databases. After removing 931 duplicates, conference papers, and review articles, 416 articles remained that met the inclusion and exclusion criteria. These articles were then screened based on their titles and abstracts, leading to the exclusion of 327 irrelevant studies. The remaining articles underwent full-text screening, ultimately resulting in the final selection of 31 studies, as summarized in Table 2.

Study characteristics

Among the 31 articles included in this review, the studies varied in their focus on different types of non-coding RNAs (ncRNAs) and their association with HDP. Specifically, 9 studies examined the involvement of long non-coding RNAs (lncRNAs), 21 studies investigated the role of microRNAs (miRNAs), and 1 study focused on circular RNAs (circRNAs). Each of these studies clearly identified the specific type of ncRNA studied and assessed its expression levels. The findings revealed that the expression levels of these ncRNAs correlated with the

pathogenesis of HDP, highlighting their potential as biomarkers for diagnosing the disease.

Majority of the studies involved human subjects, although a few researchers utilized animal models. The studies were conducted in several countries, namely China, Egypt, the Netherlands, Iran, Hungary, the Czech Republic, Istanbul, Korea, and Bahrain. All the studies included control groups, consisting of either normotensive pregnant women or normotensive female rats

Their research designs followed a consistent and structured approach, starting with the determination of subjects and sample preparation, followed by analysis of gene expression. The gene expression was predominantly measured using real-time PCR techniques, and all studies adhered to the protocol of the manufacturers. This methodology ensured that data collection was standardized and results were reliable across all the studies.

Table II. Summary of involvement of noncoding RNA in hypertensive disorders of pregnancy.

Study No.	Authors	Title	Country	Model	Methodology	Key Findings	Conclusions
1	Abd El Gayed, Eman Masoud, Abo Shady, Heba Maged, Elhelbawy, Mohammed, El Deen Arafat, Eman S. (2022)	Study the relationship between long non-coding RNA (CCAT1) expression and CDK4 expression levels in Egyptian patients with preeclampsia	Egypt	Human	RNA expression analysis	CCAT1 expression was significantly higher in preeclampsia patients	CCAT1 may be a potential biomarker for preeclampsia
2	El Gayed, Eman Masoud Abd, Zaid, Ibrahim Fathi, El Gayed, Alaa Masoud Abd, Zaki, Aziza Mahmoud Mohamed, Fouda, Eman Abd allah Mahmoud	Biochemical study on long non coding RNA gene expression in women having preeclampsia	Egypt	Human	RNA expression study	Altered expression of lncRNAs in preeclampsia cases	lncRNA expression profiles can be used to predict preeclampsia
3	Wang, Qiuhong, Lu, Xun, Li, Chunyan, Zhang, Wen, Lv, Yan, Wang, Luyao, Wu, Lan, Meng, Li, Fan, Yuru, Ding, Hongjuan, Long, Wei, Lv, Mingming (2019)	Down-regulated long non-coding RNA PVT1 contributes to gestational diabetes mellitus and preeclampsia via regulation of human trophoblast cells	China	Human	RNA analysis, trophoblast cell study	PVT1 expression was down-regulated in preeclampsia and gestational diabetes	PVT1 may serve as a therapeutic target for these conditions
4	Lei, Di, Fang, Congcong, Deng, Na, Yao, Baozhen, Fan, Cuifang (2021)	Long noncoding RNA expression profiling identifies MIR210HG as a novel molecule in severe preeclampsia	China	Human	RNA profiling	MIR210HG is significantly overexpressed in severe preeclampsia	MIR210HG could be a potential biomarker for severe preeclampsia
5	Lip, Simone V., Boekschoten, Mark V., Hooiveld, Guido J., van Pampus, Mariëlle G., Scherjon, Sicco A., Plösch, Torsten, Faas, Marijke M. (2020)	Early-onset preeclampsia, plasma microRNAs, and endothelial cell function	Netherlands	Human	Plasma microRNA profiling	Specific microRNAs are altered in early-onset preeclampsia	Plasma microRNAs could serve as early biomarkers for preeclampsia
6	Adel, Sherihan, Mansour, Amal, Louka, Manal, F, Elmekkawi S, Swelam, Nahed (2017)	Evaluation of MicroRNA-210 and Protein tyrosine phosphatase, non receptor type 2 in Preeclampsia	Egypt	Human	MicroRNA and protein analysis	MicroRNA-210 is significantly altered in preeclampsia	MicroRNA-210 could be a potential diagnostic marker
7	Nejad, Reza Mola Ali, Saeidi, Kolsoum, Gharbi, Sedigheh, Salari, Zohreh, Saleh-Gohari, Nasrollah	Quantification of circulating miR-517c-3p and miR-210-3p levels in preeclampsia	Iran	Human	Circulating miRNA quantification	miR-517c-3p and miR-210-3p levels are significantly altered in preeclampsia	These miRNAs could be used as biomarkers for preeclampsia diagnosis
8.	Wang, Yonghong, Cheng, Keyan, Zhou, Wenli, Liu, Huiqiang, Yang, Taotao, Hou, Peiqin, Li, Xiaowei (2019)	miR-141-5p regulate ATF2 via effecting MAPK1/ERK2 signaling to promote preeclampsia	China	Human	miRNA regulation study	miR-141-5p regulates ATF2 and MAPK1/ERK2 signaling in preeclampsia	miR-141-5p may be involved in preeclampsia pathogenesis

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Study No.	Authors	Title	Country	Model	Methodology	Key Findings	Conclusions
9	Zheng, Dongying, Hou, Yue, Li, Yuanyuan, Bian, Yue, Khan, Muhanmmad, Li, Fan, Huang, Ling, Qiao, Chong (2020)	Long Non-coding RNA Gas5 Is Associated With Preeclampsia and Regulates Biological Behaviors of Trophoblast via MicroRNA-21	China	Human	RNA interaction study	Gas5 lncRNA interacts with miR-21 to affect trophoblast functions	Gas5 could be a therapeutic target for preeclampsia
10	Ghafari, Ali, Lessan Peze shki, Mahboob, Saffari, Mojtaba (2020)	MICRO RNA 155, 210, 494, 29B AND 34A EXPRESSION PROFILE IN PREECL AMPSIA AND NORMAL PREGNANCIES	Iran	Human	miRNA expression profiling	Expression of miR-155, miR-210, miR-494, miR-29B, and miR-34A is altered in preeclampsia	miRNA expression profiles can differentiate preeclampsia from normal pregnancies
11	Abdelaleem, Omayma, Mahmoud, Rania, Shaker, Olfat, Hemeda, Nada, Ahmed, Naglaa (2018)	LNC RNA HULC AS A NOVEL DIAGNOSTIC AND THERAPEUTIC TARGET IN PREECLAMPSIA	Egypt	Human	lncRNA analysis	LncRNA HULC is significantly upregulated in preeclampsia	LncRNA HULC could be used for early detection and therapy
12	Chen, Dan, He, Biwei, Zheng, Panchan, Wang, Shuying, Zhao, Xueya, Liu, Jinyu, Yang, Xingyu, Cheng, Weiwei (2021)	Identification of mRNA-, circRNA- and lncRNA-Associated ceRNA Networks and Potential Biomarkers for Preeclampsia From Umbilical Vein Endothelial Cells	China	Human	ceRNA network analysis	Identified key mRNA, circRNA, and lncRNA in preeclampsia	These molecules could be potential biomarkers for preeclampsia diagnosis
13	Lázár, Levente, Nagy, Bálint, Molvarec, Attila, Szarka, András, Rigó, János (2012)	Role of hsa-miR-325 in the etiopathology of preeclampsia	Hungary	Human	miRNA profiling	miR-325 is significantly altered in preeclampsia	miR-325 could be a novel marker for preeclampsia
14	Zhou, Dexia, Qu, Bin, Zhang, Xuan (2022)	Diagnostic value of serum miR-25-3p in hypertensive disorders in pregnancy	China	Human	miRNA profiling	miR-25-3p is upregulated in hypertensive disorders of pregnancy	miR-25-3p could be a diagnostic marker for hypertensive pregnancy disorders
15	He, Xin, Ding, Dan Ni (2022)	Expression and clinical significance of miR-204 in patients with hypertensive disorder complicating pregnancy	China	Human	miRNA expression study	miR-204 expression is altered in hypertensive disorders of pregnancy	miR-204 could serve as a diagnostic marker for hypertensive pregnancy disorders
16	He, Xin, Ding, Danni (2022)	High miR-200a-3p expression has high diagnostic values for hypertensive disorders complicating pregnancy and predicts adverse pregnancy outcomes	China	Human	miRNA profiling	miR-200a-3p is elevated in hypertensive disorders of pregnancy	miR-200a-3p may predict adverse pregnancy outcomes
17	Yang, Hai Yan, Jiang, Ling (2022)	The involvement of long noncoding RNA APOA1-AS in the pathogenesis of preeclampsia	China	Human	lncRNA study	APOA1-AS is involved in the pathogenesis of preeclampsia	APOA1-AS may be a therapeutic target for preeclampsia
18	Tang, Qiuqin, Gui, Jing, Wu, Xian, Wu, Wei (2019)	Downregulation of miR-424 in placenta is associated with severe preeclampsia	China	Human	miRNA expression analysis	miR-424 is downregulated in severe preeclampsia	miR-424 could be used as a diagnostic marker for severe preeclampsia
19	Huang, Jin, Qian, Yating, Cheng, Qing, Yang, Jing, Ding, Hongjuan, Jia, Ruizhe (2020)	Overexpression of Long Noncoding RNA Uc.187 Induces Preeclampsia-Like Symptoms in Pregnancy Rats	China	Human	lncRNA overexpression study	Uc.187 overexpression induces preeclampsia-like symptoms	Uc.187 could be a target for preeclampsia therapy
20	Hromadnikova, Ilona, Kotlabova, Katerina, Dvorakova, Lenka, Krofta, Ladislav (2019)	Postpartum profiling of microRNAs involved in pathogenesis of cardiovascular/cerebrovascular diseases in women exposed to pregnancy-related complications	Czech Republic	Human	Postpartum miRNA profiling	MiRNAs related to cardiovascular diseases are altered postpartum	Postpartum miRNA profiling could be used for predicting long-term health outcomes
21	Biró, Orsolya, Alasztics, Bálint, Molvarec, Attila, Joó, József, Nagy, Bálint, Rigó, János (2017)	Various levels of circulating exosomal total-miRNA and miR-210 hypoxamiR in different forms of pregnancy hypertension	Hungary	Human	Exosomal miRNA profiling	Circulating exosomal miRNA levels vary across different types of pregnancy hypertension	miRNA profiling could aid in the diagnosis of pregnancy hypertension
22	Gao, Zheng, Wang, Li, Wang, Jinyun, Yang, Fengyong, Qu, Jin (2017)	Molecular mechanism of miR-181b in heart disease due to pregnancy-induced hypertension syndrome	China	Rats	miRNA mechanism study	miR-181b regulates heart disease caused by pregnancy-induced hypertension	miR-181b could be a target for therapeutic intervention in heart disease during pregnancy
23	Gunel, Tuba, Hosseini, Mohammad Kazem, Gumusoglu, Ece, Kisakesen, Halil Ibrahim, Benian, Ali, Aydinli, Kilic (2017)	Expression profiling of maternal plasma and placenta microRNAs in preeclamptic pregnancies by microarray technology	Istanbul	Human	miRNA profiling	Maternal plasma and placenta miRNAs are differentially expressed in preeclampsia	miRNA profiling could help diagnose preeclampsia

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Study No.	Authors	Title	Country	Model	Methodology	Key Findings	Conclusions
24	Wu, Gui Mei, Jin, Yan, Cao, Yan Min, Li, Ji Yun (2020)	The diagnostic value and regulatory mechanism of miR-200a targeting ZEB1 in pregnancy-induced hypertension	China	Human	miRNA target study	miR-200a targets ZEB1 in pregnancy -induced hypertension	miR-200a could be a diagnostic biomarker and therapeutic target
25	Jairajpuri, Deeba S., Malalla, Zainab H., Mahmood, Naeema, Almawi, Wassim Y. (2017)	Circulating microRNA expression as predictor of preeclampsia and its severity	Bahrain	Human	miRNA profiling	Specific microRNAs are predictive of preeclampsia and its severity	Circulating miRNAs could be used as biomarkers for preeclampsia
26	Liu, D.-F, Li, S.-M, Zhu, Q.-X, Jiang, W (2018)	The involvement of miR-155 in blood pressure regulation in pregnant hypertension rat via targeting FOXO3a	China	Rats	miRNA mechanism study	miR-155 regulates blood pressure during pregnancy by targeting FOXO3a	miR-155 could be a potential therapeutic target in hypertensive pregnancies
27	Kim, Suji, Park, Minsik, Kim, Ji Yoon, Kim, Taesam, Hwang, Jong Yun, Ha, Kwon Soo, Won, Moo Ho, Ryoo, Sungwoo, Kwon, Young Guen, Kim, Young Myeong (2020)	Circulating miRNAs Associated with Dysregulated Vascular and Trophoblast Function as Target-Based Diagnostic Biomarkers for Preeclampsia	Korea	Human	miRNA analysis	Dysregulated miRNAs in circulation are associated with vascular and trophoblast dysfunction	These miRNAs could be biomarkers for preeclampsia diagnosis
28	Hromadnikova, Ilona, Kotlabova, Katerina, Ondrackova, Marketa, Kestlerova, Andrea, Novotna, Veronika, Hympanova, Lucie, Doucha, Jindrich, Krofta, Ladislav (2013)	Circulating C19MC MicroRNAs in preeclampsia, gestational hypertension, and fetal growth restriction	Czech Republic	Human	MicroRNA profiling	C19MC microRNAs are differentially expressed in preeclampsia and related conditions	C19MC microRNAs could serve as biomarkers for pregnancy-related complications
29	Fan, Xufei, Lou, Jianyi, Zheng, et al. (2021)	Interference with lncRNA NEAT1 promotes the proliferation, migration, and invasion of trophoblasts by upregulating miR-411-5p and inhibiting PTEN expression	China	Human	lncRNA interference study	NEAT1 upregulates miR-411-5p and promotes trophoblast cell activity	NEAT1 may be a therapeutic target for trophoblast dysfunction
30	Hromadnikova, Ilona, Kotlabova, Katerina, Hympanova, Lucie, Krofta, Ladislav (2016)	Gestational hypertension, preeclampsia and intrauterine growth restriction induce dysregulation of cardiovascular and cerebrovascular disease associated microRNAs in maternal whole peripheral blood	Czech Republic	Human	miRNA profiling	Pregnancy complications lead to dysregulation of miRNAs associated with cardiovascular diseases	Maternal blood miRNAs could predict long-term health risks
31	Hany, Ayman M, Nasser, Yasser H, Ahmed, Hanan H, Rashed, Laila A, Mostafa, Mostafa M, Ibrahim, Walaa, Sanad, Salah A (2019)	Expression of Micro RNAs 206 and 133b and serum IL-17 levels in preeclamptic females	Egypt	Human	miRNA and IL-17 expression study	miR-206 and miR-133b levels are altered in preeclampsia	miR-206 and miR-133b could serve as biomarkers for preeclampsia

DISCUSSION

This scoping review highlights the significant roles of long non-coding RNAs (lncRNAs), microRNAs (miRNAs), and circular RNAs (circRNAs) in predicting cardiovascular diseases (CVD) associated with hypertensive disorders of pregnancy (HDP). By systematically reviewing 31 studies, we identified substantial evidence supporting the involvement of these non-coding RNA species in the pathogenesis and potential diagnosis of HDP-related cardiovascular complications.

Functions and Mechanisms of Long Non-Coding RNAs in HDP

Among the nine studies focusing on lncRNAs, a common theme is their regulatory role in gene expression, articularly in pathways relevant to HDP pathophysiology. LncRNAs influence endothelial function, inflammation, oxidative stress, and vascular remodeling, all of which are pivotal in HDP development and its long-term cardiovascular consequences. Elevated or reduced expression levels of specific lncRNAs were consistently associated with key biomarkers of HDP and its progression to CVD. These findings suggest that lncRNAs may serve as early predictors of CVD, allowing for timely intervention to mitigate cardiovascular risk. The reviewed studies highlighted the diverse regulatory functions of lncRNAs.

Many lncRNAs interact with chromatin-modifying proteins, DNA, or histones to influence gene expression epigenetically. They can recruit chromatin modifiers, such

as histone methyltransferases or demethylases, to specific genomic loci, resulting in chromatin remodeling and subsequent activation or repression of target genes. Additionally, some lncRNAs act as transcriptional regulators by interacting with transcription factors or other DNA-binding proteins. They can act as molecular scaffolds, guiding the formation of transcriptional complexes or acting as decoys by sequestering transcriptional regulators away from their target sites.[6]

Some lncRNAs participate in the regulation of RNA processing, including alternative splicing, RNA editing, and RNA stability. They can interact with splicing factors, RNA-binding proteins, or small nuclear ribonucleoprotein particles (snRNPs), influencing the processing and maturation of various RNA species. Some lncRNAs function as molecular scaffolds that facilitate the assembly of ribonucleoprotein complexes. By interacting with proteins and RNA molecules simultaneously, lncRNAs can bring together multiple components to form functional complexes involved in diverse cellular processes. lncRNAs can localize to specific subcellular compartments, such as the nucleus, cytoplasm, or specific organelles. Their subcellular localization plays a role in their functional specificity and regulatory roles.[7]

Long non-coding RNAs are a diverse group of RNA molecules characterized by their extended nucleotide sequences and lack of protein-coding potential. While early genomics research primarily focused on protein-coding genes, the realization that a substantial portion of the genome is transcribed into non-coding RNAs, including lncRNAs, has stepped up new avenues of investigation.

Long non-coding RNAs (lncRNAs) have emerged as versatile players involved in a diverse array of vital biological processes. To enhance our understanding of their functionality and delve deeper into the wealth of transcribed sequences, it is advantageous to categorize lncRNAs into distinct groups. In this review, we present a summary of classification methods for lncRNAs based on four major features: their genomic location and context, the effects they exert on DNA sequences, the mechanisms through which they function, and their targeting mechanisms.

By combining these classification criteria with existing functional annotations, we aim to uncover potential connections between different categories and provide a comprehensive analysis of the biological characteristics exhibited by lncRNAs within each category. This systematic approach not only aids in simplifying the interpretation of lncRNA functionality but also promotes in-depth exploration of their roles in various biological processes.

The above classifications facilitate the identification of commonalities and distinctions among lncRNAs, which can be crucial in formulating new hypotheses based on their unique features and understanding the intricate mechanisms underlying lncRNA functionality.[8]
The precise mechanisms through which lncRNAs influence gene expression is not fully comprehended. Some lncRNAs serve as scaffolds or guides for protein complexes, while others regulate gene expression by binding to DNA or RNA molecules. However, the exact workings of many lncRNAs are yet to be uncovered. Furthermore, lncRNA expression is often highly specific to certain tissues and cell types, posing a challenge to the study of their functions and regulatory mechanisms in a broader context.

Functions and Mechanisms of MicroRNAs in HDP

MicroRNAs (miRNAs) are major regulators of endothelial dysfunction, angiogenesis, and inflammation, major causes of HDP and CVD. Among the 21 studies reviewed, miRNAs such as miR-21 and miR-126 control vascular integrity, nitric oxide bioavailability, and inflammatory signaling, making them valuable diagnostic biomarkers for HDP-associated cardiovascular risks.

MiRNAs regulate gene expression post-transcription by inhibiting protein synthesis or triggering mRNA degradation, modulating cell proliferation, differentiation, apoptosis, and homeostasis. Their dysregulation plays a role in cancer, neurodegenerative disorders, and CVD, making them as potential therapeutic targets.[9]

In hypertension and endothelial dysfunction, miR-21 and miR-155 contribute to inflammation, oxidative stress, and reduced nitric oxide (NO) availability-features of vascular dysfunction. Angiogenesis and vascular repair are regulated by miR-126 and miR-155, while miR-29 and miR-143/145 regulate the renin-angiotensin-aldosterone system (RAAS), affecting vascular tone and fluid balance. Owing to their tissue-restricted expression, miRNAs are very specific biomarkers yet hard to detect and analyze functionally. The role of miRNAs in endothelial function defines therapeutic approaches directed to miRNA pathway blockade for the prevention of hypertension and reduction of cardiovascular risks. Continued investigation unraveled miRNA-mediated regulatory pathways, promising new cardiovascular interventions.[10]

Functions and Mechanisms of Circular RNAs in HDP

Circular RNAs (circRNAs) play roles in gene regulation and have been put forward as biomarkers in and essential hypertension. Despite the paucity of research into circRNAs in HDP, their stability and function as microRNA (miRNA) sponges suggest that they may modulate pathways significant in oxidative stress and endothelial dysfunction. Their resistance to degradation and tissue-specific expression patterns makes them perfect candidates for diagnostic and prognostic research in HDP-related cardiovascular disease.

CircRNAs regulate gene expression post-transcriptionally by sequestering miRNAs, preventing them from downregulating target mRNAs, and interacting with RNA-binding proteins. They influence cell proliferation, differentiation, apoptosis, immune responses, and are implicated in various diseases, including cancer and neurological disorders. Their stable circular structure enhances their potential as reliable biomarkers.[11]

In primary hypertension, circRNAs are involved in inflammation, oxidative stress, and endothelial dysfunction. They have been proposed to have diagnostic potential in studies, circRNA_15698, which was significantly upregulated in hypertensive patients. Their clinical utility, however, awaits confirmation and standardization of detection methods.

Despite the relative stability of circRNAs, degradation mechanisms are not known. They are expressed at low levels with high tissue specificity, and their quantitation and detection are challenging. Inspite of these limitations, circRNA research continues to expand, yielding novel information on gene regulation and disease mechanisms. Their potential involvement in the early diagnosis and therapy of hypertension indicates the need for further investigation to establish their application in the clinical setting.

LIMITATION

This scoping review examines the role of non-coding RNAs (ncRNAs) in Hypertensive Disorders of Pregnancy (HDP). However, several limitations specific to the topic must be considered. One key challenge is the variability of ncRNA biomarkers across different populations, as the studies reviewed included diverse sample types, such as human and animal models, which may impact the generalizability of the findings. Moreover, the available data on ncRNAs in HDP remains limited, with many studies focusing on individual ncRNAs rather than offering a comprehensive understanding of their overall role. Additionally, there is no consensus on the most reliable and validated ncRNA biomarkers for predicting cardiovascular outcomes in HDP, which complicates their clinical application. Lastly, the use of varying methodologies and techniques for ncRNA detection and analysis across studies may contribute to inconsistencies in the results, hindering the ability to draw definitive conclusions.

CONCLUSION

This scoping review underscores the pivotal roles of non-coding RNAs (lncRNAs, miRNAs, and circRNAs) in predicting cardiovascular diseases (CVD) linked to hypertensive disorders of pregnancy (HDP). LncRNAs are crucial in regulating endothelial function, inflammation, oxidative stress, and vascular remodelling, positioning them as potential early biomarkers for cardiovascular risk in HDP. MiRNAs are key regulators of endothelial dysfunction, angiogenesis, and inflammation, offering promise as non-invasive diagnostic tools for HDP-related cardiovascular complications.

Although circRNAs are less studied, their stability and ability to modulate miRNA activity highlight their potential for further exploration in the diagnosis of HDP and CVD. These findings emphasize the need for more focused research, particularly on circRNAs, to fully understand their mechanisms and clinical applications. Advancing the knowledge of ncRNAs and their diagnostic and prognostic roles could lead to earlier identification and intervention for individuals at-risk, ultimately improving maternal cardiovascular health outcomes.

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ORIGINAL ARTICLE

Genetic Variation of the BCL-2 Gene and its Relation to Breast Cancer in Iraqi Women

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ABSTRACT

INTRODUCTION: B-cell lymphoma-2 (BCL-2) is a key regulator of apoptosis, and its dysregulated expression contributes to cancer cell survival in several malignancies, including breast cancer. The BCL-2 gene, specifically rs2279115, has been found to significantly modulate transcriptional activity and affect BCL-2 protein expression in various tissues and diseases. Genetic differences affecting apoptotic pathways may therefore contribute to the susceptibility and progression of breast cancer. The present study aims to investigate variation in the BCL-2 genotype in humans, determine the nucleotide sequence of the gene, and determine whether this correlates with the incidence of breast cancer in 45 women. **MATERIALS AND METHODS:** This case–control study included 30 women with breast cancer and 15 an age-matched group of healthy women controls. The genetic polymorphism of the BCL-2 gene in situ (rs2279115) was determined using the tetra-primer amplification refractory mutation system-polymerase chain reaction technique. Nucleotide sequencing of the amplified fragments was performed using DNA sequencing technology. Fisher's exact test was used to compare the genotype and allele frequencies between patients and controls. **RESULTS:** There is genetic variation of the BCL-2 gene in patients with breast cancer, with three genotypes, CC, CT, and TT, in comparison with one genotype in healthy controls. The percentage of incidence of the T allele was 25% in breast cancer patients compared to 0% in controls. The sequencing test for the amplified BCL-2 gene reported multiple nucleotide variations in the breast cancer samples compared with controls. **CONCLUSION:** The present study showed a possible genetic variation with multiple mutations in the BCL-2 gene in patients with breast cancer, which needs to be confirmed by further larger cohorts.

Keywords:
BCL-2 Gene; breast cancer; genetic variation; mutation; nucleotide sequencing

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INTRODUCTION

Breast cancer is a malignant tumour in which mammary gland epithelial cells proliferate out of control due to different carcinogenic factors. The incidence of this cancer has increased and is considered a threat to women's lives and health. For instance, in the USA, breast cancer accounts for approximately 30% of women's malignant tumours. It has been approved that breast cancer is a heterogeneous tumour and, multiple genes have been confirmed to affect the course of disease progression.[1] In addition to the important role of mutation, deletion, or activation of several key oncogene and tumour suppressor genes in the development of the tumour, the inhibition of apoptosis has been implicated in breast cancer progression.[2]

The *BCL-2* gene (rs2279115) is responsible for the expression of the antiapoptotic *BCL-2* protein family. In addition, *BCL-2* has a significant role in ensuring normal tissue development and function by maintaining the balance between cellular survival and death. It plays a role in preventing high cellular death in different physiological conditions.[3] Normal breast epithelial cells are tightly modulated by balanced pro-apoptotic and anti-apoptotic signals, while disturbance of this balance can play a crucial

role in tumorigenesis and anticancer treatment resistance.[4] Additionally, mutation of the genes has an important impact on health because a devastating genetic disorder or a beneficial adaptation can occur due to a single base change.[5,6]

The rs2279115 variation in the promoter region has garnered interest for its possible impact on transcriptional activity among its regulatory polymorphisms. A case-control study of women from England revealed no association between the rs2279115 polymorphism and breast cancer risk or overall survival, indicating its minor role in Caucasian populations.[7] A thorough meta-analysis of several studies indicated that the C allele of rs2279115 may be linked to an elevated risk of several types of cancer, including breast, lung, and prostate malignancies.[8] However, the same study reported that rs2279115 could be correlated with a significantly higher risk of malignancy in Asia but not for Caucasians, which potentially supports the use of rs2279115 as a tumour marker for cancer therapy in Asia. Given these population-dependent and inconsistent findings, it is necessary to perform sequencing of the amplified BCL-2 gene region in addition to genotyping to identify potential additional nucleotide variations that may coexist with rs2279115 and contribute to altered gene regulation and breast cancer incidence. This study aimed to investigate the hypothesis that the genetic variation of the BCL-2 gene, particularly the rs2279115 polymorphism, is attributed to the incidence of breast cancer and to determine the nucleotide sequencing of this gene.

MATERIALS AND METHODS

Study Design

The study design is a case-control study. The study has been conducted on 45 women of different ages, ranging from 39 to 76 years. The participants are categorized into two groups: 15 individuals who are healthy and considered as a control group, and 30 women with diagnosed breast cancer upon visiting the Hospital of Nuclear Medicine Oncology in the city of Mosul/Iraq, during the period from December 2023 to February 2024. The participants are identified as having breast cancer at stages (I to IV) by histopathology, following clinical evaluation and imaging. They are then managed by an oncologist at the aforementioned hospital. The control participants were selected to match the cases in terms of age and were further screened to exclude individuals with a family history of cancer or any major chronic diseases to minimize potential confounding bias. This study has been performed according to formal approval from the Ethics Committee of the University of Mosul

Sample Size Calculation

The sample size was computed under the assumption of a case-control study to determine the significant relationship between the polymorphism of the BCL-2 gene and the occurrence of breast cancer. In the computation of the sample size, it is assumed to have a confidence level of 95%, 80% statistical power, and an effect size based on prior similar studies. However, the final sample size used in the study consists of 30 breast cancer-affected individuals and 15 control subjects, since the study faced constraints in the selection of the participants.

Collection of Blood Samples and DNA Extraction

Blood samples were collected from all participants using EDTA tubes. DNA has been extracted from the whole blood samples using a Whole Blood Genomic DNA Extraction Kit (ADD BIO, Korea) in accordance with the manufacturer's guidelines. The quality of the extracted DNA was evaluated by measuring absorbance at two wavelengths (260 and 280) using a nanodrop spectrophotometer. DNA was isolated from the blood of all 45 samples included in the study, and, then all extracted DNA samples were stored at −20°C for future experiments.

The tetra-primer amplification refractory mutation system-polymerase chain (Tetra–ARMS-PCR) Reactions
The DNA concentration in each sample was adjusted with TE buffer solution (10mM Tris-HCl containing 1mM EDTA•Na_2) to 25 ng/µl for PCR amplification. For primer reactions, four primers were used, including F-outer and R-outer throughout the gene. For the mutant allele, the forward outer-reverse inner primers are

used, instead of those for the normal allele. Nucleic acid from each sample was mixed with appropriate primers for the targeted mutations and the master mix components to form the PCR reaction blend in 0.2-ml PCR tubes. This mixture was quickly centrifuged to achieve optimal components. Then, the PCR tubes were cycled in a thermocycler using customized procedures for particular mutations. The reaction product (at 2% concentration) was loaded into the wells of a prepared agarose gel after a DNA ladder from BIOLAB Company was injected into specified wells. After 40 minutes of electrophoresis used to migrate the samples, the bands were imaged using a gel-electrophoresis apparatus. Tetra-ARMS-PCR was used to assess the genetic variation of the *BCL-2* gene at locus (rs2279115).

Determination of genetic variation of the *BCL-2* gene in situ (rs2279115) using Tetra–ARMS-PCR technique

Tetra–ARMS-PCR technique was performed to detect any mutation in the *BCL-2* gene. Template DNA (4 µl = 100 nanogram) and each mutation-specific primer for the *BCL2* gene (1 µl = 10 picomol), supplied by Macrogen (Korea), have been added to the contents of the master mix.[9] The primers used to determine genetic mutation at the locus (rs2279115) are shown in Table 1. Then, to conduct the multiplication reaction, the reaction tubes were inserted into the thermocycler. The amplification refractory mutation system ARMS-PCR technique was used to identify the mutation (rs2279115) (Table 2).

Table 1: The primers which are used to deduce the genetic mutation at the locus (rs2279115) via PCR technology.

Locus	primer	Sequence	Band size	annealing
rs2279115 for *BCL2*	F-outer	5- CCGGCTCCTTCATCGTCTCC-3	300 bp	58°C
	R-outer	5- CCCAGGAGAGAGACAGGGGAAA-3		
	F-inner	5- AATAAAACCCTCCCCCACCACCT-3	220bp	
	R-inner	5- CCCTTCTCGGCAATTTACACGC-3	121 bp	

In this reaction, 58C° was considered an optimal temperature for the primer bonding, depending on the Gradient program in the thermocycler device. Then, 2% agarose gel was used to separate the products resulting from the PCR reaction.

Table 2: The program adopted in the amplification refractory mutation system ARMS-PCR technique to identify the mutation (rs2279115)

No.	Stage	Locus	Temperature	Time	Cycle number
1	Initial denaturation	for all sites	95°C	6 min.	1
2	Denaturation	for all sites	95°C	45 sec.	35
3	Annealing	(rs2279115)	58°C	1 min.	
4	Extension	for all sites	72°C	1 min.	
5	Final extension	for all sites	72°C	5 min.	1
6	Stop reaction	for all sites	4°C	5 min.	1

Measurement of nucleotide sequencing for the amplified fragments via DNA sequencing technology

The PCR products, which are amplified using specific primers (initiators) targeted to the BCL-2 genes, were analysed to determine the sequence of the nitrogenous bases of the gene. The resulting DNA fragments were sequenced to identify the mutations. The 3130 Genetic Analyzer instrument (Hitachi, Japan) was used to read the sequence of the genes. Then, matching of the reported gene sequences in this study with the gene sequences documented in the National Centre for Biotechnology Information (NCBI) was performed, and the findings were analysed using the Basic Local Alignment Search Tool (BLAST) program.

Statistical analyses

P-values, confidence intervals (CIs) value, and odds ratios (ORs) were calculated using MedCalc statistical software, version 20.009 https://www.medcalc.org . Fisher's exact test was utilised to evaluate the association between genotypes or alleles and breast cancer. The value of a statistically significant difference was $P<0.05$. The following frequencies were calculated based on the following dependency: Allelic frequency of the normal allele=2 (number of homozygous individuals) + (number of heterozygous individuals)/2 (total number). The allelic frequency of the mutant allele=2 (number of heterozygotes) + (number of heterozygotes)/2(total number).

RESULTS

Extraction of DNA from blood samples

The results showed the genome packages that were extracted from blood samples (Figure 1). The purity of

the DNA sample ranged between (1.5-1.7), and the concentration ranged from (50-125 ng/µl).

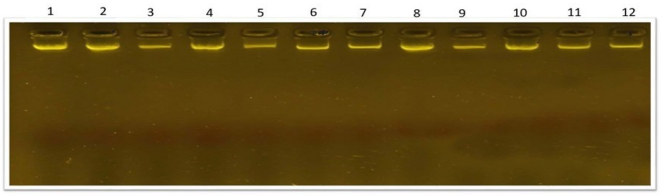

Figure 1: Genomes extracted from blood samples and separated by agarose gel at a concentration of 1%.

Determination of genetic variation of the *BCL*-2 gene in situ (rs2279115) using Tetra–ARMS-PCR technique

The results showed that there is a relationship between women who suffer from breast cancer and the genetic variation in the *BCL*-2 gene at the site (rs2279115) on chromosome 18 (Figure 2). It has been found from the PCR reaction that the genetic variation of the gene appears in the three genotypes CC, CT, and TT, whereas in control samples, there was no genetic variation in the *BCL*-2 because only one main gene has been found, as shown in Table 3.

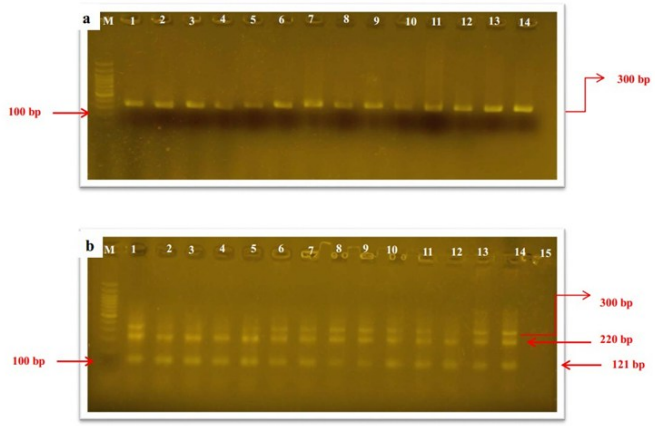

Figure 2: The product of the PCR reaction of the genetic variation (rs2279115) of the *BCL*2 gene. M denotes to the Ladder which was prepared by Biolabs with a size of 100 bp, and separated by 2% agarose gel. A: The control samples showed only one band of 300 bp size for the main gene. B: The samples from patients of breast cancer showed 3 bundles, the first with a size of 300 bp for the main gene, the second with a size of 121 bp for the natural allele, and the third bundle with a size of 220 bp for the mutant allele.

Table 3 shows the frequency of the different genotypes of the *BCL*2 gene with the percentage of allelic observations at the site (rs2279115). The present study found that the women with breast cancer had the highest frequency of the mutant genotype (TT) (16.7%) in comparison with the same mutant genotype in the healthy control group (0%).

Table 3: Distribution of allelic viewing and genotype of the *BCL*-2 gene at the locus (rs2279115) among the healthy women group and women with breast cancer group, where the C allele is the normal allele and the T allele is the mutant allele.

Comparison	Patients (n=30)	Controls (n=15)	OR	95% CI	P-value*
CC vs. (CT+TT)	20 (66.6%)	15 (100.0%)	3.75	0.40 – 35.54	0.249
CT vs. (CC+TT)	5 (16.7%)	0 (0.0%)	-	-	0.3
TT vs. (CC+CT)	5 (16.7%)	0 (0.0%)	-	-	0.3
C vs. T	C = 45 (75%) T = 15 (25%)	C = 30 (100%) T = 0 (0.0%)	3.17	0.97 – 10.35	0.056

*Fisher's exact test was used to compute the p-value.

In contrast, the women with breast cancer had the lowest percentage of the normal genotype (CC) (66.6%) in comparison with the healthy control group, which showed a 100% for the normal genotype. However, the percentage of the variant genotype (CT) was high in the experimental group (16.7%) compared to the control group (0%).

In addition to that, the present study showed that the percentage of the presence of the mutant T allele was higher in the women with breast cancer (25%) in comparison with the healthy control group (0%). In contrast, the percentage of presence of the normal allele in patients was only 75% versus 100% in the control group.

The results of the study also showed that there are suggestive trends of association between breast cancer and the mutations of the *BCL*-2 gene because the value of odds ratio (OR) for the mutant genotype TT was 3.75, and for the mutant allele OR was 3.17.

Measurement of the nucleotide sequencing for the amplified fragments via DNA sequencing technology for the *BCL*-2 gene

The sequencing test for the amplified *BCL*-2 gene reported differences in some nucleotides in the studied gene in comparison with the original gene documented in NCBI (the accession number is LC802665.1). In addition, different types of genetic variations were reported for the *BCL*-2 gene in breast cancer patients after comparing them with the gene sequences at the NCBI site using a sequencing test.

DISCUSSION

BCL-2 Genetic Variants and Breast Cancer Susceptibility

A link has been established between gene variants and different diseases.[10–13] Additionally, the *BCL-2* gene and its variants have relationships with some diseases and syndromes such as Alzheimer's disease, schizophrenia, and depression.[14–16] However, the direct association between rs2279115 and other known variants with breast cancer remains unclear. In the current study, it is hypothesized that genetic variation in BCL-2, which is a key regulator of apoptosis, could affect susceptibility to breast cancer, considering its role in tumour progression and therapy resistance. So, the study selected BCL-2 (rs2279115) and focused on the potential functional significance in breast cancer pathogenesis.

The present study is the first to investigate the link between the *BCL-2* gene polymorphism (rs2279115) and breast cancer risk in women from Mosul and the northern Iraq region. This novel localized genetic study is critical because allele frequencies and genotype distributions are different between populations due to ethnic, environmental, and lifestyle factors. The present genetic findings may clinically lead to the development of personalized screening strategies, especially if future studies confirm that certain alleles are associated with a higher risk in this population. The present findings underscore the significance of regional genetic research as a foundation for accurate oncology initiatives in underrepresented populations. These findings are fundamental in understanding the relationship between the transformation of some genes, the incidence of specific pathological conditions, and the development of future therapeutic strategies.

BCL-2 Polymorphism, Expression, and Prognostic Implications

The role of *BCL*-2 gene in breast cancer is still controversial. Some reports found that *BCL*-2 gene expression can reduce breast cancer incidence via blocking apoptosis, prolonging the cell cycle, and delaying tumour cell growth.[17] In addition, good pathophysiological behaviour in breast cancer patients was linked to increased expression of the *BCL*-2 gene, which makes the gene a promising indicator to predict the progression of lymph node metastasis.[18] In addition, reports are showing that there is no correlation between the BCL-2 promoter polymorphism and the prognosis of breast cancer.[8] Population-specific differences may be the reason for these discrepancies. It is important to note that genetic diversity, environmental influences, and lifestyle differences can vary across different populations. The present study focuses on Iraqi women, a population that may have distinct genetic and environmental backgrounds compared to those examined in other studies. It is highly recommended to further research in different populations to confirm the impact of BCL-2 promoter polymorphisms on breast cancer prognosis.

Furthermore, the type of breast cancer may be responsible for the variation in the findings. Breast cancer could be hormone receptor-positive or hormone receptor -negative. Hormone receptor-positive tumours are dependent in their growth on estrogen or progesterone because they have estrogen or progesterone receptors on the breast cancerous cells. In contrast, hormone receptor-negative tumours have no estrogen and progesterone receptors, so their proliferation does not depend on hormones.[19] *BCL*-2 has been reported as a significant prognostic marker for breast cancer because it is overexpressed in approximately 75% of this malignant tumour.[20] However, a better prognosis in patients with luminal breast cancer has been linked to high expression of the *BCL*-2 gene in hormone receptor-positive tumors.[21] In contrast, in hormone receptor-negative or triple-negative tumours showed that overexpression of the *BCL*-2 gene could be regarded as an independent poor prognostic marker.

Genotyping, Sequencing Findings, and Methodological Considerations

The present study showed genetic variations in the *BCL*-2 gene in patients with breast cancer, while in healthy women, there was only one gene without variation. The present study found that the women with breast cancer had the highest frequency of the mutant genotype (TT) in comparison with the absence of the same mutant genotype in the healthy control group, who had only the

normal genotype (CC). In addition, the variant genotype (CT) has present only in breast cancer patients. It has been proved by RNA-seq data that *BCL*-2 gene is the most frequently mutated gene in germinal center B-cell (GCB). Schuetz and co-authors found that there is a high level of *BCL*-2 mutations in follicular lymphoma and GCB, whereas in activated B-cell diffuse large B-cell lymphoma, mantle cell lymphoma, peripheral T-cell lymphoma and small lymphocytic leukaemia, the *BCL*-2 mutations were low. Moreover, no *BCL*-2 mutations have been found in GC centroblasts in the same study.[22] T-ARMS-PCR was selected as the primary method for genotyping in this current study due to its high specificity, well-established reliability, and accuracy in detecting targeted SNPs. This technique is suitable for resource-limited settings and population-specific studies because it is cost-effective and requires relatively simple laboratory infrastructure. However, the use of more advanced methods of multi-omics approaches or high-throughput technologies, such as next-generation sequencing, could provide a broader genomic context and enhance the overall depth of analysis.

