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Acknowledgements:
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Brain health is heart health

Liew Boon Seng

Department of Neurosurgery, Hospital Sungai Buloh, Selangor, Malaysia

We celebrated "World Brain Day" on 22nd July 2026 with the theme "Brain health: Access for all". This month, on 29th September, we celebrate World Heart Day under the theme "Don't Miss a Beat," to recognise hidden signs and symptoms of cardiovascular disease.

Both the brain and heart are vital organs, and their functions are closely interconnected through the heart–brain axis. One of the earliest clinical observations demonstrating this interaction was the presence of inverted wide T waves on the electrocardiogram following acute neurogenic dysfunction. This abnormality is termed "cerebral T waves or "Neurogenic T waves".[1] The cardiac–cerebral reflex represents an important component of this bidirectional relationship. The continuous linkage between cardiac sensory information and the central nervous system via the autonomic regulatory centre influences heart rate, cardiac conduction, and myocardial excitability.[2] The brain regulates cardiac function predominantly through the sympathetic and parasympathetic nervous system.[3] The central neurogenic pro-inflammatory signals from the hypothalamus and brainstem may influence vascular function and its circulation.[4] Emotional trauma, physical shock or sequelae of ischemic and haemorrhagic stroke led to sudden and excessive sympathetic discharge that may cause myocardial stunning and transient left ventricular dysfunction. This phenomenon is clinically recognised as "Takotsubo cardiomyopathy". The relationship between autonomic imbalance and Takotsubo syndrome has generated interest in therapies aimed at restoring autonomic equilibrium. Transcutaneous vagus nerve stimulation (VNS), which enhances parasympathetic activity, has been investigated in several clinical trials.[5]

The hypothalamic–pituitary–adrenal (HPA) axis represents an important component of the heart–brain axis, providing a neuroendocrine pathway through which chronic psychological or physiological stress can influence cardiovascular function.[3] During psychological stress, physiological stress, and alterations in circadian rhythm, neural signals activate the paraventricular nucleus of the hypothalamus, resulting in the release of corticotropin-releasing hormone (CRH) and arginine vasopressin. These hypothalamic hormones stimulate the anterior pituitary to secrete adrenocorticotropic hormone (ACTH), which subsequently acts on the adrenal cortex to promote the synthesis and release of glucocorticoids, predominantly cortisol. Under physiological conditions, the HPA axis is tightly regulated through a negative-feedback mechanism in which circulating glucocorticoids suppress CRH and ACTH secretion. Chronic stress, exogenous therapy, or endocrine disorders are associated with glucocorticoid excess. Prolonged glucocorticoid excess leads to obesity, metabolic syndrome, hypertension, and increases the risk of developing cardiomyopathies and subsequent heart failure.[6]

The brain and heart share many common vascular mechanisms, and systemic inflammation may contribute to vascular injury affecting both organs. Although cerebral small-vessel disease (SVD) and coronary atherosclerosis are distinct pathological entities, they share several important biological pathways, including endothelial dysfunction, chronic inflammation and oxidative stress. Furthermore, "microvascular angina" due to SVD of the heart was reported in patients with acute ischemic stroke. Berry et al., concluded in their paper that SVD is a multisystem disorder with a common pathophysiological basis that differentially affects the heart and brain in some patients.[7] Progressive changes in the intracranial vascular wall may contribute to arterial stenosis and, in selected conditions, aneurysm formation.[8] Diabetes mellitus further amplifies this vascular vulnerability through metabolic dysfunction, endothelial injury, oxidative stress, and impaired immune and inflammatory regulation. Modern neuroimaging, such as high-field magnetic resonance imaging (MRI), may detect subclinical cerebral vascular and microstructural abnormalities that reflect underlying small-vessel disease and may serve as a marker of systemic vascular risk. Microstructural changes intracranially can be detected by using high-tesla MRI, such as 3-Tesla or 7-Tesla, which demonstrates T2-weighted hyperintense white-matter lesions which may represent subclinical chronic small-vessel ischemic injury (silent micro-strokes).[9] Furthermore, high-resolution intracranial vessel-wall MRI High-resolution 3D T1-weighted black-blood vessel-wall MRI sequences with both pre- and post-contrast administration, combined with 3D T2-weighted sequences, provide detailed assessment of the arterial wall and can identify features of intracranial atherosclerotic disease that may not be apparent on conventional lumen-based angiographic imaging.[10] Avoidance of tobacco and nicotine exposure is important. Cigarette smoking and vaping cause endothelial injury affecting the vascular systems of both the heart and brain.[11-12]

The human brain receives approximately 20% of the body's total cardiac output. Changes in cardiac function and systemic haemodynamics can significantly affect cerebral perfusion and cognitive function.[13] Cardiovascular disorders such as atrial fibrillation (AF) and heart failure may

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adversely affect the brain through multiple mechanisms, including impaired cardiac output and abnormal cerebral perfusion. AF is particularly important because it substantially increases the risk of cardioembolic ischemic stroke. In this issue of the Medical Journal of Malaysia, Chee et al., discussed the benefits and challenges of anticoagulant therapy in elderly patients with AF for the prevention of recurrent stroke.[14] Although advanced age is associated with an increased risk of bleeding and other treatment-related complications, appropriate anticoagulation remains an important component of secondary stroke prevention in carefully selected elderly patients, with treatment decisions requiring an individualised assessment of both thromboembolic and bleeding risks.[14] For stroke-associated pneumonia, routine use of preventive antibiotic therapy is not recommended for all patients. Initiate antibiotic treatment promptly when pneumonia is clinically diagnosed, and follow local antimicrobial guidelines and microbiological considerations.[15] In this issue, Zulkfli et al. highlight the considerable burden of antimicrobial resistance among patients with pneumonia, emphasising the importance of targeted infection-control measures and effective antimicrobial stewardship.[16] Long-term brain health monitoring after stroke should incorporate comprehensive assessment and modification of vascular risk factors, lifestyle modification and psychosocial health assessment.[17-18]

Following neurological injury, neurorehabilitation provides an important mechanism for restoring functional connectivity. Passive limb movement can provide sensory input to the central nervous system and engage sensorimotor feedback pathways. Repeated, task-oriented rehabilitation may facilitate adaptive neuroplasticity and support the reorganisation of neural networks after stroke or other neurological injury.[19] Neuromodulation represents another emerging component of neurorehabilitation. VNS, with its ability to modulate autonomic and central neural networks, may have therapeutic potential in cognitive and functional recovery following ischaemic stroke.[20-21] The close relationship between cognitive decline and cerebrovascular health has also been highlighted by the Lancet Commission on dementia prevention, intervention and care. The 2024 Commission emphasised that a substantial proportion of dementia risk may be associated with potentially modifiable factors across the life course, including hypertension, smoking, physical inactivity, diabetes, excessive alcohol consumption, obesity, depression, social isolation, hearing impairment, traumatic brain injury and air pollution.[22]

Chronic mental exhaustion and prolonged psychological or physical stress can lead to persistent activation of the body's stress-response systems. Sustained activation of the sympathetic nervous system and HPA axis may contribute to hypertension, endothelial dysfunction, metabolic disturbances and chronic low-grade inflammation, thereby increasing cardiovascular and cerebrovascular vulnerability. These processes may be particularly relevant in ageing-related chronic inflammatory conditions.[23] Repetitive stress and prolonged overwork may also alter central nervous system processing. These factors can produce maladaptive neural plasticity, including central sensitisation and alterations in facilitatory and inhibitory neural systems.[24] Depression, chronic psychological stress and autonomic imbalance have been associated with adverse effects on cardiovascular function, including altered heart-rate variability and increased sympathetic activity.[25] Recognition and management of psychological stress should therefore form part of comprehensive cardiovascular and cerebrovascular risk reduction.