Mutation Patterns and Comparative Evidence

Identifying the genomic sites that undergo frequent mutation in human tumours is considered an efficient way to discover the causative genes in oncogenesis. So then, DNA is isolated from samples of both controls and patients with breast cancer, and analysed using a polymerase chain reaction (PCR)-mismatch technique for rapid identification of potential point mutations in the *BCL*-2 gene. Interestingly, multiple point mutations have been reported in the *BCL*-2 gene of patients with breast cancer. In line with the present finding, DNA sequencing in a previous study has confirmed the high incidence of a total of six mutations in the *BCL*-2 gene in 3 out of 5 patients with lymphoma or leukemia tumors.[23] It is noteworthy that the multiple mutations in this gene were reported for the first time in this sample population, Iraqi women.

Previous studies have shown controversial findings about the relationship between *BCL-2* polymorphism (rs2279115) and breast cancer. Several studies on different populations worldwide have focused on investigating various polymorphisms within the *BCL-2* gene and their association with breast cancer, resulting in inconsistent outcomes on a global scale. Some studies on different populations, including Asians, Middle Eastern, and European populations, have shown that different populations exhibit different allele and genotype distributions for various *BCL-2* gene polymorphisms, including rs2279115, which may play an important role in Breast cancer risk and prognosis.[8] A recent study on 175 Turkish population showed no relationship between (rs2279115) gene polymorphisms and breast cancer.[24] In contrast, another study on 110 breast cancer patients identified that the AA genotype of *BCL-2* is associated with advanced tumor stage, lymph node metastasis, and elevated Ki67 index, indicating its involvement in tumor growth.[25] In Africa, specifically in Egypt, there was a relationship between genetic polymorphism of *BCL-2* (rs2279115) and increased susceptibility to cancer.[26] These inconsistent outcomes which may occurred probably due to ethnic, and environmental factors highlight that investigations on different populations worldwide need to be carried out to understand the role of *BCL-2* gene mutation in breast cancer development and progression.

Study Limitations and Future Directions

The limitations of the study are the relatively small sample size. This was due to the expensive materials and techniques used in this self-funded study. Future studies with larger cohorts could provide a greater statistical power and generalizability, and a better understanding of genetic vulnerability to breast cancer. Despite the observed correlation between *BCL*-2 mutations and the incidence of breast cancer chromosomal mapping, it is unknown whether it would be possible to target this specific gene mutation with drugs and improve the pathological condition. Chromosomal mapping is recommended as a future study to confirm and further explore the correlation between the genetic variation and breast cancer. Additionally, the present study included cases of all cancer stages (I-IV). This may require future investigation to determine whether a specific stage show higher percentage of mutation. In addition, future studies

are required to address the functional consequences of these genetic variations, correlate genotypic data with some clinical indicators (e.g., BCL-2 expression, and tumour markers CA 15-3 and CA 27.29), protein function and apoptosis mechanism, and highlight the most effective treatment that regulates this gene and prevents or reduces the incidence and progression of the disease. The effect of different anticancer drugs on *BCL-2* gene should be addressed because these medications can adversely affect different biological parameters.[27,28] Finally, future study of the *BCL-2* allele polymorphism with other clinicopathological parameters and other tumours is recommended.

CONCLUSION

The current study demonstrated a possible association between genetic variation in the *BCL-*2 gene and patients with breast cancer. The mutations in the gene involved multiple mutations in nucleotides. These findings suggest that genetic variation in BCL-2 may contribute to breast cancer susceptibility; however, any potential stratification of breast cancer patients based on *BCL-2* mutational status requires further validation. The therapeutic response and prognosis of the disease in *BCL-*2 -mutant patients should be studied extensively and compared with *BCL-*2 -nonmutant patients.

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ORIGINAL ARTICLE

Prevalence and Factors Associated with Loneliness Among Urban-Dwelling Older Persons in Kuala Lumpur

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Loneliness, older persons, screening, social support, urban.

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ABSTRACT

The World Health Organization (WHO) declared loneliness as a global public issue. Each individual faces this psychological state in some stages of their lives as people from all age categories, including older persons may experience it. In this study, we aimed to determine the prevalence and factors associated with loneliness among older persons in Kuala Lumpur. **MATERIALS AND METHODS:** This cross-sectional study was conducted at government health clinics located in two districts located in Kuala Lumpur, Malaysia between October 2024 and March 2025. 423 older persons were recruited. The De Jong Gierveld Loneliness Scale (DJGLS-6), Duke Social Support Index (DSSI-11), Lubben Social Network Scale (LSNS-6), Geriatric Depression Scale (GDS-14) and self-rated health (SRH) questionnaires were used for data collection. Ordinal logistic regression was used to identify significant factors. **RESULTS:** The mean age of participants was 67.80 (±5.75) years. Analysis of the collected data indicated a 47.0% prevalence of loneliness among participants. Ordinal logistic regression found that female [adjusted odds ratio (AOR)=1.50; 95% confidence interval (CI): 1.04–2.19], age (AOR= 1.03; 95% CI: 1.00–1.07) and functional social support (AOR=0.92; 95% CI:0.89 – 0.96) were significantly associated with loneliness. **CONCLUSION:** Based on these findings, social and community programmes can be tailored to reach older persons at greater risk of experiencing loneliness. Identification of these individuals can be informed by their sociodemographic, health, and interpersonal characteristics highlighted in this study.

INTRODUCTION

Loneliness is defined as a distressing subjective experience that occurs when a person perceives that their social relationships do not meet the level they desire in terms of number or quality or both.[1,2] This experience reflects a perceived mismatch between their social expectations and the actual lived social connections. Recognising the prevalence and health burden of loneliness, the World Health Organization (WHO) declared it as a global public health concern.[3] Persons who experience loneliness face an increased likelihood of developing chronic health issues such hypertension and cardiovascular disease as well as mental health issues such as depression and cognitive decline.[4-7] Individuals of all age groups may encounter loneliness and these associated health implications.[3] Nonetheless, relative to younger cohorts, older persons are more significantly impacted by this psychological state.[8] Priority has therefore been given to managing the issue of loneliness among older persons, particularly in high-income countries with large ageing populations, such as the United Kingdom and the United States, as part of efforts to improve their health and well-being.[9] Based on a global systematic review and meta-analysis covering 113 countries, loneliness shows a clear age gradient, with older persons most affected.[10] In Europe, the prevalence is 2.9–7.5% among young adults, 2.7–9.6% among middle -aged adults and the highest at 5.2–21.3% among older persons. However, in low- and middle-income countries outside of Europe, whilst the prevalence among adolescents is 9.2% in South-East Asia to 14.4% in the

Eastern Mediterranean, data on other older age groups are scarce.

Malaysia is witnessing a demographic shift towards an ageing population.[11] Currently, 7.2% of Malaysians are aged 65 years and above, classifying the country as an ageing nation.[11] An increase in the ageing population will lead to a rise in chronic illnesses, loneliness, and other social challenges among older persons.[3] Nonetheless, most studies on this issue have been performed in suburban and rural areas in Malaysia whilst there is a scarcity of data highlighting it specifically in urban environments.[12-15] For instance, studies by Mahmud and Teh were conducted in community settings with samples drawn from non-urban or mixed localities with prevalence of loneliness reported at 35.7% and 53.4% respectively.[14,15] Similarly, studies by Hussein and Azam were conducted in rural agricultural settings of Malaysia with no involvement of urban population.[12,13] Several unique challenges to social connectedness are faced by urban-dwelling older persons such as high living expenses, erosion of family support, income inequalities, and accessibility issues in high-rise housing.[16] At the same time, older persons across the country also frequently visit government health clinics for several reasons such as routine check-ups, management of chronic conditions, or acute health concerns.[17] This provides an ideal opportunity for regular screening for loneliness thus ensuring that individuals at risk can be identified. Examining loneliness in a primary care setting also generates evidence that can inform future screening and intervention strategies targeted to these reachable urban primary healthcare service users. Thus, in this study, we aim to determine the prevalence and factors associated with loneliness among urban-dwelling older persons attending government health clinics in Kuala Lumpur, Malaysia.

MATERIALS & METHODS

Study Design and Setting

This study was conducted using a cross-sectional design at government health clinics in two urban districts of Kuala Lumpur, Malaysia between October 2024 and March 2025. A cluster sampling approach was employed whereby two district health offices (DHOs) were randomly selected from the four DHOs in Kuala Lumpur, namely Cheras, Kepong, Lembah Pantai, and Titiwangsa. The selected clusters were Lembah Pantai DHO and Titiwangsa DHO. All primary health clinics under these DHOs were included as data collection sites. Data were therefore collected at Kuala Lumpur, Setapak, and Dato' Keramat Health Clinics under Titiwangsa DHO, and Tanglin, Muhibbah, and Petaling Bahagia Health Clinics under Lembah Pantai DHO.

Participants' Eligibility Criteria

Individuals aged ≥60 years attending the selected government health clinics were screened for eligibility. The inclusion criteria required participants to be Malaysian citizens with the ability to comprehend Malay or English language. Adults who are not physically and/ or mentally capable of independent face-to-face communication, due to conditions such as stroke or dementia, were excluded. Although older persons with dementia or stroke-related communication impairment may experience loneliness, meaningful participation in a face-to-face interview requires sufficient ability to comprehend questions and articulate subjective emotional states. Inclusion of these participants without adapted instruments could therefore introduce bias towards lower prevalence of loneliness rather than capturing the underlying burden. For this reason, these groups were excluded to preserve the validity of self-reported outcomes.

Sampling Strategy and Data Collection

A systematic random sampling method was used to select participants from designated health clinics. Recruitment of participants was facilitated by nurses or assistant medical officers stationed at the triage counter. At the beginning of each data collection session, the starting point was selected by generating a random number using an online random number generator. The eligible older person matching this randomly generated position at the triage counter was approached as the first participant. Subsequently, every other patient triaged (n2 sampling interval) and met the inclusion criteria was approached for face-to-face data collection. Relevant

information was then gathered via pre-designed online questionnaire forms and entered accordingly into REDCap application using interviewers' electronic devices.

Sample Size Calculation

Sample size was calculated using OpenEpi Version 3.01. Determination of the required sample size was based on prevalence of loneliness and odds ratios of factors associated with loneliness among older persons reported in the literature. Calculation based on the prevalence utilised the formula $n = [Z^2 \times p(1-p) / d^2$ in which *n* is the sample size required, *Z* is the 95% confidence (1.96), *p* is the expected prevalence and *d* is the margin of error (0.05). Taking into 80% power and findings from a recent Malaysian study which reported a prevalence of 35.7% among older persons, this yielded a required sample size of 353.[14] Additionally, an odds ratio of 1.95 for age group as a predictor of loneliness as reported in a study by Grover corresponded to a required sample size of 316 participants.[18] Between the two calculated sample sizes, the larger number (353) was selected to support reliable estimation in subsequent analyses.

Study Variables

Loneliness was measured using the translated 6-item De Jong Gierveld Loneliness Scale (DJGLS-6).[19] This instrument evaluates social and emotional components of loneliness through its two subscales comprising 3 questions for each component.[20] This version of the DJGLS has been translated and validated in Bahasa Malaysia for its use among older persons.[19] The total score, after adjustment for negatively phrased items ranges from 0 (least lonely) to 6 (most lonely).[19] Scores of 0-1 indicate respondents are not experiencing loneliness whereas scores of 2-6 are indicative of some degree of loneliness.[21]

The independent variables collected were:

1. Sociodemographic characteristics. These include participants' age, sex, ethnicity, marital status, education level, living arrangement, mode of transportation, number of children, and monthly household income.
2. Physical and mental health status. Participants were asked if they had been diagnosed with chronic diseases such as hypertension, diabetes, cancer, and others.[22] Screening for depression was also performed using the Malay version of the 14-item Geriatric Depression Scale (M-GDS-14).[23] M-GDS-14 scores of 0 to 5 are deemed as normal and scores of 6 and above denote depression.[23] Furthermore, participants were asked to self-report on their overall health status using a single question.[24]
3. Two measures of social support were collected namely structural and functional social support. Locally validated Lubben Social Network Scale (LSNS-6) was utilised to assess objectively how much social support participants were receiving.[25,26] This instrument consists of six items, split equally into two subscales, with three questions in each subscale pertaining to social support from family and friends.[26] Higher total scores indicate a broader and stronger social network. A total score of 12 or less indicates inadequate structural social support among older persons.[25] Additionally, functional social support was also evaluated in this study using the 11-item Duke Social Support Index (DSSI).[27] In contrast to the LSNS-6 which quantifies objective structural support, the DSSI-11 evaluates the subjective perception of help availability and the satisfaction derived from social ties. Higher scores on the DSSI signify stronger functional social support.[27] The classification of functional social support comprises three categories, namely low-to-fair (11–26), high (27–29), and very high (30–33).[27] Both structural and functional social support were measured in this study as they represent related but distinct aspects of social relationships. This is because loneliness is shaped by perceived unmet needs rather than network size alone thus making assessment of both dimensions theoretically important. [28]

Statistical analysis

All statistical analyses were performed using Statistical Package for Social Sciences (SPSS IBM Corp., Chicago,

IL; Version 25.0). Missingness was evaluated for all variables. Two observations were found to have missing information on monthly household income and LSNS-6 scores. Given the minimal missingness, listwise deletion was used to exclude these observations thus leaving 423 cases for final analysis. Descriptive statistics were used to present participants' sociodemographic details, physical and mental health status, and levels of social support. Univariable analysis was conducted using simple ordinal logistic regression. Variables with a $p < 0.25$ in the univariable stage were included in the multiple ordinal logistic regression model. When both continuous and categorical forms of a variable were available, the continuous form was selected for inclusion in the final model to minimise loss of information from categorisation. The final model was assessed for key assumptions and multicollinearity was considered absent when the variance inflation factor (VIF) was <5.0 and the tolerance value was >0.2. Model fitness of the final model was evaluated using Brant's test (test of parallel lines) for proportional odds assumptions.

RESULTS

Sociodemographic characteristics of the participants are shown in Table I. The participants' average age was 67.8 (SD: ±5.75) years. Of all the participants, 249 (59%) were female, 273 (65%) were between the ages of 60 and 69, 196 (46%) were Malays, 289 (68%) were married and 174 (41%) lived only with a spouse. Nearly one-quarter 102 (24%) made less than RM1000, while 152 (36%) made between RM1000 and RM1999. A number of these participants reported having three or more chronic medical conditions [60 (14%)], and 135 (31.9%) had just one. Depressive symptoms were identified in a small proportion of them [16 (4%)] whilst most of the participants self-reported that they are in a good state of health [205 (49%)]. When comparing sex of participants, 127 (51%) females reported feeling lonely, higher compared to 72 (41.4%) males. As people get older, loneliness became more common whereby participants aged 80 years old and older reported higher proportion of loneliness [9 (64.3%)] compared to those aged 60 to 69 [122 (44.7%)]. Furthermore, there was higher proportion of participants with loneliness among those with low functional social support [93 (58.5%) than in those with very high functional social support 50 (29.2%).

Table I. Sociodemographic Characteristics of Participants and Proportions of Loneliness

Characteristics	n (%), Mean (SD)	Experiencing Loneliness*	
		No, n (%)	Yes, n (%)
Sex			
Male	174 (41.1)	102 (58.6)	72 (41.4)
Female	249 (58.9)	122 (49.0)	127 (51.0)
Age (years)			
- 69	273 (64.5)	151 (55.3)	122 (44.7)
70 – 79	136 (32.2)	68 (50.0)	68 (50.0)
≥ 80	14 (3.3)	5 (35.7)	9 (64.3)
Ethnicity			
Malay	196 (46.3)	112 (57.1)	84 (42.9)
Chinese	133 (31.2)	65 (49.2)	67 (50.8)
Indian	89 (21.3)	43 (47.8)	47 (52.2)
Others	5 (1.2)	4 (80.0)	1 (20.0)
Marital status			
Married	289 (68.3)	163 (56.4)	126 (43.6)
Never Married	39 (9.2)	19 (48.7)	20 (51.3)
Widowed	34 (8.0)	14 (41.2)	20 (58.8)
Divorced	61 (14.4)	28 (45.9)	33 (54.1)
Household Monthly Income			
0 – 999	102 (24.1)	56 (54.9)	46 (45.1)
1000 - 1999	152 (35.9)	77 (50.7)	75 (49.3)
2000 – 2999	82 (19.4)	45 (54.9)	37 (45.1)
3000 – 3999	50 (11.8)	27 (54.0)	23 (46.0)
≥ 4000	37 (8.7)	19 (51.4)	18 (48.6)
No. of Chronic Medical Conditions			
0	103 (24.3)	51 (49.5)	52 (50.5)
1	135 (31.9)	68 (50.4)	67 (49.6)
2	125 (29.6)	70 (56.0)	55 (44.0)
≥ 3	60 (14.2)	35 (58.3)	25 (41.7)
Living Arrangement			
Living with spouse and children	109 (25.8)	63 (57.8)	46 (42.2)
Living with spouse only	174 (41.1)	96 (55.2)	78 (44.8)
Living with children only	73 (17.3)	35 (47.9)	38 (52.1)
Living with other people	23 (5.4)	12 (52.2)	11 (47.8)
Living alone	44 (10.4)	18 (40.9)	26 (59.1)
Mode of Transportation			
Public transportation	64 (15.1)	29 (45.3)	35 (54.7)
Own transport	190 (44.9)	103 (54.2)	87 (45.8)
Brought by other people	157 (37.1)	87 (55.4)	70 (44.6)
Walking	12 (2.8)	5 (41.7)	7 (58.3)
Number of Children			
0	60 (14.2)	29 (48.3)	31 (51.7)
1	30 (7.1)	15 (50.0)	15 (50.0)
2	124 (29.3)	65 (52.4)	59 (47.6)
3	81 (19.1)	45 (55.6)	36 (44.4)
4	55 (13.0)	31 (56.4)	24 (43.6)
≥ 5	73 (17.3)	39 (53.4)	34 (46.6)
Level of Education			
No formal education	72 (17.0)	36 (50.0)	36 (50.0)
Primary	74 (17.5)	37 (50.0)	37 (50.0)
Secondary	138 (32.6)	72 (52.2)	66 (47.8)
Tertiary	139 (32.9)	79 (56.8)	60 (43.2)
Structural Social Support			
Adequate	307 (72.6)	153 (49.8)	154 (50.2)
Inadequate	116 (27.4)	71 (61.2)	45 (38.8)
Functional Social Support			
Low to Fair	159 (37.6)	66 (41.5)	93 (58.5)
High	93 (22.0)	37 (39.8)	56 (60.2)
Very High	171 (40.4)	121 (70.8)	50 (29.2)
Depression			
No	407 (96.2)	217 (53.3)	190 (46.7)
Yes	16 (3.8)	7 (43.8)	9 (56.3)
Self-rated Health			
Very good	16 (3.8)	8 (43.8)	8 (50.0)
Good	205 (48.5)	120 (58.5)	85 (41.5)
Moderate	166 (39.2)	80 (48.2)	86 (51.8)
Not good	27 (6.4)	10 (37.0)	17 (63.0)
Very bad	9 (2.1)	6 (66.7)	3 (33.3)

*Proportions of loneliness among participants were presented in row percentages

Table II shows the overall prevalence of loneliness among study participants. From the 423 respondents, 199 [47% (95% CI: 42.3–51.8)] of them reported experiencing some degree of loneliness, while 224 individuals [53% (95% CI: 48.2–57.7)] reported no loneliness. The proportions of respondents in both categories were closely comparable. Loneliness was reported by nearly half of the participants, while just over half indicated no loneliness.

Table II. Prevalence of loneliness among older persons

Loneliness status	N	Prevalence (%)	95% Confidence Interval
No Loneliness	224	53	48.2 – 57.7
Presence of Loneliness	199	47	42.3 – 51.8

Several variables were associated with loneliness among older persons through ordinal logistic regression analysis (Table III). Female sex, age, living alone, marital status and lower functional social support were significantly associated with greater odds of loneliness in the univariable (unadjusted) model. In the multivariable (adjusted) model, three factors remained significant after controlling for confounders. Women were more likely to experience loneliness than men [adjusted odds ratio (AOR)=1.50; 95% confidence interval (CI): 1.04–2.19, p=0.032].

Furthermore, age also emerged as a significant predictor of loneliness among older persons whereby each additional year of age was associated with a 3.4% increase in the odds of reporting a higher level of loneliness (AOR=1.034, 95% CI: 1.00–1.07, p=0.038). In contrast, functional social support demonstrated a strong protective effect. For each one-unit increase in the functional social support score, the odds of reporting higher loneliness decreased by 8% (AOR = 0.92, 95% CI: 0.89–0.96, p < 0.001).

DISCUSSION

In Malaysia, loneliness among older persons has been reported in several studies and national surveys. The present study provides additional evidence with a prevalence of 47%. This figure is comparable to the findings of a previous large scale Malaysian study

Table III. Univariable and Multivariable Ordinal Logistic Regression

Characteristics	COR	95% CI	p-value	AOR	95% CI	p-value
Sex						
Male [a]	1	-	-	1	-	-
Female	1.700	1.203 - 2.402	0.003**	1.505	1.035 - 2.189	0.032**
Age (years)				-	-	-
– 69 [a]	1	-	-			
70 – 79	1.300	0.898 - 1.883	0.164*			
≥ 80	2.891	1.150 – 7.271	0.024**			
Age (Continuous scale in years) [+]	1.039	1.009 - 1.070	0.011**	1.034	1.001 – 1.069	0.038**
Ethnicity						
Malay [a]	1	-	-	1	-	-
Chinese	1.209	0.818 - 1.786	0.343	1.057	0.693 - 1.612	0.797
Indian	1.363	0.873 - 2.130	0.170*	1.503	0.949 - 2.382	0.079
Others	0.347	0.059 – 2.032	0.229*	0.246	0.038 – 1.578	0.135
Marital status						
Married [a]	1	-	-	1	-	-
Never Married	1.291	0.727 - 2.292	0.384	1.539	0.496 - 4.775	0.441
Divorced	1.920	1.000 - 3.687	0.050*	2.057	0.735 - 5.759	0.158
Widowed	1.630	0.978 - 2.715	0.061*	1.686	0.677 - 4.198	0.259
Monthly Income (MYR)				-	-	-
0 – 999	1	-	-			
1000 – 1999	0.737	0.340 - 1.594	0.438			
2000 – 2999	0.773	0.382 - 1.566	0.475			
3000 – 3999	0.870	0.451 - 1.678	0.678			
≥ 4000 [a]	0.852	0.429 - 1.691	0.646			
Monthly Income (Continuous scale in MYR)	1.000	1.000 - 1.000	0.731	-	-	-
No. of Chronic Medical Conditions						
0 [a]	1	-	-	1	-	-
1	1.033	0.660 - 1.617	0.887	0.963	0.605 - 1.533	0.875
2	0.750	0.470 - 1.196	0.226*	0.693	0.423 - 1.136	0.142
≥ 3	0.806	0.461 - 1.411	0.451	0.849	0.472 - 1.526	0.584
Living Arrangement						
Living with spouse and children [a]	1	-	-	1	-	-
Living with spouse only	1.233	0.804 - 1.891	0.338	1.241	0.798 - 1.930	0.338
Living with children only	1.665	0.974 - 2.849	0.063*	0.863	0.346 - 2.153	0.752
Living with other people	1.354	0.589 - 3.115	0.476	0.855	0.240 - 3.054	0.799
Living alone	1.964	1.038 - 3.716	0.038**	1.052	0.358 - 3.088	0.924
Mode of Transportation				-	-	-
Public transportation [a]	1	-	-			
Own transport	0.811	0.487 - 1.350	0.420			
Brought by other people	1.582	0.520 - 4.813	0.419			
Walking	0.814	0.483 - 1.372	0.439			
Number of Children				-	-	-
≥ 5 [a]	1	-	-			
4	0.835	0.451 - 1.546	0.572			
3	0.856	0.482 - 1.519	0.589			
2	1.073	0.635 - 1.814	0.788			
1	1.354	0.647 - 2.832	0.430			
0	1.403	0.780 - 2.523	0.273			
Level of Education				-	-	-
Tertiary [a]	1	-	-			
Secondary	1.079	0.711 - 1.638	0.719			
Primary	1.257	0.754 - 2.098	0.381			
No formal education	1.223	0.742 - 2.015	0.430			
Structural Social Support				-	-	-
High [a]	1	-	-			
Low	0.732	0.498 - 1.076	0.109*			
Structural Social Support (Continuous scale) [+]	1.031	0.980 - 1.084	0.233*	1.048	0.994 - 1.105	0.076
Functional Social Support				-	-	-
Very High [a]	1	-	-			
High	2.812	1.784 - 4.434	<0.001**			
Low to Fair	3.315	2.221 - 4.948	<0.001**			
Functional Social Support (Continuous scale) [+]	0.926	0.892 - 0.961	<0.001**	0.921	0.885 - 0.956	<0.001**
Depression				-	-	-
No [a]	1	-	-			
Yes	0.908	0.402 - 2.050	0.831			
Depression (Continuous scale)	1.037	0.948 - 1.134	0.446	-	-	-
Self-rated Health				-	-	-
Very good [a]	1	-	-			
Good	0.593	0.246 - 1.429	0.255			
Moderate	0.807	0.333 - 1.959	0.643			
Not good	1.566	0.513 - 4.779	0.420			
Very bad	0.462	0.101 - 2.113	0.302			

COR: Crude odds ratio, AOR: Adjusted odds ratio, CI: Confidence Interval
** p-value < 0.05, * p-value < 0.25 (for Univariable Model)a reference group, + continuous form of variable chosen (for Multivariable Model)
Brant's test of parallel lines was insignificant (p-value = 1.000)

(n=1,791) which analysed data from the 2004 Malaysian Population and Family Survey.[15] It reported that 53.4% of older respondents experienced loneliness with 32.5% sometimes feeling lonely and 20.9% always feeling lonely.[15] More recently, a larger dataset from the 2014 Malaysian Population and Family Survey (n = 3,710) was analysed and it was found that 35.7% of older persons perceived themselves as lonely.[14] Variations in the methods used may contribute to differences in prevalence across surveys. These include measures of loneliness utilised and sample characteristics of participants recruited at the time of data collection. However, the current estimate of 47% emphasises loneliness among older persons has not declined in recent times. Loneliness persists among older Malaysians despite shifts in demographics and urban living. More than 70% of Malaysians now live in cities, making Malaysia one of the most urbanised countries in Southeast Asia.[29] Although living in a city provides better access to infrastructure and healthcare, it may change the way people interact with each other and weaken family and community support systems.[16]

Additionally, this study found that loneliness was significantly associated with age of older persons. The greater odds of loneliness due to increase in age are closely related to declining health and functional limitations.[30] Older individuals experience higher levels of loneliness because functional limitations are more common at their age compared to relatively younger persons.[30] However, the evidence in Malaysia remains mixed. While a study reported that age of older persons was significantly associated with loneliness, two other separate studies found no such association between age and loneliness.[14,15,31] A key reason for these differences may be attributable to the varying age distributions of participants across studies as some had fewer respondents of more advanced age thus limiting the ability to detect significant associations. The results of the present study also showed that older women were more likely than their male counterparts to experience loneliness. Multiple studies in Malaysia and other countries support this finding.[15,30,32] Several factors may be attributed to women's increased likelihood of experiencing loneliness. For instance, the relatively longer life expectancy of Malaysian women places them at greater risk of entering widowhood with a decline in companionship and support.[8,11] Furthermore, women may communicate their emotional needs in an open manner, which may lead to the detection of loneliness.[33] These combined demographic and sociocultural factors may therefore account for the identification of female sex as a significant determinant of loneliness.

In this study, structural social support which reflects the number of social contacts or the size of one's network was not significant in both the univariable and multivariable models. Interpersonal factors comprising emotional closeness and dependable support have greater influence on loneliness as older persons with lower levels of functional support were observed to be more likely to experience loneliness. This association can be explained by the protective role that supportive relationships play in providing emotional support to older persons thereby reducing feelings of isolation. In this present study, functional social support was measured using the DSSI-11 questionnaire which primarily assesses the perceived quality and adequacy of supportive relationships.[27] The items include emotional aspects such as being understood and listened to, able to share problems, feeling useful to others, and satisfaction with one's relationships. It encompasses not only ties with family and friends but also with broader social connections such as community or organisational contacts. The findings of this study align with the evidence that the emotional dimension of functional social support is essential in protecting against loneliness. This explains why participants with weaker emotional closeness and less adequate supportive ties (lower DSSI scores) were more likely to report higher feelings of loneliness. These findings highlight the need for strong functional social support within families while also strengthening friendships and community networks to prevent loneliness in older age.

The results of this study offer greater comprehension on the problem of loneliness among Malaysian older persons. Loneliness among older persons has been brought into focus through its prevalence, thus offering

insights into the gravity of this issue. Furthermore, screening for loneliness for at-risk older persons can be integrated into government health clinics. Brief tools such as the DJGLS-6 can be administered at triage by clinic staff, recorded, and used to trigger targeted follow-up. This aligns with Ministry of Health mental health integration priorities by translating a positive screening of loneliness into action.[34] Pertinent government and non-governmental organisation (NGO) stakeholders can improve the current Senior Citizens Club and Senior Citizens Activity Centre (PAWE) social networking programs and community support services for referral to these initiatives. However, participation metrics of these programmes alone may not be adequate indicators of older persons' social well-being. A structured buddy system or befriending component with a consistent volunteer matched to the same older person over time may encourage reciprocity and mutual recognition rather than passive presence. This may help reduce loneliness as it restores a sense of being needed and can fill the social void that activity alone does not reach.

This study has several noteworthy strengths. A cluster random sampling approach was used to ensure a good representation of senior citizens who visit Kuala Lumpur's government primary health clinics. Additionally, participants at the various clinics were randomly selected, which helped lessen selection bias. Nevertheless, this study has some limitations. This study is a cross-sectional study thus it is unable to examine the temporal relationship between loneliness and independent variables because they were both investigated simultaneously. Despite their ability to determine associations, cross-sectional studies are unable to definitively investigate cause-and-effect relationships. Additionally, because the data for this study were derived from in-person interviews, there might be issues with social desirability bias in the questionnaire replies. In terms of variables selection, this study focused on depressive symptoms without assessing anxiety, which is another psychological condition commonly associated with loneliness in later life.[4] Depression was prioritised given its strong and consistently documented link with loneliness, as well as its routine assessment in primary care settings.[35] However, the absence of anxiety measures may have led to an incomplete characterisation of the psychological correlates of loneliness and future studies should consider incorporating it for broader assessments of mental health.

CONCLUSION

In conclusion, loneliness remains a prevalent concern among older persons with nearly half of the study population affected. Female sex, increasing age, and lower levels of functional social support were significant determinants of loneliness. These findings emphasise the importance of recognising how demographic and social factors influence the experience of loneliness in later life. Strengthening functional support from family and friends is particularly crucial as it provides day-to-day emotional and social assistance. Targeted strategies addressing these determinants are needed to reduce loneliness and improve the overall well-being of older persons. While strategies addressing these determinants are needed, future research should adopt longitudinal designs to examine how loneliness changes over time, particularly around key life events. Such studies may help distinguish persistent from transient loneliness and better capture its longer-term implications for health and well-being in later life.

INSTITUTIONAL REVIEW BOARD (ETHICS COMMITTEE)

This study was registered with the National Medical Research Registry (NMRR), Malaysia and its ethical approval was granted by the Medical Research and Ethics Committee (MREC), Ministry of Health, Malaysia (NMRR ID-24-00839-KZJ). Written informed consent was obtained from all participants prior to data collection

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.

ORIGINAL ARTICLE

Health-Related Quality of Life in Young Adults with Hypertension: A Comparative Cross-Sectional Study in Malaysia

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ABSTRACT

INTRODUCTION: Hypertension in young adults is associated with a prolonged disease course and elevated lifetime cardiovascular risk, significantly affecting quality of life (QoL). Despite its growing prevalence and potential to affect multiple QoL dimensions, this relationship remains understudied in Malaysia. This study aimed to compare QoL between normotensive (NT) and hypertensive (HTN) young adults. **MATERIALS AND METHODS:** A cross-sectional study involving 124 participants (64 NT and 60 HTN) aged 18-39 years. QoL was assessed using the validated WHOQOL-BREF questionnaire across four domains: physical health, psychological well-being, social relationships, and environmental satisfaction. Body mass index, waist-to-hip ratio, and sociodemographic data were also collected. **RESULTS:** The HTN group demonstrated significantly lower scores than the NT group in physical health (67.5±14.5 vs 73.67±15.5, p=0.024) and in environmental domains (71.0±12.4 vs 75.5±11.3, p=0.037). Waist-to-hip ratio was the only consistent factor across all QoL domains, showing significant negative associations with physical health (B=-33.920, p=0.025), psychological well-being (B=-27.444, p=0.049), social relationships (B=-35.662, p=0.048), and the environmental domain (B=-38.132, p = 0.001). Body mass index was negatively associated with physical health (B=-0.495, p=0.045), and employment status was significantly associated with psychological well-being (B=-7.931, p=0.022). **CONCLUSION:** Hypertension management in young adults should extend beyond blood pressure control to encompass broader QoL considerations, particularly addressing central obesity and psychosocial determinants of health.

Keywords
Hypertension, Employment status, Quality of life, Waist-to-hip ratio, Young adults

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INTRODUCTION

Hypertension affects approximately 1.3 billion adults globally and is a leading risk factor for cardiovascular diseases (CVD), including heart failure, coronary artery disease, and stroke.[1] While traditionally considered a condition mainly affecting older adults, emerging evidence has shown that even young adults are increasingly at risk.[2] The latest 10-year risk prediction model estimates that 28.5 million young adults in the United States without a history of cardiovascular or kidney disease are at high risk of hypertension.[3] In Asia, the prevalence of hypertension among adolescents and younger adults is increasing, signalling early-onset cardiovascular risk and a growing long-term health burden.[4] In Malaysia, the Young-Onset Hypertension (YOH) study reported a consistent prevalence of YOH over the past decade, with 17.7% in 2006, 17.0% in 2011, and 18.4% in 2015.[5] Multiple factors contribute to this rise, including sedentary lifestyles, poor diets, biological sex differences, global obesity increase, and healthcare disparities across socioeconomic groups.[2] In addition to these risks, young

adults often have limited awareness of hypertension, its health consequences, and therapeutic management strategies.[6] Existing research predominantly examines elderly populations, resulting in a notable gap in knowledge regarding how hypertension affects younger age groups.[7]

Health-related quality of life (HRQoL) plays a crucial role in young adulthood, a period marked by significant transitions, including enrolling in university, gaining independence in living arrangements, and establishing a career.[8] QoL is a multidimensional concept encompassing physical health, psychological state, level of independence, social relationships, and relationships with relevant environmental features.[9] Previous research has reported mixed findings, with some studies demonstrating substantial negative effects of hypertension on QoL, while others suggest minimal impact.[10] These inconsistencies may be due to variations in measurement tools, population characteristics, or the severity of hypertension.[10] The World Health Organisation Quality of Life-Brief version (WHOQOL-BREF) instrument provides a comprehensive assessment of QoL across four domains, including physical health, psychological well-being, social relationships, and environment.[11] This validated tool is widely used across populations and conditions, suitable for examining QoL differences between HTN and NT individuals. Thus, this study aimed to compare QoL across all four WHOQOL-BREF domains between young adults with NT and HTN and to identify factors associated with QoL.

MATERIALS AND METHODS

Study design and participants

A cross-sectional study was conducted at the Cardiology Department of Hospital Canselor Tuanku Muhriz in Kuala Lumpur. Participants were recruited through community advertisements in the Klang Valley, and those who responded visited the department for all assessments. A trained research assistant screened respondents for eligibility and obtained written informed consent prior to enrolment. Eligible individuals were young adults aged 18 to 39 years who were either diagnosed with essential hypertension with systolic blood pressure (SBP) of 140 mmHg or greater and/or a diastolic blood pressure (DBP) of 90 mmHg or greater,[2] or were currently taking antihypertensive medication. Exclusion criteria were pregnancy, secondary hypertension, and major comorbidities such as cancer, heart failure, end-stage renal disease, and Type 2 Diabetes Mellitus, all identified through self-report on a structured screening checklist.

Demographic and physical activity

Demographic data included age, gender, education level, marital status, and current employment status. Physical activity levels were assessed using the validated Malay Version of the International Physical Activity Questionnaire -Short Form (IPAQ-SF)[12], which classifies participants into low, moderate, or high activity categories based on metabolic equivalent (MET) scores.

Cardiometabolic markers

High-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and C-reactive protein (CRP) were analysed. CRP was measured to assess systemic inflammation, and haemoglobin A1c (HbA1c) was measured to indicate long-term glycaemic control and diabetes risk. All blood samples were collected prospectively at the study visit following an 8-10 hour overnight fast.

Anthropometric and blood pressure measurement

Anthropometric measurements, including SBP, DBP, body mass index (BMI), and waist-to-hip ratio (WHR), were taken by a single trained research assistant. Blood pressure was measured using a calibrated OMRON Automatic Blood Pressure Monitor (HEM-7156T-A) in accordance with standardised protocols outlined in the Malaysian Clinical Practice Guidelines: Management of Hypertension (2018). Participants were instructed to rest for at least five minutes before measurement to ensure accuracy.[13] Three consecutive measurements were taken, and the average of the last two was recorded for the final analysis. BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2), while WHR was calculated as waist circumference divided by hip circumference.

WHOQOL-BREF assessment

The participants' QoL was assessed using the validated Malay version of the WHOQOL-BREF, with excellent internal consistency (Cronbach's alpha = 0.89).[14] This instrument includes 26 items that provide a comprehensive evaluation of participants' perceived well-being across various life domains. The questionnaire comprises two global items assessing participants' overall QoL and general health satisfaction. The remaining 24 items are systematically organised into four other core domains: physical health (7 items), psychological well-being (6 items), social relationships (3 items), and environmental factors (8 items). Responses were recorded on a 5-point Likert scale, allowing participants to indicate their levels of agreement or satisfaction with their current life situation. Domain scores were calculated by computing the mean of all items within each domain and then multiplying the result by four. These scores were transformed into a standardised 0-100 scale to facilitate interpretation and ensure comparability with the original WHOQOL-100 instrument.[9]

Statistical analysis

A total of 124 participants (60 HTN, 64 NT) were recruited based on the sample size determined by the parent study's primary outcome. Sample size calculation was performed using G*Power 3.1, referencing Galderisi et al. (2010), with a significance level of α=0.05 and a power of 80%.[15] Statistical analyses used SPSS 28.0. Descriptive statistics used means ± SD for continuous data and frequencies and percentages for categorical data. Independent t-tests compared WHOQOL-BREF scores between HTN and NT groups, chi-square tests assessed categorical associations, and multiple linear regression identified QoL factors. Significance was set at $p<0.05$. Risk factors included gender, education, marital status, employment, CRP, HbA1c, BMI, and WHR.

RESULTS

Participant characteristics

The demographic and clinical characteristics are presented in Table I. The HTN group was significantly older ($p<0.001$) and predominantly male ($p=0.010$). Compared with the NT group, the HTN group had lower rates of tertiary education ($p=0.011$), higher rates of marriage ($p<0.001$), and higher employment rates ($p=0.005$). Cardiometabolic markers revealed lower HDL-C ($p=0.002$), higher CRP ($p=0.011$), and higher HbA1c ($p=0.020$) in the HTN group, as well as higher BMI ($p<0.001$) and WHR ($p<0.001$).

Table I: Demographic and Clinical Characteristics of Participants

Demographic	Hypertensive (HTN) (n = 60)	Normotensive (NT) (n = 64)	p-value
Age, (mean ± SD)	31.5±4.2	28.4±4.2	<0.001*
Gender, n (%)			0.010*
Male	40 (66.7)	28 (43.8)	
Female	20 (33.3)	36 (56.2)	
Education level, n (%)			0.011*
Secondary	20 (33.3)	9 (14.1)	
Tertiary	40 (66.7)	55 (85.9)	
Marital status, n (%)			<0.001*
Not married	21 (35.0)	41 (64.1)	
Married	39 (65.0)	23 (35.9)	
Employment status, n (%)			0.005*
Unemployed	7 (11.7)	21 (32.8)	
Employed	53 (88.3)	43 (67.2)	
Physical activity level, n (%)			0.429
Low	16 (26.7)	24 (37.5)	
Moderate	25 (41.7)	22 (34.4)	
High	19 (31.7)	18 (28.1)	
Smoking status, n (%)			0.518
Yes	11 (18.3)	9 (14.1)	
No	49 (81.7)	55 (85.9)	
Cardiometabolic markers, (mean±SD)			
HDL-C, mmol/L	1.2±0.3	1.4±0.4	0.002*
LDL-C, mmol/L	3.4±1.0	3.1±0.9	0.167
CRP, mg/L	6.6±7.5	3.5±5.6	0.011*
HbA1c, NGSP (%)	5.5±1.6	5.0±0.9	0.020*
Anthropometric (mean±SD)			
BMI, kg/m²	30.8±5.6	25.1±5.1	<0.001*
WHR	0.90±0.1	0.84±0.1	<0.001*
Duration of hypertension, years	3.2±2.7	-	-

BMI, Body mass index; CRP, C-reactive protein; HbA1c, Haemoglobin A1c; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; WHR, Waist-to-hip ratio.
*Statistically significant, $p<0.05$

Comparison of WHOQOL-BREF domain scores

Table II presents WHOQOL-BREF domain scores for both groups. The HTN group scored significantly lower than the NT group on physical health ($p=0.024$) and on environmental domains ($p=0.037$). No significant differences were observed in psychological ($p=0.925$), social relationships ($p=0.443$), or overall QoL scores ($p=0.669$). Both groups scored highest in the environmental domain.

Table II: Comparison of WHOQOL-BREF Domain Scores Between HTN and NT groups.

Domain	Hypertensive (HTN) (n = 60)	Normotensive (NT) (n = 64)	p-value
Physical Health	67.5±14.5	73.67±15.5	0.024*
Psychological	67.98±14.5	68.2±14.4	0.925
Social Relationships	68.8±20.0	71.2±15.6	0.443
Environment	71.0±12.4	75.5±11.3	0.037*
Overall QoL	68.3±21.0	66.7±18.9	0.669

QoL, Quality of Life. Values are presented as mean ± SD.
*Statistically significant, p<0.05

Factors associated with HRQoL

Multiple linear regression analysis was performed to identify factors associated with each QoL domain (Table III). WHR was the only consistent predictor across all QoL domains, showing significant negative associations with physical health (B=-33.920, 95% CI:-63.464, -4.377, p=0.025), psychological well-being (B= -27.444, 95% CI: -54.781, -0.106, p=0.049), social relationships (B=-35.662, 95% CI:-71.003, -0.322, p=0.048) and environmental domain (B=-38.132, 95% CI:-60.700, -15.563, p=0.001). BMI was associated with physical health (B=-0.495, 95% CI:-0.978, -0.012, p=0.045), while employment status was associated with psychological well-being (B=-7.931, 95% CI:-14.690, -1.172, p=0.022). Gender, marital status, CRP, and HbA1c were not significant predictors of QoL in any domain. Figure 1 illustrates the consistent negative association between WHR and all QoL domains.

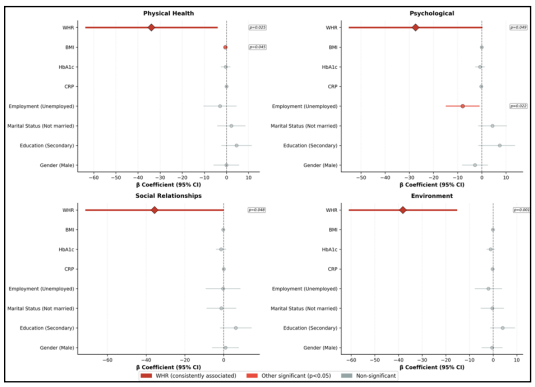

Figure 1: Forest plots of multivariable linear regression showing associations between anthropometric, metabolic, and sociodemographic factors and quality of life domains. Values represent β coefficients with 95% confidence intervals

DISCUSSION

Key Findings

This study yielded several noteworthy findings. WHR, rather than BMI, demonstrated a consistent association with HRQoL across all four WHOQOL-BREF domains, suggesting that central adiposity has a broader impact on well-being than total body mass. Furthermore, hypertension primarily affected the physical health and environmental domains in this young adult cohort, unlike older populations, where psychological and social domains tend to be more affected. Additionally, employment status was independently associated with psychological QoL, underscoring the critical role of occupational engagement in the mental health of young adults with hypertension.

In demographic analysis, significant differences were observed between the HTN and NT groups in age and gender. Although the age difference was statistically significant, both groups fell within the 18-39 year age range, qualifying them as young adults according to the 2024 European Society of Cardiology (ESC) Guidelines for the Management of Elevated Blood Pressure and Hypertension.[2] To the best of our knowledge, this is the first study to investigate HRQoL among young adults with hypertension in Malaysia. The predominance of males in the HTN group is consistent with findings from the Malaysian hypertension prevalence study, which reported that males are nearly twice as likely to have hypertension compared to females.[5] Men, who are often the primary earners, tend to face greater work-related stress and have higher smoking rates, raising their risk of hypertension.[16] In this study, one-third of the HTN group had only secondary-level education, whereas the NT group was predominantly composed of university graduates. These findings support earlier research indicating that lower levels of education are typically associated with a limited understanding of health information and decision-making.[17,18] Meanwhile, higher education is associated with lower risk and better health outcomes.[18-25] Greater educational attainment may be associated with a decreased risk of hypertension, potentially attributable to improved health literacy and awareness of blood pressure regulation techniques.[24]

Marital status was also significantly associated with hypertension status, with the majority in the HTN group being married. This finding is consistent with earlier results from the MyCoSS study on Malaysian adults, which reported that most hypertensive individuals are married, a trend also observed in other countries.[18,20,21,26]

Table III: Multiple Linear Regression Analysis for Factors Associated with Domains of Quality of Life.

Variable (Reference)	Physical Health			Psychological			Social Relationships			Environment		
	B	95% CI	p-value	B	95% CI	p-value	B	95% CI	p-value	B	95% CI	p-value
Gender (Male)	-0.084	-5.661, 5.493	0.976	-2.819	-7.980, 2.342	0.282	0.949	-5.722, 7.621	0.779	-0.447	-4.708, 3.813	0.836
Level of Education (Secondary)	4.517	-2.121,11.154	0.180	7.426	-1.284, 13.568	0.218	6.284	-1.656, 14.224	0.120	3.992	-1.078,9.063	0.122
Marital Status (Not married)	2.170	-4.027, 8.367	0.489	4.434	-1.300, 10.168	0.128	-1.184	-8.597,6.229	0.752	-0.362	-5.095,4.372	0.880
Employment status (Unemployed)	-2.933	-10.238, 4.371	0.428	-7.931	-14.690, -1.172	0.022*	-0.306	-9.044, 8.432	0.945	-2.012	-7.592,3.568	0.477
CRP, mg/L	-0.024	-0.447, 0.398	0.909	-0.259	-0.650, 0.132	0.193	0.068	-0.438, 0.573	0.791	-0.225	-0.547,0.098	0.171
HbA1c, %	-0.373	-2.371, 1.624	0.712	-0.734	-2.582, 1.115	0.433	-1.352	-3.741, 1.037	0.265	-1.088	-2.614,0.438	0.161
BMI, kg/m²	-0.495	-0.978, -0.012	0.045*	-0.068	-0.515, 0.379	0.763	-0.240	-0.818, 0.338	0.413	-0.140	-0.509,0.229	0.455
WHR	-33.920	-63.464, -4.377	0.025*	-27.444	-54.781, -0.106	0.049*	-35.662	-71.003, -0.322	0.048*	-38.132	-60.700, -15.563	0.001*

BMI, Body mass index; CRP, C-reactive protein; HbA1c, Haemoglobin A1c; WHR, Waist-to-hip ratio.
*Statistically significant, $p<0.05$
Multicollinearity was assessed prior to each regression model using Variance Inflation Factors (VIF). All VIF < 5.0; no significant interactions detected. R^2: Physical Health = 0.106; Psychological = 0.137; Social Relationships = 0.063; Environment = 0.156

A 2025 study from China found that, in women, factors like age and financial status may influence how marital status relates to hypertension.[27] In India, an individual's hypertension status was consistently related to their spouse's condition across various socio-demographic groups.[28] On the other hand, in our study, most NT participants were not married. This variation could be attributed to the sampling method, as the NT group likely included recent graduates who had just started working and were not yet married.

HDL-C levels were significantly higher in the NT group than in the HTN group, consistent with its inverse relationship with hypertension.[29,30] Although our study did not include measurements of high-sensitivity CRP, standard CRP levels were significantly elevated among participants with hypertension. Elevated CRP levels may contribute to hypertension by reducing nitric oxide production, upregulating vasoconstrictors, and impairing blood vessel relaxation.[31] HbA1c, a biomarker of long-term glycaemic control, was also significantly higher in the HTN group. This finding is consistent with the understanding that higher levels of this biomarker can increase cardiovascular risks, including hypertension. The BiomarCaRE prospective cohort study, conducted across Europe, investigated the association between HbA1c levels and cardiovascular outcomes in 36,180 participants. It found that both cardiovascular disease and overall mortality rates rose as HbA1c levels increased among individuals without diabetes.[32] Similarly, a study from the China Health and Nutrition Survey (CHNS) observed a positive relationship between HbA1c and hypertension incidence in 4,074 participants. [33]

Comparison of HRQoL between HTN and NT

This study explored HRQoL differences between NT and HTN groups, finding that both scored highest in the environmental domain, consistent with earlier research on hypertensive individuals.[34,35] This domain includes financial resources, personal freedom, safety, health, social care (access and quality), home environment, learning and leisure opportunities, and physical aspects of surroundings.[11] Most participants likely resided in the Klang Valley, an urban area characterised by good safety, healthcare, social services, leisure facilities, and transportation. Healthcare accessibility varies considerably by location, with urban centres such as the Klang Valley benefiting from higher physician density per capita.[16] A study in Malaysia shows urban residents benefit from well-maintained facilities like public transportation, parking, and health services, which enhance QoL needs.[36]

A significant difference was found in average scores, with the HTN group scoring lower than the NT group. This indicates that those with normal blood pressure might have better access to or satisfaction with health-supporting resources. Conversely, hypertensive individuals may face limited recreational access due to fewer exercise programs, exercise limits, medication side effects such as fatigue and dizziness, or fear of adverse events. A study found that hypertensive individuals had fewer leisure

opportunities and lower QoL, as evidenced by their mean QoL scores.[35] The International Society of Hypertension (2024) recommends initiating lifestyle modifications, including increased physical activity (≥150 min/week of moderate aerobic activity [brisk walking, cycling, or swimming]) and resistance training 2-3 times/week, early in life as a primary strategy to prevent and control hypertension.[37]

Meanwhile, the physical health domain has the lowest HRQoL score in the HTN group, consistent with previous research findings.[21,34,38,39] Although some earlier studies reported that elderly populations tend to have the lowest physical health scores in this domain, a study assessing HRQoL among young adults on the rural west coast of Peninsular Malaysia reported similar results, indicating that young adults may also experience reduced physical health scores.[38] Hypertension can negatively impact physical health through several factors, including medication use, pain, work limitations, sleep disturbances, and reduced energy levels.[11] A study on patients' experiences with hypertension found that most report symptoms and challenges in daily activities.[40] There is also evidence of a bidirectional association between hypertension and insomnia, with hypertension predicting higher insomnia risk (OR =1.20, 95% CI: 1.08-1.32) and vice versa (OR =1.11, 95% CI: 1.07-1.16).[41] Furthermore, insufficient sleep increases prehypertension risk,[42] and hypertensive individuals often experience poor sleep, affecting their QoL, especially physically.[34] Inadequate sleep triggers sympathetic activation that impairs cardiovascular regulation by preventing normal nighttime blood pressure drops or causing nocturnal increases.[37] These findings are especially important for young adults in Malaysia, as some young workers do shift work, leading to irregular sleep patterns and an elevated risk of hypertension.[43]

Interestingly, we found no significant differences between NT and HTN in psychological and social domains. Both had average scores, implying that hypertension may have a smaller effect on HRQoL in young adults. This finding aligns with the understanding that hypertension initially presents as an asymptomatic condition in younger populations.[44] The asymptomatic nature of early-stage hypertension means that young adults often do not experience noticeable physical symptoms that would directly affect their psychological well-being or social functioning. In Malaysia, almost 29.2% of people suffer from high blood pressure, but about 11.9% are unaware of their condition. This lack of awareness is particularly prevalent among younger age groups, especially those aged 18 to 39.[45] Consequently, their HRQoL in these areas tends to be similar to that of normotensive individuals.

Factors associated with HRQoL between HTN and NT

Regression analysis indicated that WHR was negatively associated with HRQoL across all four domains. WHR is a measure of central or abdominal obesity that reflects visceral fat accumulation.[46] In contrast, BMI showed a specific association only with physical health. This finding is consistent with a previous study of Filipinos, which reported that WHR was more strongly associated with decreased HRQoL than BMI.[47] Similarly, a multicity study from China found that abdominal obesity had a greater impact on physical health compared with mental health.[48] In Malaysia, the prevalence of abdominal obesity among adults has increased significantly from 2011 to 2023, raising major public health concerns that can impact overall QoL.[45] The Ministry of Health's Clinical Practice Guidelines recommend annual screening for BMI and waist circumference, using culturally appropriate cut-off values for the Malaysian population.[49] This differential pattern between BMI and WHR reinforces the importance of body fat distribution over total body mass. Central obesity appears to have broader implications for HRQoL, while peripheral or overall obesity primarily affects physical capabilities.

The significant association between employment status and psychological domain scores confirms that occupational engagement is important for mental health. This finding is consistent with previous research indicating that unemployment can significantly reduce QoL.[17,18,38] The association between unemployment and lower psychological well-being may reflect the loss of role identity, social interaction, and sense of purpose that employment provides.[18,38] That this association was

confined to the psychological domain suggests that employment primarily influences mental health rather than all aspects of life.

Nevertheless, several limitations should be acknowledged. The cross-sectional design prevents establishing a causal relationship between hypertension and HRQoL. The lack of sociodemographic matching between groups means residual confounding cannot be excluded despite regression adjustment, and future studies should consider a matched or propensity-score design. Although the sample size was sufficient for the primary analyses, it may not have had adequate power to detect minor effects. Additionally, self-reported questionnaire data carry an inherent risk of response bias, and potential confounders, including dietary habits, stress levels, and sleep quality, were not assessed. Considering early hypertension onset and its impact on HRQoL, comprehensive cardiovascular evaluations, including advanced imaging modalities such as echocardiography and carotid ultrasound, should be considered to detect subclinical damage and enable timely intervention before complications arise.

CONCLUSION

This study demonstrates that hypertension reduces HRQoL in young adults, particularly in the physical health and environmental domains. It emphasises the need for hypertension management strategies that address not only blood pressure control but also broader HRQoL concerns. Current evidence suggests community-based physical activity programmes, workplace wellness initiatives, WHR-targeted dietary and exercise counselling, and health literacy campaigns within routine care are associated with better HRQoL outcomes in young adults with hypertension. Longitudinal studies are needed to confirm the causal direction of these associations.

INSTITUTIONAL REVIEW BOARD (ETHIC COMMITTEE)

This study was approved by the Research Ethics Committee of the National University of Malaysia (JEP-2023-510).

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ORIGINAL ARTICLE

Caregiver Perception in Supporting Communication for People with Dementia

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ABSTRACT

INTRODUCTION: Dementia progressively impairs cognitive abilities and negatively affecting communication between people with dementia (PWD) and their caregivers. This study explored caregivers' experiences in communicating with PWD. **MATERIALS AND METHODS:** This qualitative study received ethical approval from Universiti Kebangsaan Malaysia (JEP-2024-266). Sixteen family caregivers of PWD were purposively recruited from the Psychiatric Clinic, Occupational Therapy Unit, and Speech Therapy Unit at a public university hospital. Semi-structured face-to-face interviews were conducted individually, lasting 30–40 minutes, and were recorded via Microsoft Teams. The transcripts were analysed using thematic content analysis. Coding reliability achieved 81.33% agreement, and discrepancies were resolved through discussion. **RESULTS:** Two main themes were identified: Communication Challenges (CC) and Strategies to Support Communication (SSC). The CC theme comprised of four subthemes: cognitive deficits, other PWD-related factors, communication difficulties, and impacts on caregivers' personal lives. The SSC theme comprised of three subthemes: comprehensive support, active engagement, and the use of communication aids. Communication breakdowns, behavioural issues, coexisting health conditions, and limited family support contributed to caregiver stress, whereas memory support, emotional reassurance, cognitive stimulation, and multimodal communication strategies improved interaction. **CONCLUSION:** Caregivers' wellbeing is affected by the cognitive and behavioural challenges of PWD as well as the availability of family support. External support, engagement activities, and communication aids may enhance caregiver–PWD interaction and strengthen social connections. The findings highlight the need for culturally tailored interventions and caregiver training programs to improve communication experiences and overall quality of life for both caregivers and PWD.

Keywords
family caregivers, social perception, communication disorders, dementia, Alzheimer's disease

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INTRODUCTION

Dementia is a progressive neurological condition that affects cognitive and communication functions, posing significant challenges for people who are experiencing dementia and their caregivers.[1] Cognitive deficits affect communication abilities, including language, memory, and attention, making it more challenging to comprehend, process, and express oneself during communication.[2] Family caregivers play a central role in supporting people with dementia (PWD) as the disorder progresses.[3] The adaptation of communication strategies is essential to maintain the quality of interaction, relationships, and emotional connections.[4] This study explored the perceptions of Malaysian family caregivers regarding their communication with PWD, the challenges they faced, and the strategies they employed to enhance interaction.

MATERIALS AND METHODS

Study Design

This study employed a qualitative approach involving individual face-to-face interviews with family caregivers of PWD. Ethical approval was granted by the Universiti Kebangsaan Malaysia's Research Ethics Committee (JEP-2024-266).

Participants

A total of 16 family caregivers were recruited based on predefined inclusion and exclusion criteria, namely individuals who: (a) have a family member diagnosed with dementia by a medical doctor, (b) serve as caregiver of the PWD, (c) able to communicate in Malay or English, and (d) have never been diagnosed with mental health disorders. Participants were recruited through purposive sampling at the Psychiatric Clinic, Occupational Therapy Unit, and Speech Therapy Unit of a public university hospital.[4]

Study Sites

All interviews were conducted in person at a public university hospital in a private consultation room to ensure confidentiality.

Data Collection Tools and Procedure

A participants' background questionnaire was constructed to gather sociodemographic data. A semi-structured interview guide was also developed to facilitate the exploration of the caregivers' roles, challenges, and communication strategies. Individual face-to-face interviews were conducted, each lasting approximately 30 to 40 minutes. All sessions were audio-recorded using the Microsoft Teams application and securely stored in password-protected cloud storage. Before participation, caregivers were screened to ensure they met the inclusion criteria. Written informed consent was obtained from each participant.

Data Analysis

Interview recordings were transcribed verbatim and analysed using a thematic content analysis approach to identify the main ideas that addressed the study objectives. In the analysis, each transcript was segmented into meaningful units. A specific code was given to each segment. A list of initial codes was generated. The codes were grouped into categories, which were then used to identify themes and subthemes. To ensure reliability, an independent coder conducted coding on two transcripts based on the initial code list. The codes between the two coders were evaluated for agreement.

RESULTS

The age of participants ranged from 20 to 77 years, with a mean of 54.25 and a standard deviation of 14.7. The participants included spouses (31.25%), children (62.5%), and other family members (6.25%). The sample included caregivers of Chinese (68.75%), Malay (18.75%), and Indian (12.5%) ethnicities. The duration of providing care to PWD ranged from 10 months to 14 years, with a mean of 4.86 and a standard deviation of 4.07. The sociodemographic data are summarised in Table I.

Table I: Sociodemographic Characteristics of Participants (n=z16)

Participant	Age	Ethnicity	Relationship with PWD	Occupation	Duration of Caregiving
1	72	Chinese	Husband	Retired	2 years
2	47	Indian	Daughter	Assistant editor	2 years
3	60	Indian	Son	Retired	2 years
4	50	Chinese	Daughter	Pediatrician	3 years
5	77	Malay	Husband	Retired	3 years
6	75	Chinese	Wife	Retired	6 years
7	20	Chinese	Grandson	Student	14 years
8	50	Chinese	Daughter	Housewife	14 years
9	52	Chinese	Daughter	Housewife	9 years
10	50	Chinese	Daughter	Finance manager	3 years
11	43	Chinese	Daughter	Beautician	2 years
12	44	Chinese	Daughter	Accountant	5 years
13	65	Malay	Wife	Retired	4 years
14	54	Chinese	Daughter	Company secretary	5 years
15	42	Chinese	Daughter	Housewife	3 years
16	67	Malay	Wife	Retired	10 months

In qualitative analysis, a list of codes was generated based on the analysis of the transcriptions. The codes were evaluated through coding reliability, resulting in 81.33% agreement. Discrepancies were resolved through discussions between the coders.

Key Themes

Thematic analysis of the interviews revealed two major themes: "Challenges in Communication with PWD" (CC) and "Strategies to Support Communication with PWD" (SSC). For the first theme (CC), four subthemes

were identified: the impact of dementia on communication, cognitive deficits, other PWD factors and the impacts on caregivers' personal life. For the second theme (SSC), three subthemes were identified: comprehensive support, active engagement, and the use of communication aids. These themes are outlined in Figure 1.

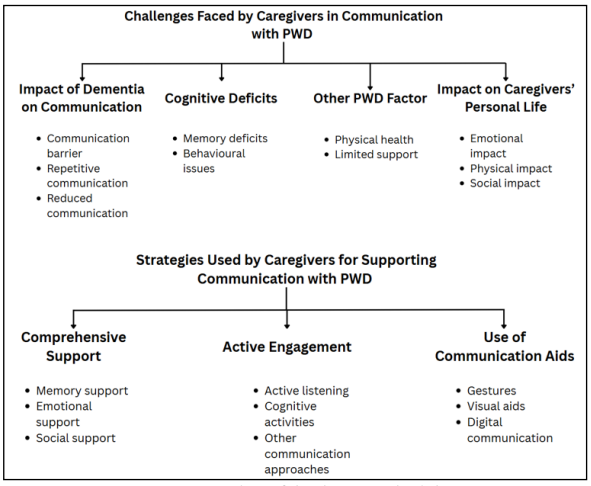

Figure 1: Overview of the themes and subthemes

Challenges Faced by Caregivers in Communication with PWD (CC)

Caregivers of PWD reported four key challenges in communication (CC). Participants' quotes and subthemes are presented in Table II. Firstly, they experienced significant impacts of dementia on communication, including barriers to understanding, repetitive speech, and reduced verbal interaction. Secondly, cognitive deficits such as memory loss and behavioural disturbances further hinder effective communication. Thirdly, other PWD factors such as hearing loss, coexisting medical conditions (e.g., stroke), and limited family support compounded these challenges. Lastly, the impact on caregivers personal lives were considerable, with many experiencing emotional stress, physical exhaustion, and social isolation due to their caregiving responsibilities.

Strategies to Support Communication with PWD (SSC)

Caregivers employed a range of strategies to support communication with PWD, which were categorised into three main areas. Participants' quotes and subthemes are presented in Table III. "Comprehensive support" involved reinforcing memory through repeated reminders, providing emotional reassurance, and fostering social interaction to enhance engagement. "Active engagement" strategies included active listening, cognitive stimulation through games or structured activities, and, when necessary, more assertive communication methods to gain the attention or cooperation of the PWD. Additionally, caregivers utilised various communication aids such as gestures, visual tools like whiteboards, and digital platforms including smartphones and messaging apps, to facilitate clearer and more consistent communication. These strategies reflect caregivers' adaptability in addressing the evolving challenges of dementia care.

Table II: Challenges Faced by Caregivers in Communication with PWD

Subthemes	Categories	Quotes
Impacts of Communication on Dementia	Communication barrier	"..right now, when you speak to her, she will find it difficult to receive what you're going to tell her" (P01) "..they want something, but you couldn't figure out what they want.." (P09)
	Repetitive communication	"Yes, she always tell story. She will repeat, repeat and repeat" (P12) "Every five minutes after that, he will ask again what time is it" (P16)
	Reduced communication	"He is quite afraid to talk because he is afraid, he will talk nonsense, so he talks less now." (P08) "It's just previously she talks alot and now I think maybe reduce to 20% to 30%." (P12)
Cognitive Deficits	Memory deficits	"She keeps on saying she wants to go home but she can't remember that this is actually her house" (P05) "My mother-in-law, she cannot remember us. If we ask her who she was living with, she said she is with her sister, when in fact, she lives with my husband, which is her son." (P08)
	Behavioural issues	"Nowadays, it is more difficult, he would always say no and be aggressive." (P02) "..she have emotion problem and then so she was sometimes certainly will very sad or very angry." (P15)
Other PWD factor	Physical health	"And then, she also used to tell me she can't hear exactly what I want to tell, maybe because of the ear" (P01) "..officially diagnosed by doctor premier HUKM with minor brain stroke. So, he seems forgetting since then." (P16)
	Limited support	"His siblings also do not want to take care of him." (P16)
Impacts on Caregivers' Personal Life	Emotional Impact	"..because you don't understand, and you tend to be very impatient and get angry and also very stress" (P06) "..quite stressful to take care of someone who is forgetting." (P14)
	Physical Impact	"It's very tiring and frustrating in a sense" (P02) "..now I am stressed, because lack of sleep to take care of him" (P16)
	Social Impact	"We talk only when it is necessary. Even if we talk many times, he will forget." (P16)

Table III: Strategies Used for Supporting Communication with PWD

Subthemes	Categories	Quotes
Comprehensive care	Memory support	"..we ask what date? Then she says can't remember. Then, we remind her again" (P03) "So you need to repeat two three times, then he will understand" (P07) "I just repeat and repeat when she was asking about my pet. I already told her many times, but she still asks" (P11)
	Emotional support	"..to comfort, to say it is okay if you have forgotten." (P13)
	Social support	"She is very happy about little children. So, there is bonding for my mother and her grandchildren. She got the initiative to communicate with them" (P09) "..he still want to go back to the same restaurant to see whether his friend is there so that he can talk around." (P10)
Active Engagement	Active listening	"..need to always listen to him.." (P10)
	Cognitive activities	"..they sort of do guessing game, try to guess what he trying to say" (P02) "Then, we prepare a menu to help in memory" (P03)
	Other communication approaches	"We just do whatever method. I will be louder and force her." (P08) "Sometimes, I need to shout to him. I guess that's the most effective which is to shout" (P16
Use of communication aids	Gestures	"..my mom and I sometimes will get irritated and point to what we are trying to say" (P02)
	Visual aids	"..only the whiteboard where I put what he is supposed to do." (P13)
	Digital communication	"But it was a good thing she actually started using phone and there was one time I think we chat about two minutes" (P04) "If he goes outside, I will always check on him via Whatsapp, which is another form of communication." (P13)

DISCUSSION

Communication breakdowns between caregivers and people with dementia (PWD) were prominently reported as major challenges in caregiving. Several participants described instances where PWD were unable to comprehend or respond appropriately, repeatedly asked the same questions, retold the same stories, forgot familiar people or surroundings, and made inappropriate requests such as asking to "go home" despite already being at home. These communication difficulties often led to frustration, reduced quality of interaction, and increased stress among caregivers.[5,6] These findings are consistent with previous research, which indicates that cognitive decline disrupts communication and is a major contributor to caregiver emotional strain.[7,8]

Interestingly, unlike past research,[9] reduced verbal interaction between caregivers and PWD was minimally reported in this study. Behavioural challenges, such as aggression and emotional instability, were also highlighted as significant stressors, adding unpredictability to caregiving situations.[10] Coexisting medical conditions, including hearing impairment or the after-effects of stroke, further complicated interactions, echoing prior findings that multimorbidity increases the complexity of dementia caregiving.[11] A lack of family support was also reported as a contributing factor to caregiver strain and social isolation.[12,13] Emotional exhaustion, frustration, and burnout were recurrent subthemes, which align with previous studies identifying communication-related stress as a core issue for caregivers.[8] Physical consequences, such as tiredness and disrupted sleep, were also described and are consistent with findings on the health impact of long-term caregiving.[14] However, social withdrawal was less frequently reported in this study compared to its recognised risk in the literature.[15,16]

In addressing these challenges, caregivers described a range of communication strategies that could be grouped into three subthemes: comprehensive care, active engagement, and the use of communication aids. Memory support strategies, such as frequent reminders and repetition, were widely used to reduce confusion among PWD, which is consistent with past studies indicating that prompting supports memory retention.[8] Emotional reassurance and fostering social interactions were also highlighted as beneficial, providing both cognitive and emotional support.[17,18] Active engagement strategies, including attentive listening and cognitive stimulation through games or tasks, were employed by several participants and are supported by previous findings showing their positive effects on communication and mental functioning.[9]

A few caregivers reported using more forceful communication methods, such as raising their voices when necessary. Although sometimes effective, such strategies must be used cautiously, as they risk increasing distress or confusion in PWD if delivered without empathy.[8] The reported use of communication aids such as gestures, whiteboards, and digital tools like messaging apps, illustrates a shift toward multimodal communication. These tools can provide structure and continuity, reflecting broader trends in the integration of technology into dementia care.[15,18]

This study has several limitations. The sample size was small and context-specific, with all participants recruited from a single university hospital in an urban area. Therefore, the findings may not be generalisable to caregivers in rural areas, where lifestyle and resources may differ. Furthermore, the data were based on self-reported experiences, which may be subject to recall bias or individual interpretation. Future studies should consider recruiting more diverse samples and triangulating caregiver narratives with observational data or professional perspectives.

CONCLUSION

This study highlights the significant communication challenges faced by caregivers of PWD, including cognitive, behavioural, and medical-related barriers. Despite these challenges, caregivers employ a variety of strategies ranging from memory support and emotional reassurance to active engagement and the use of communication aids to improve interactions with PWD. Addressing these communication challenges through culturally appropriate caregiver training programs in Malaysia is crucial. Such programs should include practical communication strategies, emotional support, and guidance on utilising digital communication tools in home care. Additionally, respite services and peer support networks can help alleviate the emotional and physical burdens faced by caregivers. Ultimately, improving communication between caregivers and PWD has the potential to enhance not only the quality of interaction but also the overall quality of life for both caregivers and PWD.

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ORIGINAL ARTICLE

Assessment Of Pain, Balance, Functional Performance, And Quality Of Life In Patients With Meniscus Lesions: A Cross-Sectional Study

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ABSTRACT

INTRODUCTION: This study aimed to compare pain, balance, functional performance, and quality of life between individuals with meniscal injury and healthy controls. To evaluate the differences in pain, balance, functional performance, and quality of life between individuals with meniscal injury and healthy controls. **MATERIALS AND METHODS**: Seventy participants were enrolled, including 35 patients with MRI-confirmed meniscal injury and 35 age- and sex-matched healthy controls. Pain was measured using the Visual Analog Scale (VAS), balance and mobility with the Berg Balance Scale (BBS) and Timed Up and Go Test (TUG), functional performance with the Five Times Sit to Stand Test (5TSTS), and quality of life with the Western Ontario Meniscal Evaluation Tool (WOMET). Muscle strength and range of motion (ROM) were also assessed. **RESULTS**: Compared with healthy controls, individuals with meniscal injury reported higher pain levels and demonstrated poorer functional performance and quality of life ($p<0.05$). The meniscal tear group reported higher pain levels ($p<0.001$) and demonstrated worse functional mobility (longer TUG and 5TSTS times) and quality of life (higher WOMET scores, $p<0.05$). A significant correlation was found between VAS and WOMET outcomes in the meniscal tear group ($p<0.05$) and between VAS and both WOMET and BBS outcomes in the control group ($p<0.05$). **CONCLUSION**: This study emphasizes the need for rehabilitation strategies addressing both physical recovery and quality of life for individuals with meniscal injuries. Future research should explore targeted pain management and rehabilitation programs to improve patient well-being.

Keywords
Meniscus tear, pain, muscle strength, balance, quality of life

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INTRODUCTION

Meniscal injury are common knee injuries affecting a broad population, from young athletes to the elderly. They often result from sports trauma or age-related degeneration. [1] These injuries not only cause local damage but also impact pain perception, balance, function, and overall quality of life.[2,3] Despite advances in diagnosis and treatment, the broader functional effects of meniscal injury —especially concerning objective evaluations— remain underexplored. The meniscus plays a key role in knee stability, shock absorption, and load distribution.[3,4] Damage can lead to biomechanical alterations, reduced stability, and increased osteoarthritis risk.[4–7]

While prior studies have primarily focused on treatment strategies, fewer have assessed daily functional implications such as postural control and fall risk.[8] To our knowledge, this study evaluates pain, balance, functional performance, and quality of life in individuals with meniscal injury using a comprehensive combination of VAS, BBS, TUG, 5TSTS, and WOMET, which have

mostly been reported individually or partially in previous studies. This comprehensive approach provides a multidimensional analysis, differing from previous studies that focus on isolated measures. The inclusion of predominantly female and older participants also adds to understanding this condition in underrepresented groups. This study aims to evaluate the functional and quality-of-life impacts of meniscal injury by comparing objective measures between patients and healthy controls. We hypothesize that patients will report higher pain, poorer function, and reduced quality of life, and that pain levels will correlate with balance and functional limitations.

MATERIALS AND METHODS

A total of 70 participants were enrolled: 35 patients with MRI-confirmed meniscal injury and 35 healthy controls. Sample size was calculated using G-Power (effect size = 0.8, power = 95%).[9]

Inclusion criteria – Meniscus group: Participants aged 18 –60 years with MRI-confirmed meniscal tear who were willing to participate and had no systemic or neurological conditions affecting assessment. All participants were evaluated during conservative (non-operative) management prior to any surgical decision. Both traumatic and degenerative meniscal tears, involving different morphologies and locations, were included without restriction on tear type.

Inclusion criteria – Control group: aged 18–60, no neurological, orthopedic, or systemic issues, and willing to participate. For the control group, individuals with no history of knee pain, trauma, surgery, or known musculoskeletal disorders were included. Participants had no current or previous knee-related symptoms and no clinical findings suggestive of meniscal pathology on physical examination. Therefore, routine radiographic (X-ray or MRI) screening was not performed, as there were no clinical indications requiring imaging.

Exclusion criteria: recent lower extremity fracture or knee surgery within the past year, autoimmune/inflammatory diseases, or recent knee rehabilitation (within 6 months).

Physical and Sociodemographic Data

Collected data included age, sex, height, weight, occupation, dominant limb, and physical activity levels, as well as symptom duration and affected side.

Pain and Range of Motion

Pain intensity was assessed using the Visual Analog Scale (VAS) during activity, rest, and at night. Knee range of motion (ROM) was measured with a goniometer, with the pivot placed on the lateral femoral condyle, using standard anatomical alignment for flexion and extension. Participants were assessed in the prone position.

Muscle Strength

Quadriceps and hamstring strength were tested using manual muscle testing (MMT) on a 5-point scale. For flexion testing, participants lay prone; for extension, they sat with hips and knees at 90°. Resistance was applied at the ankle. Pelvic stabilization was ensured during flexion, and a towel supported the thigh during extension.[10] A single experienced physiotherapist conducted all tests to ensure consistency.

Balance

Balance was assessed with the Berg Balance Scale (BBS), a 14-item tool with scores ranging from 0 to 56, where higher scores indicate better balance. Its Turkish version has been validated. [11]

Functional Performance

Functional performance was evaluated using the Timed Up and Go Test (TUG)[12] and Five Times Sit to Stand Test (5TSTS).[13] For TUG, participants stood from a chair, walked 3 meters, turned, and returned to sit; time was recorded. For 5TSTS, they rose and sat five times with arms crossed, and the total time was noted.

Quality of Life

Quality of life was assessed using the Western Ontario Meniscal Evaluation Tool (WOMET), validated in Turkish. It consists of 16 items across three subdomains: physical symptoms, emotional impact, and lifestyle/

work.[14]

Assessment of Quality of Life

The Western Ontario Meniscal Evaluation Tool was used to assess the quality of life in people with meniscus pathology (WOMET). This validated tool in Turkish consists of 16 questions divided into three categories: physical symptoms, emotional impact, and lifestyle/work. Together, these questions provide a thorough evaluation of the individual's well-being.[14]

Statistical Analyses

Data were analyzed using IBM SPSS v27.0.1.0. Categorical data were reported as counts and percentages; continuous variables as means ± standard deviation. The Chi-square test was used for group comparisons of categorical variables. The Mann-Whitney U test was used for non-normally distributed continuous variables. Spearman's correlation assessed relationships between variables. A p-value <0.05 was considered statistically significant.

RESULTS

Seventy subjects, comprising 35 with meniscus injury and 35 healthy individuals, were included in the study. Descriptive data for the participants are shown in Table 1. No statistically significant difference was found between the demographic characteristics of the groups (p>0.05).

Table I: Comparison of the physical characteristics of individuals

		Study Group	Control Group	
Variable		n (%)	n (%)	p
Sex	Female Male	24 (68.57%) 11 (31.43%)	26 (74.29%) 9 (25.71%)	0.597
Dominant Side	Right Left	5 (14.29%) 30 (85.71%)	1 (2.86%) 34(97.14%)	0.198
Age (years)		45.2 ± 9.9	44.3 ± 10.1	0.715
Height (cm)		164.6 ± 10.6	166.3 ± 8.8	0.286
Weight (kg)		79.2 ± 13.5	76.4 ± 14.0	0.455
BMI (kg/m2)		29.4 ± 4.8	27.7 ± 5.0	0.092

cm: Centimeter, kg: Kilogram, m: meter, n: sample size, Significant values $p<0.05$

The distribution of the dominant side, education level, smoking, and alcohol consumption was compared between the study group and control group. The majority of individuals in both groups were right-handed, with 85.71% in the study group and 97.14% in the control group. Education levels varied, with the largest portion of the study group having completed primary education (62.86%), while the control group showed a more diverse educational background, including a higher percentage of participants with bachelor's degrees (34.29%). Smoking habits were less common in both groups, with 80% of the study group and 71.43% of the control group not engaging in smoking. Alcohol consumption was also low among participants, with the vast majority not consuming alcohol at all (91.43% in the study group and 94.29% in the control group). However, the differences between groups in these categories were not statistically significant, indicating similar demographic and lifestyle characteristics among participants.

Regarding meniscal tear characteristics in the study group, 74.3% of patients had medial meniscus injury , while 22.9% had lateral injury and 2.9% had combined medial and lateral involvement. The posterior horn was the most commonly affected location (82.9%), followed by the anterior horn (17.1%). In terms of tear morphology, horizontal injury were the predominant type (80%), whereas other tear types were observed less frequently.

Table II: Comparison of muscle strength and ROM findings between groups

Measurement		Study Group (n=35) +/- SD (Min-Max)	Control Group (n=35)	p-value
Knee Joint Flexion	Right	127.1±10.2 (95-140)	128.5±7.6 (110-140)	0.901
	Left	127.5±9.9 (100-140)	128.0±8.6 (105-140)	0.906
Knee Joint Extension	Right	1.30±2.74 (-10-5)	0.69±1.05 (0-4)	0.009*
	Left	1.77±1.55 (0-5)	0.69±0.96 (0-3)	0.002*
Knee Flexor Strength	Right	4.66±0.48 (4-5)	4.89±0.40 (3-5)	0.012*
	Left	4.60±0.55 (3-5)	4.89±0.47 (3-5)	0.003*
Knee Extensor Strength	Right	4.51±0.66 (3-5)	4.89±0.40 (3-5)	0.003*
	Left	4.49±0.70 (3-5)	4.83±0.38 (4-5)	0.024*

*Mann-Whitney U Test, °: degree, X±SD: Mean ± Standard Deviation, Min-Max: Minimum – Maximum, ROM:Range of motion; n: sample size, Significant values are represented in bold, $p < 0.05$

Knee flexion range of motion did not differ significantly between the meniscus tear group and the control group. However, knee extension range of motion was significantly greater in the meniscus tear group on both sides. In addition, knee flexor and extensor muscle strength were significantly lower in the meniscus tear group compared with healthy controls.

Table III: Comparison of balance, physical performance, and VAS findings between groups.

Variable	Study Group (n=35)	Control Group (n=35)	p-value
BBS Score	54.1 ± 2.0, Range: 47-56	54.3 ± 2.6, Range: 45-56	0.227
TUG Time (seconds)	9.11 ± 1.41 Range: 6.8-12.46	8.53 ± 3.24,Range: 6.38-24.99	0.003*
5TSTS Time (seconds)	11.2 ± 3.0, Range: 7.4-20	10.5 ± 4.7, Range: 7.12-30	0.035*
VAS Rest	2.23 ± 2.04, Range: 0-7	0.49 ± 1.46, Range: 0-6	<0.001*
VAS Activity	5.60 ± 2.26, Range: 0-10	2.00 ± 2.57, Range: 0-7	<0.001*
VAS Night	3.26 ± 3.63, Range: 0-10	0.91 ± 2.15, Range: 0-8	0.001*

BBS: Berg Balance Score; TUGT: Timed Up and Go Test; 5TSTS: Five Times Sit to Stand Test; VAS: Visual Analog Scale

No significant difference was observed between groups in Berg Balance Scale scores. However, individuals with meniscus injury demonstrated significantly longer Timed Up and Go and Five Times Sit to Stand test completion times, indicating reduced functional performance. Furthermore, pain intensity at rest, during activity, and at night was significantly higher in the meniscus tear group.

Table IV: Comparison of WOMET scores.

WOMET	Study Group (n=35)	Control Group (n=35)	p- value
WOMET-A (Physical Symptoms)	Average: 246.9, Range: 20-740, Median: 220	Average: 113.4, Range: 0-420, Median: 70	<0.001*
WOMET-B (Sports/Recreation)	Average: 182.9, Range: 0-400, Median: 180	Average: 69.7, Range: 0 -300, Median: 30	<0.001*
WOMET-C (Emotions)	Average: 99.4, Range: 0-240, Median: 100	Average: 41.1, Range: 0 -180, Median: 0	<0.001*
WOMET Total Score	Average: 529.1, Range: 20-1260, Median: 470	Average: 224.3, Range: 0-750, Median: 150	<0.001*

WOMET: Western Ontario Meniscal Evaluation Tool

Table 4 shows the results of the Western Ontario Meniscal Evaluation Tool (WOMET) which assesses the impact of meniscus injury on physical symptoms, sports/recreation activities, emotions, and overall quality of life. Across all sections (A for physical symptoms, B for sports/recreation, and C for emotions) and the total score, the study group (with meniscus injury) reported significantly higher impacts than the control group. The differences were statistically significant, and the p-values were less than 0.001 across all categories.

VAS scores at rest showed a weak and non-significant correlation with BBS, TUGT, and 5TSTS, suggesting minimal association with balance and physical performance. However, there was a moderate positive correlation with WOMET-B (r=0.341, p=0.045), indicating that higher rest pain levels are associated with worse outcomes in the WOMET-B domain.

Activity-related VAS scores demonstrated moderate to strong positive correlations with all WOMET subscales, particularly WOMET-Total (r=0.613, p<0.001), suggesting that pain during activity significantly impacts all aspects of quality of life as measured by the WOMET. Nighttime VAS scores also showed moderate to strong positive correlations with WOMET-A, WOMET-B, WOMET-C, and WOMET-Total, with the highest correlation observed with WOMET-Total (r=0.630, p<0.001).

DISCUSSION

In our study, we compared individuals with isolated meniscus injury , without additional pathologies, to healthy individuals of similar age groups in terms of pain, balance, functional performance, and quality of life. Pain, ROM, postural control, and fall risk assessed by the Berg Balance Scale (BBS), and bilateral knee joint flexion angles were closely matched between the two groups. However, when evaluating balance and functional performance with the Five Times Sit to Stand Test (5TSTS) and the Timed Up and Go Test (TUGT), as well as quality of life with the Western Ontario Meniscal Evaluation Tool (WOMET) scores, differences were found between the two groups. There is a lack of studies evaluating postural balance, fall risk, functional performance, and quality of life in patients with meniscus lesions.

Meniscus tear risk increases with age.[15] One study reported a mean age of 36,[16] while ours was 48, consistent with literature.[17] Prior studies noted male predominance in meniscal injuries.[18-20] In contrast, 68% of our study group and 74% of controls were female, likely reflecting the patient profile of our clinic.

High BMI is a known risk factor.[21,22] A previous study reported an average BMI of 30.5 kg/m²; [21]our study group had a mean BMI of 29.4 kg/m², with no significant difference between groups.