Brain health can be broadly defined as preserving neurological function by preventing or reducing factors that may cause brain injury, promoting recovery after neurological insult, and enhancing compensatory neural mechanisms through neuroplasticity and neuromodulation.[26-27] Nutrition represents an important modifiable determinant of both brain and cardiovascular health. A balanced, nutrient-rich diet can help reduce metabolic dysfunction, systemic inflammation, excess weight gain and vascular injury. A brain- and heart-healthy diet includes intake of leafy greens, berries, whole wheat, nuts and fish rich in omega-3 fatty acids. Conversely, excessive consumption of highly processed foods, added sugars, saturated fats and alcohol should be minimised.[28] Regular physical activity provides another important link between cardiovascular fitness and brain health. Activities such as walking, yoga, strength training, and balance exercises can improve cardiovascular fitness, peripheral and cerebral circulation and vascular function.[29] They can also promote neuroplasticity and support cognitive and functional health.[30] Sleep is another essential component of the heart–brain axis. Adequate restorative sleep, particularly sufficient deep sleep, supports neuronal recovery, memory consolidation, metabolic homeostasis and autonomic regulation. Conversely, persistent sleep disruption may adversely affect cardiovascular and neurological health.[31-32]

Maintaining brain health requires a proactive approach to the early identification and management of neurological and vascular risk factors. Brain health monitoring includes assessment of cognitive function, brain structure and volume, neurovascular status and neurofunctional assessment.[33] Key strategies for maintaining brain health and stroke prevention include controlling modifiable risk factors such as hypertension, diabetes, atrial fibrillation and smoking.[34] Metabolic health should also be addressed through appropriate control of blood glucose, lipid levels and body weight, as diabetes, dyslipidaemia and obesity contribute substantially to both cerebrovascular and cardiovascular disease.

Effective pharmacological management, however, depends not only on prescribing appropriate treatment but also on treatment adherence and implementation. In this issue, Devaraj et al., reported that the use of single-pill combination (SPC) therapy among hypertensive patients in a cross-sectional study was only 27.9%. Although single-pill combinations may simplify treatment regimens and potentially improve adherence and blood-pressure control, their utilisation remained limited and was influenced by factors including the presence of chronic kidney disease, physician preference and the absence of diabetes mellitus.[35] In this issue too, Ang et al., reported that medications acting on the cardiovascular system accounted for 39.6% of

returned medications and highlighted medication adherence as an important factor associated with this problem.[36]

Despite increasing recognition of the heart–brain axis, important knowledge gaps remain. Current evidence does not yet fully explain how subtle cardiovascular abnormalities translate into structural and functional alterations within the brain, particularly before the development of clinically overt cardiovascular or neurological disease.[37] Further research integrating cardiovascular imaging, neuroimaging, autonomic assessment, biomarkers and longitudinal cognitive and functional outcomes will be necessary to better define these bidirectional pathways.

In conclusion, the heart and brain should not be considered as independent organs. Neurological injury can profoundly affect the heart, while cardiovascular dysfunction can, in turn, compromise cerebral perfusion and neurological function. Understanding this bidirectional heart–brain axis is therefore increasingly important in the prevention, diagnosis, and management of both cardiovascular and neurological disease.

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Outcomes of complex older patients with acute ischaemic stroke and atrial fibrillation: A comparison study with and without the use of oral anticoagulants for secondary stroke prevention

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ABSTRACT

Introduction: Direct oral anticoagulants (DOACs) have become the mainstay of stroke prevention in patients with atrial fibrillation (AF). Decision to anticoagulate frail and post-stroke patients with AF may be challenging and complex. This study aimed to compare the outcomes of complex older patients with acute ischaemic stroke and AF who were treated with and without oral anticoagulants for secondary stroke prevention.

Materials and Methods: This is a retrospective observational study of all older persons (≥65 years) admitted to the geriatric medicine ward in our university hospital with acute ischaemic stroke and AF from January 2016 - December 2021. The inclusion criteria in our study were patients discharged alive from hospital post-ischaemic stroke with AF. Exclusion criteria were those who died as inpatient, those undergoing end-of-life care or with very severe frailty which are contraindication to anticoagulation. Comparison was done between patients who were anticoagulated and patients who were eligible for anticoagulation but were not anticoagulated for various reasons.

Results: There were 539 patients with ischaemic stroke, of whom 110 (21%) had AF. Among them, 29 patients were excluded due to death during hospitalization (19), end-of-life (4), and very severe frailty (6). While 65 (80%, mean age 84.1 ± SD 6.3) were discharged on anticoagulation, 16 (20%, mean age 88.3 ± SD 4.3, p=0.388) were discharged without anticoagulation. The median clinical frailty score was six in both groups. Among the anticoagulated, 59 (91%) were commenced on DOACs and six (9%) were on warfarin. The main reasons recorded for not commencing anticoagulants in eligible patients were patient/family did not agree to start (8), high bleeding risk (7), and poor social support (1). Mortality was significantly higher in the non-anticoagulated group (n=10, 63%) compared to the anticoagulated group (n=22, 32%) (p=0.036).

Conclusion: Although frail older persons are perceived to have a poorer benefit/risk ratio when anticoagulated, our study demonstrated lower mortality in post-stroke anticoagulated complex older AF patients compared to those who were not anticoagulated. However, given the small numbers of participants in our study, further studies are required to determine characteristics of patients who may have better outcomes or lower risk of adverse events on anticoagulants. These findings also underscore the pressing need for a standardized, frailty-prescribing and monitoring protocol to maximise benefit and minimise risks of adverse outcomes.