Horizontal tears are common, often in the posterior horn.[23] Medial tears occur more frequently than lateral ones.[23-25] In one study of 103 cases, horizontal tears were

among the most common.[26] Similarly, 80% of our participants had horizontal tears, mostly posterior (82.9%) and medial (74.3%). This supports the notion that horizontal tears result from age-related degeneration. Knee pain negatively affects daily function.[27] In our study, participants' knee pain was assessed with the Visual Analog Scale (VAS). A total of 102 patients with meniscal injury , treated either surgically or conservatively, were evaluated, and the average pain intensity according to VAS was reported as 5.[28] In another study with 24 participants with radial and bucket-handle meniscus tears, the average pain level during activity was more than 5, and the pain at rest was more than 3.[29] In our study, VAS values were also significantly higher in the study group compared to the control group.

A decrease in the range of motion in flexion is reported in previous studies.[5] We did not find such a difference in our study group and both groups' range of motion in flexion and extension were in the normal range. However, the results for both knee extension movements were significantly different. As restricted motion is associated with acute lesions, our study did not account for the acute and chronic knee pain, which may be an explanation for this difference.

The role of the quadriceps femoris muscle is significant in knee function and joint stability.[30] A significant relationship was found for both parameters, with a 30% decrease in extensor muscle strength and a 17% decrease in flexor muscle strength in the knee with a meniscus tear compared to the healthy knee.[31] Another study found that quadriceps femoris muscle strength following knee injuries was lower in the side with meniscal injury.[32] In our study, the examination of muscle strength in both healthy and patient groups also revealed a significant difference between the knee flexor and extensor muscle groups.

Although BBS is commonly used for balance,[33] we found no group difference. Previous studies reporting poor stability did not use BBS.[34] To our knowledge, this is the first study applying BBS in meniscal tear cases, indicating the need for further research.

A study of 252 patients with osteoarthritis and meniscus tears found that lower extremity muscle strength positively impacted pain and mobility, with TUG time averaging 10 seconds.[35] In our study, the TUG time was significantly longer in the study group (9.11 s) than in controls (8.3 s). 5TSTS results also showed significantly delayed performance in the meniscus tear group.

WOMET assesses the quality of life in meniscal injuries. It consists of 16 questions under 3 main headings to evaluate physical findings (A), lifestyle(B), and mood(C) in individuals with meniscal tears. In a study examining the preoperative symptoms of patients with degenerative meniscal tears, two groups were examined, those with and without mechanical symptoms, and no significant difference was found between the WOMET scores of these groups.[36] WOMET was used to examine the short-term clinical outcomes of arthroscopic partial meniscectomy in terms of quality of life, and preoperative assessment results showed high scores parallel to the VAS score.[37] We also compared the scores of the three main sections and the total scores of the Western Ontario Meniscal Evaluation Tool (WOMET) between groups. In Sections A, B, C, and the overall score, the meniscus tear group outperformed the control group. The meniscus tear group scored considerably higher in Section A, which could be connected to the group's high VAS ratings. Section B, which measures quality of life, and Section C, which analyzes the effect of knee difficulties on mood, again showed a significant difference between the groups, with higher scores in the meniscus tear group. Overall, the data show a significant negative relationship between pain and a decrease in meniscus-related quality of life, as criticized by the WOMET, particularly during physical activity and at night. These results highlight how crucial it is to treat pain in meniscus-related individuals in order to improve their overall quality of life.

We employed multiple objective tools-VAS, BBS, TUG, 5TSTS, WOMET-providing a comprehensive comparison between meniscus patients and healthy controls. To our knowledge, this is the first study combining all these tools in one cohort.

Nonetheless, several limitations should be noted. The lack of proprioception assessment restricts conclusions regarding postural balance. Gender imbalance, with more females than males, may affect generalizability. The wide age range, without subgroup analysis, could have masked age-related effects. Additionally, the absence of MRI in the control group raises concerns about undetected asymptomatic pathology. Although BMI values were relatively high in both groups, radiographic screening for early osteoarthritis was not performed in asymptomatic controls, which should be considered when interpreting the findings. Finally, the observed differences should be interpreted cautiously, as meniscal tear type and time elapsed since injury were not analyzed as separate subgroups. These factors may influence functional performance and pain outcomes and should be addressed in future studies.

CONCLUSİON

Significant differences were observed between groups in pain, joint mobility, muscle strength, functional performance, and quality of life. Pain appeared to negatively influence multiple outcome parameters, highlighting the importance of effective pain management strategies to improve functional capacity and overall well-being in individuals with meniscal injuries. These findings may support the development of exercise-based rehabilitation programs targeting pain reduction. Future research should include long-term follow-up, proprioceptive assessment, broader populations, and comparative analyses between patients receiving structured rehabilitation and those without rehabilitation to further clarify treatment-related outcomes.

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CONFLİCTS OF INTEREST

The authors declare no conflicts of interest.

CONSENT

Written informed consent from the patients was obtained.

INSTITUTIONAL REVIEW BOARD (ETHICS COMMITTEE)

Ethical approval for the study was granted by the Biruni University Ethics Committee for Non-Interventional Clinical Investigations on 27.05.2022, under decision number 2022/70-25, and written informed consent was obtained from all participants

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ORIGINAL ARTICLE

Evaluation of Anaesthesia Information Provision on Pre-Operative Anxiety in Patients Undergoing Planned Surgery in a Tertiary Centre

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ABSTRACT

INTRODUCTION: Pre-operative anxiety is associated with physiological and psychological implications in the peri-operative period. Pre-operative education and anaesthesia information provision help alleviate concerns and anxiety regarding anaesthesia for planned surgeries. This study aims to compare differences in levels of anxiety with anaesthesia information provision and factors contributing to anxiety. **MATERIALS AND METHODS**: Seventy patients, aged between 18 and 65, with American Society of Anesthesiologists classes I or II undergoing planned surgery were recruited into this study. They were divided into Group A, which received regular pre-anaesthetic counselling one day prior to surgery, and Group B, which received the counselling and an anaesthesia information sheet (AIS). Both groups were then given an Amsterdam Preoperative Anxiety Information Scale (APAIS) questionnaire at the end of the pre-anaesthetic visit and again on the morning of the planned surgery. The scores were calculated to determine the level of anxiety. **RESULTS**: Group B showed a significant reduction in anxiety levels compared to Group A [Difference (95% CI): -1.51 (-1.96, -1.07); p< 0.001]. For the information desire component, a significant decrease was observed in both Group A (p = 0.037) and Group B (p< 0.001). Group B demonstrated a greater decrease [Difference (95% CI): - 1.17 (-1.62, -0.73)] compared to Group A [Difference (95%CI): -0.40 (-0.77, -0.03)]. Past surgical history was a factor shown to be of statistical significance [coeff (95% CI): -2.39 (-4.21, -0.57); p= 0.011]. **CONCLUSION**: Provision of AIS significantly reduced the level of anxiety in patients undergoing planned surgery and has been shown to alleviate concerns in patients with no past surgical history.

Keywords
Anxiety, Anaesthesia, Information, Pre-operative

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INTRODUCTION

The definition of anxiety, as per the American Psychological Association, is an emotion characterised by feelings of tension, worried thoughts, and physical changes like increased blood pressure. Patients who undergo surgery are shown to experience anxiety pre-operatively, with a prevalence of around 60-80% in previously done studies.[1,2]

Pre-operative anxiety is related to multiple physiological and psychological changes. Physiological changes include an increased stimulation of the sympathetic nervous system, which manifests as increased blood pressure, tachycardia, and activation of the stress response, which causes increased glucocorticoid secretion and associated depression of the immune system.[3,4,5,6] This leads to increased requirements of anaesthetic and analgesic drugs intra- and post-operatively, a delayed healing process, a higher incidence of post-operative pain scores, slower wound healing, and a longer hospital stay.[7] Anxiety also plays a part in cognition, which affects the process of

thinking, understanding, and accepting information, and affects the ability to make informed judgments.[1,8] In the current era of Enhanced Recovery After Surgery (ERAS), patient education and counselling are emphasised pre-operatively. Routine use of anxiolytic pre-medication is not favoured due to variability in response to differing doses of anxiolytic medication and an anticipated delay in post-operative recovery due to impaired cognitive and motor function.[9] As part of ERAS, preoperative education, minimising fasting times, and pre-operative carbohydrate loading have also been shown to reduce pre -operative anxiety.[10]

The causes of anxiety include fear of surgery, effects of anaesthesia, a lack of understanding of potential complications and side effects, as well as fear of poor recovery post-operatively, and are shown to contribute to pre-operative anxiety.[11] Provision of information during pre-medication rounds by anaesthesia medical officer to discuss anaesthesia, its related effects, and possible side-effects is shown to reduce anxiety and help with the mental preparation for surgery.[12] However, this does not apply in emergency surgeries as counselling usually occurs in the operating room, which leads to reduced levels of mental preparation.[13] The amount of information provided to patients pre-operatively has been shown to provide reassurance and guidance regarding what is expected during the day of surgery.[14]

Confounding factors that can affect levels of anxiety include age, gender, level of education, co-morbidities, previous history, or experience of having procedures/ surgeries before, economic status, and pain tolerance.[15] Studying the prevalence of anxiety and learning where it is most prevalent may assist anaesthetists to improve pre-operative preparation of patients and achieve earlier recovery post-operatively.

There are many validated questionnaires which have been used to assess anxiety in patients, namely the State Trait Anxiety Inventory (STAI), Hospital Anxiety and Depression Scale (HADS), Multiple Affect Adjective Checklist (MAACL), Visual Analogue Scale (VAS), as well as the Amsterdam Preoperative Anxiety Information Scale (APAIS).[1,16] The APAIS questionnaire has been translated and used in different countries, including Mexico, Germany, Korea, Japan, and Malaysia.[17] The use of APAIS scores in previous studies has shown comparative results to assess the incidence of anxiety in patients pre-operatively.[18]

This study aims to compare the differences in levels of anxiety with the provision of an anaesthesia information sheet (AIS) and to determine the effect of information provision pre-operatively on the levels of anxiety in patients, as well as factors contributing to anxiety.

MATERIAL AND METHODS

Patients aged between 18 and 65 years, American Society of Anesthesiologists (ASA) physical status I or II, who were planned for surgery under either general anaesthesia (GA), regional anaesthesia (RA) or both (GA+RA), were recruited into the study. Patients who had pre-existing psychiatric illnesses, a history of consuming anxiolytic medications, those diagnosed with clinical anxiety who were on treatment or follow-up, as well as those who were unable to comprehend English or Malay languages were excluded. Written informed consent was obtained from patients who were eligible to be enrolled in the study during premedication visits. Patients were randomized into two groups, Group A and Group B, using computer-generated randomized numbers.

Both groups of patients received standard pre-anaesthetic visits by the anaesthesia medical officer in charge, and underwent pre-operative assessment, counselling, and consent for anaesthesia was obtained. No pre-medication with anxiolytic agents was given to either group. Both groups of patients received an APAIS questionnaire at the end of the session. In addition, Group B patients also received an anaesthesia information sheet (AIS) upon completion of the APAIS questionnaire at the end of the session for personal reference. Both groups of patients were then informed that they would receive a subsequent APAIS questionnaire to be completed on the morning of surgery, prior to being wheeled into the operating room. The enrolment into the study and completion of the APAIS questionnaire were done by the primary

investigator to standardise the time spent with the patient and avoid bias in terms of information provided during assessment of pre-operative anxiety levels.

On the morning of surgery, upon arrival at the waiting bay of the operating theatre complex, patients were assessed by the anaesthesia medical officer in charge via the APAIS questionnaire. A data collection sheet, which contained demographic information as well as information on level of education, history of previous surgery and anaesthesia either under GA, RA, GA and RA, or local anaesthesia (LA), planned surgery for current admission, and duration of surgery was also filled by the medical officer in charge. The APAIS questionnaire, the data collection sheets were then compiled and passed back to the researcher at the end of each day. Patients were considered as drop-outs if they could not complete the questionnaire during the anaesthesia visit or on the day of surgery, or due to cancellation of surgery.

The APAIS questionnaire is a validated self-assessment questionnaire, consisting of six questions. It has two questions related to anxiety about anaesthesia, two questions related to anxiety about surgery, and the final two questions related to the desire to obtain more information about surgery and anaesthesia. The APAIS questionnaire took about five minutes to complete. All responses were recorded based on a Likert scale from a score of 1 (not at all) to 5 (extremely). Questions 1, 2, 4, and 5 were anxiety-related and had a range of scores from 4 (not anxious) to 20 (highly anxious). A cut-off value of ≥ 11 was used to denote significant anxiety, as quoted in the original paper used in developing the APAIS questionnaire.[16] Questions 1 and 2 were about anaesthesia-related anxiety, and the scores were added to form sum A. Questions 4 and 5 were about surgery-related anxiety, and the scores were added to form sum S. Sums A + S = sum C, which denoted the total anxiety score. Questions 3 and 6 were related to the information desire components (IDC) and added together to form the sum IDC, which ranged from a score of 2 (no need for information) to 10 (high requirement of information). The APAIS questionnaire was distributed in both English and Malay versions. Both versions of the APAIS questionnaires were used with permission.

The AIS provided for patients was divided into three main components comprising information on anaesthesia pre-, during, and post-surgery. The first component consisted of information provided regarding anaesthesia, different types of anaesthesia, and what would happen the day before surgery. The second component involved explanation regarding the day of surgery, which covered what was to be expected during arrival to the operating theatre, being wheeled into the operating room, what would happen before induction of anaesthesia, and further explanation on how anaesthesia would ensure the patient was kept comfortable and safe throughout surgery. The third component described what was routinely carried out at the end of surgery, including monitoring in the recovery area and prior to discharge to the ward. The information provided a general idea to the patient and allowed the patient to refer back to the AIS should they require any further information or clarification. The AIS was constructed based on local practices, with a focus mostly on general and regional anaesthesia. Explanations were kept simple to allow patients to understand easily. The content of the AIS was validated by four anaesthetic specialists currently practicing in HCTM. The AIS was prepared in English and Malay versions in a pamphlet form. The Malay version was translated by a certified translator via 'Institut Terjemahan & Buku Malaysia Berhad'.

A pilot study was conducted prior to the actual study to determine the sample size. Twelve patients received the AIS while another nine patients did not during the preoperative visit. Following preoperative assessment and obtaining anaesthesia consent, they were assessed for their anxiety scores using the APAIS questionnaire on the day before as well as shortly prior to being wheeled in for surgery. These scores were then collected and used to calculate an appropriate sample size to conduct this study. The power of this study was set at 80%, α-value of 0.05, and using the Snedecor and Cochran formula.[19] A total of 70 patients were required, including the 10% drop-out rate, with 35 patients in each group.

The data was analysed using the SPSS (Statistical Package for the Social Sciences) version 26.0 and STATA version 14.0. Descriptive statistics were used to present the data. The distribution of continuous variables was explored using a histogram and presented as mean and standard deviation if the data were normally distributed, otherwise median (25th percentile, 75th percentile). Categorical variables were presented as frequency and percentage. The differences in patient characteristics between control and intervention groups were explored using an independent sample T test, Mann-Whitney U test, Pearson chi-squared test, and Fisher Exact test, whichever was appropriate. Comparison of anxiety and sum IDC pre and post treatment between the two groups was explored using an independent sample T test as well, and further tested to adjust for age, ASA class, and past surgical history using ANCOVA. On the other hand, the changes in anxiety and sum IDC pre and post treatment in each control and treatment group, respectively, were explored using a paired sample t-test. The factors associated with anxiety were explored using linear regression models. All the tests were two-sided, and statistical significance was denoted as $p< 0.05$.

RESULTS

A total of 72 patients were recruited into this study. However, two patients were considered drop-outs due to the cancellation of surgery. The characteristic data of the patients in both groups are shown in Table I. Out of 70 patients that were recruited into the study, 35 were allocated to Groups A and B, respectively.

In our study, the prevalence of anxiety in a population of 70 patients, only 32 patients (46%) had anxiety scores ≥ 11. Group A had 12 patients (35%), whereas Group B had 20 patients (57%). The difference in scores relating to anxiety (sum C) and information desire component (sum IDC) was then compared between Groups A and B pre- and post-intervention, as shown in Table II. No significant difference was observed between the two groups in both the univariable model and the multivariable model adjusted for age, ASA status, and past surgical history.

Table I: Demographic data, surgical and anaesthesia characteristics.

Characteristics	Group A (n=35)	Group B (n=35)	p Value
Age (in years)	42.89 ± 13.24	34.89 ± 11.80	0.010[a]
Gender			
Female	19 (54.3)	19 (54.3)	>0.950[c]
Male	16 (45.7)	16 (45.7)	
Race			
Malay	24 (68.6)	27 (77.1)	0.510[d]
Chinese	9 (25.7)	3 (8.6)	
Indian	1 (2.9)	4 (11.4)	
Others	1 (2.9)	1 (2.9)	
ASA class			
I	12 (34.3)	23 (65.7)	0.009[c]
II	23 (65.7)	12 (34.3)	
BMI (kg/m²)	26.54 ± 5.46	25.74 ± 2.58	0.546[a]
Level of education			
Secondary	6 (17.1)	6 (17.1)	0.858[c]
Tertiary	20 (57.1)	18 (51.4)	
Higher	9 (25.7)	11 (31.4)	
Duration of surgery			
< 1 hour	1 (2.9)	2 (5.7)	
< 2 hours	18 (51.4)	13 (37.1)	0.507[d]
< 3 hours	10 (28.6)	16 (45.7)	
< 4 hours	5 (14.3)	4 (11.4)	
< 5 hours	1 (2.9)	0 (0.0)	
Mode of anaesthesia			
GA	26 (74.3)	28 (80.0)	0.745[d]
RA	6 (17.1)	6 (17.1)	
GA+RA	3 (8.6)	1 (2.9)	
Past surgical history			
No	7 (20.0)	16 (45.7)	0.022[c]
Yes	28 (80.0)	19 (54.3)	
Number of past surgery(s)	2 [1-3]	2 [1-3]	0.360[b]
Type of anaesthesia in previous surgery(s)			
GA	20 (71.4)	11 (57.9)	0.315[d]
LA	1 (3.6)	2 (10.5)	
RA	1 (3.6)	3 (15.8)	
GA+LA	0 (0.0)	1 (5.3)	
GA+RA	4 (14.3)	2 (10.5)	
GA+RA+LA	2 (7.1)	0 (0.0)	

Data expressed as mean ± standard deviation and frequency (percentage). P values obtained are denoted based on the type of test used [[a] independent sample t test; [b] Mann-Whitney U test; [c] Pearson chi-squared test, [d] Fisher Exact test].

Table II: Difference in anxiety and IDC scores between Groups A & B between the day prior to and on the morning of surgery.

	Group A (n=35)	Group B (n=35)	[a]p value	Difference (95% CI)	[b]p value
The day prior to surgery					
Anxiety score (Sum C)	10.00 ± 3.80	11.06 ± 3.65	0.239	-0.72 (-2.79, 1.35)	0.492
Information desire component score (sum IDC)	6.60 ± 2.13	7.09 ± 2.11	0.341	-0.82 (-2.06, 0.43)	0.195
Day of surgery					
Anxiety score (Sum C)	10.31 ± 3.47	9.54 ± 3.05	0.327	0.93 (-0.86, 2.72)	0.302
Information desire component score (sum IDC)	6.20 ± 1.84	5.91 ± 1.63	0.495	0.09 (-0.93, 1.12)	0.858

Data expressed as mean ± standard deviation.
[a]p-value- independent sample t-test.
[b]p value- ANCOVA (adjustments made for age, ASA status, and past surgical history status).

Within each group, Group B showed a significant decrease in the level of anxiety with the provision of AIS [Difference (95% CI): -1.51 (-1.96, -1.07); $p<0.001$] compared to Group A, as shown in Table III. For the IDC, a significant decrease was observed in both Group A ($p=0.037$) and Group B ($p<0.001$). Group B, however, demonstrated a greater decrease [Difference (95% CI): -

1.17 (-1.62, -0.73)] compared to Group A [Difference (95%CI): -0.40 (-0.77, -0.03)].

Table III: Within-group changes of Anxiety and IDC Score in control and intervention groups.

	Group A (n=35)			Group B (n=35)		
	Mean ± SD	Difference (95% CI)	p value	Mean ± SD	Difference (95% CI)	p value
Anxiety Score						
The day before surgery	10.00 ± 3.80	0.31 (-0.09, 0.72)	0.125	11.06 ± 3.65	-1.51	<0.001
Morning of surgery	10.31 ± 3.47			9.54 ± 3.05		
IDC Score						
The day before surgery	6.60 ± 2.13	-0.40 (-0.77, -0.03)	0.037	7.09 ± 2.11	-1.17 (-1.62, -0.73)	<0.001
Morning of surgery	6.20 ± 1.84			5.91 ± 1.63		

Data expressed as mean ± standard deviation (SD).

Factors associated with levels of anxiety were also studied using the control group data via linear regression models, as shown in Table IV. It was observed that patients with a history of previous surgery(s) had lower anxiety levels compared to those without [coeff (95% CI): -2.39 (-4.21, -0.57); p= 0.011].

Table IV: Factors associated with levels of anxiety.

	SIMPLE LINEAR REGRESSION		
	coeff	95% CI	p value
Age	-0.02	-0.09, 0.05	0.610
Gender			
Female	Ref		
Male	1.20	-2.98, 0.57	0.181
Race			
Malay	Ref		
Chinese	-2.11	-4.47, 0.25	0.079
Indian	0.66	-2.79, 4.10	0.704
Others	-3.44	-8.74, 1.86	0.199
ASA class			
I	Ref		
II	-0.25	-2.05, 1.54	0.776
BMI	0.09	-0.07, 0.26	0.249
Level of education			
Secondary	Ref		
Tertiary	0.94	-1.54, 3.42	0.451
Higher	1.52	-1.22, 4.25	0.272
Duration (hours)			
< 1 hour	Ref		
< 2 hours	-1.04	-5.58, 3.50	0.648
< 3 hours	-0.26	-4.60, 4.55	0.991
< 4 hours	-2.33	-7.34, 2.67	0.355
< 5 hours	-2.33	-11.00, 6.34	0.593
Mode of anaesthesia			
GA	Ref		0.225
RA	1.42	-0.89, 3.73	0.050
GA+RA	-3.75	-7.50, 0.00	
Past surgical history, n (%)			
No	Ref		0.011
Yes	-2.39	-4.21, -0.57	

DISCUSSION

We aim to study the effect of providing AIS in relation to the alleviation of anxiety or reduction in pre-operative levels of anxiety faced by patients. The results obtained show that patients in Group B who received the AIS had lower anxiety and desire for information scores compared to Group A. Interestingly, Group A patients also showed lower scores for information desire on the morning of surgery compared to the day prior, albeit not as much as Group B. This suggests that additional information provision does help alleviate concerns regarding the lack of anaesthesia information. This was similarly seen in a study which showed lower levels of anxiety in patient groups who received anaesthesia information sheets as compared to the group that received verbal counselling.[6] Another study conducted via perusal of an audiovisual aid during preoperative counselling showed reduced levels of anxiety in patients compared to those who were not exposed to the material.[20] However, in this study, patients were obstetric in origin and planned for caesarean sections, and thus multimedia aid provision was constructed in accordance with a focus on the process of a Caesarean section. In view of the general pool of cases involved in our study, a tailored approach for each surgical type or anaesthetic technique of concern was not feasible.

Most previous studies done about pre-operative anxiety and its contributing factors saw female patients, those with lower levels of education, and those with no prior surgical history exhibiting higher anxiety levels. In our study, there were no significant predisposing factors to higher scores in relation to gender or educational status.[1,13,15,21] An interesting point to note was that in the population of 70 patients, everyone had a minimum of secondary school education, which correlated to a better understanding and comprehension, possibly leading to reduced levels of anxiety. Group B patients (57%) had a significantly higher number of patients who had higher pre-operative anxiety scores on the day before surgery compared to Group A (32%). While age was not a primary variable studied regarding levels of anxiety in itself, Group B patients were generally younger, and this may have been a possible reason for higher anxiety levels due to uncertainty regarding surgery and anaesthesia, as well as better understanding and comprehension with counselling, which led to lower scores on the morning of surgery with the provision of AIS. The significant findings from our study show that those with past surgical history had lower levels of anxiety, further

proving that those who were naïve to surgery tended to have greater anxiety. This was also seen in a study that showed higher pre-operative anxiety scores in patients who had no previous surgical history.[2] The common concerns in patients who were undergoing surgery for the first time were related to a fear of complications, post-operative pain, poor recovery, impact post-operatively, and fear of death.[2,8] The duration of surgery did not correlate with higher levels of anxiety, which is likely attributable to the heterogeneity of cases. No previous studies have studied the levels of anxiety in relation to varying anticipated operative duration.

Anaesthetic pre-operative visits are a vital part of pre-operative assessment, optimization, and planning. The time spent between an anaesthetist and the patient is invaluable in recognizing co-morbidities and other related issues that may hinder a smooth peri-operative surgical period and good recovery. Pre-operative assessments allow patients to get sufficient information as to what they are going to be exposed to or what to expect on the day of surgery and after. While verbal communication is important, the ability of patients to retain sufficient information and comprehension of all delivered information may not always be possible.[6] Perusal of other methods of information delivery via pamphlets, audio aids, videos, as well as simulated walk-throughs, has been shown to help patients understand better, as well as reduce their anxiety and clear worries before proceeding with surgery.[6,20] In some centres, patients were screened up to two or three weeks before surgery and received videos regarding anaesthesia via post prior to being seen in a clinic.[14] However, a study conducted over two decades ago highlighted that the availability of media players to view the video guide was not widely available to all patients.[14] The ability to provide information in an accessible, easily available format enables better delivery of material to the patient. Another study had also shown a greater reduction in anxiety levels in patients post-operatively when given a multimedia aid compared to those who did not receive the same in a population of patients undergoing procedures under regional anaesthesia.[22] This helped patients understand better, ask directed questions, and seek answers to matters of particular concern. In our centre, in view of the ongoing pandemic of COVID-19 during the data collection period, cases were generally planned on a week-to-week basis based on availability of theatres and operating time, and hence screening patients beforehand was more challenging than usual.

We compared anxiety levels and information desire components as a whole, and the subdivisions of each component were not broken down for individual assessment. This is because we aimed to compare the general prevalence of anxiety and its alleviation based on information provision. A possible follow-through would be to assess individual anxiety scores based on surgical versus anaesthetic-related anxiety. A possible improvement would be to choose surgical specialties with particular types of surgeries and compare the patient population within that group to obtain better demographic data and comparison. Another potential concern with the use of information sheets in a diverse population is their applicability to patients who cannot comprehend either English or the Malay language. This may necessitate multi-lingual versions to apply it in a more rural setting. In ideal pre-operative preparatory methods, all patients should be seen in a pre-operative anaesthetic clinic and receive adequate counselling and information, allowing discussions regarding anaesthesia and its associated concerns. However, in view of the pandemic and a reduction of planned cases and operating room slots, this was of limited use and practicality in our centre.

CONCLUSION

Provision of AIS significantly reduced the level of anxiety in patients undergoing planned surgery and has been shown to alleviate concerns in patients with no past surgical history.

CONFLICT OF INTEREST

The authors have no conflicts of interest to report.

INSTITUTIONAL REVIEW BOARD (ETHIC COMMITTEE)

This prospective, observational, randomized study was conducted after obtaining institutional ethics committee

approval (JEP-2022-225) between May and November 2022 at Hospital Canselor Tuanku Muhriz (HCTM), Universiti Kebangsaan Malaysia (UKM).

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ORIGINAL ARTICLE

Unravelling the Potential of Trans-3-Hydroxycinnamic Acid on Metabolic Indices, Biochemical, and Haematological Parameters in Rats with Metabolic Disturbances

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ABSTRACT

INTRODUCTION: Metabolic disturbances caused by high-calorie diets contribute significantly to global mortality. *Trans-3*-hydroxycinnamic acid (HCA), a bioactive antioxidant, may offer protective effects against such imbalances. This study evaluated the metabolic, biochemical, and haematological effects of HCA in rats fed a high-fat, high-fructose (HFHF) diet. **MATERIALS AND METHODS:** Male Sprague Dawley rats aged 7-8 weeks were fed with HFHF diet for 6 consecutive weeks. Rats with metabolic disturbances received HCA at 15 mg/kg, 30 mg/kg, or 60 mg/kg, and were continuously fed with HFHF diet for another 6 weeks. Normal control rats received normal pellets. The effects of HCA on metabolic indices, biochemical, and haematological parameters were evaluated. **RESULTS:** HCA treatment for 6 weeks ameliorates metabolic indices, including weight gain, Lee obesity index, abdominal and thoracic circumferences, TC/HDL ratio, glucose, and fat pad deposition. Improved AST and ALT levels indicated the hepatoprotective effect of HCA, supported by decreased fat vacuolation. The most significant effects were observed at 30 mg/kg. No significant haematological or renal toxicity was detected. **CONCLUSION:** Our results indicated HCA at 30 mg/kg is the optimum dose that exerts its ameliorative effects in reducing metabolic indices, along with no severe biochemical and haematological changes.

Keywords
trans-3-hydroxycinnamic acid, metabolic indices, biochemical, haematological, metabolic disturbance

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INTRODUCTION

Metabolic disease is a constellation of metabolic risk factors, including obesity, hyperlipidaemia, elevated glucose associated with insulin resistance, and elevated blood pressure.[1] The incidence is escalating rapidly, hence become the main priority among healthcare professionals due to its substantial health implications and fatality risk. The pathological state may develop into hepatic steatosis, atherosclerotic cardiovascular disease, kidney failure, gallbladder stones, and cancers.[2] A high-calorie diet coupled with a sedentary lifestyle has significantly contributed to increasing metabolic indices pertaining to body weight, lipid profiles, glucose, and insulin levels.[3,4]

Given the substantial morbidity and mortality burden related to metabolic disease complications, which show no abating signs, there is significant interest in identifying novel compounds with high pharmacological targets that could be effective in reducing the complications of metabolic disease. At present, treatment of metabolic disease relies on multiple drugs, which have multiple side effects.[5] Hence, a safer, cost-effective agent needs to be explored. Phenolic compounds have been exploited to promote health and serve as a potential source for discovering new therapeutic or preventive drugs.[6,7]

Trans-3-hydroxycinnamic acid (HCA), also known as *m*-coumaric acid, is one of the naturally occurring polyphenols found in a variety of plant-based foods. We previously found a high composition of *trans-3*-HCA in fermented bee bread harvested from the *Heterotrigona itama* bee species.[8] HCA exhibits potent antioxidant capacity by scavenging free radicals via its phenolic hydroxyl group and has demonstrated a positive effect in modulating glucose and lipid metabolism.[9,10,11] However, the *in vivo* evidence regarding the metabolic benefits of HCA remains sparse and inconsistent, primarily due to variations in animal models, dosage regimens, and treatment durations. Therefore, the present study was designed to evaluate the optimal dose of *trans-3*-HCA and assess its ameliorative effects on the metabolic indices, biochemical, and haematological parameters in rats fed a HFHF diet. The findings aim to provide foundational data supporting the potential therapeutic application of HCA in managing metabolic disturbances.

MATERIAL AND METHODS

Preparation of hydroxycinnamic acid

HCA with >98% purity was purchased from Sigma-Aldrich (France) and freshly dissolved in saline solution prior to each administration. A certificate of analysis was obtained from the supplier.

Preparation of high-fat high-fructose (HFHF) diet

The HFHF diet was formulated using a mixture of 62% normal pellet (Gold Coin, China), 32% animal ghee (Cripto, Malaysia), 6% powdered milk, 12% cholesterol powder (Nacalai Tesque, Japan), and 300 IU of vitamin C and D (Eurobio Biocal D Complex, Malaysia). This formulation provided 560.09 kcal/100g and consisted of 11.93% protein, 40.47% fat, 37.03% carbohydrate, 6.68% moisture, and 3.89% ash. A 10% fructose drink was prepared weekly in a dilution with distilled water. The HFHF diet used in this study was a modified high-fat diet with increased caloric density, adapted from our previously established obesity model.[12]

Animals

Twenty-five male Sprague-Dawley rats (7-8 weeks old), weighing 220-250 g, were obtained from the Animal Research and Service Centre (ARASC), Universiti Sains Malaysia, Kelantan. Each rat was housed separately in a polypropylene cage with a 12-hour light-dark cycle, a regulated temperature of 22±2 °C, and a controlled humidity level of 55±10%. All experimental procedures were approved by the UniSZA Animal and Plant Research Ethics Committee (UAPREC/008/010), and followed the guidelines provided by the Faculty of Medicine, Universiti Sultan Zainal Abidin, and the National Institute of Health (NIH), Malaysia.

Experimental design

Following a one-week acclimatisation period, rats were fed either a normal pellet (n=5) or a high-fat high-fructose (HFHF) diet plus 10% fructose in drinking water (n=20) for 6 weeks. Metabolic disturbance was confirmed by increases in the Lee obesity index, total cholesterol (TC), and glucose, and by an abnormal total area under the curve following an oral glucose tolerance test. Rats with metabolic disturbances were randomly allocated into four groups, with the first group as a positive control group. Another three groups of rats were administered HCA at 15 mg/kg, 30 mg/kg, or 60 mg/kg via oral gavage for 6 weeks. All groups were allocated five animals each as follows.

- The normal Control group was fed with normal pellets and administered 1 mL of distilled water via oral gavage.
- The metabolic disturbances (MD) group was fed with a high-fat diet and 10 % fructose solution (HFHF diet), and 1 mL of distilled water.
- The MD+HCA1 group was fed with the HFHF diet and received HCA at 15 mg/kg body weight.
- The MD+HCA2 group was fed with the HFHF diet and received HCA at 30 mg/kg body weight.
- The MD+HCA3 group was fed with the HFHF diet and received HCA at 60 mg/kg body weight.

HCA doses were selected based on the previous study.[13] Body weight of the rats was monitored weekly throughout the experimental period. Body weight changes were recorded after the differences between the

initial and final body weights of the rats.

Blood collection and tissue sampling

The animals were anaesthetised with ketamine 90 mg/kg and xylazine 5 mg/kg via intraperitoneal injection after 16 hr of fasting period. Blood samples were collected from the posterior vena cava and centrifuged at 4000 rpm for 15 min. The obtained serum was aliquoted and stored at – 80 °C for subsequent biochemical analysis. The adipose tissue from the abdominal, epididymal, retroperitoneal, pericardial, and perirenal regions was carefully excised and weighed in grams (g). The liver, kidney, heart, and aorta samples were dissected and preserved in 10% formalin for histopathological examination.

Anthropometrical analysis

The body weight of the rats was measured weekly using a digital weight balance. Naso-anal length was determined by measuring the longitudinal axis of the naso-anal. The abdominal circumference was determined by the circumference length of the midpoint between the anterior and posterior legs. The thoracic circumference was determined by measuring the circumference length immediately behind the foreleg region. The Lee obesity index was determined by dividing the cubic root of body weight (g) by the naso-anal length (cm).[14]

Biochemical analysis

Determination of oral glucose tolerance test

Rats were fasted for 16 hr overnight and orally loaded with glucose at 2 g/kg/bw. Blood glucose was determined from the acquired blood sample of the tail vein using a glucometer (Accu-Chek, Malaysia) before (at 0 min) and after glucose loading (at 30, 60, 90, and 120 min). A total of glycaemic responses to OGTT were determined from the calculation of total area under the curve (AUC) following completion of 120 min observation period using the trapezoidal method.[15]

Determination of serum lipid profile

The protocols for serum total cholesterol (TC) and triglyceride (TG) levels were performed via an enzymatic colorimetric method according to the provided commercialised kit protocol provided (ARCHITECT c kit, Abbott, IL, USA). Low-density lipoprotein (LDL) levels were determined using the formula provided by the previous protocol: LDL (mmol/L)=(TC-HDL-(TG/5)).[16] High-density lipoprotein (HDL) was determined after removal of LDL cholesterol, chylomicron, and VLDL cholesterol.

Determination of liver function and renal function tests

Serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) were determined according to the method provided by the International Federation of Clinical Chemistry (IFCC) using standard spectrophotometric methods (Abbott Architect Ci8200, Abbott Park, IL, USA). The renal function test was evaluated using a standard calibrator machine, which comprised several methods involving an indirect ion-selective electrode, the urease method, phosphomolybdate, and uricase.

Determination of serum full blood count

The Multi-Angle Polarized Scatter Separation (MAPSS) system, a flow cytometric technology, was used to assess haematological parameters. This method characterises red blood cells (RBC), platelets (PLT), white blood cells (WBC), and nucleated other cells (NOC) in detail.

Histological analysis

The liver, heart, kidney, and aorta were stored in 10% formaldehyde solution. The grossed tissues were serially processed in an automated processor and embedded with paraffin wax into a block. The sample blocks were serially sectioned (5 μm) using a microtome and mounted on slides before being stained with Haematoxylin and Eosin. The images were analysed under an optical microscope (Olympus, Tokyo, Japan).

Statistical analysis

All the data obtained from the experimental findings are provided as mean (S.E.M). Data were statistically measured with GraphPad Prism 9.0. One-way ANOVA

with post-hoc Tukey test was applied to analyse the mean differences between multiple groups. A *P* value of less than 0.05 is considered to be statistically significant.

RESULTS

Effects of trans-3-hydroxycinnamic acid on anthropometrical parameters

As shown in Table I, rats in the MD group exhibited significantly higher weight gain compared to the Control group after 12 weeks of the HFHF diet. Following 6 weeks of HCA treatment, the MD+HCA1 and MD+HCA2 groups showed significant reductions in body weight gain compared with the MD group. Additionally, the Lee obesity index, abdominal and thoracic circumferences of the MD group were significantly higher than those of the Control group, indicating the successful induction of obesity. Administration of HCA, particularly at doses of 15 and 30 mg/kg, significantly decreased these parameters, suggesting attenuation of HFHF-induced adiposity.

Table I: Effects of trans-3-hydroxycinnamic acid on anthropometrical parameters.

Parameter	Control	MD	MD+HCA1	MD+HCA2	MD+HCA3
Body weight gain	185.72 (6.40)	245.93 (2.55)*	153.62 (2.82)**	179.28 (12.36)**	210.61 (9.36)***
Rate of body weight gain	0.38(0.02)	0.47(0.04)*	0.41(0.00)*	0.38(0.02)*	0.48(0.03)
Lee obesity index	321.76 (1.98)	369.91 (8.39)*	319.06 (9.26)**	329.77 (8.33)**	343.70 (4.85)
Abdominal circumference	17.75 (0.75)	20.17 (0.93)*	17.50 (0.50)**	18.00 (1.00)**	19.00 (0.58)
Thoracic circumference	17.00 (0.20)	18.38 (0.43)*	16.67 (0.33)**	17.00 (0.29)**	17.33 (0.73)

Data are presented as means (S.E.M.), *n*=5/group. Statistical analysis performed using ANOVA with Tukey's post hoc test for multiple comparisons. * p<0.05 in comparison with Control group, ** p<0.05 in comparison with MD group, *** p<0.05 in comparison to MD+HCA1 group. Control: rats fed with normal pellet, MD: metabolic disturbance rats fed with high-fat high-fructose diet, MD+HCA1: metabolic disturbance rats with HCA at 15 mg/kg, MD+HCA2: metabolic disturbance rats with HCA at 30 mg/kg, MD+HCA3: metabolic disturbance rats with HCA at 60 mg/kg. MD, metabolic disturbances; HCA, *trans-3*-hydroxycinnamic acid.

Effects of *trans-3-hydroxycinnamic* acid on oral glucose tolerance test (OGTT) and fasting serum glucose

The OGTT was performed in the final week of the experimental period. No significant changes were observed in the area under the curve and fasting blood glucose levels across all experimental groups.

Effects of trans-3-hydroxycinnamic acid on lipidomic profile

Figure 2 illustrates the lipidomic profiles of all experimental groups. Total cholesterol and low-density

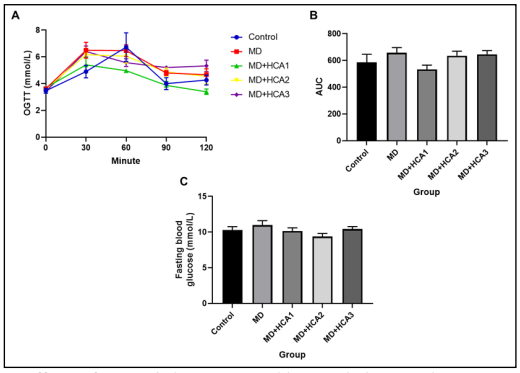

Figure 1. Effects of *trans-3-hydroxycinnamic* acid on oral glucose tolerance test and fasting blood glucose in metabolic disturbance rats. Data are expressed as mean with S.E.M. (*n*=5). Statistical analysis performed using ANOVA with Tukey's post hoc test for multiple comparisons. AUC: area under the curve, Control: rats fed with normal pellet, HCA, *trans-3*-hydroxycinnamic acid, MD: metabolic disturbance rats fed with high-fat high-fructose diet, MD+HCA1: metabolic disturbance rats with HCA at 15 mg/kg, MD+HCA2: metabolic disturbance rats with HCA at 30 mg/kg, MD+HCA3: metabolic disturbance rats with HCA at 60 mg/kg, OGTT: oral glucose tolerance test. MD, metabolic disturbances.

lipoprotein in the MD, MD+HCA1, and MD+HCA2 groups were significantly higher than in the Control group. Conversely, the MD+HCA2 group showed a marked suppression of these lipid markers (Figure 2A, 2C). Additionally, the MD group showed a significant increase in TC/HDL ratio when compared to the normal Control group, with a significant reduction elicited in the MD+HCA2 group (Figure 2E). Meanwhile, no significant changes were observed in TG levels across all experimental groups (Figure 2B).

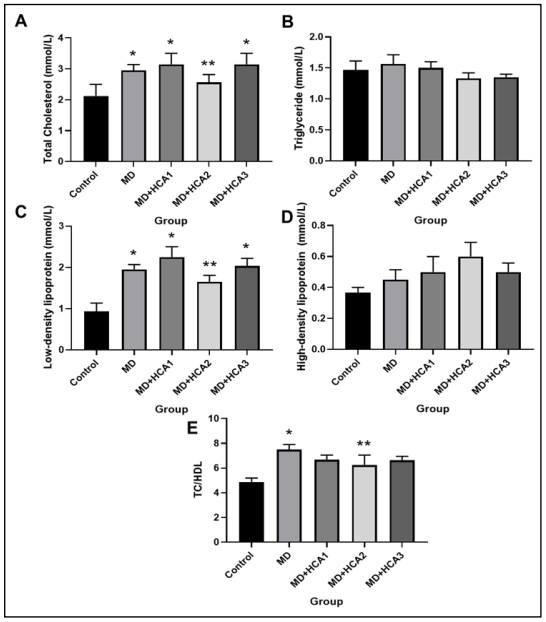

Figure 2. Effects of *trans-3*-hydroxycinnamic acid on lipidomic profile in metabolic disturbance rats. Data are expressed as mean with S.E.M. (*n*=5). Statistical analysis performed using ANOVA with Tukey's post hoc test for multiple comparisons. * p<0.05 in comparison with Control group, ** p<0.05 in comparison with MD group. Control: rats fed with normal pellet, MD: metabolic disturbance rats fed with high-fat high-fructose diet, MD+HCA1: metabolic disturbance rats with HCA at 15 mg/kg, MD+HCA2: metabolic disturbance rats with HCA at 30 mg/kg, MD+HCA3: metabolic disturbance rats with HCA at 60 mg/kg. MD, metabolic disturbances; HCA, trans-3-hydroxycinnamic acid.

Effects of trans-3-hydroxycinnamic acid on full blood count

Table 2 exhibited notable variations in full blood count parameters across all groups. Haemoglobin concentration was highest in the Control group, but consistently decreased across metabolic groups, with a significantly notable value observed in the MD+HCA3 group compared to the Control group. A similar trend was also seen for MCV value in the MD+HCA3 group. Other parameters were negligible across all groups.

Table II: Effects of *trans-3*-hydroxycinnamic acid on full blood count

Parameter	Control	MD	MD+HCA1	MD+HCA2	MD+HCA3
Total RBC (x10^12 /L)	7.17(0.09)	7.30(0.30)	7.55(0.35)	7.67(0.13)	6.67(0.99)
Haemoglobin (gm/L)	141.25 (2.95)	131.33 (2.85)	130.00 (1.00)	130.33 (2.40)	129.67 (0.67)*
PCV (L)	0.36(0.01)	0.34(0.00)	0.340 (0.01)	0.34(0.01)	0.30(0.04)
MCV (fl)	50.00(0.58)	46.00 (0.58)	46.00 (1.00)	45.75 (1.25)	45.33 (0.88)*
MCH (pg)	20.00(0.58)	18.00 (1.00)	17.50 (0.50)	17.00 (0.00)	20.33 (3.33)
MCHC (g/L)	393.33 (8.82)	385.00 (5.00)	380.00 (10.00)	376.67 (3.33)	446.67 (66.67)
RDW (%)	14.43(0.33)	14.70 (0.10)	15.30 (0.20)	15.33 (0.62)	13.97 (1.26)
WBC (x10^9 / L	12.07(0.61)	10.40 (1.80)	10.80 (1.60)	9.73(1.13)	8.55(1.39)
Polymorphs (%)	16.33(3.93)	18.00 (2.00)	21.00 (4.00)	17.67 (4.67)	20.67 (6.23)
Lymphocytes (%)	78.33(2.73)	77.00 (3.00)	72.00 (2.00)	76.00 (3.61)	73.33 (6.17)
Monocytes (%)	5.00(1.00)	5.00(1.00)	7.00(1.00)	6.00(1.00)	5.67(0.33)
Eosinophils (%)	0.33(0.33)	0.00(0.00)	0.50(0.50)	0.33(0.33)	0.330.33)
Basophils (%)	0.00(0.00)	0.00(0.00)	0.00(0.00)	0.00(0.00)	0.00(0.00)
Platlet Count x10^9 /L	1083.00 (101.49)	1064.50 (150.00)	969.00 (226.00)	1108.00 (30.66)	844.67 (263.44)

Data are presented as means (S.E.M.), *n*=5/group. Statistical analysis performed using ANOVA with Tukey's post hoc test for multiple comparisons. * p<0.05 in comparison with the control group. Control: rats fed with normal pellet, MD: metabolic disturbance rats fed with high-fat high-fructose diet, MD+HCA1: metabolic disturbance rats with HCA at 15 mg/kg, MD+HCA2: metabolic disturbance rats with HCA at 30 mg/kg, MD+HCA3: metabolic disturbance rats with HCA at 60 mg/kg. MD, metabolic disturbances; HCA, *trans-3*-hydroxycinnamic acid.

Effects of trans-3-hydroxycinnamic acid on liver function test and renal profile

Table 3 summarises the effects of various doses of HCA on liver function tests and renal profile. Significant elevations in AST, ALT, and ALP levels were observed in the MD group compared with the Control group. Treatment with HCA2 and HCA3 substantially attenuated the AST levels. A notable reduction in ALP level was observed only in the HCA2 group. Whereas a substantial reduction of the elevated ALT was also observed in the HCA1 and HCA2 groups. The data on biochemical levels of renal profile indicated no significant alterations compared to the Control group.

Table III: Effects of *trans-3*-hydroxycinnamic acid on liver function test and renal profile in metabolic disturbance rats.

Parameter	Control	MD	MD+HCA1	MD+HCA2	MD+HCA3
Total protein (g/L)	62.33(1.20)	63.00 (1.53)	67.33 (2.85)	65.00 (2.08)	63.33 (1.20)
Albumin (g/L)	25.33(0.88)	27.00 (0.58)	27.67 (1.33)	28.67 (0.33)	26.67 (0.33)
Globulin (g/L)	40.00(0.00)	36.67 (3.33)	40.00 (0.00)	36.67 (3.33)	40.00 (0.00)
AG Ratio	0.63(0.03)	0.77 (0.07)	0.67 (0.03)	0.77 (0.07)	0.67 (0.03)
AST (U/L)	128.00 (7.09)	168.00 (13.99)*	159.67 (25.50)	124.00 (3.79)**	108.67 (16.60)**
ALT (U/L)	54.80(4.89)	109.67 (3.53)*	115.00 (26.84)*	109.67 (6.06)*	94.67 (13.68)
ALP (U/L)	126.33 (16.70)	384.20 (60.01)*	356.67 (45.11)	295.00 (45.70)**	365.50 (29.50)
Sodium (mmol/L)	140.00 (0.58)	140.33 (0.88)	140.00 (1.53)	140.33 (1.20)	142.00 (1.00)
Potassium (mmol/L)	5.80 (0.38)	5.43 (0.38)	6.27 (0.88)	5.03 (0.20)	4.87 (0.33)
Chloride (mmol/L)	103.00 (1.00)	102.33 (0.88)	104.00 (0.58)	104.00 (0.58)	105.00 (0.58)
Urea (mmol/L)	7.13 (0.14)	3.60 (0.61)	3.57 (0.57)	3.80 (0.10)	3.73 (0.42)
Creatinine (µmol/L)	51.33 (1.45)	55.33 (1.76)	52.67 (5.78)	50.33 (3.18)	49.00 (1.73)
Uric acid (µmol/L)	108.00 (21.63)	92.00 (17.09)	104.00 (17.44)	84.00 (3.46)	82.00 (5.29)

Data are presented as means (S.E.M.), *n*=5/group. Statistical analysis performed using ANOVA with Tukey's post hoc test for multiple comparisons. *p<0.05 in comparison with Control group, ** p<0.05 in comparison with MD group. Control: rats fed with normal pellet, MD: metabolic disturbance rats fed with high-fat high-fructose diet, MD+HCA1: metabolic disturbance rats with HCA at 15 mg/kg, MD+HCA2: metabolic disturbance rats with HCA at 30 mg/kg, MD+HCA3: metabolic disturbance rats with HCA at 60 mg/kg. MD, metabolic disturbances; HCA, *trans-3*-hydroxycinnamic acid.

Effects of trans-3-hydroxycinnamic acid on adipose tissue deposition

Table 4 revealed notable differences in various adipose tissue deposition among experimental groups. Abdominal, epididymal, retroperitoneal, and perirenal fat pads were significantly higher in the MD group compared with the Control group. Co-treatment with HCA1 and HCA2 markedly mitigated these effects. The MD+HCA1 group showed a substantial decrease in abdominal, epididymal, and retroperitoneal fat pads when compared to the MD group. Similarly, the MD+HCA2 group also demonstrated a significant reduction in these fat depositions, with extensive reduction of perirenal fat when compared to the MD group. Whereas, the MD+HCA3 group exhibited a significant reduction in retroperitoneal fat deposition when compared to the MD group and did not achieve statistical significance in all areas. Differences in pericardial fat were minimal across all experimental groups.

Table IV: Effects of *trans-3*-hydroxycinnamic acid on adipose tissue deposition

Parameter	Control	MD	MD+HCA1	MD+HCA2	MD+HCA3
Abdominal (g)	4.13 (1.07)	11.37 (1.48)*	4.478(0.63)**	6.46(0.28)**	7.57(1.09)
Epididymal (g)	4.47 (0.85)	7.91(0.52)*	4.08(0.05)**	4.44(0.50)**	5.50(0.64)
Retroperitoneal (g)	0.48 (0.15)	1.42(0.16)*	0.51(0.16)**	0.54(0.08)**	0.67(0.09)**
Pericardial (g)	0.15 (0.05)	0.34(0.09)	0.18(0.05)	0.19(0.03)	0.18(0.04)
Perirenal (g)	0.16 (0.04)	0.55(0.11)*	0.21(0.09)	0.19(0.07)**	0.20(0.05)

Data are presented as means (S.E.M.), *n*=5/group. Statistical analysis performed using ANOVA with Tukey's post hoc test for multiple comparisons. * p<0.05 in comparison with Control group, ** p<0.05 in comparison with MD group. Control: rats fed with normal pellet, MD: metabolic disturbance rats fed with high-fat high-fructose diet, MD+HCA1: metabolic disturbance rats with HCA at 15 mg/kg, MD+HCA2: metabolic disturbance rats with HCA at 30 mg/kg, MD+HCA3: metabolic disturbance rats with HCA at 60 mg/kg. MD, metabolic disturbances; HCA, *trans-3*-hydroxycinnamic acid.

Effects of trans-3-hydroxycinnamic acid on histopathological analysis

The liver, kidney, heart, and aorta in the Control group demonstrated a normal arrangement of histological architecture. The MD group showed a series of morphological alterations with multiple fat vacuoles in the liver, tubular dilatation in the renal cortex, disarray and hypertrophy of the myocardium, and rough endothelial surface of the aorta. Whereas these metabolic alterations seem to be ameliorated in HFHF diet rats that received HCA at various doses (Figure 3).

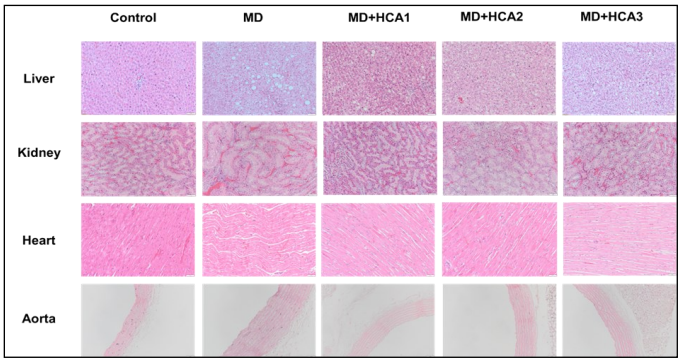

Figure 3. Illustrates the effects of *trans-3* hydroxycinnamic acid on histological analysis of liver, kidney, heart, and aorta on Haematoxylin and Eosin staining, at x100 magnification (scale). The MD group exhibited morphological alterations, including fat vacuolation in the liver, tubular dilatation in the renal cortex, myocardial disarray and hypertrophy, and a roughened endothelial surface of the aorta. Control: rats fed with normal pellet, MD: metabolic disturbance rats fed with high-fat high-fructose diet, MD+HCA1: metabolic disturbance rats with HCA at 15 mg/kg, MD+HCA2: metabolic disturbance rats with HCA at 30 mg/kg, MD+HCA3: metabolic disturbance rats with HCA at 60 mg/kg. MD, metabolic disturbances; HCA, *trans-3*-hydroxycinnamic acid.

DISCUSSION

Metabolic disease is a worldwide problem, affecting most developed and industrialised countries.[17] The alteration in metabolic parameters is associated with high-fat diet intake, thus implicated in cellular and biochemical changes that deviate from the normal body homeostasis. These resulted in increased metabolic-related complications such as obesity, diabetes mellitus, hypertension, and hyperlipidaemia.[18] In the present study, the HFHF diet was administered for 12 weeks, with a concomitant HCA treatment delivered during the latter 6 weeks of the experimental period. We aimed to determine the ameliorative effects of HCA, a potential bioactive compound, on metabolic indices, biochemical, and haematological parameters in rats fed with the HFHF diet.

In the present study, rats fed with an HFHF diet for 12 weeks developed notable signs of metabolic disturbances, as evidenced by significant increases in body weight gain and Lee obesity index, as demonstrated in the MD group. This was associated with the significant increase in abdominal and thoracic circumferences, which serve as a key indicator for central obesity. The obesogenic effects are further supported by increased adiposity in abdominal, epididymal, retroperitoneal, and peri-renal regions. These findings are in agreement with a previous study showing that a prolonged high-calorie and high-fat diet can contribute to the accumulation of total and visceral fat mass, with ectopic deposition in the liver, heart, and muscle.[19] Furthermore, the high calories provided by the HFHF diet used in the present study could promote rapid lipid accumulation and systemic metabolic disturbances. These obesogenic effects could also be attributed to prolonged fructose intake that stimulates the lipogenic molecules through the activation of sterol regulatory element-binding protein 1 (SREBP-1) and carbohydrate-responsive element-binding protein (ChREBP), enhancing TG synthesis and fat accumulation.[20] Interestingly, our results indicated that the HCA-treated group mitigated anthropometrical parameters and obesogenic effects, with the most compelling outcome observed in the HCA2 (30mg/kg) group. The actual mechanism by which HCA ameliorates obesity and anthropometrical parameters is not entirely clear. Studies postulate a few established mechanisms related to the inhibition of adipocyte deposition and differentiation, upregulation of lipolysis factors, or inhibition of pancreatic lipase.[21,22]

Measuring lipid profiles and deposition is crucial for determining metabolic health.[23] Our results demonstrated high serum TC and LDL levels in the MD group, which were also associated with a high TC/HDL ratio. This lipidaemic effect is also associated with significant fat accumulation across multiple areas in the MD group. Fructose contains lipogenic nutrients, and its consumption has been associated with metabolic dyslipidaemia resulting from the mass production of hepatic and intestinal lipoprotein particles. Fructose can be further metabolised into glycerol, which is a precursor for TG and lipid accumulation.[24] This could justify the presence of fat vacuolation in the liver, a primary target of metabolic organs, in rats administered with the HFHF diet. The obesogenic and lipidemic effects of HFHF-diet render other morphological alterations, including dilatation of the renal tubules, hypertrophy of the myocardium, and rough endothelial surface of the aorta, which was demonstrated in the MD group. Simultaneously, treatment with HCA1 and HCA2 was particularly effective in countering these increments, which were notably seen in abdominal, epididymal, and retroperitoneal fat pad regions. This could indicate anti-adipogenic or fat-reducing activity of HCA, potentially by modulating lipid metabolism and energy expenditure.

In terms of glucose metabolism, the AUC level in the MD group showed a higher trend compared to the Control group, indicating an impairment of insulin sensitivity. This may be related to the activity of lipid by-products, which mediate the insulin target cells, leading to blockage of the insulin signal.[25] Fructose consumption in clinical and experimental animal studies has been associated with alterations in metabolic parameters related to glucose tolerance, insulin, and obesity.[26] Few findings also postulate that products of glucosamine and other hexosamine derivatives could potentially induce glucose intolerance and insulin resistance.[27] In contrast, the MD+HCA1 and MD+HCA2 groups exhibited a decrement in glucose peak level, with glucose levels returning closer to baseline within 120 minutes, suggesting an improvement in glucose clearance capacity and enhancement of metabolic control. This effect was more pronounced in the MD+HCA1 group, indicating its superior efficacy in mitigating glucose intolerance. These outcomes may be attributed to the role of HCA in enhancing glycogen synthesis and inhibiting gluconeogenesis, thereby reducing hepatic glucose output. [28]

In addition to metabolic outcomes, haematological and biochemical parameters were also assessed to determine the safety and toxicity of different dosages of HCA.[29] All haematological parameters revealed no significant abnormality, except for a significant decrease in RBC and MCV values in the MD+HCA3 group when compared to the Control group. Higher doses of HCA may elicit a suppressive effect on erythropoiesis or excessive destruction of the red cell, resulting from pro-oxidant effects.[30] We observed a biphasic effect of administered HCA on metabolic disturbance in rats. HCA at low to moderate doses may exert protective or compensatory hematopoietic effects, whereas HCA at high doses appears to exert a detrimental effect on erythrocytes. However, further mechanistic studies concentrating on oxidative stress biomarkers and red blood cell membrane stabilisation could clarify these haematological alterations. Prolonged high-fat diet intake is associated with an increase in ALT, AST, and ALP, indicating ongoing liver injury that could potentially lead to liver damage. This damaging effect is significantly observed in the MD group, with the reversal effect being more pronounced in the MD+HCA2 group compared to other treated groups, supporting its hepatoprotective role. HCA1 and HCA3 exert a minimal ameliorative effect with partial restoration of the metabolic balance. As shown in Table 3, albumin levels were lower than globulin levels in both control and experimental groups. This pattern is consistent with the physiological characteristics of rodents, which typically exhibit relatively higher globulin fractions [31,32.] The A/G ratios observed in the present study remained within the reported physiological reference ranges for male *Sprague-Dawley* rats, indicating preserved hepatic synthetic function. In addition, recent work highlighting analytical considerations and reference interval derivation for serum protein fractions supports the reliability of albumin and globulin measurements used

in this study, further strengthening interpretation of the observed protein profiles [33,34].

Whereas all the electrolyte levels (sodium, potassium, and chloride) remained largely unchanged across groups, indicating stable electrolyte homeostasis. These results indicate that HCA at various doses following 12 weeks of the experimental period does not possess any toxic effect on the experimental animal.

A limitation of the present pilot study is the absence of direct measurements of oxidative stress and inflammatory markers, which are known contributors to the pathogenesis of metabolic disease. As this study was designed primarily for dose optimisation and histopathological assessment, sample availability precluded additional biochemical analyses. Future studies will incorporate oxidative stress and inflammatory parameters to further elucidate the mechanistic basis of *trans-3-HCA*'s protective effects.

CONCLUSION

In summary, our data demonstrate that trans-3-hydroxycinnamic acid (HCA), a phenolic compound, has promising therapeutic potential for mitigating metabolic disturbances in rats fed the HFHF diet. Supplementation with HCA, particularly at 30 mg/kg, significantly improved body weight regulation, visceral fat accumulation, lipid profiles, and liver enzymes. It also ameliorated histopathological changes in key metabolic organs, including the liver, kidney, heart, and aorta, while demonstrating hepatoprotective and cardioprotective effects. Furthermore, HCA at various doses does not exhibit any toxic effect on the experimental animal. These findings suggest that HCA may serve as a valuable candidate for further development as a nutraceutical or adjunct therapy in managing metabolic syndrome and its associated complications.

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AUTHORS CONTRIBUTION

Study concept and design: ZAO and MM; acquisition of data: ASA, BAI; analysis and interpretation of data: ASA, BAI; drafting of the manuscript: ASA, ZAO; critical revision of the manuscript: ZAO, ZZ, and MM; statistical analysis: ZZ, NAS, NAAB; obtained funding: ZAO; administrative, technical, or material support: NAS, NAAB; and study supervision: ZAO, NAS.

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CONFLICTS OF INTEREST

The authors declare that the research was conducted without any commercial or financial relationships that could be interpreted as a potential conflict of interest.

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ORIGINAL ARTICLE

Mapping Health Influencers on Social Media: A Bibliometric Analysis of Trends and Challenges (2010–2024)

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ABSTRACT

INTRODUCTION: Social media platforms such as YouTube, Instagram, and TikTok have become vital tools for health communication, with influencers shaping public perceptions, promoting healthy behaviours, and addressing global health challenges. **MATERIALS AND METHODS**: This bibliometric analysis examined the evolving role of health influencers between 2010 and 2024, through 516 Scopus-indexed peer-reviewed publications, comprising 479 original research articles and 37 reviews. Bibliometric measures, including citation analysis, institutional mapping, and keyword co-occurrence, were applied using Bibliometrix, Biblioshiny, and VOSviewer. **RESULTS**: The most productive year was 2024 with 92 publications (2199 citations). The United States of America (USA) contributed the most citations (49.81%), with Fishman E.K. from Johns Hopkins University as the most prolific author. The most cited article had 602 citations (40.1 citations/year). The Journal of Medical Internet Research led in publications. Medicine accounted for 66.4% of publications. Dominant themes included misinformation, content quality, health promotion, and medical education. While USA and Canada dominate, international collaboration remains limited, highlighting underrepresentation from low- and middle-income countries. **CONCLUSION**: This analysis highlights the intersection of social media, health communication, and public engagement strategies. Health influencers hold potential to amplify health promotion, but issues of misinformation, ethical concerns, and unequal global participation persist. For policymakers, the findings highlight the need for regulatory frameworks to ensure content accuracy and credibility. For practitioners, the study highlights opportunities to collaborate with health influencers to promote evidence-based, culturally sensitive health messaging. Future research should broaden database coverage, evaluate health influencer's behavioural impact, and establish guidelines for ethical, evidence-based health communication.

Keywords
Attitude to Health, Bibliometrics, Data Visualization, Health Promotion, Communications Media

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INTRODUCTION

In the present digital age, social media has become a transformative platform for health communication, enabling widespread dissemination of health-related information to a global audience. The rise of health influencers, a term that organically evolved as social media grew in prominence within the healthcare and wellness sectors to describe individuals or professionals who use social media platforms to promote health knowledge and practices, has played a pivotal role in this evolution. Platforms such as Instagram, YouTube, and TikTok have provided novel avenues for health education, engagement, and even intervention, particularly among the younger and tech-savvy demographics.[1-3] The influence of health-related content on social media is profound, with studies documenting its potential to shape public perceptions, encourage health-seeking behaviours, and disseminate

evidence-based practices. For instance, research on TikTok videos addressing mental health and acute medical conditions has highlighted the platform's ability to attract high engagement, albeit with variability in the quality and reliability of content.[4,5] Similarly, YouTube has emerged as a resource for public health initiatives such as smoking cessation campaigns, offering diverse content that resonates with its audience.[6]

Despite the growing prominence of health influencers, there is limited bibliometric analysis exploring trends in social media-based health communication. Previous systematic reviews and descriptive studies have primarily focused on specific platforms or health topics, leaving gaps in understanding the broader landscape of what is trending and why certain themes garner attention.[1,2] Understanding these trends is crucial for optimising the use of social media in public health strategies and mitigating potential risks associated with misinformation or low-quality content.

This bibliometric analysis aims to address these gaps by examining trends in health influencer-related research from 2010 to 2024. By analysing publication patterns, thematic focus areas, and engagement metrics, this study seeks to elucidate the factors driving the popularity and impact of health influencers on social media by answering the following research questions:

1. What are the publication trends and citation patterns in the study of health influencers on social media?
2. Who are the most influential contributors (authors, institutions, and countries) advancing research in this field?
3. What are the most highly cited works, and how have they shaped the development of the field?
4. What key themes, topics, and research directions emerge from keyword and content analyses of the literature on health influencers in social media?

The findings will provide valuable insights for researchers, healthcare professionals, and policymakers looking to harness the potential of social media as a tool for health promotion and education.

Previous studies on bibliometric analysis of social media and health

Several bibliometric studies have examined the role of social media in health-related communication, focusing primarily on misinformation and its impact on public health. One study conducted a bibliometric analysis of scientific literature on medical and health-related misinformation, revealing a surge in research during the COVID-19 pandemic; it also identified key contributors and trends but was limited by its lack of platform-specific analyses.[7] Another study examined social media's role in mental health research, identifying thematic trends such as its impact on mental well-being and advocacy efforts. While this study innovatively combined bibliometric and content analysis, it was limited by its narrow focus on mental health, excluding broader public health concerns.[8] Another significant contribution analysed the role of social media in spreading misinformation during the COVID-19 pandemic. Their findings highlighted the significant influence of misinformation on vaccine hesitancy and public behaviour but were constrained by their focus on pandemic-related contexts, neglecting misinformation in other health domains.[9] These studies were also restricted to a broad definition of social media, focused on specific aspects of health, and did not investigate the role of health influencers or their influence on content quality and audience engagement (Table I).

Table I: Summary of previous bibliometric studies of social media and health

Author	Domain/Search Strategy	Data Source & Scope	TDE	Bibliometric Attributes Examined
Yeung et al., 2022[7]	ALL=(misinformati* OR "wrong informati*" OR disinformati* OR "misleading informati*" OR "fake news*") AND ALL=(medic* OR illness* OR disease* OR health* OR pharma* OR drug* OR therap*) AND ALL=("social media*" OR Facebook* OR Twitter* OR Instagram* OR YouTube* OR Weibo* OR Whatsapp* OR Reddit* OR TikTok* OR WeChat*)	Web of Science Core Collection	529	- Publication and citation counts of contributors in terms of author, institution, country, and journal. - Publication and citation counts of terms and keywords, and identified the top 10 most cited papers. - Citations per paper (CPPs) - n-gram analysis
Azizan, 2024[8]	"social network*" OR "Social media" OR "Facebook" OR "Instagram" OR "Twitter" OR "LinkedIn" OR "TikTok" AND "Mental Health" OR "psychological well-being" OR "Mental Disorder" OR "Mood Disorder*" OR "Depression" OR "affective disorder*" OR "Affective Symptom*" OR "Depressive" OR "psych*" OR "anxiety" OR "Stress" OR "Psychological."	Scopus and Web of Science	3119	- publication numbers -primary research themes -top countries -subject areas -frequently used author keywords -preferred sources -institutional data
Adebesin et al., 2023[9]	("Health*" OR "Medical") AND ("Misinformation" OR "Disinformation" OR "Fake News") AND ("Social media" OR "Twitter" OR "Facebook" OR "YouTube" OR "WhatsApp" OR "Instagram" OR "TikTok") AND ("Pandemic*" OR "Corona*" OR "Covid*")	SCOPUS	943	- top trending keywords - niche topics - authors - publishers

TDE='Total documents examined

MATERIALS AND METHODS

Search strategy

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart (Figure 1) to conduct our analysis. On 21st December 2024, we gathered data from the Scopus database publications from 2010 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, abstract and keywords. 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 ("health influencers" OR "medical influencers") OR TITLE-ABS-KEY (medical AND content AND social AND media) AND TITLE-ABS-KEY (engagement OR audience)) AND PUBYEAR > 2009 AND PUBYEAR < 2025 AND (LIMIT-TO (SRCTYPE , "j")) AND (LIMIT-TO (PUBSTAGE , "final")) AND (LIMIT-TO (SUBJAREA , "MEDI") OR LIMIT-TO (SUBJAREA , "HEAL") OR LIMIT-TO (SUBJAREA , "NURS") OR LIMIT-TO (SUBJAREA , "PSYC") OR LIMIT-TO (SUBJAREA , "PHAR") OR LIMIT-TO (SUBJAREA , "IMMU") OR LIMIT-TO (SUBJAREA , "NEUR") OR LIMIT-TO (SUBJAREA , "DENT")) AND (LIMIT-TO (DOCTYPE , "ar") OR LIMIT-TO (DOCTYPE , "re")) AND (LIMIT-TO (LANGUAGE , "English")) A total of 644 articles were initially identified by the Scopus database.

Data screening

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. Papers from conference proceedings, books, book chapters, and other non-journal publications were excluded from our analysis. Irrelevant publications defined as those not focused on social media or health influencers were excluded. The initial screening and selection of articles were undertaken by the first author, with any ambiguous or uncertain cases discussed and resolved by consensus among all authors. Following these criteria, a total of 516 scientific journal articles and reviews were chosen for the bibliometric analysis. These selected articles provide a comprehensive overview of the literature on health influencers and social media spanning from 2010 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 health influencers on social media. 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 Analyze 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. We also utilised Bibliometrix, an R-based package designed for quantitative bibliometric analysis and accessed the web interface Biblioshiny to analyse the .csv file. Furthermore, VOSviewer was used to visualise the findings, mapping keyword co-occurrences with a minimum of five keyword occurrences and a minimum cluster size of five, ensuring robustness and clarity of the visualised 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.

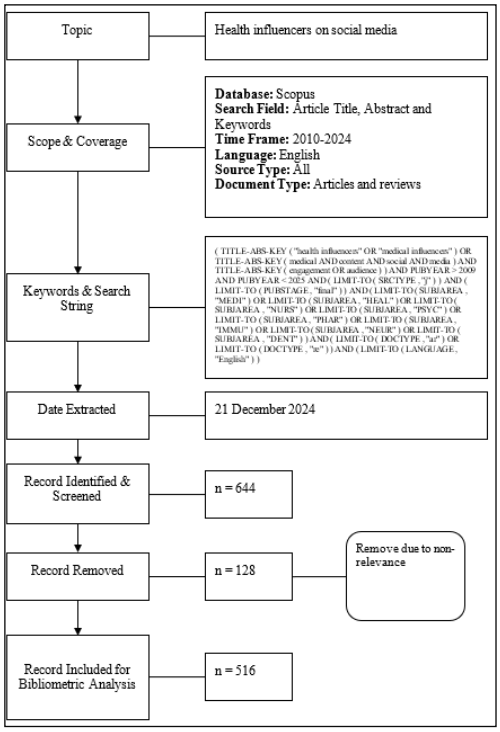

Figure 1. Flow diagram of the search strategy following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol.

RESULTS

Documents profiles and trends

We retrieved a total of 479 original articles and 37 reviews. All were journal articles written in English. These articles were published in 161 different journals. Most of the publications covered fields: Medicine (66.4%), Health Professions (5.4%), Social Sciences (4.9%), Nursing (3.1%), and Biochemistry, Genetics and Molecular Biology (2.8%) as the topics. Overall, the number of publications per year has increased over time with a slight temporary decrease in 2023, possibly reflecting delays in the publication process following the surge of COVID-19-related research or shifting editorial priorities.[10] The highest number of publications was in 2024 with 92 articles published that year. The number of citations per year has also increased over time with a peak of 2199 in 2024 (Figure 2).

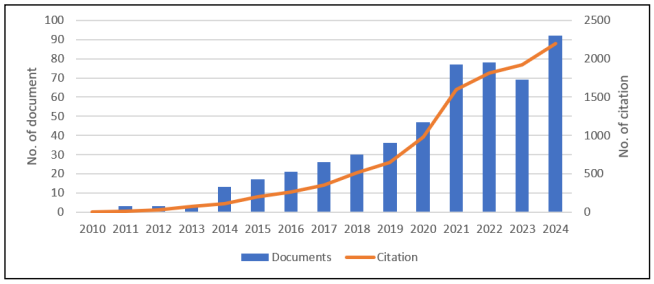

Figure 2. Total Publications and Citations by Year

Most productive Authors and Institutions

Table 2 shows the most productive authors, while Table 3 shows the most productive institutions publishing papers on health influencers in social media. Among authors, Fishman E.K. from Johns Hopkins University School of Medicine (USA) leads with 7 publications and 59 total citations, followed by Kauffman L. and Weisberg E.M., both from the same institution, with 6 publications each. Sloniewski P. from Gdanski Uniwersytet Medyczny (Poland) stands out with 5 publications and a high citation impact of 124 total citations, reflecting strong influence in the field.

Although institutions in the USA dominate the research landscape, the University of Toronto (Canada) leads in productivity with 21 publications and 512 citations, demonstrating a high citation-per-publication (C/P) rate of 24.4. The University of Pennsylvania (USA) follows with 16 publications and an impressive total of 738 citations, achieving a remarkable C/P rate of 46.1. Harvard Medical School (USA) shows the highest impact with 11 publications and 848 citations, averaging 77.1 citations per publication. Other notable institutions include the University of Michigan, Johns Hopkins University School of Medicine, and the University of California, all contributing significantly with high-quality research and citation impacts.

Table II. Most Productive Authors with a minimum of five publications

Author's Name	Affiliation	Country	TP	NCP	TC	C/P	C/CP	h
Fishman E.K.	Johns Hopkins University School of Medicine	USA	7	6	59	8.4	9.8	5
Kauffman L.	Johns Hopkins University School of Medicine	USA	6	5	51	8.5	10.2	4
Weisberg E.M.	Johns Hopkins University School of Medicine	USA	6	5	51	8.5	10.2	4
Sloniewski P.	Gdanski Uniwersytet Medyczny	Poland	5	5	124	24.8	24.8	4

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

Table III. Most productive institutions with minimum of ten publications

Affiliation	Country	TP	NCP	TC	C/P	C/CP	h
University of Toronto	Canada	21	21	512	24.4	24.4	10
University of Pennsylvania	USA	16	15	738	46.1	49.2	8
University of Michigan	USA	14	13	218	15.6	16.8	7
University of Toronto Faculty of Medicine	Canada	13	13	285	21.9	21.9	7
University of California	USA	13	13	249	19.2	19.2	8
Johns Hopkins University School of Medicine	USA	12	9	273	22.8	30.3	6
Harvard Medical School	USA	11	10	848	77.1	84.8	6
University of Colorado Medical School	USA	11	9	124	11.3	13.8	6
UCSF School of Medicine	USA	11	11	168	15.3	15.3	7
NYU Langone Health	USA	11	11	169	15.4	15.4	7
University of Michigan Medical School	USA	11	11	184	16.7	16.7	7
The University of British Columbia	Canada	10	9	202	20.2	22.4	7

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

Publications by countries

The USA leads as the top contributor with 257 articles (49.8%), reflecting its dominant role in the field, although with relatively low international collaboration (11.3% MCP or multiple country publications). Canada (7.8% MCP) and the United Kingdom (UK) (6% MCP) follow, with the UK exhibiting a high level of international collaboration (45.2% MCP). European countries such as Germany (55.5% MCP), Switzerland (50% MCP), Austria (100% MCP), and Norway (75% MCP) stand out for their strong MCP percentages, highlighting their focus on global research partnerships. In contrast, countries like Turkey, China, Poland, Malaysia, and Hong Kong emphasise domestic research, as shown by their 100% single-country publications (SCP). Italy (28.6% MCP) balances domestic and international efforts, while smaller contributors like Saudi Arabia (20% MCP), Spain (20% MCP), and Denmark (25% MCP) show moderate collaboration levels.

Publications by source titles

The Journal of Medical Internet Research is the most productive source, contributing 48 articles. The International Journal of Environmental Research and Public Health follows with 13 articles. BMC Public Health and World Neurosurgery each contributed nine articles. Journals like Current Problems in Diagnostic Radiology, Digital Health, JMIR Formative Research, JMIR Public Health and Surveillance, Journal of the American College of Radiology, and Vaccine each contributed six articles.

Citation metrics

A total of 516 papers have been published in this period, with 446 papers collectively garnering 10815 citations, which translates to an average of 721 citations per year. The average number of C/P of 24.2. An h-index of 50 indicates that at least 50 papers have received 50 or more citations each.

Highly cited documents

The top ten highly cited articles are listed in Table 4. The most cited article, with 602 citations, explores how diabetes patients use Facebook for communication.11 Other highly cited studies include one on the impact of COVID-19 rumours and misinformation on social media (514 citations), a review on X's role in health research, and studies on the reliability of YouTube content regarding rheumatoid arthritis and anorexia.[12-17] Additional studies cover health communication strategies via X and Pinterest, the use of video-sharing platforms for hypertension information, and TikTok's role in COVID-19 communication.[18-20]

Table IV. Top ten highly cited articles

No	Authors	Title	Cites	Cites per Year
1	Greene et al. (2011)[11]	Online social networking by patients with diabetes: A qualitative evaluation of communication with Facebook	602	40.1
2	Tasnim et al. (2020)[12]	Impact of rumours and misinformation on COVID-19 in Social Media	514	34.3
3	Sinnenberg et al. (2017)[13]	Twitter as a tool for health research: A systematic review	487	32.4
4	Singh et al. (2012)[14]	YouTube for information on rheumatoid arthritis - A wakeup call?	453	30.2
5	Syed-Abdul et al. (2013)[15]	Misleading health-related information promoted through video-based social media: Anorexia on YouTube	251	16.7
6	Loeb et al. (2019)[16]	Dissemination of Misinformative and Biased Information about Prostate Cancer on YouTube	220	14.7
7	Park et al. (2016)[17]	Tweeting as health communication: Health organizations use of twitter for health promotion and public engagement	174	11.6
8	Guidry et al. (2015)[18]	On pins and needles: How vaccines are portrayed on Pinterest	165	11.0
9	Kumar et al. (2014)[19]	Are video sharing Web sites a useful source of information on hypertension?	136	9.1
10	Li et al. (2021)[20]	Communicating COVID-19 information on TikTok: A content analysis of TikTok videos from official accounts featured in the COVID-19 information hub	127	8.5

Top keywords

Analysis of top author keywords with minimum occurrence of five keywords revealed that social media is the dominant theme, appearing in 21.4% of the total 1,333 keywords. Among specific platforms, X (5.3%) and YouTube (4.7%) are the most frequently studied, followed by Facebook (2.9%) and Instagram (2.4%). The presence of Covid-19 (3.2%) and misinformation (1.7%). Additionally, health communication (2.8%) and content analysis (2.0%).

Co-occurrence analysis of author's keywords

The co-occurrence analysis of author keywords reveals that "social media" is the central theme, with platform-specific focuses on YouTube, Instagram, and X. Key areas of interest include health communication, content analysis, and engagement. Five distinct research areas were identified (Figure 3): public health promotion and community engagement (e.g., mental health and adolescents), misinformation and content quality (e.g., vaccine hesitancy), medical education and health literacy, broader educational themes (e.g., surgical education), and pandemic-related topics like COVID-19.

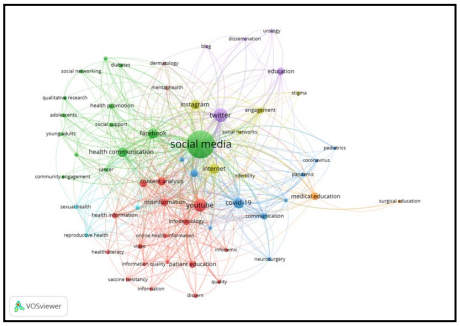

Figure 3. Network visualisation of the author's keywords. The size of the label and the node of an item is determined by the weight of the item. The colour of an item is determined by the cluster to which the item belongs. Lines between items represent co-occurrence links between terms. Link strength indicates the number of publications in which two terms occur together. Source: VOSviewer

Co-occurrence analysis of terms based on title and abstract

The co-occurrence analysis of terms in titles and abstracts in Figure 4 highlights two main thematic clusters. The red cluster focuses on community engagement, communication strategies, and platform-specific activities, with key terms such as community, communication, post, and platform names. The green cluster emphasises content evaluation, engagement metrics, and content quality, featuring terms such as video, quality, and reliability.

Strong interconnections exist between the clusters through terms like patient and source. Key themes include platform-specific studies, audience engagement, content credibility, and educational applications.

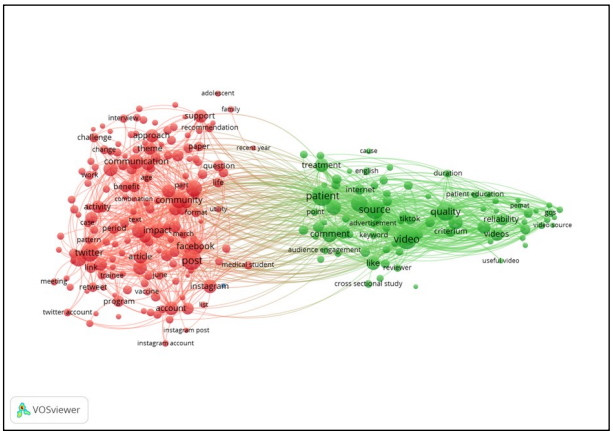

Figure 4. Network visualisation of a term co-occurrence network based on title and abstract fields. The size of the label and the node of an item is determined by the weight of the item. The colour of an item is determined by the cluster to which the item belongs. Lines between items represent co-occurrence links between terms. Link strength indicates the number of publications in which two terms occur together. Source: VOSviewer

DISCUSSION

The rise of health influencers in public health communication

Research on health influencers on social media has expanded significantly since 2010, reflecting their growing influence in shaping public perceptions of health. This trend is evident in the increasing number of publications and citations over time, as ascertained in this bibliometric analysis.

Health influencers break traditional communication barriers by delivering accessible and relatable health messages. Through platform-specific engagement strategies, they simplify complex health topics to make them more appealing.[21] A previous bibliometric analysis examined social media marketing tools for healthy eating, but its scope was limited. The present study provides a broader overview of health-related influencer research across social media platforms.[22]

While health influencers contribute to public health advocacy and education, they also inadvertently facilitate the spread of misinformation. Co-occurrence analysis discovered clusters related to medical misinformation,

emphasising concerns about content accuracy.[18,20] A previous bibliometric analysis on medical and health-related misinformation in social media reported significant platform-specific topic preferences, with X, YouTube, and Facebook being the most frequently studied. While our study did not specifically analyse misinformation, we similarly observed concerns being raised on other platforms, including Instagram, highlighting the wider relevance of this issue across social media channels.[23]

Health influencers are increasingly shaping not only public health awareness but also medical education and professional discourse, although algorithm-driven content amplification creates new challenges.[24] Further research is needed to understand how health influencers build credibility, how audiences assess trustworthiness, and how regulatory frameworks can adapt to the rapidly evolving digital landscape.[25]

Trending Topics and Research Hotspots

Research on health influencers has shifted from platform-specific studies, such as X and blogging, to broader investigations into "social media," reflecting the increasing integration of multiple platforms in health communication.[26,27] Co-occurrence analysis identifies two primary thematic clusters: community engagement and communication strategies, and content evaluation, including engagement metrics and quality assessment. These shifts mirror broader trends in the social media landscape, with platforms like TikTok and Instagram becoming prominent for video-based health communication. The emergence of terms such as "misinformation" and "healthcare personnel" post-2020 highlights the COVID-19 pandemic's influence, amplifying concerns about the spread of inaccurate information and the role of medical professionals online. These issues align with prior studies on misinformation trends and influencer engagement strategies.[12,21] Strong links between engagement metrics and content credibility reflect ongoing debates about the reliability and ethical responsibilities of health influencers. Furthermore, changes in platform usage patterns also shape research trends. Twitter's 2023 rebranding to X and the rise of newer platforms such as Threads may have encouraged researchers to adopt more generalised terminology.[28]

Among publication sources, the Journal of Medical Internet Research is the most prolific, followed by the International Journal of Environmental Research and Public Health, BMC Public Health, and World Neurosurgery. This distribution highlights an interdisciplinary approach, encompassing public health, medicine, digital health, and surgical education.[29]

Platforms, Algorithms, Policies, and Content Quality

This bibliometric analysis also highlights TikTok and YouTube as key platforms for digital health communication. Co-occurrence analysis confirms "social media" as the dominant theme, alongside specific platforms such as YouTube, Instagram, and X. For instance, one study examined COVID-19 vaccine misinformation on X, while another explored attitudes toward pregnant fitness influencers on Facebook.[30,31] These studies reflect sustained interest in platform functionality and content credibility.