KEYWORDS:
Anticoagulation, stroke, atrial fibrillation, frail, older persons, geriatric

INTRODUCTION

Atrial fibrillation (AF) is a common arrythmia in frail, complex older persons. The prevalence of AF increases with age, affecting up to 4.2% of those aged 60–70 years and 17% of those aged 80 years or older.[1] People with AF have increased risk of stroke.[2] In the Framingham study, the annual risk of stroke in patients with AF was 1.5% in those aged 50–59 years and 23.5% in those aged 80–89 years.[3]

Frailty is a clinically identifiable state of diminished physiological reserve and increased vulnerability to a broad range of adverse health outcomes.[4] For frail older patients, stroke is associated with an increased risk of severe functional decline and loss of health-related quality of life.[5]

Older persons with AF have more favourable outcomes on direct oral anticoagulants (DOACs) than without, and on DOACs than on vitamin K antagonists (VKA).[6-7] The net clinical benefit for DOACs declines with advanced age due to competing risks for bleeding and death but is maintained longer with DOACs than VKA.[8] When given anticoagulation, older age is an accepted risk for haemorrhage and bleeding complications are likely to be higher in people with frailty. In the 2021 European Heart Rhythm Association (EHRA) practical guide on the use of DOACs, the benefit over risk ratio is greater in the fit older person with the ratio reducing with increasing levels of frailty.[9] The EHRA guide suggests that very severe frailty and terminal illness typically indicate a contraindication to anticoagulation.[10] In this EHRA practical guide where the Clinical Frailty Scale (CFS) was used, very severe frailty is defined as completely dependent for personal care and approaching end-of-life and typically they could not recover even from a minor illness.

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Despite the evident benefits of anticoagulants in preventing stroke, there are many considerations in starting anticoagulation in older frail persons, which include multiple chronic diseases, polypharmacy, drug-drug interactions, pharmacokinetics and pharmacodynamics which can all be affected by ageing.[11] A study by Mant et al. in 2007 in a population of over the age of 75 years clearly supports the use of anticoagulation therapy for people who have AF.[12] However, Perera et al (2009) concluded that frail older inpatients with AF are significantly less likely to receive anticoagulation than those who are non-frail and appear more vulnerable to adverse clinical outcomes, with and without antithrombotic therapy.[13] Nishimura et al. (2023) demonstrated in his study that increasing levels of frailty, the incidence of the composite bleeding outcome increased rapidly: for patients classified as "not frail," the incident rate of bleeding was 11.2 per 100 person-years, while this nearly doubled to 21.0 per 100 person-years for patients with severe frailty, mainly driven by an increase in nonmajor bleeding events.[14] Meanwhile Nguyen et al.'s study in 2016 found that frailty status had no independent impact on pharmacological treatment of AF, but the rate of major bleeding complications may reflect careful patient selection and management of anticoagulation.[15] Hence the decision of prescribing can be complex and individualised. This study is aimed to determine the characteristics and outcomes of older persons with AF and ischaemic stroke who were anticoagulated compared to those who were eligible for anticoagulation but were not anticoagulated.

MATERIALS AND METHODS

Study Population

This was a retrospective observational study approved by the ethics committee of our university hospital (MEC ID: 201312-0636). All older persons aged 65 years old and above who were admitted to the geriatric medicine ward in our university hospital from January 2016 – December 2021 with an acute ischaemic stroke and a background medical history or new diagnosis of AF were included. Exclusion criteria were those who died as an inpatient, very severe frailty (CFS of 8), and those who were undergoing end-of-life care (CFS of 9) which are contraindications to anticoagulation. The index date is defined as when the patient was first admitted for the acute ischaemic stroke. The follow-up period was defined as the duration from the index date until the death of the patient, or until the end date of the study period (December 31, 2024) which was 3 years after the end of recruitment period.

Patients' characteristics, medications, and outcomes were collected using our university hospital's in-house Electronic Medical Record system. Patient's frailty status was determined according to the Rockwood CFS version 2, based on the functional, and dependency status of the patient before stroke and upon discharge from the stroke admission. Very severe frailty was defined as completely dependent, approaching end-of-life, and could not recover even from a minor illness. End-of-life was defined as progressive life-limiting disease with a prognosis of months or less.[16] The subsequent outcome and complications were based on reports in our electronic medical record, with at least one follow-up visit to our hospital after discharge. The degree of disability or dependence in the daily activities were also recorded using modified Rankin scale (mRS), a standardized and validated measure for assessing the impact of a new stroke.[17]

Statistical Analysis

Results were presented as mean (SD) ± standard deviation, compared using t-tests, and correlation test. Counts and percentages were analysed using c^2 and Fisher's exact test. All tests were two-sided, with the level of significance set at $p<0.05$, performed using SPSS statistic version 23 for Windows©.

Outcome

The primary outcome of interest was the overall mortality. Secondary outcomes were the complications associated with anticoagulation: major bleeding, clinically relevant non-major bleeding (CRNMB), non-clinically consequential minor bleeding and recurrent ischemic stroke. There was also composite secondary outcome of all 3 categories of bleeding combined.

The above classification of severity of bleeding is according to the International Society on Thrombosis and Haemostasis (ISTH)'s definition of bleeding in non-surgical patients. It can be divided into major bleeding, CRNMB, and non–clinically consequential minor bleeding event. Major bleeding is defined as having a fatal bleeding, symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome.[18] A CRNMB is defined as any sign or symptom of haemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for the ISTH definition of major bleeding but does prompt a clinical response, which leads to one of the following: a hospital admission, a physician guided medical or surgical treatment for bleeding, prompting a face to face evaluation.[19] A non-clinically consequential minor bleeding event is defined as bleeding that is not actionable. A decrease of haemoglobin of 2g/dL or more is considered major bleeding by ISTH, this is often encountered during assessment after initiation of anticoagulant but there is no obvious source of bleeding identified.

RESULTS

There were 539 patients with stroke who were admitted to the geriatric medicine ward in our university hospital from January 2016 - December 2021 (Figure 1), of whom 110 (20%) had AF (paroxysmal or persistent). Among the 110, 73 were commenced on anticoagulation for secondary stroke prevention, but eight died during the admission, leaving 65 discharged (80%, mean age 84.1 ± SD 6.3). On the other hand, 37 were not prescribed anticoagulation. Among them, 11 died during the admission period, four were undergoing end-of-life care due to stroke, and six had very severe frailty post-stroke. At last, there were 16 who were eligible for anticoagulation but discharged without anticoagulation (20%, mean age 88.3 ± SD 4.3). Those not anticoagulated were significantly older (median: 88 vs 84, p=0.016) and had

Table I: Characteristics of participants with and without anticoagulants

Characteristic	Anticoagulated n =65	Non-anticoagulated n = 16	p-value
Sex			
Male	28 (43%)	5 (31%)	0.388
Female	37 (57%)	11 (69%)	
Median age ± IQR Year	84.0 ± 9	88.5 ± 6	0.016*
Body weight (kg)	57.2 ± 11.1	44.8 ±7.18	0.001*
No. of comorbidities	3.8 ± 1.3	3.7 ± 1.4	0.863
Types of anticoagulation			
Apixaban	38 (58%)		
Dabigatran	20 (31%)		
Rivaroxaban	1 (2%)		
Warfarin	6 (9%)		
Median CFS (pre-stroke)	5 ± 1	5 ± 1	0.829
Median CFS (Post-stroke)	6 ± 1	6 ± 1	0.357
mRS	4.0 ± 0.9	4.2 ± 0.9	0.459
No. of medications	6.6 ± 3.1	4.7 ± 1.7	0.021*
CHA2DS2-VASc Score	5.6 ± 1.6	5.6 ± 1.1	0.954
HAS-BLED Score	2.8 ± 0.9	2.9 ± 0.8	0.909
CKD stage	2.3 ± 0.9	2.0 ± 0.6	0.357

*Statistically significant.
Abbreviation: IQR = Interquartile range. CFS = Clinical Frailty Score. CHA2DS2-VASc = Score for Atrial fibrillation stroke risk. HAS-BLED = Score for Major bleeding risk on anticoagulant. mRS = modified Rankin Scale. CKD = chronic kidney disease.