TikTok and Instagram employ education-entertainment strategies, making health content accessible, particularly to younger audiences.[32] However, this accessibility raises concerns about misinformation, as engagement-driven algorithms prioritise viral content over accuracy. Research on ophthalmology-related TikTok videos revealed significant portions of misleading content, potentially influencing patient decisions.[33] This analysis may under-represent algorithm-focused studies because it was limited to Scopus-indexed publications.

Algorithmic biases also shape content visibility, amplifying certain health messages while suppressing others, particularly less mainstream or evidence-based perspectives.[34] During global crises such as COVID-19, misinformation often gained greater traction than credible sources.[35] Platform policies and algorithmic biases can also marginalise health influencers presenting alternative viewpoints.[36] Addressing these disparities requires greater collaboration between healthcare professionals and health influencers to promote evidence -based content while countering misinformation.[37,38]

Global Contributions and Research Collaboration

This analysis found that the USA dominates research on health influencers, benefiting from strong academic infrastructure and funding.[39] However, its relatively low international collaboration suggests a domestically focused research agenda echoing previous bibliometric studies that identified Anglocentric dominance and domestic preference in medical publishing.[40] In contrast, countries such as the UK and Germany demonstrate higher cross-border partnerships, facilitating knowledge exchange. Our findings are also consistent with earlier bibliometric analyses showing that while the USA leads in publications and citations, institutional collaboration networks are gradually expanding from high-income to emerging market countries.[41] In our dataset, emerging regions such as Turkey, Malaysia, and China show increasing contributions, though limited engagement from low- and middle-income countries overall raises concerns about inclusivity.[25,42] Expanding global collaboration and encouraging participation from underrepresented regions would provide valuable insights into diverse socio-cultural perspectives on health communication, thereby enhancing the diversity and applicability of the field.[43]

CONCLUSION

This bibliometric analysis (2010–2024) highlights the growing role of health influencers on social media in shaping public health narratives, with platforms such as Instagram, YouTube, and TikTok being central to this trend. While research output is led by the USA and Canada, global participation is increasing, though low- and middle-income countries remain underrepresented. Social media is a powerful tool for disseminating health information, but challenges around content accuracy and misinformation persist. The findings emphasise the importance of collaboration between healthcare professionals and health influencers to ensure evidence-based, credible content, particularly in sensitive domains such as mental health and cosmetic surgery, where ethical considerations are paramount.

For policymakers, these insights highlight the need for regulatory frameworks that safeguard against misinformation while supporting the creation of reliable, engaging health content. For practitioners and health communicators, the results highlight opportunities to harness influencer-driven platforms for health promotion, provided that content is both scientifically accurate and culturally appropriate.

Limitations of this study include the restriction to Scopus -indexed, English-language publications and the use of simplified thematic categorisation, which may overlook relevant work published in other languages, indexed in different databases, or addressing more nuanced subthemes. Future research should expand coverage to additional platforms and databases, examine the behavioural impact of influencer-led health communication, and further investigate mechanisms to promote evidence-based and ethical content creation.

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ORIGINAL ARTICLE

Hand Strength Differences Across Cardiometabolic Conditions: A Cross-Sectional Comparative Study

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ABSTRACT

INTRODUCTION: Handgrip and pinch strength are critical indicators of upper limb function and health, and may be affected by cardiometabolic conditions such as type 2 diabetes mellitus (T2DM), hypertension (HPT), and hyperlipidemia (HPL). This study aimed to compare handgrip and pinch strength among healthy adults, individuals with T2DM+HPT, and those with T2DM+HPT+HPL in a Malaysian population. **MATERIALS AND METHODS**: A cross-sectional study was conducted with 204 adults (n=68 per group), matched by age, gender, and health condition. Handgrip and pinch strength were assessed using the Jamar Hydraulic Dynamometer and Pinch Gauge following the American Society of Hand Therapists (ASHT) protocol. Statistical analyses included One-way ANOVA and Pearson correlation. **RESULTS**: Hand strength differed significantly across groups ($p<0.001$). Healthy adults demonstrated higher grip and pinch strength than participants with T2DM+HPT and T2DM+HPT+HPL. Strength measures showed strong bilateral correlations (0.85-0.92, $p<0.001$). Weak positive associations were observed between random blood sugar and grip/pinch strength ($r=0.239$-0.271), while diastolic blood pressure showed weak associations with grip strength only ($r=0.239$-0.265). HbA1c was not significantly associated with hand strength. **CONCLUSION**: Cardiometabolic conditions are associated with reduced hand strength, particularly when T2DM coexists with HPT and HPL. Grip and pinch strength may serve as accessible functional markers for clinical assessment and early intervention in at-risk populations.

Keywords
Hand Strength, Type 2 Diabetes Mellitus, Hypertension, Hyperlipidemia, Functional Assessment

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INTRODUCTION

Hand function plays a critical role in daily living, enabling both fine and gross motor activities. In particular, handgrip and pinch strength are essential for prehensile and precision tasks.[1,2] Beyond their mechanical role, handgrip strength also serves as a biomarker that reflects the integrity of various physiological systems and is associated with chronic disease risk and premature mortality.[3] Biomarkers, as defined by the World Health Organization, are objective indicators of medical status based on body function, structure, or participation.[4]

Adults aged 18-65, whether healthy or living with conditions such as Type 2 Diabetes Mellitus (T2DM), hypertension (HPT), or hyperlipidemia (HPL), may exhibit varying levels of handgrip and pinch strength. These measures are predictive of future morbidity, functional disability, and mortality.[5] Individuals with T2DM often experience muscle weakness, particularly in handgrip and pinch strength, due to impaired glucose regulation and insulin resistance.[6] Similarly, hypertension has been associated with reduced muscle strength, likely due to the effects of elevated blood pressure on vascular and muscular function.[7] In contrast, individuals without T2DM or HPT tend to have stronger hand strength, which may reflect better overall muscle function.[8]

Previous studies have primarily compared handgrip strength between healthy and diabetic individuals or between healthy and hypertensive individuals, with limited research examining the combined effects of T2DM, HPT, and HPL, particularly within the Malaysian population.[7,9] Therefore, this study aimed to compare handgrip and pinch strength across cardiometabolic groups, and examine correlations with biomarkers including random blood sugar, HbA1c, and blood pressure.

MATERIALS AND METHODS

A total of 204 participants were recruited using purposive sampling and divided equally into three groups: healthy controls (n=68), adults with Type 2 Diabetes Mellitus and hypertension (T2DM+HPT, n=68), and adults with T2DM, HPT, and hyperlipidemia (T2DM+HPT+HPL, n=68). Participants with cardiometabolic conditions were recruited from Sungai Buloh Health Clinic while healthy controls were recruited in Kuantan area. Participants were matched based on age group, gender, and health condition to minimize potential confounding factors.

Exclusion criteria included individuals with current or previous hand injuries, Type 1 Diabetes Mellitus (T1DM), upper limb pain, cardiovascular disease, or other comorbidities beyond the specified group classifications. Demographic data, body weight, and height were recorded prior to strength testing. Additionally, relevant clinical parameters such as random blood sugar (RBS), fasting blood sugar (FBS), HbA1c, and blood pressure readings were obtained from medical records or measured at the clinic to profile the cardiometabolic status of participants.

Handgrip and pinch strength were assessed using a Jamar Hydraulic Hand Dynamometer and a Jamar Hydraulic Pinch Gauge. All measurements adhered to the American Society of Hand Therapists (ASHT) protocol, with participants seated upright, shoulders adducted and neutrally rotated, elbows flexed at 90°, forearms in a neutral position, and wrists positioned between 0° and 30° extension. Three trials were performed for each hand, with a 30-second rest between trials, in accordance with standardized testing protocols. The mean of the three trials was used for analysis. [10]

Data were analyzed using IBM SPSS Statistics version 28.0. Descriptive statistics were calculated, followed by One-Way Analysis of Variance (ANOVA) to compare group differences, and Pearson correlation tests to examine relationships between strength measures and physiological markers.

RESULTS

Out of 204 participants who met the inclusion criteria, three equal groups were formed: healthy controls (n=68), individuals with Type 2 Diabetes Mellitus and hypertension (T2DM+HPT, n=68), and individuals with T2DM, hypertension, and hyperlipidemia (T2DM+HPT+HPL, n=68). Table I summarizes the demographic and clinical characteristics of each group. Participants were matched by age and gender. Clinical variables such as body mass index (BMI), blood pressure, random blood sugar (RBS), fasting blood sugar (FBS), and HbA1c were collected to describe the cardiometabolic profile of each group.

Table I: Demographic and Clinical Characteristics of Participants by Group (N=204)

Characteristics	Healthy Controls (n=68)	T2DM + HPT (n=68)	T2DM + HPT + HPL (n=68)
Age (years)	44.75 ± 12.70	51.09 ± 10.72	51.65 ± 9.96
Gender - Female	24 (35.3%)	24 (35.3%)	24 (35.3%)
Gender - Male	44 (64.7%)	44 (64.7%)	44 (64.7%)
Dominant Hand - Right	61 (89.7%)	59 (86.8%)	53 (77.9%)
Dominant Hand - Left	7 (10.3%)	9 (13.2%)	15 (22.1%)
BMI - Underweight	4 (5.9%)	0 (0.0%)	0 (0.0%)
BMI - Normal	25 (36.8%)	23 (33.8%)	26 (38.2%)
BMI - Overweight	32 (47.1%)	26 (38.2%)	24 (35.3%)
BMI - Obese	7 (10.3%)	19 (28.0%)	18 (26.5%)
RBS (mmol/L)	-	7.83 ± 3.84	8.31 ± 3.94
FBS (mmol/L)	-	7.02 ± 3.43	6.92 ± 2.83
HbA1c (%)	-	6.84 ± 1.82	6.95 ± 1.54

Descriptive Measurements of Grip and Pinch Strength

Table II shows handgrip and pinch strength by age group in the healthy control group. Among young adults (18-39 years), the mean right-handgrip strength was 33.58 kgf (SD=12.76), while the left-handgrip strength was 30.86 kgf (SD=10.86). Right and left pinch strengths were 5.83 kgf (SD=1.65) and 5.02 kgf (SD=1.57), respectively.

Middle-aged adults (40-59 years) showed slightly lower grip strength values, with 32.85 kgf (SD=11.58) on the right and 30.25 kgf (SD=11.95) on the left. However, their pinch strength was slightly higher than that of the younger group. Older adults (60-65 years) demonstrated the lowest grip and pinch strength across all measures.

Table II: Handgrip and pinch strength by age group in healthy controls

Age Group	Strength Measure	Female (n, %)	Male (n, %)	Mean ± SD
Young (18-39)	Grip Right	7 (43.75%)	9 (56.25%)	33.58 ± 12.76
	Grip Left	7 (43.75%)	9 (56.25%)	30.86 ± 10.86
	Pinch Right (Lateral)	7 (43.75%)	9 (56.25%)	5.83 ± 1.65
	Pinch Left (Lateral)	7 (43.75%)	9 (56.25%)	5.02 ± 1.57
Middle-aged (40-59)	Grip Right	14 (31.82%)	30 (68.18%)	32.85 ± 11.58
	Grip Left	14 (31.82%)	30 (68.18%)	30.25 ± 11.95
	Pinch Right (Lateral)	14 (31.82%)	30 (68.18%)	6.62 ± 1.89
	Pinch Left (Lateral)	14 (31.82%)	30 (68.18%)	6.16 ± 1.89
Older (60-65)	Grip Right	3 (37.50%)	5 (62.50%)	26.88 ± 5.88
	Grip Left	3 (37.50%)	5 (62.50%)	25.67 ± 8.56
	Pinch Right (Lateral)	3 (37.50%)	5 (62.50%)	4.85 ± 2.07
	Pinch Left (Lateral)	3 (37.50%)	5 (62.50%)	5.02 ± 2.52

Table III shows the hand strength levels in the T2DM+HPT group. Young adults showed lower strength than their healthy counterparts, with right-handgrip strength averaging 26.67 kgf (SD=10.41) and left-handgrip 24.62 kgf (SD=10.94). Pinch strength was also reduced. Middle-aged participants demonstrated further declines, with slightly reduced grip and pinch strength on both sides. Among older adults (60-65 years), hand strength remained relatively low and showed limited variation.

Table III: Handgrip and pinch strength by age group in adults with T2DM and hypertension (T2DM+HPT)

Age Group	Strength Measure	Female (n, %)	Male (n, %)	Mean ± SD
Young (18-39)	Grip Right	7 (43.75%)	9 (56.25%)	26.67 ± 10.41
	Grip Left	7 (43.75%)	9 (56.25%)	24.62 ± 10.94
	Pinch Right (Lateral)	7 (43.75%)	9 (56.25%)	4.01 ± 1.36
	Pinch Left (Lateral)	7 (43.75%)	9 (56.25%)	3.54 ± 1.11
Middle-aged (40-59)	Grip Right	14 (31.82%)	30 (68.18%)	21.10 ± 8.54
	Grip Left	14 (31.82%)	30 (68.18%)	21.71 ± 8.54
	Pinch Right (Lateral)	14 (31.82%)	30 (68.18%)	3.41 ± 1.17
	Pinch Left (Lateral)	14 (31.82%)	30 (68.18%)	3.57 ± 1.21
Older (60-65)	Grip Right	3 (37.50%)	5 (62.50%)	22.75 ± 5.72
	Grip Left	3 (37.50%)	5 (62.50%)	20.25 ± 8.06
	Pinch Right (Lateral)	3 (37.50%)	5 (62.50%)	3.63 ± 0.83
	Pinch Left (Lateral)	3 (37.50%)	5 (62.50%)	3.27 ± 1.05

Table IV shows hand strength values for the T2DM+HPT+HPL group. Young adults in this group showed slightly higher grip strength than those in the T2DM+HPT group, but still below healthy controls. Middle-aged participants displayed a decline in both grip and pinch strength. Interestingly, older adults showed slightly better strength than middle-aged participants in some measures, though the differences were small and within the margin of variation.

Table IV: Handgrip and pinch strength by age group in adults with T2DM, hypertension, and hyperlipidemia (T2DM+HPT+HPL)

Age Group	Strength Measure	Female (n, %)	Male (n, %)	Mean ± SD
Young (18-39)	Grip Right	7 (43.75%)	9 (56.25%)	27.17 ± 10.85
	Grip Left	7 (43.75%)	9 (56.25%)	26.71 ± 10.52
	Pinch Right (Lateral)	7 (43.75%)	9 (56.25%)	3.64 ± 1.65
	Pinch Left (Lateral)	7 (43.75%)	9 (56.25%)	3.41 ± 1.30
Middle-aged (40-59)	Grip Right	14 (31.82%)	30 (68.18%)	22.10 ± 8.20
	Grip Left	14 (31.82%)	30 (68.18%)	21.87 ± 8.47
	Pinch Right (Lateral)	14 (31.82%)	30 (68.18%)	3.57 ± 1.34
	Pinch Left (Lateral)	14 (31.82%)	30 (68.18%)	3.40 ± 1.34
Older (60-65)	Grip Right	3 (37.50%)	5 (62.50%)	25.17 ± 5.14
	Grip Left	3 (37.50%)	5 (62.50%)	21.08 ± 4.77
	Pinch Right (Lateral)	3 (37.50%)	5 (62.50%)	4.19 ± 1.23
	Pinch Left (Lateral)	3 (37.50%)	5 (62.50%)	3.96 ± 0.62

Differences in Hand and Pinch Strength Between Groups

One-way ANOVA revealed statistically significant differences in hand strength across the three groups. For right-handgrip strength, the F-statistic was 20.224 with a p-value of less than 0.001. Left-handgrip strength also showed a significant difference with an F-value of 12.365 ($p<0.001$). Differences in pinch strength were even more obvious, with the right lateral pinch showing an F-value of 64.931 and the left lateral pinch an F-value of 51.232, both statistically significant at $p<0.001$.

Post hoc Tukey tests indicated that healthy individuals had significantly greater handgrip and pinch strength than participants with T2DM and hypertension (T2DM+HPT), who in turn had higher strength levels than those with additional hyperlipidemia (T2DM+HPT+HPL). These findings confirm a clear, graded decline in hand strength corresponding with increasing cardiometabolic burden. Figure 1 displays boxplots of handgrip and pinch strength (right/left) across groups, illustrating the group differences.

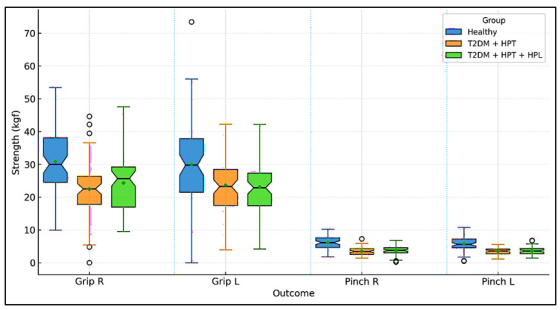

Figure 1: Boxplots of handgrip and pinch strength (right/left) across groups ($p<0.001$).

Correlation with Clinical Biomarkers

HbA1c showed no significant correlations with right-handgrip strength ($r=0.129$, $p=0.297$), left-handgrip strength ($r=0.157$, $p=0.205$), left pinch strength ($r=0.073$, $p=0.559$), or right pinch strength ($r=0.094$, $p=0.451$).

RBS demonstrated weak but statistically significant positive correlations with right-handgrip strength ($r=0.251$, $p=0.039$), left-handgrip strength ($r=0.239$, $p=0.049$), left pinch strength ($r=0.260$, $p=0.032$), and right pinch strength ($r=0.271$, $p=0.025$). SBP was not significantly correlated with any grip or pinch strength measure. Correlations were weak and non-significant for right grip strength ($r=0.006$, $p=0.962$), left grip strength ($r=-0.052$, $p=0.673$), right pinch strength ($r=0.029$, $p=0.815$), and left pinch strength ($r=-0.113$, $p=0.359$). In contrast, diastolic blood pressure (DBP) demonstrated weak but statistically significant positive correlations with right-handgrip strength ($r=0.265$, $p=0.029$) and left-handgrip strength ($r=0.239$, $p=0.049$). No significant associations were observed between DBP and left pinch strength ($r=0.130$, $p=0.290$) or right pinch strength ($r=0.206$, $p=0.093$). Figure 2 provides a visual summary of these correlations.

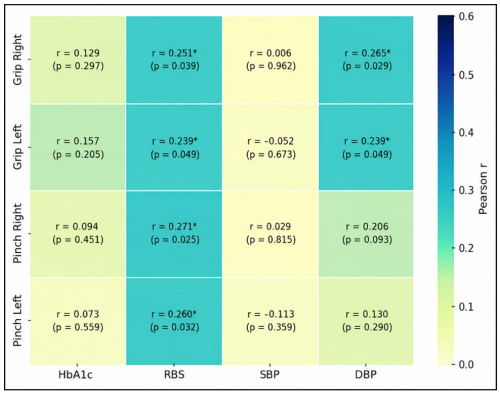

Figure 2: Pearson's correlations (r) between hand strength measures and cardiometabolic biomarkers (n=68) (**p < 0.01).

DISCUSSION

This study aimed to compare handgrip and pinch strength across different cardiometabolic conditions, assess age-related differences, and examine correlations with clinical biomarkers, including random blood sugar (RBS), HbA1c, and blood pressure (BP). The findings demonstrate that cardiometabolic disease status significantly affects hand strength, with greater functional decline observed in individuals with combined T2DM, hypertension, and hyperlipidemia. Descriptive patterns also suggested age-related differences in strength, consistent with prior literature.[11,12] Additionally, random blood sugar demonstrated weak positive associations with both grip and pinch strength, while diastolic blood pressure showed weak associations with grip strength only.

Age-related reductions in hand strength were most evident among healthy controls, whereas patterns were less consistent in participants with cardiometabolic conditions. While age-related decline in strength has been well documented in previous literature, our study observed a similar trend across age strata.[11,12] This trend may be more evident in individuals with chronic conditions such as Type 2 Diabetes Mellitus (T2DM) and hypertension (HPT), where aging is compounded by metabolic and vascular impairments.[13]

In addition to age, disease status significantly influenced hand strength. Participants with both T2DM and HPT demonstrated lower grip and pinch strength compared to healthy controls, while those with additional hyperlipidemia (T2DM+HPT+HPL) exhibited the most pronounced deficits. These findings suggest a cumulative negative effect of comorbid cardiometabolic conditions on muscle function. Specifically, hyperlipidemia may exacerbate insulin resistance, impairing glucose uptake in skeletal muscle and reducing cellular energy availability, thereby weakening contractile ability.[14] Furthermore, elevated lipid levels can accelerate atherosclerotic processes, restricting blood flow and oxygen delivery to muscle tissues. This ischemia may result in muscle fatigue and reduced function, contributing to the strength impairments observed in this group.[14]

These findings are consistent with previous studies reporting lower grip strength in individuals with T2DM and HPT compared to healthy counterparts. For example, significantly reduced hand strength has been observed in diabetic adults, as well as in individuals with hypertension.[9,15,16] Muscle strength reduction in T2DM has been attributed to both metabolic dysfunction and neuromuscular impairment, further supporting this study's results.[17,18] Moreover, the underutilization of hand function assessments in diabetes care has been highlighted in recent literature, highlighting the importance of incorporating grip and pinch evaluations into routine practice to detect functional decline early.[19] This aligns with emerging research emphasizing that diabetic peripheral neuropathy can significantly compromise hand function and daily activity performance.[20] Therefore, integrating simple hand strength measures may complement existing clinical tools to assess disability risk and functional impairment in people with DM and related comorbidities.

Beyond group comparisons, this study also examined correlations between hand strength and physiological markers. Strong bilateral correlations were observed between right and left hand strength measures, indicating substantial symmetry in upper limb strength performance. Notably, random blood sugar (RBS) demonstrated weak positive correlations with both grip and pinch strength, whereas diastolic blood pressure (DBP) showed weak positive correlations with grip strength only. In contrast, HbA1c, which reflects long-term glycemic control, showed no significant association with grip or pinch strength. This aligns with findings that HbA1c may not be a reliable indicator of muscle performance in diabetic populations.[8] These results suggest that acute metabolic and vascular factors, rather than chronic glycemic levels, may have a more modest influence on hand strength. The positive correlations between RBS and strength were weak and should be interpreted cautiously, as they do not imply a beneficial effect of hyperglycaemia on muscle function. Residual confounding, treatment effects, or variability in acute glucose measurements may explain these associations.

Clinically, these findings highlight the importance of evaluating hand strength in individuals with T2DM, HPT, and HPL. Reduced grip and pinch strength not only reflect musculoskeletal decline but may also indicate broader metabolic and cardiovascular dysfunction. Early detection of hand strength deficits can support timely rehabilitation planning, guide functional goal setting, and potentially improve long-term outcomes. Routine hand strength assessment may offer a practical, non-invasive method for identifying individuals at elevated risk of disability, enabling targeted intervention to preserve independence and enhance quality of life.

CONCLUSION

This study demonstrated that healthy adults exhibited significantly greater handgrip and pinch strength compared to individuals with T2DM+HPT and those with T2DM+HPT+HPL. RBS was weakly and positively correlated with both grip and pinch strength, whereas diastolic blood pressure showed weak positive correlations with grip strength only. HbA1c was not significantly associated with hand strength measures. These findings highlight the impact of cardiometabolic conditions on upper limb strength and support the utility of grip and pinch strength as functional indicators in clinical assessments. Although limited by the small number of young adults with comorbidities, the study provides important reference data for clinicians in evaluating and managing patients with diabetes and hypertension. Future research should adopt longitudinal designs and recruit more diverse populations to validate hand strength as a biomarker for chronic disease burden and functional decline.

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CONFLICT OF INTEREST

None declared.

ETHICS APPROVAL

This study was approved by the Human Research Ethics Committee of Universiti Teknologi MARA (Ref No: FERC/FSK/MR/2023/00288) and Medical Ethics and Research Committee of Ministry of Health Malaysia (Ref No: NMRR-ID-24-00274-N8M-(IIR))

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ORIGINAL ARTICLE

Mental Health Help-Seeking Attitude and its Associated Factors among Chinese International University Students in Malaysia

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ABSTRACT

INTRODUCTION: Amid growing concerns about mental health in academic settings, especially among international students facing cross-cultural stress and stigma, understanding factors associated with mental health help-seeking attitudes is crucial for effective strategies. This study aimed to examine mental health help-seeking attitudes and associated factors among Chinese international university students in Malaysia. **MATERIALS AND METHODS:** A cross-sectional study was conducted from October 2024 to July 2025 among Chinese international students selected through convenience sampling. Data were collected using a questionnaire comprising socio-demographic characteristics, the Attitude Toward Seeking Professional Psychological Help-Short Form (ATSPPH-SF), the Language Proficiency subscale of the Revised Sociocultural Adaptation Scale (SCAS-R), the Self-Stigma of Seeking Help Scale (SSOSH-3), the Stigma Scale for Receiving Psychological Help (SSRPH), and the Multidimensional Scale of Perceived Social Support (MSPSS). Data were analysed using descriptive statistics and multiple linear regression. **RESULTS:** A total of 222 participants were analysed. The median help-seeking attitude score was 16.5 (IQR: 14-21). Self-stigma (adjusted β=-0.550, p<0.001) and students from health and life sciences field (vs. science and technology) (adjusted β=-2.533, p=0.027) were significant negative predictors, age (adjusted β=0.148, p=0.030) and social support (adjusted β=0.072, p=0.011) were significant positive predictors. **CONCLUSION:** Personal and environmental factors were associated with mental health help-seeking attitudes. Universities may improve attitudes by strengthening support systems. Future studies are recommended to further explore strategies to improve mental health help-seeking attitudes among international university students.

Keywords
Mental Health, Mental Health Help-seeking, Attitude, Chinese, International University Students

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INTRODUCTION

Mental health problems have become a highly prevalent public health concern, especially among university students.[1] Mental health problems among university students are widespread worldwide. In a large international survey involving 14,000 students across 19 universities in eight countries, 35% of the university students met the diagnostic criteria for at least one common mental health disorder. Furthermore, university students demonstrated 12.9% higher levels of depressive symptoms than the general population.[2] University students are considered to be particularly vulnerable during the transition from high school to university, as they face the developmental challenges associated with emerging adulthood, placing them at heightened risk for mental health problems.[3]

As a distinct subgroup of university students, international university students face additional challenges, including

language barriers, social isolation, and difficulties with cross-cultural adjustment. Compared with domestic students, international students are more likely to experience stress and negative emotions, which may further increase their risk of mental health problems.[4] Moreover, the mental health problems of international students show a relatively high degree of severity and lead to serious consequences. In a study among 42,428 domestic students and 2,423 international students in universities in the United States, international students were more likely to feel overwhelmingly depressed and report suicide attempts.[5]

Universities worldwide have introduced a wide range of mental health support services, including counselling services, healing sessions, peer support activities, group therapy and mindfulness-based approaches.[6] However, despite the availability of these services, many students remain reluctant to seek professional help, even when experiencing serious mental health problems. Barriers to help-seeking appear to be particularly pronounced among international students, who demonstrate lower levels of mental health service utilisation and higher thresholds for seeking professional support.[7] A study conducted in the United States reported a significant difference in mental health service utilisation rates between international students (32.0%) and domestic students (49.8%).[8]

Mental health help-seeking attitude refers to an individual's overall evaluation of seeking help from a mental health professional, which may influence the utilisation of professional mental health services among university students. Attitudes are considered predictors of behaviour and may influence both students currently experiencing mental health problems and those without current mental health problems.[9] According to the Planned Behaviour Theory, behavioural intention is the most immediate determinant of actual behaviour, and intention is influenced by three key constructs: attitude toward the behaviour, subjective norms, and perceived behavioural control. Based on this theory, mental health help-seeking attitudes are important factors of help-seeking intention, which may subsequently influence the actual utilisation of mental health services.[10] Prior studies have identified several associated factors. For individual-level factors, stigma was a factor that many studies mentioned.[11] For social factors, social support also mentioned as an associated factor, as university students often prefer seeking informal support from family and friends than professional mental health help.[12] For cultural factors, cultural background and length of stay abroad may further affect international students' mental health help-seeking attitudes, with longer stays often leading to better adaptation.[13]

In recent decades, China has become one of the world's largest sources of international university students.[14] Due to geographical proximity, cultural ties, and relatively affordable education, Malaysia has emerged as a key destination, hosting a rapidly growing population of Chinese international students.[15] Despite their increasing presence, research on the mental health help-seeking attitudes of Chinese international students in Malaysia remains scarce. Existing studies have primarily focused on local students or international students in general, with insufficient empirical evidence specifically addressing Chinese international students as a distinct group.

To address this research gap, the present study aimed to understand the level of mental health help-seeking attitude and its associated factors among Chinese international university students in Malaysia. This study contributes to the existing literature by providing empirical evidence on mental health help-seeking attitudes and their associated factors among Chinese international university students in Malaysia, a population that remains underrepresented in current research. By identifying the roles of language proficiency, stigma-related factors, and social support, the study expands current understanding of the cultural and psychosocial determinants influencing help-seeking attitude among international students. The findings also provide practical implications for Malaysian universities and higher education institutions. Specifically, the results may assist universities in developing culturally sensitive mental health services and targeted intervention strategies to enhance the prevention, early identification, timely treatment, and recovery of mental health

problems among international students.[16] Furthermore, this study offers a useful foundation for future researchers to conduct longitudinal, cross-cultural, and intervention-based studies on mental health help-seeking among international student populations.

MATERIALS AND METHODS

Study Design, Sampling Method and Selection Criteria

This cross-sectional study was conducted from October 2024 to July 2025 among Chinese international university students at a public university in Malaysia. Ethical approval and questionnaire preparation were completed in March 2025, and the pre-test was conducted in early April 2025. Data collection was conducted from April to May 2025, while data organization and statistical analyses were performed between June and July 2025.

The name list of Chinese international university students was not accessible due to the university's confidentiality policy regarding students' personal information. Therefore, considering the study timeline, accessibility, and resource constraints, a convenience sampling method was used to select the participants, which allowed efficient access to a defined population of Chinese international students.

The inclusion criteria were as follows: i) Students aged 18 years or above. ii) Students who had resided in Malaysia for more than three months to ensure sufficient exposure to the host country environment and university setting. Previous studies of international student adaptation suggest that the initial months after arrival are often characterized by acute transitional stress and early sociocultural adjustment, which may temporarily influence attitudes toward mental health help-seeking.[17] Therefore, the three-month criterion was considered appropriate to avoid these potential confounding variables. iii) Students who were citizens of China with Chinese nationality. iv) Students whose primary place of residence before studying in Malaysia was China. The exclusion criteria were as follows: i) Students who are studying at the branch campus. ii) Students currently receiving treatment for a diagnosed mental illness.

Sample Size

The sample size was calculated using the formula for estimating a population mean proposed by Lwanga and Lemeshow (1991): $n=Z^2(1-\alpha/2)\times\sigma^2/d^2$, with a significance level (α) of 0.05, a 95% confidence level ($Z_{(1-\alpha/2)}=1.96$), and a desired precision (d) of 0.6, where the estimated standard deviation (σ) of 4.34 was derived from a previous study conducted among 113 Chinese international university students in the United States examining mental health help-seeking attitudes.[18] $n=(1.96^2\times4.34^2)/0.6^2=201$. Considering a 30% non-response rate, the required sample size of this study is 201/(1-30%) = 288.

Study Instruments

The study instrument was a self-administered questionnaire developed in the English and consisted of five sections.

Section A collected socio-demographic information, including age, gender, field of study, academic level, marital status, and length of stay in Malaysia.

Section B utilised Attitude Toward Seeking Professional Psychological Help-Short Form (ATSPPH-SF) to assess mental health help-seeking attitudes among participants. The ATSPPH-SF is a 10-item scale, using a four-point Likert scale (0 = disagree, 3 = agree), with several reverse -scored items. Total scores range from 0 to 30, with higher scores indicating more positive help-seeking attitudes. The ATSPPH-SF comprises three dimensions, and a sum score above 20 across all 10 items, as well as a score above 10 on each dimension, indicates a positive mental health help-seeking attitude; otherwise, it reflects a negative attitude.[19] The ATSPPH-SF has demonstrated good reliability (Cronbach's $\alpha=0.86$) among university students,[20] along with strong test-retest reliability ($r=0.84$) with a reported construct validity coefficient of 0.87.[21]

Section C employed the Language Proficiency subscale of the Revised Sociocultural Adaptation Scale (SCAS-R) to measure self-perceived language proficiency. The Language Proficiency subscale of the SCAS-R is a 2-item

subscale, using a 5-point Likert scale (1 = not at all competent, 5 = extremely competent). Higher scores reflect better language proficiency. A previous study among international university students reported strong reliability (Cronbach's *a*=0.90) and satisfactory predictive and incremental validity.[22]

Section D assessed both self-stigma and public stigma associated with mental health help-seeking. Self-stigma was measured using the ultra-brief version of Self-Stigma of Seeking Help Scale (SSOSH-3). The SSOSH-3 contains 3 items rated on a 5-point Likert scale (1 = strongly disagree, 5 = strongly agree). Higher scores indicate greater self-stigma associated with help-seeking. The SSOSH-3 demonstrated good internal consistency (Cronbach's *a*=0.87) and strong content validity (mean CVR=1.00; mean CVI>0.80).[23] Public stigma was measured by Stigma Scale for Receiving Psychological Help (SSRPH). The SSRPH is a 5-item measure using a 4-point Likert scale (0 = strongly disagree, 3 = strongly agree) to assess perceived public stigma. Higher scores indicate greater perceived stigma. The SSRPH showed good internal consistency (Cronbach's *a*=0.74),[24] and good construct validity, with confirmatory factor analysis supporting a single-factor structure and excellent model fit (χ^2=6.8, *df*=5, *p*=0.24; CFI=0.975; TLI=0.926; RMSEA=0.048).[25]

Section E utilised the Multidimensional Scale of Perceived Social Support (MSPSS) to measure social support. The MSPSS is a 12-item instrument measuring perceived social support, using a 7-point Likert scale (1= very strongly disagree, 7= very strongly agree).[26] The MSPSS displayed excellent internal consistency (Cronbach's *a*=0.938) and demonstrated good construct validity, with confirmatory factor analysis supporting the three-factor structure and showing acceptable to good model fit (RMSEA=0.08, 90% CI:0.07-0.09; CFI=0.97; TLI=0.96).[27]

Prior to the main data collection, a pre-test was conducted among 21 Chinese international university students to assess the clarity, feasibility, and internal consistency of the questionnaire. The overall questionnaire demonstrated acceptable internal consistency (Cronbach's α=0.742). The Cronbach's α of ATSPPH-SF was 0.731, the Language Proficiency subscale of the SCAS-R was 0.728, SSOSH-3 was 0.970, SSRPH was 0.968, and MSPSS was 0.962.

Data Collection

Data were collected from April to May 2025 using self-administered paper-based questionnaires. The survey was conducted in the main library of the public university in Malaysia, a central study area frequently used by students. Participants were recruited using convenience sampling during regular academic hours. Chinese international students who appeared to meet the eligibility criteria were approached individually by the researcher and briefly informed about the purpose and procedures of the study. Before participation, students were provided with an information sheet explaining the study objectives, inclusion criteria, voluntary nature of participation, assurance of confidentiality, and the right to withdraw at any time without any consequences. Students who agreed to participate provided written informed consent before completing the questionnaire. The questionnaire was self-administered and completed anonymously in the library environment, and required approximately 10 minutes to complete. Completed questionnaires were returned directly to the researcher upon completion. A total of 288 questionnaires were distributed, of which 222 were fully completed and included in the final analysis, yielding a response rate of 77.1%. The data were used solely for research purposes and were kept strictly confidential, and only the research team had access to them.

Data Analysis

Data were analysed using IBM SPSS Statistics version 29.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarise the data. Categorical variables were presented as frequencies and percentages, whereas continuous variables were expressed as medians and interquartile ranges (IQRs) due to their non-normal distribution. Variables with a *p*-value <0.25 in the simple linear regression analysis were entered into the multiple linear regression model to identify significant predictors, statistical significance was set as $p<0.05$, using a 95%

confidence interval. Prior to model interpretation, the assumptions of multiple linear regression were assessed, including normality of residuals, linearity, homoscedasticity, and absence of multicollinearity.

RESULTS

Characteristics of Participants

Table I presents the characteristics of the participants. A total of 288 students were invited to participate, and 222 completed and returned the questionnaires, yielding a response rate of 77.1%. Participants' median age was 25 years (interquartile range [IQR]: 23-27). More than half of the participants were female (57.7%). Academic disciplines were classified into three major fields based on the International Standard Classification of Education (ISCED).[28] Most participants (75.2%) were from the humanities and social sciences field. In addition, two-thirds of the participants were postgraduate students (66.7%), and the majority were single (59.0%). The participants' median length of stay was 17 months (IQR: 12-24). Meanwhile, the median language proficiency score was 8 (IQR: 6-9). The median self-stigma score was 9 (IQR: 6-13), and the median public stigma score was 8.5 (IQR: 4-12). The median score for perceived social support was 68 (IQR: 61-73). Moreover, the median mental health help-seeking attitude score was 16.5 (IQR: 14-21).

Table I: Descriptive characteristics of the participants (n = 222)

Variables	n (%)
Age (years old)	25 (23–27)*
Gender	
Male	94 (42.3)
Female	128 (57.7)
Field of study	
Science and technology	28 (12.6)
Humanities and social sciences	167 (75.2)
Health and life sciences	27 (12.2)
Academic level	
Undergraduate	74 (33.3)
Postgraduate	148 (66.7)
Marital status	
Single	131 (59.0)
Non-single	91 (41.0)
Length of stay (months)	17 (12–24)*
Language proficiency (Language Proficiency Subscale of the SCAS-R score)	8 (6–9)*
Self-stigma (SSOSH score)	9 (6–13)*
Public stigma (SSRPH score)	8.5 (4–12)*
Social support (MSPSS score)	68 (61–73)*
Mental health help-seeking attitude (ATSPPH-SF score)	16.5 (14–21)*

Note: *Median (IQR)

Predictors Contributing to Mental Health Help-Seeking Attitudes of Participants

Table II presents the results of the simple and multiple linear regression analyses examining the predictors of mental health help-seeking attitude among participants. In the simple linear regression analysis, gender (p<0.05), students from the humanities and social sciences field compared with those from the science and technology field (p<0.05), self-stigma (p<0.001), public stigma (p<0.001), and social support (p<0.05) were significantly associated with mental health help-seeking attitude.

Table II: Results of simple and multiple linear regression analysis predictors of mental health help-seeking attitude

		Simple Linear Regression		Multiple Linear regression		
Variables		**Crude β (95% CI)[a]**	**p-value**	**Adjusted β (95% CI)[b]**	**p-value**	**VIF**
Age		0.100 (-0.026, 0.226)	0.12	0.148 (0.015, 0.281)	0.03*	1.492
Gender	Female vs. Male[c]	1.743 (0.630, 2.855)	0.002*	0.112 (-1.080, 1.304)	0.853	1.487
Field of study	ref = Science and technology[c]					
	Humanities and social sciences[c]	-1.868 (-3.563, -0.174)	0.031*	-0.706 (-2.287, 0.875)	0.380	1.996
	Health and life sciences[c]	-1.668 (-3.906, 0.570)	0.143	-2.533 (-4.776, -0.289)	0.027*	2.304
Academic level	Undergraduate vs. Postgraduate[c]	0.736 (-0.451, 1.924)	0.223	0.409 (-0.810, 1.629)	0.509	1.417
Marital status	Single vs. Non-single[c]	0.545 (-0.711, 1.802)	0.393			
Length of stay		0.036 (-0.018, 0.089)	0.190	-0.021 (-0.071, 0.030)	0.420	1.184
Language proficiency		-0.338 (-0.681, 0.004)	0.053	-0.018 (-0.375, 0.340)	0.923	1.449
Self-stigma		-0.572 (-0.710, -0.434)	<0.001*	-0.550 (-0.832, -0.267)	<0.001*	4.356
Public stigma		-0.390 (-0.506, -0.275)	<0.001*	-0.038 (-0.251, 0.175)	0.723	3.807
Social support		0.059 (0.002, 0.116)	0.044*	0.072 (0.017, 0.127)	0.011*	1.250

Notes: VIF = variance inflation factor; [a]Simple linear regression; [b]Multiple linear regression; [c]The reference category;R^2=0.291; *Adjusted* R^2=0.257; *significant at p<0.05

In the multiple linear regression analysis, age was identified as a significant positive predictor of mental health help-seeking attitude. For each one-year increase in age, the help-seeking attitude score increased by 0.148 points (adjusted β=0.148, 95% CI: 0.015 to 0.281, p=0.030). Compared with students from the science and technology field (reference group), those from the health and life sciences field had significantly lower help-seeking attitude scores (adjusted β=-2.533, 95% CI:-4.776 to -0.289, p=0.027). Self-stigma was a significant negative predictor of help-seeking attitude. Each one-unit increase in self-stigma score was associated with a 0.550-point decrease in help-seeking attitude score (adjusted β=-0.550, 95% CI:-0.832 to -0.267, p<0.001). Conversely,

social support was a significant positive predictor. Each one-unit increase in social support score was associated with a 0.072-point increase in help-seeking attitude score (adjusted β=0.072, 95% CI:0.017 to 0.127, =0.011). The final model explained 29.1% of the variance in mental health help-seeking attitude (R^2=0.291), and 25.7% after adjustment for the number of predictors (*Adjusted* R^2=0.257). Collinearity diagnostics indicated no multicollinearity issues among the variables (all VIFs <5).