Table II: Clinical outcomes among patients with and without anticoagulation

Complication	Anticoagulated n = 65	Non-anticoagulated n = 16	p-value
Major bleed	17 (26%)	1 (6%)	0.086
CRNMB	7 (10%)	3 (18%)	0.385
Combined bleed	22 (34%)	3 (19%)	0.242
Recurrent ischemic stroke	10 (15%)	4 (25%)	0.362
Death	22 (32%)	10 (63%)	0.036*
Ischemic Stroke	4	1	0.989
Intracranial bleed	2	0	0.477
GI bleed	2	0	0.477
Sepsis	8	2	0.888
Malignancy	1	0	0.618
Heart failure	2	0	0.474
HHS	0	1	0.043*
Undetermined cause	3	6	

* Statistically significant
Abbreviation: CRNMB = clinically relevant non-major bleeding, Hb = Haemoglobin, GI = Gastrointestinal, HHS = Hyperosmolar hyperglycaemic syndrome.

a lower mean body weight 44.8kg vs 57.2kg (p=0.001) with fewer medications (6.6 vs 4.7, p=0.021). The average length of follow-up was 30 months (±SD 20 months). The median Clinical Frailty Score v2.0 post stroke was six in both groups of those with and without anticoagulation. In the anticoagulated group, 65 (89%) were commenced on DOACS and eight (11%) on warfarin (Table I). The reported anticoagulants used were apixaban (38/65, 58%), dabigatran (20/65, 31%), rivaroxaban (1/65, 2%) and warfarin (6/65, 9%). With the 59 who were discharged with DOACs, 56 (95%) were prescribed with appropriate dose and three were prescribed with off-label inappropriately reduced dose based on the treating physicians' clinical judgement due to bleeding history.

For the 16 patients who were discharged without anticoagulant, the main reason recorded for not commencing on anticoagulant was because family members or patient did not agree to start (8/16, 50%). The reasons for not agreeing to anticoagulation could not be determined from the medical notes. The second reason was perceived high bleeding risk (7/16, 44%), which was evident in patients with high HAS-BLED score (≥3), history of major bleeding with anticoagulation or antiplatelet, and cancer imposing the patient with higher bleeding risks.[20] Only one (1/16, 6%) was not started on anticoagulation due to poor social support.

For the overall mortality, the outcome of death was significantly higher in the non-anticoagulated group (10/16, 63%) compared to the anticoagulated group (22/65, 32%, p=0.036). The occurrence of major bleed (26% vs 6%, p=0.086), CRNMB (10% vs 18%, p=0.385), and combined bleed (34% vs 19%, p=0.242) were similar in the anticoagulated group compared to non-anticoagulated group. There was no non–clinically consequential minor bleeding event reported in our study. Despite given anticoagulation, 10 out of 65 patients (15%) experienced

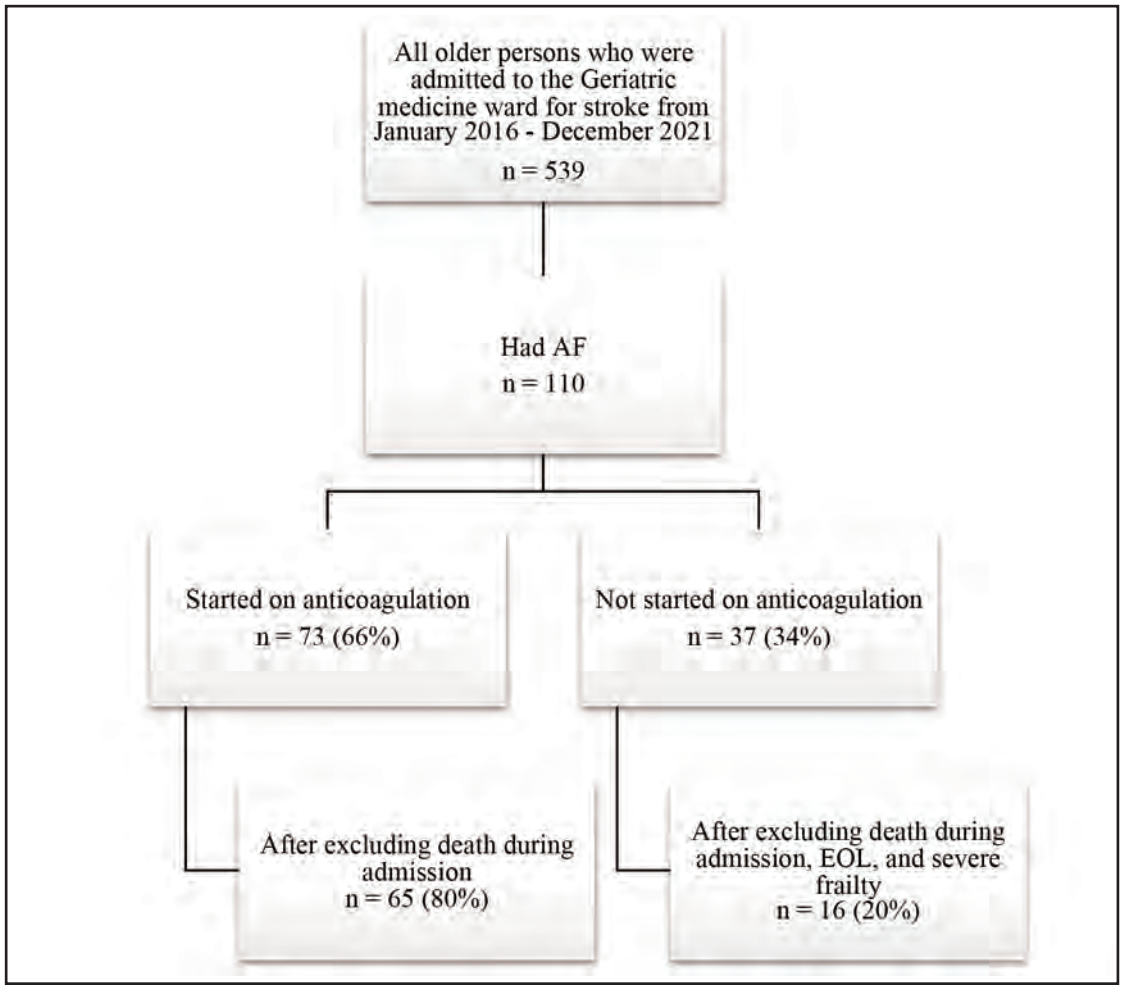

Fig. 1: Flow chart of subjects included in the study following inclusion and exclusion criteria. Abbreviation: AF = Atrial fibrillation, EOL = End of life

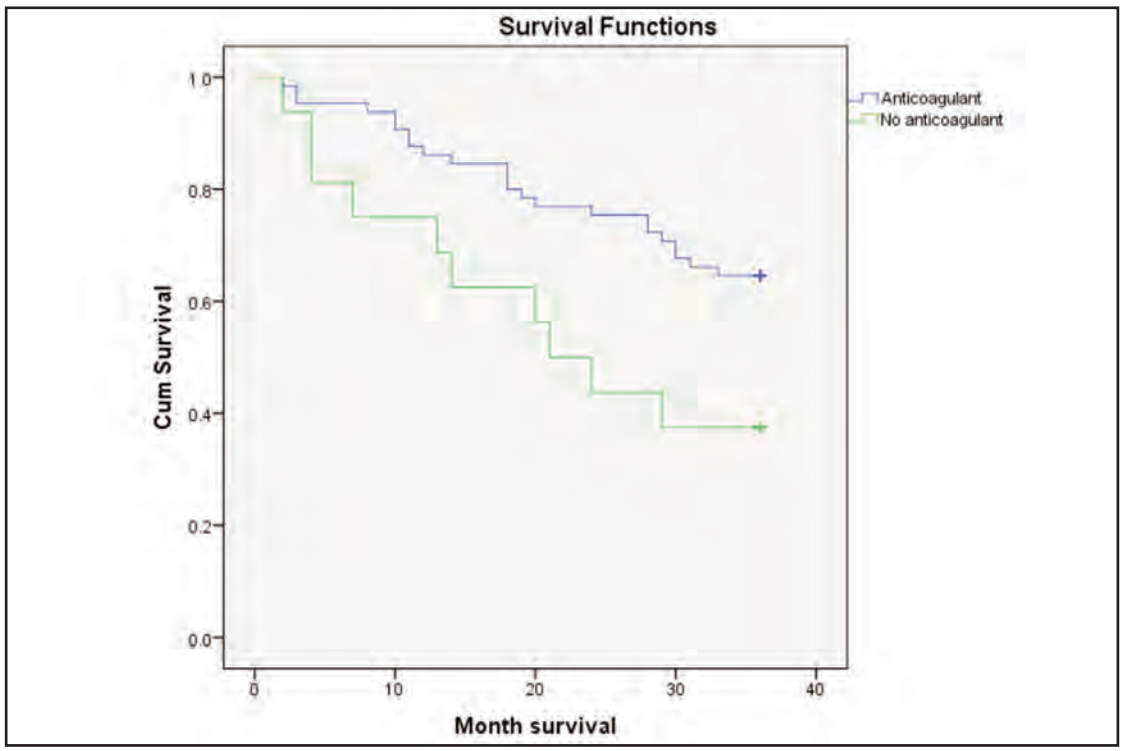

Fig. 2: Kaplan-Meier curve shows the survival between anticoagulant group (blue line) and non-anticoagulant group (Green line). Y-axis represents cumulative survival probabilities, and X-axis shows the number of months of survival

recurrent ischemic stroke, while four out of 16 (25%, p=0.362) had recurrent ischemic stroke in the non-anticoagulated group (Table II).

The causes of death are listed below the row of death. Most died due to sepsis (eight in the anticoagulated group vs two in the non-anticoagulated group). Four anticoagulated patients had deadly recurrent ischemic stroke compared to one in the non-anticoagulated group. There were four deaths due to major bleeding (intracranial bleed and gastrointestinal bleed) in the anticoagulated group, while none in the non-anticoagulated group. There were deaths due to undetermined cause when patients were dead on arrival, or cause of deaths were not clearly be found in the record.

To compare the time to survival rate in anticoagulated and non-anticoagulated participants, the Kaplan–Meier estimator was employed to compute survival curves over three years (36 months) follow-up period (follow-up intervals varied depending on individuals' condition and prognosis, usually on a four to six monthly basis), and differences between anticoagulated and non-anticoagulated groups were assessed using log rank tests (Figure 2). The curve showed significant difference (log-rank: 0.021), showing higher survival rate of 68% in the anticoagulated group compared to 37% in the non-anticoagulated group in the three years period analysed for survival. However, given the extreme imbalance in group sizes and the very small denominator in the untreated arm, this analysis was underpowered, and the survival estimates were unstable and prone to heavy influence by individual outliers. In the anticoagulated group, six (6/22, 27%) were cardiovascular deaths, and 16 (73%) were non-cardiovascular deaths.

DISCUSSION

The management of AF in frail, older patients who have already suffered an ischemic stroke presents a profound clinical dilemma. AF-related strokes tend to be more severe, generally presenting with greater disability and higher mortality compared to non-AF stroke.[21] Patients with AF had poorer survival and more stroke recurrences during one year of follow-up. A study by Lin et al. showed that the AF subjects had lower mean Barthel index scores acutely (29.6 versus 58.6, p<0.01) and at three months p=0.005), six months (p=0.003), and 12 months (p=0.130) after stroke among survivors.[22] A meta-analysis by Huang et al. showed the prevalence of frailty and prefrailty in stroke patients to be 27% (95% CI: 22.9–31.1%, <0.01) and 47.9% (95% CI: 42.5–53.3%, p<0.01) respectively.[23] The increased frailty associated with these strokes leads to higher adverse events including major bleeds, ischemic stroke and death.[24]

Our study directly reflects this vulnerable population and highlights a critical disconnect between perceived clinical risk and actual mortality outcomes. We observed a significantly lower overall mortality rate in frail, post-stroke patients who were discharged on anticoagulation compared to those who were eligible for anticoagulation but not anticoagulated (32% vs. 63%, p=0.036), which was also reflected in the survival curve demonstrating a significant 68% survival rate at three years for the anticoagulated cohort versus only 37% for the non-anticoagulated group (log-rank: 0.021).

More importantly, this substantial survival benefit was achieved despite the anticipated risks of anticoagulation in an older demographic. Physicians frequently harbour deep worries about prescribing anticoagulants to frail patients due to bleeding concerns. Indeed, in our non-anticoagulated cohort, a perceived high bleeding risk was driven by high HAS-BLED scores, previous bleeding history, or concurrent cancer. While our findings did show an upward trend in bleeding complications among anticoagulated patients (such as major bleeding at 26% vs. 6%), these differences did not reach statistical significance, likely limited by our small sample size.

The critical interpretation of these findings is that the survival benefit of anticoagulation in this cohort appears to heavily outweigh the bleeding risks. The fear of iatrogenic harm (bleeding) often overshadows the natural, highly lethal progression of untreated AF. By withholding anticoagulation, we may be inadvertently subjecting these patients to a much higher risk of all-cause mortality.