DISCUSSION

In this study, participants demonstrated less positive mental health help-seeking attitudes. Comparable findings have been reported among university students in Türkiye,[6] and Malaysian university students, including both local and international students.[29] Developmentally, university students are at a transitional life stage characterized by increasing autonomy, independence, and identity formation. During this stage, seeking professional mental health services may be perceived as a sign of personal weakness, emotional instability, or reduced self-reliance.[30] These challenges may be further intensified among Chinese international university students studying in Malaysia. Besides academic pressures, international students are also required to adapt to a new sociocultural and educational environment while living away from their established family and social support systems. Many students may feel pressure to appear emotionally resilient and independent while studying abroad, particularly due to family expectations and financial investment associated with overseas education. Consequently, students may avoid expressing mental distress or seeking professional help to avoid worrying their families or being perceived as unable to cope with overseas life.[31] Furthermore, the Malaysian multicultural environment may also influence students' attitudes toward mental health help-seeking. Malaysia comprises of diverse ethnic and religious groups, and perceptions of mental health problems may vary across cultural contexts.[32] As a result, Chinese international students may experience uncertainty regarding how mental health issues are viewed within the local community and university environment. Limited interaction with local students, unfamiliarity with available mental health services, and concerns about cross-cultural communication may further discourage professional help-seeking.

Nevertheless, some previous studies have reported more positive help-seeking attitudes, such as among international students in the United States.[33] Differences in the accessibility of mental health services may explain this discrepancy. Compared with developed countries where mental health awareness campaigns, counselling services, and psychological support systems are more openly promoted and normalized, international students in Malaysia may encounter fewer opportunities for open mental health discussions and less familiarity with professional psychological services.[34] These differences may influence students' help-seeking attitudes and their willingness to access professional mental health support.

Regarding the factors associated with mental health help-seeking attitudes in this study, greater self-stigma and students from the health and life sciences field compared with students from the science and technology field were the negative predictors, and older age and higher level of social support were the positive predictors of mental health help-seeking attitudes.

For age, the result is consistent with previous studies among students and public population.[35,36] Previous studies have suggested that, as individuals grow older, they become more aware of mental health services.[37] Older individuals are also more likely to have had prior exposure to mental health services, which may reduce fear, uncertainty, or misconceptions regarding professional psychological help-seeking. University students are still in the stage of forming their personality and concepts. Compared with younger people, older individuals tend to have more established beliefs and attitudes. The different opinions of others have less influence on older people's decision-making, which also make older individuals more willing to seek professional mental health help.[38]

For students from health and life sciences field compared with students from the science and technology field a

more negative mental health help-seeking attitude was observed. This finding differs from the common finding that students in health-related disciplines tend to demonstrate more positive attitudes. One possible explanation is that students from health-related disciplines may perceive themselves as having greater knowledge about mental health problems, which could lead to overconfidence in self-management and a reduced perceived need for professional mental health support.[39] Another explanation is that students in health-related fields may experience greater concern about professional image or career implications associated with mental health problems, which may discourage help-seeking attitudes.[40]

For self-stigma, the result is consistent with findings reported among teachers and nursing students.[24,41] In cultures that value autonomy and self-reliance, seeking professional mental health help may be perceived as a sign of weakness or personal failure.[42] Individuals with high self-stigma often internalise such stereotypes, resulting in feelings of shame, embarrassment, and reluctance to seek mental health help.[24] Among Chinese international students, traditional cultural values may further strengthen the influence of self-stigma on help-seeking attitudes. In Chinese culture, the concept of "saving face" is highly valued, and mental health problems may be perceived as bringing shame not only to the individual but also to the family.[43] As a result, students may avoid disclosing emotional difficulties or seeking professional mental health help in order to maintain personal and family honour.[44] In addition, the host-country environment may also contribute to self-stigma and reluctance to seek professional help. Collectivist cultural norms are widely present within Malaysian society, where such norms encourage emotional restraint and endurance of personal distress rather than openly expressing mental problems.[45] As Chinese international university students adapt to the Malaysian sociocultural environment, they may become increasingly aware of the collectivist cultural norms that emphasise social harmony and concern for others' opinions. This may contribute to concerns about social judgement and loss of social image, thereby discouraging professional mental health help-seeking. Therefore, universities may consider implementing culturally sensitive and inclusive mental health promotion strategies, such as establishing campus peer-support groups and support circles, allowing students with prior experiences of professional mental health service utilisation to share their experiences may help normalise help-seeking behaviours and improve mental health help-seeking attitudes among Chinese international university students in Malaysia.[46]

For social support, the result is consistent with previous studies among both international students and university students.[47,48] Individuals typically turn first to family, friends, or other social networks when facing mental health challenges. These networks can provide emotional comfort, share relevant information, and reduce mental health-related stigma, thereby making professional mental health help-seeking more acceptable.[49] According to the stress-buffering model, social support mitigates the negative effects of stress by providing emotional and practical resources. Support from friends, family, or significant others can lessen the emotional burden of stigma and normalise help-seeking behaviours, thereby increasing individuals' acceptance of and confidence in seeking professional psychological assistance.[50] Conversely, a contrasting study among older adults reported a negative association between social support and mental health help-seeking attitudes, suggesting that individuals with strong informal support may also rely on family or community networks instead of professional services.[51] Therefore, universities should strengthen campus-based support systems while also emphasising the unique and irreplaceable role of professional mental health services. Strategies such as integrating mental health education into university orientation programmes and providing accessible counselling services may help improve mental health help-seeking attitudes among international students.[52]

Despite yielding valuable insights, this study has several limitations. First, the use of convenience sampling restricts the generalizability of the findings. Second, the scope of the sample, restricted to Chinese international students at one of the public universities, may not represent the broader population of Chinese international

university students in Malaysia. Third, the use of an English-only questionnaire may still have introduced potential comprehension bias. Although all participants were required to provide proof of English proficiency equivalent to at least IELTS 6.0 prior to admission, as non-native English speakers, some participants may not have fully understood certain questionnaire items or expressions, which could have affected the accuracy of their responses. Fourth, social desirability bias may have influenced participants' responses to the questionnaire. Participants may have tended to provide socially acceptable answers, which could have resulted in underreporting of stigma and overreporting of positive help-seeking attitudes.

Based on the findings and limitations of this study, several directions for future research are recommended. Future studies could compare Chinese international students with international students from other cultural backgrounds to examine how cultural differences influence help-seeking attitudes. Qualitative studies are also recommended to obtain more in-depth perspectives. Moreover, future studies could evaluate the effectiveness of targeted interventions, such as bilingual mental health promotion programmes and campus-based peer-support initiatives, and examine how these interventions influence mental health help-seeking attitudes among Chinese international university students.

CONCLUSION

This cross-sectional study among Chinese international university students in Malaysia revealed generally less positive mental health help-seeking attitudes. Older age, lower self-stigma, and higher social support emerged as significant positive predictors of mental health help-seeking attitudes. In contrast, being a student from the health and life sciences field (compared with the science and technology field) was a significant negative predictor. These findings advance the understanding of mental health help-seeking attitudes among international student populations, highlighting the importance of both intrapersonal and contextual influences. From a practical perspective, the results suggest several targeted strategies: strengthening social support systems and improving culturally responsive mental health services. Universities may also consider implementing early mental health screening and peer support networks to foster more positive attitudes toward seeking help.

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ORIGINAL ARTICLE

Characteristics, Risk Factors, and Maternal-Foetal Outcomes of Pregnant Women with COVID-19 Admitted to Hospital Sungai Buloh, Malaysia: A Single-Centre Retrospective Cohort Study

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ABSTRACT

INTRODUCTION: Malaysia was hit by one of the biggest waves of COVID-19 in year 2021, the worst-case morbidity and mortality since the pandemic started in 2020. Hospital Sungai Buloh (HSB), Selangor was the first hospital designed to treat COVID-19 cases only and was the referral centre for COVID-19 in the Klang Valley, hence all pregnant patients with COVID-19 in Selangor was referred here for treatment and care. This study aims to describe the characteristics and outcomes of pregnant women with COVID-19 admitted to HSB, and to identify the risk factors associated with severe outcomes. **MATERIALS AND METHODS:** This study is a single centre, retrospective cohort study whereby electronic records of pregnant patients with COVID-19 admitted to HSB from May to August 2021 were searched and data on sociodemographic and clinical characteristics, management, complication and outcomes of the mother and foetal were retrieved. **RESULTS:** Out of 282, 66 women had severe covid-19 (stage 4 &5) and 216 had non-severe COVID-19 (stage 1-3). We found that pregnant patients with severe COVID-19 infection are more likely to be obese, have lower absolute lymphocyte counts and higher C-reactive protein (>50) on admission, and higher day of illness on admission. **CONCLUSION:** Severe COVID-19 resulted in longer hospital stay, associated with higher disease related complications and adverse maternal and foetal outcomes. However, vertical transmission is rare although possible in COVID-19. Our study provides a valuable local data from a single COVID-19 centre in Malaysia

Keywords
COVID-19, Pregnancy, Maternal-fetal outcomes, Risk factors, Retrospective cohort study

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INTRODUCTION

Hospital Sungai Buloh (HSB) was the referral centre for COVID-19 in the Klang Valley, Selangor,Malaysia at the start of the pandemic. Between March to June 2021, 3396 pregnant women were diagnosed with COVID-19 in Malaysia and the number continued to rise.[1] Approximately 3-5.5% of these women required intensive care unit (ICU) admissions and as of 9th Aug 2021, a total of 70 maternal deaths due to COVID-19 had been reported in Malaysia.[2] Pregnant women are at slightly increased risk of becoming having severe illness when infected with COVID-19, as physiological adaptations during pregnancy may predispose them to a more severe course of pneumonia.[3]

Previous studies have identified obesity, pre-existing diabetes, and other cardiometabolic comorbidities as important risk factors for severe COVID-19 in pregnancy. Ethnic disparities in disease severity have also been reported globally, suggesting the influence of both biological and socio-economic factors.[4] Understanding the characteristics, risk factors, and outcomes can facilitate optimal resource allocation to address COVID-19-related concerns effectively. Despite numerous studies examining the effects of COVID-19 on maternal and neonatal outcomes,[5] there remains a scarcity of data from Malaysia on these aspects. This study aims to describe and compare the characteristics and outcomes of pregnant women with

COVID-19 admitted to HSB, and to identify risk factors associated with severe disease.

MATERIALS AND METHODS

This was a single-centre retrospective cohort study involving pregnant women with COVID-19 who were admitted to HSB between May and August 2021. Pregnant patients with SARS-CoV-2 infection confirmed by either polymerase chain reaction (PCR) testing or a rapid test kit (RTK) during this period were included. Data on sociodemographic characteristics, clinical variables, laboratory parameters, management, complication as well as pregnancy and neonatal outcomes were extracted from electronic records. Clinical severity of COVID-19 is as in Appendix 1. Clinical deterioration was defined as an increase in the World Health Organization (WHO) ordinal scale during hospitalisation (Appendix 2). Regarding foetal outcomes, miscarriage was defined as pregnancy loss at ≤20 weeks of gestation, while stillbirth was defined as pregnancy loss occurring after 20 weeks of gestation. Sample size was determined using the events per variable (EPV) principle. With an EPV of ≥10 and four predictors in the model, at least 40 pregnant women with severe COVID-19 were required.[6,7]

Statistical analysis

Variables were summarised as mean (SD) or median (IQR) for continuous data and frequencies (%) for categorical data. Clinically relevant variables were compared between non-severe and severe COVID-19 groups using independent t-test or Mann–Whitney U test for continuous variables and chi-square or Fisher's exact test for categorical variables.

Variables applicable only to patients with severe COVID-19 such as markers of disease progression during hospitalisation, oxygen therapy requirements, intensive care utilisation, and selected laboratory biomarkers measured during clinical deterioration were analysed descriptively. The pattern of missing data was assessed using Little's test for Missing Completely at Random (MCAR). A non-significant result (p>0.05) indicated consistency with the MCAR assumption.

To identify factors associated with severe COVID-19, multivariable logistic regression analysis was performed. Stepwise variable selection was applied to identify variables for inclusion in the final model. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were reported to describe the associations between potential risk factors and severe COVID-19 outcomes. The discriminative performance of selected variables and the final multivariable model in identifying severe COVID-19 was evaluated using receiver operating characteristic (ROC) curve analysis.

Complete case analysis was used for the multivariable regression model. To assess the potential impact of exclusions due to missing data, baseline characteristics of participants included in the final regression model were compared with those excluded because of missing data. All statistical analyses were performed using Stata version 16,[8] and a two-sided p value <0.05 was considered statistically significant.

RESULTS

Sample Characteristics

A total of 282 pregnant patients admitted with COVID-19 to HSB from May to August 2021, out of which 66 (23.4%) were severe cases and 216 were non-severe. The mean age of all patients was 30.55 (5.53) with the average BMI of 28.21 (6.43) kg/m^2 (Table I). A total of 77.3% were Malays and the most common comorbidities were diabetes mellitus. Majority of the respondents were non-smokers and in third trimester with 37 as median week of gestation.

Characteristics by COVID-19 Severity

When comparing by severity status, severe patients were older, but the difference was not statistically significant. The percentage of patients with obesity was significantly higher in the severe group (p value=0.001).

The median gestation age at admission was lower among patients with severe COVID-19 A higher percentage of unvaccinated patients in the severe group (90.9%) compared to the non-severe group (81.0%) (p value= 0.026).

Patients with severe COVID-19 presented to hospital at day 6 of illness, compared to the non-severe patients who present at day 4 of illness (p value <0.001). Non-severe disease was defined as clinical stage 1-3 (needing no oxygen therapy), while severe disease comprised clinical stage 4-5 (pneumonia needing variable oxygen therapy). Out of 66 patients with severe COVID-19 (Stage 4 & 5), only 16 of them admitted initially with severe disease, whereas 50 of them came in with initial diagnosis of COVID-19 stage 1& 2 before becoming severely ill (Stage 4&5) afterwards (as depicted in table 1- stage on admission and table 3-highest stage achieved during hospitalisation).

Patients with severe COVID-19 had lower Absolute Lymphocyte Count (ALC) at admission, higher CRP and higher Neutrophil to Lymphocyte Ratio (NLR). About 45.9% of patients with severe COVID-19 has CRP of more than 50 mg/L at admission, compared to only 7.1% in the non-severe group (p value <0.001).

Clinical management and hospital course severe COVID-19 patients

Table II presents the clinical management, and hospital course of severe COVID-19 patients (n=66). More than half required ICU admission, occurred at a median of day 5 after hospitalisation and 9 days from illness onset with deterioration occurring around day 8 of illness.

Eight severe patients had positive blood culture. All of them were mechanically ventilated except for 1 patient who were just on NPO2 (she had CoNS). Meanwhile, among the mechanically ventilated, eleven had positive tracheal aspirate-9 had multi-resistant Acinetobacter baumannii, 1 Pseudomonas aeruginosa and 1 mixed growth.3

The median ICU stay of the patients was 11 days. Among severe cases, a substantial proportion required mechanical ventilation, while others received varying levels of oxygen support, including nasal prongs, face mask, and HFNC. In term of highest oxygen requirements among the patients with severe disease, 42.4% were mechanically ventilated, 33.3% received only NPO2, 13.7% received up to facemask oxygenation and 10.6% had up to HFNC. Median day of receiving oxygen support was 8 days and among the mechanically ventilated patients (n=28), median ventilation was 8 days. Mean D-dimer was highly elevated at 1198.5, however the mean ferritin was normal at 251.

Table I: Sociodemographic, Clinical, and Laboratory Characteristics at Admission and During Clinical Deterioration Among Pregnant Women with COVID-19 by Disease Severity

Variable	Total	Non-severe	Severe	P value
Age, years, mean (SD) (n=282)	30.55 (5.53)	30.20 (5.50)	31.70 (5.50)	0.054
Race				
Malay	218 (77.3%)	166 (76.9%)	52 (78.8%)	
Indian	14 (4.96%)	11 (5.1%)	3 (4.5%)	
Chinese	14 (4.96%)	12 (5.6%)	2 (3.0%)	0.930
Others	3 (1.06%)	2 (0.9%)	1 (1.5%)	
Non-Malaysian	33 (11.7%)	25 (11.6%)	8 (12.1%)	
BMI, mean (SD) (n=200)	28.21 (6.43)	27.34 (±5.90)	30.82 (7.27)	<0.001
Obesity	71 (25.2%)	46 (21.3%)	25 (37.9%)	0.007
Diabetes Mellitus	102 (36.2%)	77 (35.6%)	25 (37.9%)	0.740
Bronchial asthma	14 (5%)	10 (4.6%)	4 (6.1%)	0.640
Pulmonary disease	2 (0.7%)	2 (0.7%)	0 (0.0%)	0.430
Cardiac disease	1 (0.4%)	1 (0.5%)	0 (0.0%)	0.580
Renal disease	4 (1.4%)	4 (1.9%)	0 (0.0%)	0.270
Smoking status (n=157)				
Current	3 (1.9%)	0 (0%)	3 (5%)	0.040
Never	154 (98.1%)	91 (100%)	63 (95%)	
Vaccination status (n=192)				
Not vaccinated	162 (84.4%)	102 (81.0%)	60 (90.9%)	
One dose	17 (8.8%)	11 (8.7%)	6 (9.1%)	0.026
Two doses	13 (6.8%)	13 (10.3%)	0 (0.0%)	
Trimester (n=279)				
First trimester	7 (2.5%)	6 (2.8%)	1 (1.5%)	
Second trimester	15 (5.3%)	6 (2.8%)	9 (13.6%)	0.002
Third trimester	260 (92.2%)	204 (94.4%)	56 (84.8%)	
Gestation week	37 (4)	37 (2)	34 (7)	<0.001
Day of illness	4 (3)	4 (3)	6 (3)	<0.001
COVID-19 Stage at admission				
Stage 1	102 (36.2%)	98 (45.4%)	4 (6.1%)	
Stage 2	156 (55.3%)	112 (51.9%)	44 (66.7%)	
Stage 3	8 (2.8%)	6 (2.8%)	2 (3.0%)	<0.001
Stage 4A	14 (5%)	0 (0%)	14 (21.2%)	
Stage 5A	1 (0.4%)	0 (0%)	1 (1.5%)	
Stage 5B	1 (0.4%)	0 (0%)	1 (1.5%)	
ALC at admission (n=250)	1.38 (1.02- 1.78)	1.5 (1.15-1.93)	1.00 (0.79-1.29)	<0.001
NLR at admission (n=249)	4.15 (3.0-6.1	3.80 (2.73-5.2)	5.93 (4.85-7.3)	<0.001
CRP at admission, No (%), (n=230)				
≥ 50 mg/L	40 (17.4%)	12 (7.1%)	28 (45.9%)	<0.001
CRP at deterioration (n=69)	6.6 (4.7- 9.5)	3.35 (3.2-4.7)	7.80 (6-11)	<0.001
NLR at deterioration (n=69)	6.2 (3.7 – 9.1)	3.66 (3.1-4.4)	6.6 (4.9-9.7)	0.008
Highest creatinine (n=4)	154.5 (82.5- 243.5)	82.5 (58-107)	243.5 (202 -285)	0.120
Highest ALT (n=22)	157 (138- 356)	153 (127 - 433)	159 (140-323)	0.857

Note: Data are presented as median (Q1-Q3) unless stated. ALC: Absolute Lymphocyte Counts, NLR: Neutrophils to Lymphocyte Ratio, ALT: Alanine transaminase

Disease progression during hospitalisation and maternal–foetal outcomes

Among severe cases, dexamethasone was the most commonly used and only 7 patients received Tocilizumab, and none had Baricitinib. Antibiotic use was more frequent in severe than non-severe cases. Overall, in patients with severe COVID-19, most of them were in stage 4A and 5B.

Table II: Clinical management and hospital course among pregnant women with severe COVID-19 (n=66)

Variable	Statistics
Ferritin on deterioration (n=47)	251 (161-406)
D-dimer on deterioration (n=50)	1198.5 (848 -1614)
Highest level of oxygen requirement	
NP	22 (33.3%)
FM	9 (13.7%)
HFNC	7 (10.6%)
MV	28 (42.3%)
Total days on oxygen support (n=66)	8 (4-15)
Total days on HFNC (n=29)	2 (2-3)
Total days on MV (n=28)	8 (3 - 14.5)
Day of illness on deterioration into higher stage (n=59)	8 (7- 9)
ICU admission	35 (53%)
ICU length of stay (days) (n=35)	11 (6 -15)
Day of illness at ICU admission (n=36)	9 (7- 10)
Day of hospitalisation at ICU admission (n=35)	5 (3 - 6)
Positive blood culture (n=8)	
Acinetobacter baumanii (ACBM)	1 (12.5%)
Multi-drug resistant ACBM	3 (37.5%)
Coagulase Negative Staphylococcus	3 (37.5%)
Enterococcus faecium	1 (12.5%)
Positive tracheal aspirate culture (n=11)	
Group 1 beta lactamase pseudomonas	1 (9.1%)
Multi-drug resistant ACBM	9 (81.8%)
Mixed growth	1 (9.1%)

Note: Data are presented as median (Q1-Q3) or number (%), as appropriate. MV: Mechanical Ventilation, HFNC: High Flow Nasal Cannula, NP: Nasal Prongs, FM: Face Mask, O2: Oxygen, ICU: Intensive Care Unit

In terms of complications 50% had Pulmonary Embolism (PE) confirmed by Computed Tomography Pulmonary Angiography (CTPA) 25.8% had liver impairment, 6.1% had pneumothorax and pneumomediastinum, respectively. Only one patient needed Renal Replacement Therapy (RRT), had ACS and pericardial effusion respectively. A total of 40 (60.7%) patients with severe COVID-19 had Organizing Pneumonia (OP), based on CTPA and/or HRCT. A total of 13 (19.7%) patients had mild OP, 7 (10.6%) moderate OP and 20 (30.3%) had severe OP. Surprisingly, 4 (1.9%) patients with non-severe COVID-19 had OP reported on their CT scans.

Severe disease was significantly associated with prolonged hospitalisation and all maternal deaths occurred in the severe group. Among seven maternal death, their foetuses survived except for one stillbirth. In the non-severe group, two miscarriages in early pregnancy, the rest were delivered alive. Obstetric and neonatal outcomes also differed by disease severity.

Table III: Disease progression during hospitalisation and maternal–foetal outcomes

Variable	Total (n=282)	Non-severe (n=216)	Severe (n=66)	P value
Treatment received				
Dexamethasone	61 (21.6%)	6 (2.8%)	55 (83.3%)	
Antibiotics	82 (29.1%)	36 (16.7%)	46 (69.7%)	
Prednisolone	39 (13.8%)	0 (0%)	39 (59.1%)	
Methylprednisolone	38 (13.5%)	0 (0%)	38 (57.6%)	
Hydrocortisone	31 (11%)	1 (0.5%)	30 (45.5%)	
Tocilizumab	7 (2.5%)	0 (0%)	7 (10.6%)	
Highest COVID-19 stage reached				
Stage 1	85 (30.1%)	85 (39.4%)	-	
Stage 2	113 (40.1%)	113(52.3%)	-	
Stage 3	18 (6.4%)	18 (8.3%)	-	
Stage 4A	32 (11.3%)	-	32 (48.5%)	
Stage 5A	6 (2.1%)	-	6 (9.1%)	
Stage 5B	28 (9.9%)	-	28 (42.4%)	
Maternal Complications				
Needing RRT	1 (0.4%)	0 (0%)	1 (1.5%)	
Renal impairment	4 (1.4%)	1 (0.5%)	3 (4.5%)	
Liver impairment	21 (7.4%)	4 (1.9%)	17 (25.8%)	
Pneumothorax	4 (1.4%)	0 (0%)	4 (6.1%)	
Pneumomediastinum	4 (1.4%)	0 (0%)	4 (6.1%)	
Pulmonary embolism	35 (12.4%)	2 (0.9%)	33 (50%)	
Cardiac complications				
ACS	1 (0.4%)	0 (0%)	1 (1.5%)	
Pericardial Effusion	1 (0.4%)	0 (0%)	1 (1.5%)	
Organising pneumonia diagnosed on CTPA/HRCT	44 (15.6%)	4 (1.9%)	40 (60.6%)	
Mild	17 (6%)	4 (1.9%)	13 (19.7%)	
Moderate	7 (2.5%)	0 (0%)	7 (10.6%)	
Severe	20 (7.1%)	0 (0%)	20 (30.3%)	
Total days of hospitalisation, median (Q1-Q3)	8 (6-10)	7 (5.5-8.5)	16 (9-21)	<0.001
Obstetric and foetal outcomes				
Maternal outcome (n=282)				<0.001
Alive	275 (97.5%)	216 (100%)	59 (89.4%)	
Death	7(2.5%)	0 (0%)	7 (10.6%)	
Mode of delivery (n=160)				0.020
Vaginal delivery	35 (21.9%)	31 (26.5%)	4 (9.3%)	
LSCS	125 (78.1%)	86 (73.5%)	39 (90.7%)	
Apgar score, median (Q1-Q3) (n=155)	9 (9-9)	9 (9 – 9)	9 (4.5-9)	<0.001
Gestational age at birth, week, median (Q1-Q3) (n=165)	38 (37-39)	38 (37 - 39)	37 (34-38)	<0.001
Foetal birthweight, kg, mean (SD) (n=153)	2.82 (0.58)	2.89 (0.53)	2.61 (0.68)	0.058
Foetal death (n=212)				
Miscarriage	2 (0.9%)	2 (1.3%)	0 (0%)	
Stillbirth	1 (0.5%)	0 (0%)	1 (1.6%)	
Alive	209 (98.6%)	148 (98.7%)	61 (98.4%)	
Foetal COVID status (n=151)				
Positive	1 (0.6%)	0 (0%)	1 (2.6%)	

Women with severe COVID-19 were more likely to undergo caesarean delivery (p=0.020) and delivered at a significantly earlier gestational age (p<0.001). Neonates born to mothers with severe disease had significantly lower Apgar scores (p<0.001).

Obstetric and neonatal outcomes also differed by disease severity. Women with severe COVID-19 were significantly more likely to undergo caesarean delivery and delivered at a significantly earlier gestational age. Neonates born to mothers with severe disease had significantly lower Apgar scores (p<0.001). Birthweight tended to be lower among severe cases, although this difference did not reach statistical significance.

Table IV : Risk factors for severe COVID-19 in pregnant women (n=159)

Variable	Adjusted OR (95% CI)	SE	z	P value
BMI	1.12 (1.02, 1.22)	0.05	2.33	0.020
CRP ≥50 mg/L at admission	16.96 (3.20, 89.8)	14.42	3.33	0.001
Day of Illness at admission	1.30 (1.05, 1.61)	0.14	2.45	0.014
ALC on admission	0.04 (0.01, 0.22)	0.04	-3.75	<0.001
Vaccination status (yes)	0.24 (0.04, 1.51)	0.22	-1.53	0.127

Note: Adjusted odds ratios were obtained from multivariable logistic regression analysis

Risk factors for severe COVID-19 in pregnant women

Complete case analysis approach was used for multivariable logistic regression in determining the risk factors for severe COVID-19. Five variables were chosen by stepwise method to include in final model. After excluding participants with missing data in any of the variables included in the regression model, 159 participants were retained for the multivariable analysis.

The proportions of data for key variables not included in the regression model were as follows: BMI (21%), vaccination status (17%), day of illness (44%), CRP (31%), and ALC (36%). Characteristics of participants included in and excluded from the multivariable analysis due to missing data were compared. No statistically significant differences were observed for the key factors included in the final model, suggesting that exclusion due to missing data was unlikely to introduce substantial bias. In addition, a non-significant result (p>0.05) of Little's test for Missing Completely at Random (MCAR) indicating that the missing data were consistent with the MCAR assumption.

As shown in Table IV, individuals with a higher BMI were more likely to experience severe COVID-19. Those with a C-reactive protein (CRP) level above 50 were 17 times more likely to develop severe outcomes. Each additional day of illness increased the likelihood of severe outcomes by 30%. Conversely, those with a higher ALC at admission were less likely to develop severe outcomes. Vaccinated pregnant women had reduced odds of developing severe COVID-19, although this association did not reach statistically significant. The area under ROC curve of the regression model was 0.897.

DISCUSSION

One of the significant findings of our study was that the patients with severe disease had a higher BMI compared to the non-severe group. Higher BMI was significantly associated with severe COVID-19 in pregnancy,[9,10] likely reflecting the combined effects of obesity-related chronic inflammation, impaired respiratory mechanics, increased thrombotic risk, and clustering of metabolic comorbidities. Our finding regarding obesity is consistent with the study by Knight et al.[11]

More than 80% of pregnant patients were unvaccinated, particularly among those with severe disease. As pregnant women were excluded from initial COVID-19 vaccine clinical trials, there were no clear early guidelines regarding the safety of COVID-19 vaccination during pregnancy. Consequently, a high proportion of pregnant women remained unvaccinated. In Malaysia, pregnant women at that time were generally advised to defer vaccination until the second trimester or, if already in the third trimester, to postpone vaccination until after delivery, which likely contributed to the low vaccination uptake observed.

Subsequently, multiple studies demonstrated that maternal COVID-19 vaccination has no adverse effects on pregnancy outcomes, and that the benefits of vaccination outweigh potential risks. Vaccination during pregnancy was later recommended by the WHO, the Centres for Disease Control and Prevention (CDC), and major international guidelines, including those from the Royal College of Obstetricians and Gynaecologists

(RCOG), regardless of gestational age.[12,13] In our study, although vaccination appeared to be protective against severe COVID-19, this association did not statistically significance, possibly due to the limited number of vaccinated patients during the study period.

The median day of clinical deterioration occurred on day 8 of illness. This finding is consistent with previous studies describing deterioration patterns in COVID-19, in which the highest risk period occurs between days 5 and 10, with severe disease commonly developing after day 8.[14,15] This highlights the importance of close monitoring for clinical deterioration from day 5 onwards in symptomatic patients with risk factors.

Viral infections are generally associated with a reduction in total lymphocyte count, resulting in lymphopenia, which is a well-recognised feature of COVID-19 infection. Conversely, the NLR increases in states of infection, inflammation, and sepsis. Previous data during the COVID-19 pandemic have identified laboratory markers associated with increased disease severity and mortality, including lymphopenia, neutrophilia, and elevated serum ALT, AST, LDH, CRP, and ferritin levels.[16,17,18] In our study, severe COVID-19 patients had lower ALC, higher NLR, and higher CRP levels (>50 mg/L) on admission. Throughout their illness, severe patients demonstrated lower ALC, higher NLR, and elevated CRP levels compared to those with non-severe disease. However, ferritin levels were found to be normal despite severe disease. This is likely because ferritin is an unreliable biomarker of hyperinflammation in pregnancy due to physiological iron depletion, hepcidin suppression, immune modulation, and plasma volume expansion, resulting in lower ferritin levels even in clinically severe disease. These findings are supported by other international studies.[19,20]

Severe COVID-19 is known to be associated with respiratory failure and acute respiratory distress syndrome (ARDS).[21] In our study, 42% of patients with severe disease required mechanical ventilation, pulmonary embolism (PE) occurred in 50% of patients with severe COVID-19, while 61% developed organising pneumonia and 6% developed pneumothorax or pneumomediastinum. Given the synergistic prothrombotic effects of pregnancy and COVID-19, all severe disease patients underwent CTPA, which may partly explain the exceptionally high rate of PE detection. In addition to heightened diagnostic surveillance, the high prevalence of PE likely reflects combined hypercoagulability from pregnancy and SARS-CoV-2–induced endothelial injury, compounded by critical illness and suboptimal thromboprophylaxis early in the pandemic.

Patients admitted to the ICU were more likely to develop complications compared to non-ICU patients. Liver impairment was also common, with 26% of patients demonstrating elevated liver enzymes. Elevated ALT is recognised as a biochemical marker associated with severe COVID-19. Notably, four patients in the non-severe group (category 3) had organising pneumonia detected incidentally on CT imaging. This aligns with previous study, which reported that 74.5% of patients with organising pneumonia were in the non-severe group, while 25.5% were in the severe group.[22] Patients with severe disease demonstrated more extensive consolidations and involvement of multiple lobes, resulting in greater residual lung lesions on follow-up CT scans. This may explain the incidental detection of organising pneumonia in the non-severe group in our study.

Only eight patients with severe COVID-19 had positive blood cultures, three of which grew coagulase-negative staphylococci, likely representing skin contamination. Four patients had *Acinetobacter baumannii* bacteraemia, consistent with opportunistic infection in critically ill patients. Among 28 intubated patients with severe disease, 11 had positive tracheal aspirate cultures. These findings suggest that significant bacterial co-infection is relatively uncommon in COVID-19.

Our study also demonstrated that severe COVID-19 was associated with longer hospitalisation and more than half of patients with severe disease required ICU care. This highlights that severe disease not only causes significant morbidity but also results in increased healthcare utilisation and cost.

Majority of pregnant patients with severe COVID-19

received intravenous dexamethasone, followed by intravenous methylprednisolone, oral prednisolone, or intravenous hydrocortisone. A small number of patients received tocilizumab, while none received baricitinib, as it was not included in the Malaysian COVID-19 treatment guidelines at the time. The guidelines recommended oral prednisolone or intravenous hydrocortisone for pregnant patients who did not require corticosteroids for foetal lung maturation, explaining the high use of dexamethasone in our cohort. Despite limited safety data at the time, clinicians utilised tocilizumab as a rescue therapy in pregnant patients with severe disease refractory to steroids. Importantly, none of the infants born to mothers with severe COVID-19 had congenital anomalies.

Seven pregnant women with severe COVID-19 died; one of these cases was associated with stillbirth, while the remaining foetuses survived following emergency lower segment caesarean section (LSCS). Severe disease was associated with delivery at a lower gestational age, lower birthweight, and lower Apgar scores. The majority of patients underwent LSCS, largely due to the lack of negative-pressure ventilation in labour rooms. Although vaginal delivery is not contraindicated, the perceived increased risk of aerosol generation during the second stage of labour contributed to the preference for LSCS. Prematurity among neonates born to mothers with severe COVID-19 was largely iatrogenic for maternal indications. Lower birthweight and Apgar scores were likely multifactorial, predominantly driven by maternal hypoxia, placental vascular pathology (COVID-19 placentitis), thrombo-inflammation, endothelial dysfunction, placental microthrombosis, and reduced placental perfusion. Of the 209 live-born infants, only one tested positive for COVID-19, indicating that vertical transmission is possible but rare.

Several limitations should be considered when interpreting our findings. First, this was a single-centre study, which may limit generalisability. Secondly, missing data may have affected result accuracy. A complete-case analysis approach was used; although only 159 patients with complete data on BMI, day of illness, vaccination status, CRP, and ALC were included in multivariable logistic regression, Little's MCAR test suggested that missingness was random and unlikely to introduce systematic bias.[23] Comparisons between included and excluded patients showed no significant differences, supporting the MCAR assumption and the appropriateness of complete-case analysis. Finally, the relatively small sample size limits statistical power. Larger, multi-centre studies are needed to validate these findings and improve generalisability.

CONCLUSIONS

Severe COVID-19 in pregnancy is associated with identifiable and potentially modifiable risk factors, including higher BMI, lack of vaccination, and early laboratory markers of inflammation and immune dysregulation. Elevated CRP, lymphopenia, and increased NLR ratio, on admission were associated with disease severity and clinical deterioration. Patients with severe disease experienced higher rates of thrombotic and respiratory complications, prolonged hospitalisation, and adverse maternal and neonatal outcomes, including iatrogenic prematurity, lower birthweight, and reduced Apgar scores.

These findings have direct clinical implications. Early risk stratification using readily available clinical and laboratory parameters may enable timely escalation of care, targeted thromboprophylaxis, and closer foetal surveillance in high-risk pregnant patients.

At a policy level, our results support prioritisation of pregnant women particularly those with obesity or other risk factors for vaccination, early referral, and specialised care pathways during COVID-19 surges. Collectively, severe COVID-19 in pregnancy represents a distinct high -risk clinical entity, where early identification and preventive strategies can mitigate maternal morbidity, reduce healthcare burden, and improve perinatal outcomes.

Competing interests

The authors declare there is no competing interests.

INSTITUTIONAL REVIEW BOARD (ETHIC COMMITTEE)

We obtained approval from the Medical Research and Ethics Committee (MREC) and the Ministry of Health Malaysia (MOH), registered under NMRR ID-22-00994-OKI (IIR).

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CASE REPORT

Unfortunate Series of Fractured Cannula: Rare Venous Access Complications

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ABSTRACT

Cannulas are essential medical devices that are used daily for intravenous access, facilitating fluid and medication delivery. Although complications such as phlebitis, pain, and swelling at the cannulation site are commonly observed, cannula fractures remain a rare but potentially serious complication. This case series describes four incidents of fractured intravenous cannulas, occurring within 6 months at a tertiary centre without vascular surgery services, during its early operational phase. All cases were successfully managed through prompt identification and removal under local anaesthesia. Investigations revealed contributing factors, including inappropriate cannula size selection, prolonged dwell time, insertion in high-mobility areas, and patient-related anatomical challenges. These cases highlight the need for strict adherence to intravenous catheter protocols and proper cannula selection based on indication and duration. These case series aim to raise awareness among medical professionals and manufacturers about the associated risks, promote better prevention strategies, and drive improvements in cannula design and manufacturing, ultimately enhancing patient safety.

Keywords
venous access complication, cannula fracture, fluid therapy, intravenous catheter, patient safety

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INTRODUCTION

Intravenous cannulation (IVC) is a routine procedure for medication and fluid administration, yet it carries risks ranging from pain and phlebitis to extravasation. Rarely, serious complications such as cannula fracture may occur, posing risks of embolization and tissue injury. The incidence of such fractures ranges from 0%, and 2.1%[1], often underreported due to its rarity.

Because this complication is uncommon, it may not be recognised early. In many instances, the intravenous cannula appears externally intact even when the patient complains of discomfort, and in the absence of obvious signs such as extravasation, swelling, or phlebitis, healthcare providers may assume the device is functioning normally. However, a fractured cannula tip retained within the vein can lead to serious sequelae, including tissue damage, vasculitis, migration, or embolization.[2]

Mechanically, catheter fractures may result from excessive torque, repeated flexion at the insertion site, forceful advancement against resistance, or damage from needle reinsertion.[3] Material factors include polymer degradation, loss of tensile strength, and poor bonding between the hub and the catheter shaft.[3,4] Manufacturing defects and extended cannula dwell time further increase risk.[5,6]

This case series described four cases of fractured intravenous cannulas managed in a tertiary centre without vascular access services, over 6 months, aiming to raise awareness of this rare but preventable complication.

CASE PRESENTATIONS

CASE 1

A 45-year-old woman with a BMI of 35 kgm^2 presented with giddiness and vomiting. An 18-gauge cannula was inserted into the right antecubital fossa for hydration and medication at the emergency department. On the sixth day of admission, prior to discharge, the staff nurse discovered that the catheter had fractured when the

cannula was removed. This was further confirmed by bedside ultrasound and plain radiography of the right upper limb (Figure 1). Consequently, the patient underwent vascular exploration under local analgesia, and the fractured component was successfully retrieved (Figure 2). The procedure and recovery process were uneventful.

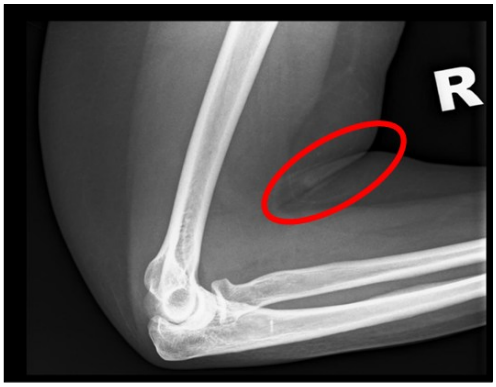

Figure 1: Radiograph of the right elbow in lateral view. An elongated hyperdense foreign body was observed in the superficial layer of the right antecubital fossa.

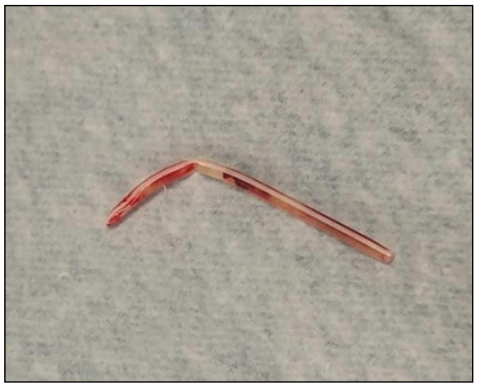

Figure 2: The retrieved fractured catheter

CASE 2

A 45-year-old male admitted for wound debridement had an 18-gauge cannula inserted in the left antecubital fossa for antibiotic therapy. After four days, the team decided to remove this peripheral line and replace it with a peripherally inserted central catheter (PICC) for long-term antibiotic administration. During the removal of the 18-gauge cannula, the staff nurse discovered that the catheter had fractured, and a segment was retained in the vein. The fragment was subsequently removed through ultrasound-guided incision and exploration under local analgesia.

CASE 3

A 61-year-old male with community-acquired pneumonia received intravenous antibiotics through a 20-gauge right antecubital fossa cannula. The same cannula remained in place for more than four days and continued to be used as it appeared externally intact, with no signs of complication. However, on the sixth day of insertion, the cannula started leaking and was removed. Upon removal, it was noted that its tip had fractured and remained inside the vein. The fractured segment was not visible on elbow radiography. A CT scan of the right upper limb revealed an elongated hyperdense structure, partly in the subcutaneous tissue and partly within the superficial vein, consistent with a fractured catheter fragment (Figure 3). The fragment was successfully removed via ultrasound-guided incision and exploration under local analgesia.

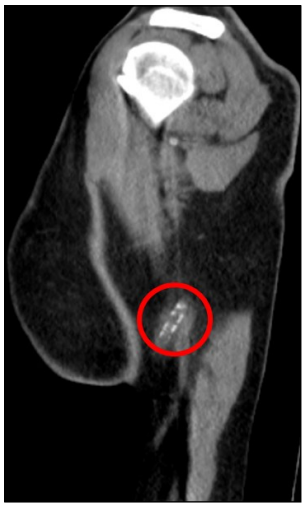

Figure 3: Elongated hyperdense structure partly in the superficial vein and partly in subcutaneous tissue representing a fractured catheter fragment.