However, this survival benefit is not absolute and must be contextualized and individualised within the spectrum of frailty. Our study design explicitly excluded patients with very severe frailty (CFS of 8) and those undergoing end-of-life care with a prognosis of less than six months (CFS of 9). In these profoundly frail individuals, the risk-benefit ratio heavily inverses, and anticoagulation is fundamentally contraindicated. This aligns tightly with the 2021 EHRA practical guide on the use of DOACs, which reinforces that while fit and moderately frail older persons benefit greatly, very severe frailty and terminal illness preclude the use of anticoagulation.

The prescription of anticoagulants in frail, older post-stroke patients demand careful consideration and individualized assessment. Our data has suggested that frailty alone should not be a barrier to treatment. Moving forward, clinical practice must shift from avoidance to active management, which includes rigorous surveillance for bleeding complications and comprehensive education for frail patients and their families regarding the true balance of risks and benefits.

STRENGTHS AND LIMITATIONS

The strengths of this study are that it comprised a sample of very old and frail people, where the risk of complications is high. This group have been under-represented in clinical trials and are at a higher risk of both stroke and bleeding complications. We used a validated Rockwood CFS version 2 which is being used worldwide. Although this study did not focus on the types of anticoagulation used and their associated bleeding risks, it aimed to overall compare patients who were anticoagulated against those who were eligible for anticoagulation but were not anticoagulated for the stated reasons.

There are several limitations of this study. First, this was a retrospective study, from which we were unable to detect compliance and adherence to treatment. Our study could have led to bias due to missing data and retrospective interpretation. Furthermore, this study was based on what was recorded in our electronic medical record, hence certain complications might not be captured if patients did not report the complications or sought treatment in other hospitals, especially non–clinically consequential minor bleeding event which tend to be under-reported by patients or their families. HAS-BLED score may underestimate the bleeding risks in frail older persons, as there were many other risk factors of bleeding which may not be captured but may influence the physicians' decision for not prescribing anticoagulation. These risk factors of bleeding include high falls risk, recent anaemia, thrombocytopenia, coagulopathy, malignancy (greatly increases both bleeding and clotting risks), and cerebral amyloid angiopathy. On the other spectrum, the inability to elicit the reasons why or family members refused anticoagulation may pose significant selection bias.

CONCLUSION

Our observational study found lower overall mortality rates in the anticoagulated group of post-stroke patients with atrial fibrillation compared to those who were not anticoagulated. Frail older patients who are anticoagulated require more surveillance in terms of anticoagulation associated bleeding risks and education to increase awareness of bleeding risks among patients.

These findings underscore the pressing need for a standardized, frailty-prescribing and monitoring protocol to maximise benefit and minimise adverse events. A structured guideline would ensure that complex, uncaptured bleeding risks, and strict DOAC pharmacokinetic dosing are formally integrated into clinical decision-making, moving subjective and hesitative local practice toward objective, decisive patient-centred care. Further studies are also required to determine characteristics of patients who may have better outcomes or lower risk of adverse events on anticoagulants.

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CONFLICT OF INTEREST

There is no conflict of interest regarding the publication of this study.

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ORIGINAL ARTICLE

8-Hydroxy-2′-Deoxiguanosine (8-OHdG) as a reliable biomarker for rheumatoid arthritis

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ABSTRACT

Introduction: Rheumatoid arthritis (RA) is a chronic, autoimmune, destructive inflammatory synovitis that ultimately affects metabolic function, the vascular system, and systemic bone. Many researchers have demonstrated that free radicals induce oxidative stress and are involved in several disease conditions. It was observed that a physiological equilibrium between oxidants and antioxidants is being disrupted by oxidative stress. Free radicals are molecules, ions, or atoms with unpaired electrons. These elements tend to be stabilized. For stabilization, they attack other molecules to get electrons. In the cells, this behavior can cause mutations or even cellular death. This study aimed to evaluate the oxidative stress marker 8-Hydroxy-2-Deoxiguanosine (8-OHdG) as a biomarker for Iraqi RA patients.

Materials and Methods: The estimation of the plasma level of this marker was achieved in human RA patients using ELISA. The current study included 132 adult individuals who were diagnosed as RA patients with joint complications, while the remaining 66 were healthy and served as controls. Blood plasma levels of 8-OHdG were estimated using a commercial ELISA kit. The resultant solution was washed after being incubated, and then a conjugate enzyme was added; finally, the results were read using an ELISA reader at 450nm.

Results: A significant increase in plasma concentration of 8-OHdG was detected in the disease group. The most significant increase in this biomarker (p = 0.001) appeared in RA patients in comparison with the healthy subjects. The significant increase of inflammatory and oxidative biomarkers highlighted in this study might point to a relationship between these biomarkers and the pathogenesis and progression of rheumatoid arthritis in adult subjects.

Conclusion: This study suggests the role of 8-OHdG as an early diagnostic marker of RA. Because 8-OHdG is a strong indicator of oxidative stress-related DNA damage, this result may have significant clinical implications.

KEYWORDS:
8-Hydroxy-2′-Deoxiguanosine (8-OHdG), Rheumatoid Arthritis, Biomarker

INTRODUCTION

Rheumatoid arthritis (RA) is one of the leading causes of disability and labor loss, a chronic autoimmune disease known for its tissue-destructive effects and unresolved synovial inflammation. It impacts between 0.2–1% of the population worldwide.[1-2] In RA, a symptomatic clinical phase after the beginning of systemic immune dysregulation in mucosal surfaces was recognized as the end of the multi-year prodromal phase. Besides causing pain and articular degeneration, the immune reactivity limits itself to the synovium and links to a wider range of comorbidities.[3-4] Persistent inflammatory synovitis, which typically affects peripheral joints in a symmetric distribution, serves as the hallmark of established RA.[5] Oxygen metabolism has an important role in the pathogenesis of many diseases and RA is one of these diseases.[6]

During normal physiological processes, reactive oxygen species (ROS) are molecules that occur when a cell is not under stress. It was detected that 98% of the respired oxygen within the electron transport chain is utilized by mitochondria. This is used to generate adenosine triphosphate (ATP).[7-8] On the other hand, in the course of cellular oxidative phosphorylation, these molecules are produced by activated phagocytic cells during oxidative bursts. When these molecules exceed a physiological buffering capacity, oxidative stress will occur, and ROS will be formed. High levels of production of ROS can damage different cellular elements like proteins, lipids, matrix components and nucleic acids.[9] Furthermore, to amplify a synovial inflammatory–proliferative response, ROS serve as crucial intracellular signaling molecules. Additionally, ROS are linked to many ageing-related disorders and are held responsible for the loss of the structure and function of proteins.[10]

The activation of the two key transcription factors, nuclear factor-κB and hypoxia-inducible factor-1α, is regulated by changes in cytokine stimulation and cellular oxygenation. These two factors are thought to be activated by the recurring cycles of hypoxia and reoxygenation linked to variations in synovial perfusion.[11-12] Furthermore, a variety of ROS molecules, including peroxynitrate, hydrogen peroxide, hydroxyl radicals, superoxide anion radicals and singlet oxygen, can oxidize nucleic acids or their constituent parts to produce a variety of precursors. As a result, the sugar moiety and heterocyclic DNA bases react strongly with the hydroxyl

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radical near or at diffusion-controlled.[13] In recent years, many researchers have confirmed that oxidative stress contributes to many chronic inflammatory conditions.[14] So, understanding the body's oxidative state is quite helpful. Thus, many oxidative stress biomarkers have been measured. Within a living organism, 8-Hydroxyguanine (8-OHGua, the base moiety of 8-OHdG) is a molecule produced as the result of an oxidation of guanine base by ROS.[15] When oxygen starts to damage cellular DNA, free radicals are generated during exposure to environmental oxidants, phagocytosis, cellular respiration, and cell injury.[16] Quanine bases in DNA are the main goal for ROS attack to form 8-hydroxydeoxyguanosine (8-OHdG). Rather than cytosine, this molecule can bind to thymidine. Based on this, the level of 8-OHdG is generally regarded as a biomarker of mutagenesis consequent to oxidative stress.[17]

At the C-8 site, 8-OHdG a product of DNA modification produced by the oxidation of deoxyguanosine, is considered the most sensitive and useful biomarker of oxidative DNA damage.[18] Oxygen derivatives that are commonly linked to RA include lipid peroxides (LOOH), lipid alkoxyl radicals (LOO-), lipid peroxyl radicals (LO-), hydroxyl free radicals (H2O2), and superoxide free radical anions (O2-). In the intense inflammatory environment, these free radicals (LOOH, LOO-, LO-, H2O2 and O2-) are excessively produced by the joints affected in RA patients.[19] One of the most prominent products of oxidative DNA damage is 8-OHdG, which was recently used as a reliable and sensitive marker of oxidative stress.[20] The oxidation potential of the guanine base is the lowest when compared to other bases.[13] This leads to the formation of 8-oxoguanosine (8oxoG) and 8-oxodeoxyguanosine (8oxodG).[21] Thus, the molecule, which is more susceptible to free radical attack, quinine, supports the formation of the 8-OHdG molecule.

Scientific researchers have focused their attention on this molecule, which is a common choice as an oxidative stress biomarker. This molecule indicates DNA damage (8-OHdG residues), which results in transversion mutation by partnering with cytosine or adenine during the replication process (GC to TA).[22] The effect of 8-OHdG is to stimulate the transversion of G-->T, which are among the most frequent somatic mutations.[23] One of the predominant forms of free radical-induced oxidative lesions that occur in nuclear and mitochondrial DNA is 8-OHdG or 8-oxodG. Thus, it has been widely used as a biomarker for oxidative stress and carcinogenesis. To mitigate the harmful effects of oxidative stress-induced DNA lesions, an efficient process removes most of 8-oxoA before the next round of replication. But, the half-life of an 8-oxoG lesion is 4.6 times longer than that of an 8-oxoA lesion induced by H2O2.[24] Thus, the biological significance of alterations in 8-OHdG levels has been investigated in many types of diseases.[25-26]

For more accurate diagnosis and monitoring of RA, many biomarkers, including symptoms, patient-reported measures and laboratory measurements have been used. However, there is no current gold standard measurement because each measure varies in strengths and weaknesses. So, no single 'best' measure of disease activity could be recommended. Protein biomarkers might provide reliable measurements reflecting pathophysiological status. However, erythrocyte sedimentation rate ESR and CRP, incorporated into clinical disease activity measures such as the Disease Activity Score (DAS) and Simplified Disease Activity Index (SDAI), are non-specific indicators because these biomarkers are influenced by age, anemia and the presence of immunoglobulins.[27] Anti-CCP can be used in the diagnosis and prediction of RA especially in recurrence cases. MBDA correlates with and might be a predictor of response to treatment.[28]

Anti-MCV may be used but with anti-CCP and RF negative. Other biomarkers, such as vascular endothelial growth factor-A (VEGF-A) and matrix metalloproteinase 3 (MMP3), are also reported to be correlated with disease activity.[29] Many studies concluded that 8-OHdG is a reliable and promising biomarker of oxidative stress and a valid predictor of functional outcomes in patients.[30-32] Saeed et al. found such a relationship in RA patients.[33] Despite the fact that oxidative stress has been extensively studied in the etiology of RA, it has been established that patients with RA exhibit a much stronger link with their plasma 8-OHdG levels.[34] Some studies have recently employed urinary 8-OHdG as a biomarker for measuring endogenous oxidative DNA damage, as well as for determining the risk of disease development and accelerated aging. Researchers consider it a good biomarker for assessing the risk of various cancers and degenerative diseases.[35]

MATERIALS AND METHODS

This study included 132 individuals (108 females and 24 males) were diagnosed with RA and 66 were healthy subjects (as control). Patients were examined and diagnosed as having definite RA according to the ACR/EULAR 2010 criteria by a specialist physician at Medical City of Baghdad. In addition to the ethical approval of the Baghdad Research Ethics Committee, informed consent was obtained from all participants. The selection of healthy controls was based on the absence of any congenital deformity, malignancy, or infectious diseases such as hepatitis C (HCV) or hepatitis B (HBV), acquired immune deficiency syndrome (AIDS).

In addition, no detection of inflammatory arthritis was made in the blood samples of the control subjects. Whereas, the subjects with a history of antibiotic therapy, corticosteroid drugs and non-steroidal anti-inflammatory drugs in the last three months were not included in this study. Furthermore, the other excluded group was individuals with any history of liver disease, cardiovascular disease, hypertension or diabetes. Smokers were also excluded from this study.

For this investigation, informed consent was obtained from each patient. All Samples were collected during the period between November 2022 and June 2024. The sera were conserved in a freezer at -20 0C until use. 8-OHdG was estimated in the sera of patients using the ELISA kit, Elabscience®, USA. According to the kit protocol, standards were prepared and followed by incubation, washing, conjugate enzyme addition, and the result was read at 450 nm. Furthermore, some blood parameters were detected, which included: white blood cells (WBC), hemoglobin (Hb), and erythrocyte sedimentation rate (ESR).