CASE 4

A 65-year-old man was admitted for septic shock secondary to community-acquired pneumonia. Intravenous inotrope was required, but as peripheral venous access was difficult, a standard 16-gauge peripheral intravenous cannula, which is normally inserted in the upper limb, was placed in the right femoral region due to poor peripheral veins. After the cannula was used for initial inotrope administration, a more secure central venous catheter was subsequently attempted. During the

removal of the earlier cannula at the femoral site on the same day of insertion, it was discovered that the cannula had fractured from the hub. Radiography of the pelvis and femur did not visualize the fragment due to vascular calcifications. Targeted ultrasound of the right femoral region revealed a 2.3 cm tubular structure in the superficial subcutaneous tissue, parallel to the femoral vessel, with its most superficial point 0.2 cm below the surface (Figure 4). The fractured fragment was removed at the bedside under local anaesthesia.

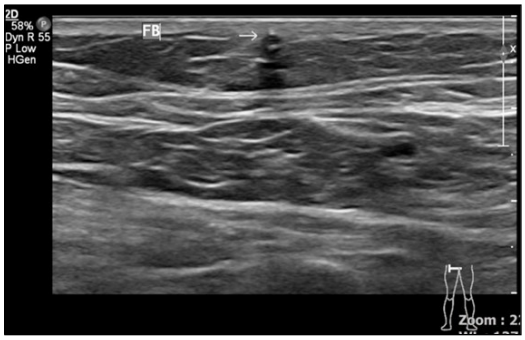

Figure 4: Targeted ultrasound over the right femoral region reveals a tubular-walled structure (white arrow) in the superficial subcutaneous tissue inthe right femoral region, located parallel to the femoral vein below.

DISCUSSION

Peripheral IVC is generally safe but carries the risk of rare complications, such as cannula fractures. While most literature focuses on common issues like thrombophlebitis and extravasation, cannula fractures are underreported, emphasizing the need for greater awareness.[7]

In managing these incidents, early identification and diagnosis were achieved through clinical examination and radiological confirmation, using X-ray, ultrasound, or computed tomography (CT) to detect the fractured cannula. In situations where the fractured cannula is not visible on radiograph or has potentially migrated to deeper tissues or embolized into central vessels, the use of a tourniquet is recommended to prevent embolization.[8] The fractured fragment is commonly embolized proximally to the central venous system; however, distal embolization can also occur.[9] In this case series, none of the broken cannulas had migrated.

Root cause analyses were conducted for all four cases, revealing several contributing factors. Cannulations were performed by experienced medical officers and nurses. Each successful insertion was documented as a single attempt at the respective site for that particular patient. In Case 4, multiple failed attempts at other sites preceded the final insertion at the femoral region; however, the femoral cannulation itself was achieved in a single attempt. Despite being classified as single attempts, subtle manipulations such as partial retraction followed by reinsertion of the needle to correct an initial malposition may have damaged the inner plastic liner.[10] Most peripheral intravenous cannulas are made of flexible polymers such as polytetrafluoroethylene or polyurethane, which can be mechanically weakened when the introducer needle is reinserted or adjusted within the catheter. Such manoeuvres may cause micro-tears or partial transection of the catheter wall, predisposing it to fracture during subsequent use or removal.[10,11] Hence, adjustment of the introducer needle within an already advanced plastic cannula should be strictly avoided.

Prolonged cannula dwell time beyond the widely recommended 72 to 96 hours, as seen in Cases 1 and 3, may also have contributed to the complication. Extended use of a single intravenous cannula can result in material fatigue[6], which weakens the polymer structure and increases the likelihood of fracture during removal. Furthermore, failure to replace the cannula within this commonly practiced interval increases the risk of catheter-related infection.

Improper insertion site selection may also have contributed to the risk of catheter fracture. High-mobility areas such as the antecubital fossa (Cases 1-3) are subject to frequent flexion and insertion, leading to repeated micromotion and increased mechanical stress on the cannula.[12,13] In case 4, a standard peripheral intravenous cannula was inserted into the femoral region. The femoral site is not recommended for short peripheral cannulas because of its depth, movement, and proximity to major vessels. Using a short, rigid cannula designed for superficial veins at this deeper location likely increased bending and material stress, predisposing to fatigue and eventual breakage.[7] If femoral access is unavoidable, a catheter with greater tensile strength and flexibility, such

Table I: Summary of Key Clinical Details

Case	Age/ Gender	BMI (kgm^{-2})	Comorbidities	Cannula Gauge & Site	Cannula Brand	Duration Before Fracture	Difficulty During Insertion	Imaging	Removal Method
1	45/ Female	42	DM, hypertension	18G, right antecubital	Brand A	6 days	Nil	X-ray, US	Local exploration
2	45/ Male	24	Osteomyelitis of the left tibia	18G, left antecubital	Brand A	4 days	Nil	US	US-guided local exploration
3	61/ Male	30	DM, hypertension, ESRF	20G, right antecubital	Brand B	6 days	Nil	X-ray, CT scan	US-guided local exploration
4	65/ Male	29	DM, hypertension, ESRF	16G, right femoral	Brand B	<1 day	Multiple attempts at other sites	X-ray, US	Local exploration

(BMI: Body Mass Index; US: Ultrasound; G: gauge; DM: diabetes mellitus; ESRF: end-stage renal failure)

as an angiographic catheter, should be used, as these are designed to resist kinking and breakage. For safer practice, ultrasound guidance may be employed to facilitate accurate insertion and minimise unnecessary tissue trauma during access.

Patient-related factors such as obesity and vascular calcification may further increase the risk. Obesity presents anatomical and technical challenges by obscuring vascular landmarks and increasing insertion depth, while calcified vessels reduce vascular compliance, limiting the flexibility needed for safe catheter advancement and adjustment.[16,17] Across our series, all patients had chronic comorbidities, and two were classified as obese.

Another recurring theme was the absence of a formalized policy on intravenous cannula management, attributed to the hospital's early operational phase, as the incidents occurred within its first two years of operation. Comprehensive guidelines on cannula selection and insertion site have not yet been established. In response, the hospital introduced several measures, including clearer directives on proper technique, stricter adherence to usage duration, and regular intravenous line training for all staff, particularly new ones. Ultrasound-guided insertion is encouraged for patients with difficult access to reduce repeated attempts. The existing venous access care and monitoring protocol was reinforced after the first incident to heighten vigilance, but subtle complications such as catheter fracture may remain undetected, as the cannula can appear intact and patients remain asymptomatic. This highlights the limitation of routine inspection alone and reinforces the need for careful technique and prevention.

Two different brands of cannulas were involved in the reported incidents. In response, we contacted the manufacturing companies to inquire about the structural integrity. Rigorous tensile strength and leak testing were conducted, and confirmed that the devices complied with ISO 10555 standards for safety and quality. Following these incidents, another cannula brand was introduced to replace the previously used devices in the hospital. Since the adoption of improvement measures, no further incidents of cannula fractures have been reported, indicating the effectiveness of these interventions.

CONCLUSION

This case series emphasises the importance of addressing the rare but significant complication of cannula fracture. Learning from these cases, particularly the contributing factors and system gaps, supports ongoing staff education, encourages safer cannulation practices, and helps prevent similar events in the future.

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CASE REPORT

Complete Hydatidiform Mole and Co-Existing Foetus with Severe Maternal Thyrotoxicosis: A Case Report

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Keywords
Hydatidiform mole, complete hydatidiform mole with normal co-twin, CHMCF, twin molar pregnancy

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ABSTRACT

Twin molar pregnancy refers to the coexistence of a complete or partial hydatidiform mole alongside a foetus. A complete hydatidiform mole with co-existing foetus (CHMCF) is an exceptionally rare obstetric phenomenon, with an incidence of approximately 1 in 20,000 to 100,000 pregnancies. Owing to its rarity, no standardized management guidelines currently exist. We report a case of a 33-year-old woman, G5P4, diagnosed with CHMCF at 15 weeks gestation, who developed severe maternal thyrotoxicosis and rapid uterine enlargement necessitating termination of pregnancy for maternal safety. Following termination of pregnancy, she was monitored closely with β-hCG surveillance due to the potential risk of gestational trophoblastic neoplasia. This case highlights the diagnostic dilemma, as well as challenges of management and post-treatment surveillance in CHMCF. Early diagnosis and multidisciplinary care are essential for optimal maternal outcomes.

INTRODUCTION

Molar pregnancy (hydatidiform mole) occurs approximately 1-3 per 1,000 pregnancies and is classified into complete or partial hydatidiform mole. Complete hydatidiform mole occurs when an empty ovum fertilized by one sperm that duplicates its paternal genome or results from when one ovum is fertilized by two sperms. Consequently, no embryonic or foetal tissue develop. Suction curettage remains the mainstay of treatment.

In contrast, CHMCF refers to the coexistence of a complete hydatidiform mole alongside a foetus. CHMCF was first described by Luker in 1914, occurring in approximately 1 in 20,000 to 100,000 pregnancies and is more common than partial hydatidiform mole with a coexisting foetus (PHMCF).[1,2] In comparison, CHMCF has a higher risk of gestational trophoblastic neoplasia (GTN) with a possibility of live birth of 40-60%, while PHMCF has a high likelihood of miscarriage or intrauterine foetal death due to severe chromosomal abnormalities.[2,3,4] Owing to its rarity and lack of standardized guidelines, CHMCH presents considerable diagnostic and management challenges.

CASE REPORT

We report a very rare case of twin molar pregnancy of the CHMCF type in Malaysia. A 33-year-old woman (G5P4) presented at 10 weeks' gestation with vaginal spotting. An ultrasound showed a single viable foetus, which corresponded to her gestational age. She was discharged and treated as threatened miscarriage.

At 12 weeks gestation, she experienced hyperthyroid symptoms, primarily palpitations. Clinical assessment showed that the uterus was larger than dates, measuring approximately 18 weeks, with a doughy consistency. Ultrasonography showed a single viable foetus corresponding to 12 weeks' gestation and the presence of multiple hypoechoic cystic lesions within the placenta. The differential diagnoses included a partial mole, a molar pregnancy with co-existing normal twin, a singleton pregnancy with placental mesenchymal dysplasia, or an exaggerated placental site tumour. Her β-hCG level was 453,800 IU/L, exceeding the normal range for a singleton pregnancy between 9 and 12 weeks (25,700-288,000 IU/

L).[5] Her thyroid function was also raised with free T4 elevated at 44.3 pmol/L. Therefore, propylthiouracil at a dose of 50 mg twice daily was initiated.

At 15 weeks gestation, the ultrasound revealed a viable foetus with two distinctive placental morphologies: anteriorly to the foetus, there was a multicystic appearance of the placenta and the presence of another normal, homogenous placenta adjacent to it extending posteriorly (Figure 1). Bilateral theca lutein cysts were observed. These findings were aligned with the ultrasound findings of CHMCF, as reported in the case series by Giorgione et al. Because the molar placenta was located anteriorly, amniocentesis was not performed due to the risk of massive bleeding.

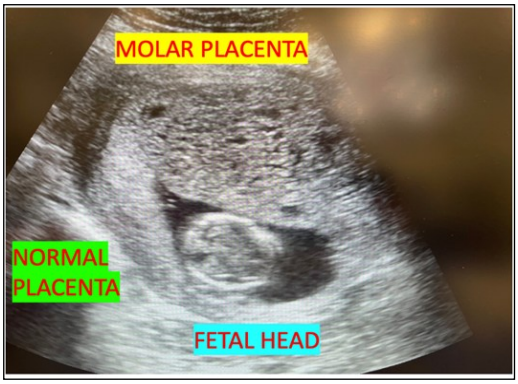

Figure 1: Transabdominal ultrasound at 15 weeks gestation demonstrating the viable fetus (F), the adjacent multicystic 'molar' placenta (MP), and the separate normal placenta (NP). Bilateral theca lutein cysts are also noted (not shown)."

Despite treatment, her clinical condition progressively deteriorated including palpitations, persistent vomiting, significant weight loss, reduced effort tolerance, and lower limb swelling. Clinical examination revealed fine tremors without overt signs of heart failure, and the gravid uterus had enlarged to a 24 weeks' size. Her β-hCG level exceeded 1,000,000 IU/L, and thyroid function tests confirmed severe thyrotoxicosis (TSH< 0.0005 mIU/L and free T4 at 42 pmol/L). Given the high risk of maternal deterioration, termination of pregnancy was advised after in-depth counselling and she was managed by a multidisciplinary team.

She underwent suction and curettage (S&C) under ultrasound guidance with cervical ripening facilitated by per vaginal misoprostol 400µg three hours prior to the procedure and was closely monitored for bleeding.

Intraoperatively, the foetus required piecemeal extraction because of the advanced gestational age using sponge forceps, followed by suction and curettage using a 10-mm Karman cannula. Oxytocin infusion was initiated at the beginning of the procedure to minimise the risk of excessive haemorrhage. The estimated blood loss was 1 litre, and she received one unit of packed red blood cells.

Post-procedural inspection revealed morphologically normal foetus with a normal placenta (Figure 2a) and vesicular tissue consistent with a molar pregnancy (Figure 2b), which was later confirmed by histopathological examination.

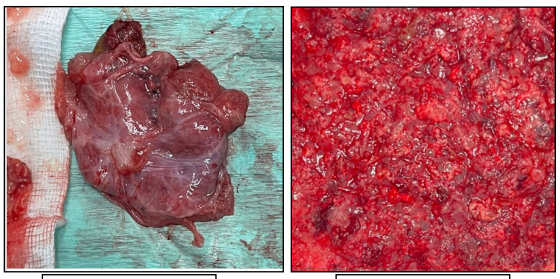

Figure 2a **Figure 2b**

Figure 2: Gross specimen of placental tissues removed during suction and curettage.
(a) Normal-appearing placental tissue with smooth chorionic surface and membranous remnants.
(b) Molar tissue showing multiple translucent vesicles of varying sizes, consistent with complete hydatidiform mole.

Initially, serial weekly β-hCG levels declined, but by the fourth week post-S&C, levels plateaued at 9,787 IU/L (Figure 3). She declined chemotherapy recommended by oncology team.

At the tenth week post-S&C, a new intrauterine lesion was detected on imaging, with a β-hCG level of 3,585 IU/L. She underwent a repeat S&C. Histopathologic examination (HPE) did not reveal any evidence of gestational trophoblastic neoplasia.

Following the procedure, her β-hCG levels declined and eventually normalised, and her thyrotoxic symptoms resolved, allowing for the gradual discontinuation of antithyroid medication.

DISCUSSION

CHMCF is a very rare and complex condition. Here, we explore the diagnostic dilemmas, prenatal testing options,

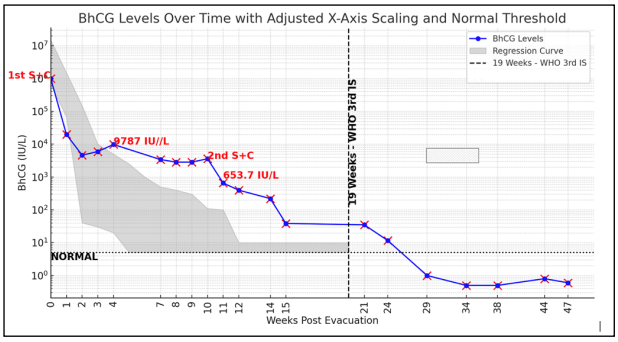

Figure 3: Post-evacuation **β-hCG trend** over time
(**X-axis:** weeks post-evacuation; **Y-axis:** β-hCG, IU/L; log scale).

DIAGNOSTIC DILEMMA

Ultrasound serves as a valuable tool for differentiating twin molar pregnancy from other placental abnormalities, such as placental mesenchymal dysplasia and exaggerated placental site reactions. Typically, the diagnosis of CHMCF is made between 12 and 14 weeks of gestation[4,7], through the concurrent visualisation of both a normal placenta and a molar placenta. Bilateral thecal lutein cysts are present in approximately one-quarter of CHMCF cases.[4,7]

β-hCG levels can aid in differentiation, as they have significantly elevated in twin molar pregnancies but only mildly increased in placental mesenchymal dysplasia.[8]

In cases where the diagnosis remains inconclusive, magnetic resonance imaging (MRI) can provide a further distinction between CHMCF and placental mesenchymal dysplasia.[9]

ROLE OF PRENATAL TESTING

Prenatal diagnosis using chorionic villous sampling, amniocentesis, or foetal cord sampling can help to differentiate between CHMCF and PHMCF. Cytogenetic analysis of CHMCF typically reveals a diploid karyotype of paternal origin in the molar placenta, while the coexisting foetus has a normal euploid karyotype. In contrast, cases of PHMCF often exhibit triploid or tetraploid karyotypes, with both the placenta and foetus being structurally abnormal and frequently resulting in miscarriage during the first trimester.

The potential role of cell-free DNA (cfDNA) in diagnosing CHMCF was described by Simon et al. in 2015. This non-invasive method can detect anomalous foetal haplotypes and paternal uniparental disomy, a key feature of a complete hydatidiform mole. As a result, cfDNA testing may reduce the need for invasive prenatal procedures, particularly in cases where the risk of bleeding is high.

EXPECTED PERINATAL OUTCOMES

CHMCF has a high risk of complications, including vaginal bleeding, pre-eclampsia, hyperthyroidism, GTN, miscarriage, preterm birth, and intrauterine foetal demise. The likelihood of achieving a live birth ranges from 40% to 60%.[2,3,4,10]

Historically, 50% to 70% of women underwent elective termination due to maternal complications.[4] However, recent retrospective cohort studies (2017 & 2024) have shown that only 8% to 23% of women opted for elective termination, while 8% to 16% underwent termination due to maternal complications.[2,10]

Maternal complication rates have remained comparable between old and recent studies. A systematic review and meta-analysis by Zilberman Sharon et al. reported an overall antenatal maternal complication rate of 80.8%, with 70% of women experiencing vaginal bleeding, 23.3% developing hyperthyroidism, and 14.3% being diagnosed with pre-eclampsia. Intrauterine foetal demise was reported in 40.1% of cases, and preterm birth accounted for 78% of live births. A French retrospective cohort study (2024) found that the mean gestational age at delivery was 32 ± 5 weeks.[10] The risk of developing GTN following a CHMCF pregnancy has remained consistently high, ranging from 27% to 46% across various studies.[2,4,10]

More favourable obstetric outcomes have been observed in pregnancies without maternal complications and with β-hCG levels below 400,000 IU/L, with a higher likelihood of achieving a live birth.[3] However, in this case, the patient experienced multiple severe complications, including vaginal bleeding, progressively worsening hyperthyroid symptoms, and extremely elevated β-hCG levels exceeding 1,000,000 IU/L. Hence, after in-depth

counselling with the couple, termination of pregnancy was carried out.

CHALLENGES IN TERMINATION OF PREGNANCY

Maternal stabilisation is a priority and requires a multidisciplinary approach. Surgical challenges include a tightly closed cervix and an enlarged uterus with the coexistence of a formed foetus and molar tissue, which increase the risk of torrential bleeding. This case also highlights the technical challenges of second-trimester uterine evacuation in CHMCF, where evacuation of a formed foetus followed by complete removal of extensive molar tissue requires meticulous surgical planning to minimise haemorrhage and reduce the risk of retained trophoblastic tissue. Cervical ripening immediately before uterine evacuation is considered a safe approach. Ultrasound guidance during the procedure is recommended to reduce the risk of uterine perforation and ensure complete evacuation. Suction and curettage (S&C) remains the preferred method of uterine evacuation unless foetal parts obstruct suction. The International Federation of Gynaecology and Obstetrics (FIGO) recommends initiating oxytocin at the start of the procedure to minimise bleeding risk. However, physicians need to balance the benefits of bleeding control with the potential risk of embolisation of molar tissue.

MONITORING POST-TERMINATION OF PREGNANCY

CHMCF has a higher risk of GTN (27-46%) compared with single molar pregnancies (15%).[2,4,10] The median time for β-hCG normalisation in CHMCF is 12-16 weeks[1], and 8 weeks for single molar pregnancies. Therefore, pre-existing β-hCG regression nomograms for single molar pregnancies are not representative of the β-hCG reduction trends in CHMCF, and the optimal timeframe for β-hCG surveillance in CHMCF remains uncertain. Rising or plateauing β-hCG levels may indicate the development of GTN. Most cases are FIGO low-risk (FIGO score 0 to 6) and respond well to first-line single-agent chemotherapy (methotrexate), with an overall cure rate of 91%.[10] For less chemo-sensitive GTN, combination chemotherapy with surgery achieves a 100% cure rate.[10]

CONCLUSION

CHMCF presents significant diagnostic challenges, often becoming more readily recognisable on ultrasound after 12 weeks' gestation, with maternal complications being more frequent and severe than in single molar pregnancies. S&C is challenging, requiring the piecemeal extraction of the normal foetus into smaller pieces to achieve complete evacuation of molar tissue.

β-hCG levels in CHMCF are markedly elevated and regress more slowly than in singleton molar pregnancies. The lack of a specific β-hCG regression nomogram further complicates post-termination monitoring and management. A multidisciplinary team approach is essential to optimise patient care.

CONFLICT OF INTEREST

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

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The authors would like to express their sincere appreciation to the patient for her permission to share this case. The authors acknowledge the Department of Obstetrics and Gynaecology and the Department of Pathology, Sultan Ahmad Shah Medical Centre, International Islamic University Malaysia (IIUM), for providing institutional support and resources that facilitated this work.

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CASE REPORT

Breast Cancer in Neurofibromatosis Type 1: Screening, Diagnostic and Therapeutic Challenges – A Case Report

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ABSTRACT

Neurofibromatosis type 1 (NF1) is a genetic disorder characterized by an increased risk of various tumours, including breast cancer, particularly in women under 50. This case report discusses a 47-year-old woman with NF1 who was diagnosed with metastatic invasive ductal carcinoma of the breast. She initially presented with respiratory symptoms, and subsequent clinical evaluation revealed a left breast ulcer and underlying mass, which the patient had attributed to NF1-related cutaneous changes. Histopathological examination confirmed bilateral hormone receptor positive, HER2-negative invasive breast carcinoma with metastatic involvement. Management options, including systemic therapy, were discussed within a multidisciplinary team, and the patient elected to proceed with endocrine therapy using Tamoxifen. This case highlights the clinical complexity of breast cancer detection in individuals with NF1, where overlapping benign cutaneous manifestations may influence symptoms interpretation. It also highlights the importance if early and regular breast cancer screening, beginning at age 30, using appropriate imaging modalities such as mammography and contrast-enhanced breast MRI. Individualised screening strategies patient education remain essential to optimise outcomes in this high-risk population.

Keywords
neurofibromatosis type 1, breast cancer, screening, early detection

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INTRODUCTION

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder that increases the risk of tumour formation. It is primarily marked by the growth of multiple neurofibromas along the peripheral nerves. The condition occurs in about 1 in 2,500 to 3,000 births.[1] While NF1 is primarily recognized for its dermatological and neurological manifestations, it also predisposes patients to various tumours, including breast cancer. Studies indicate that women with NF1 have a 3- to 5-fold higher risk of developing breast cancer, particularly those under the age of 50.[2] Diagnostic delays are common in NF1 patients due to overlapping skin lesions and atypical presentations that may obscure malignancies. Therefore, early detection through routine mammography, clinical breast examinations and patient education is essential for timely diagnosis and intervention.[3]

CASE PRESENTATION

A 47-year-old woman with a known history of neurofibromatosis type 1 (NF1), diagnosed during adolescence with generalised lesion, but not under regular follow-up, presented with respiratory symptoms and significant unintentional weight loss over five months. Further clinical assessment led to hospital admission,

where she was treated for acute pulmonary oedema related to a hypertensive emergency and subsequently followed up in a primary care setting.

Her symptoms persisted and comprehensive physical examination later revealed an ulcerated lesion in the lower outer quadrant of the left breast, associated with a firm underlying mass measuring approximately 3x3 cm (Figure 1). The patient had not previously reported this lesion, as it was initially perceived to be related to NF1-assocaited cutaneous changes. Additional history revealed that the lesion began as a pruritic area overlying a neurofibroma.

Breast imaging demonstrated a large irregular hypoechoic mass in the left breast at the 2:00–3:00 position, near the areola, measuring 2.3 x 4.2 x 5.8cm categorized as BIRADS 5. An additional irregular lesion was identified in the right breast at the 12 o'clock position, 2 cm from the nipple, measuring 0.7 x 1.0 x 0.7 cm, categorized as BIRADS 4A (Figure 2). Computed tomography of the thorax, abdomen and pelvis (CT TAP) revealed bilateral breast mass with metastases to the lung and bones.

Histopathological examination of biopsies from both breasts confirmed invasive breast carcinoma that was oestrogen receptor (ER)-positive, progesterone receptor (PR)-positive and HER2 negative. (Figure 3). The patient was managed through a multidisciplinary approach involving the breast and endocrine surgical team as well as the oncology team provided holistic management. Systemic treatment options, including palliative chemotherapy and endocrine therapy were discussed and the patient elected to proceed with endocrine therapy using Tamoxifen.

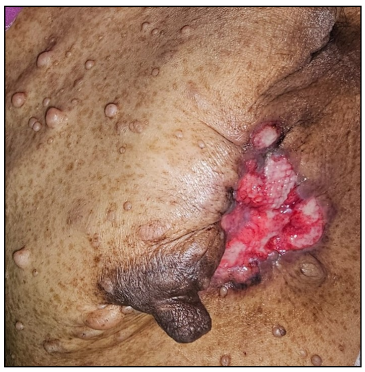

Figure 1: An irregular ulcer at the lower outer quadrant of the left breast, measuring 3x3cm with multiple cutaneous neurofibromas and café au lait spots.

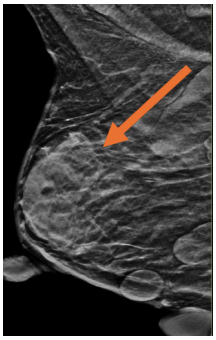

Figure 2: Mammogram of right breast shows large irregular hypoechoic mass seen at 2:00 -3:00 periareolar region, measuring 2.3x4.2x5.8cm (BIRADS 5)

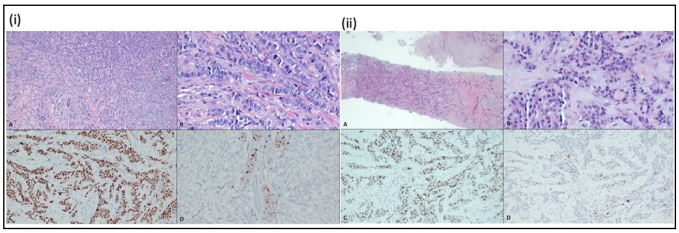

Figure 3(i and ii): Histological features of both right and left breast tumour biopsies are of same morphology. (A) The tumour is composed of malignant ductal cells arranged in cords and sheets (H&E, 10x). (B) The malignant cells show pleomorphic nuclei and inconspicuous nucleoli (H&E, 40x). The malignant cells are also positive for (C) Oestrogen receptor (IHC, 20x) and (D) Progesterone receptor (IHC, 20x).

DISCUSSION

NF1 is a hereditary illness marked by the formation of many benign tumours known as neurofibromas, as well as other symptoms such as café-au-lait spots and freckling. Approximately 50% of individuals impacted by NF1 exhibit a positive family history, whereas the other 50% are attributed to de novo mutations. Sporadic occurrences of NF1 are caused by spontaneous mutations in the NF1 gene, which can emerge in individuals with no family history of the condition.[4] In this case study, this patient has sporadic NF1, as no other family members have a similar skin condition.

People with NF1 have a heightened likelihood of developing cancerous tumours, including breast cancer, in comparison to those who do not have the condition. These malignancies can reduce the average life expectancy of people with NF1 by 10 to 15 years.[5] The NF1 gene is located on the long arm of chromosome 17, near the BRCA1 gene. Both are tumour suppressor genes with different mechanisms: NF1 regulates cell growth through the RAS pathway, while BRCA1 is involved in DNA repair. Mutations in NF1 cause neurofibromatosis type 1 and increase the risk of early-onset breast cancer. However, there is no direct genetic link between NF1 and

BRCA1.[6] Studies indicate that women with NF1 have a 3- to 5-fold higher risk of developing breast cancer, particularly those under the age of 50.[2] The predominant histological variant of breast cancer in NF1 patients is invasive ductal carcinoma.[7] They also appear to present more aggressively, with a 4-11-fold increased incidence of contralateral breast cancer.[8] In this case study patient has a bilateral breast mass, and a biopsy revealed advanced-stage invasive breast carcinoma.

The patient's advanced stage of breast cancer illustrates the significant diagnostic delays often encountered in NF1 patients. The overlapping cutaneous features of benign neurofibromas and potential malignancies can lead to misinterpretation of symptoms by both patients and their healthcare providers. Here, the patient attributed her ulcerative breast lesion to her NF1 condition, leading to a significant delay in seeking prompt medical evaluation. Additionally, more attention and intervention were focused on her distressing respiratory issues, further adding to the delay in considering other possible causes such as malignancies. This case highlights the importance of earlier breast cancer screenings in women with NF1, possibly by the age of 30, much earlier than the general population.[9] According to the National Comprehensive Cancer Network (NCCN) Guidelines (2025), annual mammography is recommended from ages 30, with consideration of contrast-enhanced breast MRI between ages 30 and 50. MRI increases the detection of cancerous lesions that may be missed during mammograms, especially in younger women with dense breast tissue.[10] This case reinforces the need for tailored cancer screening protocols in NF1 patients that consider both genetic predisposition and personal health history. Implementing standardized screening guidelines could facilitate earlier detection and improve outcomes.

Patients with metastatic breast cancer generally have a poor prognosis, with a 5-year survival rate of only 27% in the era before modern targeted therapies.[11] There is inadequate high-level evidence to support surgical excision of the primary tumour solely to increase survival in metastatic breast cancer. A multidisciplinary team approach has been shown to improve management coordination and clinical outcomes in breast cancer care.[11] The principles of breast cancer treatment are similar to those for the general population. In premenopausal women, ovarian function suppression combined with an aromatase inhibitor represents and established endocrine therapy option, supported by large, randomised trials and guideline recommendations. The NCCN Guidelines for systemic treatment of recurrent or metastatic hormone receptor–positive, HER2-negative metastatic breast cancer state that in the presence of visceral crisis - defined by severe organ dysfunction requiring rapid disease control - initial palliative chemotherapy should be considered as first-line therapy. In the absence of visceral crisis, endocrine therapy combined with CDK4/6 inhibitors is generally preferred as first-line treatment.[10] This recommendation is supported by landmark trials such as PALOMA and MONARCH, in which letrozole was commonly used as the aromatase inhibitor backbone, demonstrating significant improvements in progression-free and overall survival.[12,13] However, real-world treatment decisions are often shaped by local resource availability and patient circumstances. In Malaysia, tamoxifen remains an important and practical endocrine therapy option because of its accessibility and affordability, particularly when access to aromatase inhibitors or CDK4/6 inhibitors is limited.[10]

In this case, the patient was managed by a multidisciplinary team approach. She was initially planned for palliative chemotherapy due to a visceral crisis involving the lung, which she refused due to the side effects despite counselling and support for the treatment. Subsequently, treatment with CDK4/6 inhibitors was also suggested, which are commonly used in hormone receptor-positive and HER2-negative metastatic breast cancers, however, she declined this option. Currently, she is receiving Tamoxifen, with close monitoring for disease progression. Despite refusing further treatment, she was counselled to return promptly should she experience symptoms indicative of disease progression.

CONCLUSION

This case emphasizes the critical importance of early and regular breast cancer screening in patients with NF1. Despite multiple healthcare encounters, this patient's

breast cancer was diagnosed at an advanced stage, largely due to delays in clinical detection and underreporting of symptoms by the patient. Patients with NF1 must be informed and educated about their higher risk of breast cancer. Early recognition through modalities such as mammography, breast MRI and routine clinical examinations has the potential to significantly improve outcomes in this high-risk population. Healthcare providers must implement tailored screening protocols and enhance patient education about increased cancer risks associated with NF1. Timely diagnosis and intervention are vital to reducing morbidity and mortality linked to NF1-related breast cancer. Clinicians must maintain vigilance for malignancies in NF1 patients and proactively advocate early and regular breast cancer screenings.

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CASE REPORT

Rapid Progression From Chronic Phase to Blast Crisis: Prognostic Implications of Bone Marrow Fibrosis in Chronic Myeloid Leukemia

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ABSTRACT

Chronic myeloid leukaemia (CML) demonstrates variable responses to tyrosine kinase inhibitors (TKI). The prognostic impact of bone marrow fibrosis (BMF), particularly at diagnosis, remains under-recognised, especially in adolescent patients. We report a case of a 14-year-old male diagnosed with chronic-phase CML who progressed rapidly to blast crisis within 12 months. Despite treatment with imatinib followed by nilotinib, the patient failed to achieve a complete cytogenetic response due to severe cytopenia and frequent dose interruptions. Retrospective analysis of the initial bone marrow biopsy revealed grade 3 fibrosis. The disease remained refractory despite high-dose induction chemotherapy. This case highlights the potential prognostic relevance of BMF in adolescent CML and supports the integration of reticulin staining into the diagnostic workup to guide timely intervention.

INTRODUCTION

Chronic myeloid leukaemia (CML) is a myeloproliferative neoplasm (MPN) characterised by the BCR-ABL1 fusion gene resulting from the t(9:22) translocation. Tyrosine kinase inhibitor (TKI) has revolutionised the treatment landscape and prognosis of CML. Increasing evidence suggests that the presence of bone marrow fibrosis (BMF) at diagnosis may be associated with inferior treatment outcomes, including delayed molecular responses, suboptimal TKI efficacy, and reduced likelihood of achieving treatment-free remission.[1,2] Adolescents with CML typically exhibit a more indolent course, making early blast crisis an unusual and alarming progression. The role of BMF in paediatric or adolescent CML is rarely reported, and its prognostic relevance remains unclear in this population. We present a case of adolescent CML that progressed rapidly from chronic phase to blast crisis, highlighting the potential prognostic significance of BMF detected at diagnosis.

CASE REPORT

Initial Presentation and Diagnosis

A 14-year-old male presented with a three-month history of fatigue, poor appetite, early satiety, and significant weight loss. Physical examination revealed pallor and massive splenomegaly, palpable 15cm below the left costal margin. There was no hepatomegaly or lymphadenopathy. Initial laboratory results showed severe normochromic normocytic anaemia (haemoglobin 6.7g/dL), marked leucocytosis (white cell count 330 x 10^9/L), and thrombocytosis (platelet count 456 x 10^9/L). A peripheral blood smear showed teardrop cells, marked leucocytosis with granulocytic precursors at all stages, and 5% blasts.

The initial bone marrow aspirate was haemodiluted with no excess blasts, while the trephine biopsy showed hypercellularity with increased megakaryocytes. Reticulin staining was not performed initially due to a reagent

shortage. BCR-ABL1 rearrangement was confirmed via molecular analysis. The patient was diagnosed with chronic-phase CML, with a Sokal Index of 1.2 (intermediate risk).

Treatment Course and Challenges

Imatinib was initiated shortly after diagnosis. However, at 6 months post-diagnosis, the patient failed to achieve a complete cytogenetic response (CCyR), with persistent BCR-ABL1 positivity in 77% of cells by fluorescence in situ hybridization (FISH). Treatment was frequently interrupted and dose-adjusted due to recurrent grade 4 cytopenia. Next-generation sequencing detected no BCR-ABL1 kinase domain mutations, including T315I. Due to poor tolerability, imatinib was discontinued and replaced with nilotinib at 6 months post-diagnosis. However, similar hematologic toxicity limited dose escalation. Despite ongoing treatment, serial peripheral blood smears and bone marrow assessments confirmed persistent chronic-phase CML. Quantitative BCR-ABL1 polymerase chain reaction was not performed, as serial FISH analyses remained consistently positive.

Retrospective reticulin staining of the diagnostic trephine biopsy later confirmed grade 3 fibrosis (Figure 1). Given the high-grade fibrosis and TKI intolerance, the patient was referred for allogeneic stem cell transplantation (allo-SCT). A matched sibling donor was identified.

Progression to Blast Crisis

At approximately 12 months from initial presentation, the patient progressed to blast crisis. Bone marrow aspiration resulted in a 'dry tap', while trephine biopsy revealed diffuse infiltration by blasts (Figure 2). Immunohistochemistry demonstrated blast positivity for CD34 [Figure 3(a)], CD117 [Figure 3(b)], MPO [Figure 3 (c)], and CD61 [Figure 3(d)]. Reticulin staining confirmed persistent grade 3 fibrosis [Figure 3(e)]. Peripheral blood flow cytometry showed 45% blasts expressing CD45 dim, CD117, HLA-DR, CD34, and CD13, consistent with acute myeloid leukaemia (AML).

Induction chemotherapy was initiated per local paediatric AML protocol, comprising mitoxantrone (12 mg/m^2 daily for four days) and cytarabine (100 mg/m^2 twice daily for ten days), along with nilotinib (200 mg every other day) and prophylactic intrathecal chemotherapy. The course was complicated by a grade 5 infection, indicating poor tolerance to intensive chemotherapy. As of the time of this report, the disease remains refractory. Salvage chemotherapy is ongoing, and allo-SCT with the matched sibling donor is planned, although the timing remains uncertain.

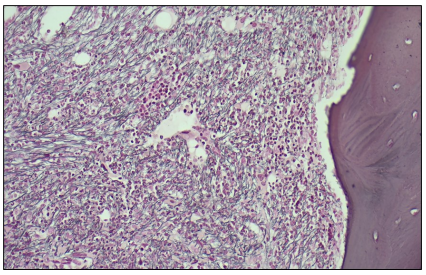

Figure 1: Retrospective reticulin stain of the diagnostic trephine biopsy showing grade 3 marrow fibrosis (400x magnification).

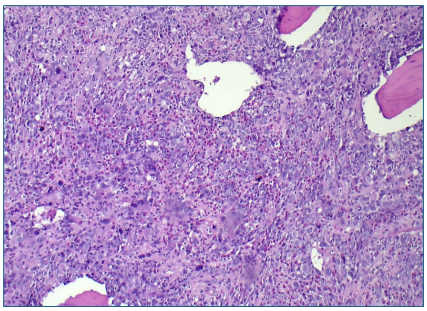

Figure 2: Trephine biopsy at blast crisis showing diffuse infiltration by blasts (Hematoxylin and Eosin stain 400x magnification).

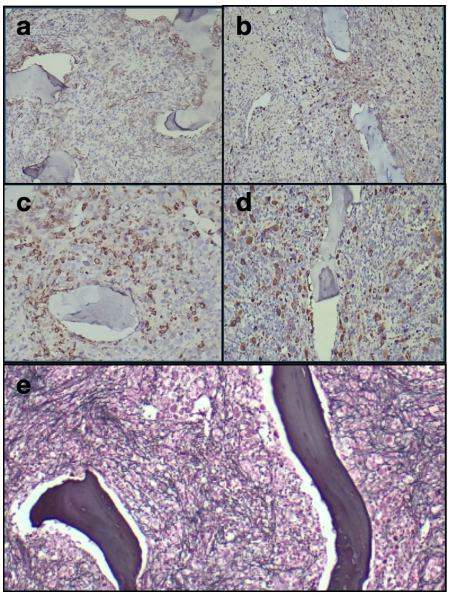

Figure 3: Immunohistochemical and reticulin staining of the trephine biopsy at blast crisis. (a) CD34-positive blasts; (b) CD117-positive blasts; (c) MPO-positive blasts; (d) CD61 highlighting megakaryocytes; (e) Reticulin stain showing grade 3 fibrosis (400x magnification for all panels).

DISCUSSION

This case raises the question of whether early identification of BMF should influence upfront TKI selection or transplant referral timing, particularly in younger patients. BMF in CML is commonly observed at diagnosis, with studies reporting grade 2-3 fibrosis in up to one-third of patients.[3] Its presence has been associated with delayed molecular responses, suboptimal TKI outcomes, and reduced likelihood of achieving treatment-free remission.[1,2,4] While it is more extensively described in adult populations, its occurrence and significance in adolescents with CML are not well established due to limited data.

The pathogenesis of BMF in CML is believed to be driven by clonal proliferation of megakaryocytes and monocytes that secrete fibrogenic cytokines such as platelet-derived growth factor and transforming growth factor-beta, leading to fibroblast activation and reticulin deposition.[5] In contrast, in other MPNs such as primary myelofibrosis, BMF is often driven by JAK2, CALR, or MPL mutations that activate the JAK-STAT signalling pathway, resulting in excessive cytokine production and marrow stromal remodelling.[6] Since JAK2 mutations are typically absent in BCR-ABL1 positive CML, the fibrotic process in CML likely arises from alternative, BCR-ABL1 -driven mechanisms.

TKI therapy has demonstrated the potential to reverse BMF, potentially mitigating its adverse prognostic effects in the TKI era.[5] Imatinib has been shown to significantly reduce fibrosis grade in many CML patients, although higher-grade fibrosis may require a longer duration to achieve optimal response.[5] However, long-term imatinib exposure has also been reported to induce new or progressive marrow fibrosis in some patients, with resolution observed after switching to second-generation TKIs.[7] Although BMF does not necessarily prevent therapeutic response, it remains associated with delayed cytogenetic and molecular responses.[1]

The rate of CCyR appears similar regardless of fibrosis severity; however, patients with moderate to severe fibrosis tend to show poorer early responses and suboptimal outcomes when treated with first-generation TKIs such as imatinib.[4] These findings suggest that significant fibrosis at diagnosis may support the early use of second-generation TKIs, though further evidence is warranted.

Currently, BMF alone does not constitute an indication for allo-SCT in CML. However, in patients with persistent high-grade fibrosis, intolerance to multiple TKIs, or progression risk, allo-SCT remains a viable and often necessary option.[8,9] In our patient, the combination of high-grade fibrosis and TKI intolerance led to early consideration of allo-SCT. Unfortunately, delays in workup due to social factors resulted in disease progression to blast crisis.

Based on this case and emerging evidence, we recommend that all newly diagnosed CML patients, especially those with atypical features or cytopenia, undergo reticulin staining as part of their baseline marrow workup. Identifying high-grade fibrosis early may help guide the intensity of monitoring, TKI selection, and timely referral for transplant consideration.

CONCLUSION

This case highlights the potential prognostic relevance of BMF in CML, particularly in adolescent patients. High-grade fibrosis at diagnosis may be associated with poor tolerance to TKI, delayed or suboptimal treatment response, and an increased risk of rapid disease progression. Although BMF may be reversible with TKI therapy, its presence warrants close molecular monitoring and should prompt timely consideration of alternative strategies, including early referral for allo-SCT. Given the potential for BMF to predict poor response and rapid disease progression in CML, incorporating reticulin staining into routine diagnostic protocols may improve risk stratification and treatment planning, particularly in adolescents.

CONFLICT OF INTEREST

The authors have no conflict of interest.

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