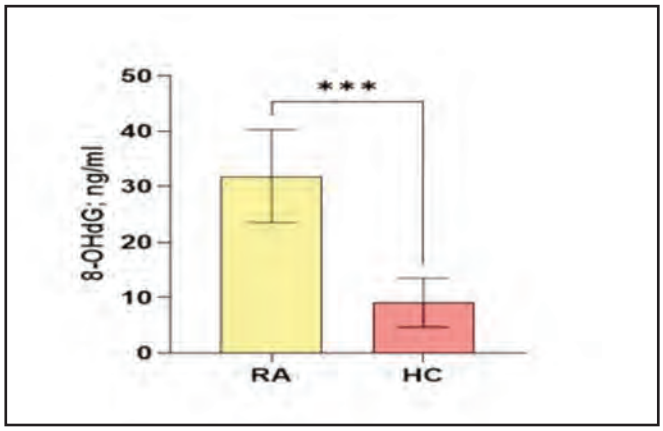

Fig. 1: Level of 8-OHdG in rheumatoid arthritis patient's sera. RA (n=66) and healthy controls HC(n=66). Values are given as mean and standard deviation, 31.9 ± 8.4 vs 9.1 ± 4.4 ng/ml; (*** p < 0.001)

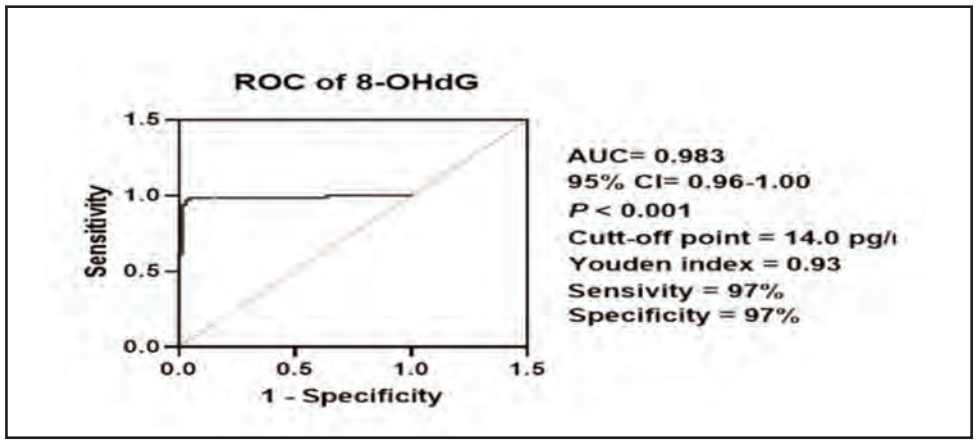

Fig. 2: Receiver operating characteristic (ROC) curve analysis. 8-OHdG in rheumatoid arthritis patients (n=66) versus healthy controls (n-66). The analysis demonstrated a high discriminatory power of 8-OHdG between patients and controls

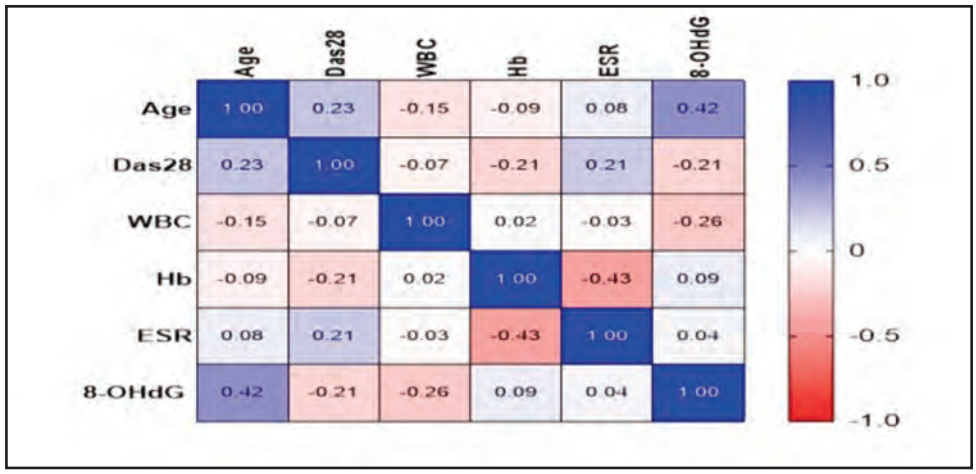

Fig. 3: Heat map matrix of correlation analysis baseline laboratory data in patients with RA. Values inside boxes indicate the correlation coefficient (rSp). The blue color indicates a positive correlation, while the red color indicates a negative correlation

Statistical analysis

The excel sheets had all of the readings, and SPSS v.16 was used to perform the statistics. The results were significant when the mean ± standard deviation ($p < 0.05$). Tests used included the Spearman correlation graph and the independent t-test.

RESULTS

Plasma level of 8-OHdG in RA patients is considered a critical biomarker of oxidative stress. The relationship between 8-OHdG level and RA was confirmed in this study. 8-OHdG measurement was achieved by the colorimetric method (ELISA Kit). The sensitivity range of this test was approximately 0.94-60 ng/ml with an assay time of two hours.

In this study, an analysis of samples aspirated from 66 RA patients revealed a significantly elevated concentration of 8-OHdG ($p = 0.001$). The levels of 8-OHdG were significantly high (31.9 ± 8.4) ng/ml at $p < 0.001$ compared with healthy controls (9.1 ± 4.4) ng/ml at $p < 0.001$ (Figure 1). High discriminatory power of 8-OHdG was shown between patients and controls (Figure 2). Some hematological parameters were studied in both patients and healthy groups in this work to explore the relationship between 8-OHdG and these parameters in RA (Figure 3). The heat map matrix of correlation analysis between baseline laboratory data in patients revealed that there was a correlation between 8-OHdG and the age of patients, but a weak link was shown with the Disease Activity Score 28 (Das28).

DISCUSSION

RA is believed to be one of the main global chronic inflammatory diseases. Its impact is estimated to be 0.5-1.0% of the world's population.[33] Our study demonstrated that a serum level of 8-OHdG is significantly elevated in patients with RA in comparison to healthy controls. Because 8-OHdG is the main oxidized product resulting from DNA damage, the results of this study pointed increase in oxidative DNA deterioration in RA patients, which may take part in the pathogenesis of the disease. The high 8-OHdG levels in patients with RA could be connected to the hyperactivation of immune cells, increased production of pro-inflammatory cytokines, and mitochondrial dysfunction. Also, continual oxidative stress may take part in DNA damage, cellular dysfunction, and apoptosis, triggering synovial inflammation and the destruction of the joint.[35] The ROC (Receiver Operating Characteristic) curve analysis for 8-OHdG in this study estimates its effectiveness in differentiating RA patients from healthy controls. The results suggest that 8-OHdG might be a highly dependable biomarker for the diagnosis of RA, with minimal false positives and false-negative results. The 97% sensitivity and 97% specificity contribute to its high accuracy; as a result, this biomarker could be used for early monitoring of disease progression. The heatmap matrix of correlation analysis between baseline laboratory data in patients with RA indicates correlation coefficients (p-value). 8-OHdG shows a positive correlation with age ($p=0.42$), which suggests that oxidative stress is increased with aging in RA patients. On the other hand, it shows a weak negative correlation with DAS28 ($p=0.21$), suggesting that oxidative stress may not strongly align with clinical disease activity. Finally, it indicates no significant correlation with inflammation markers (ESR, WBC) ($p=0.43$), indicating that 8-OHdG might be more linked to oxidative stress mechanisms than the traditional inflammatory pathway.[36]

CONCLUSION

In this study, selected RA patients' plasma levels revealed elevated levels of 8-OHdG, indicating oxidative DNA damage when compared with the plasma levels of healthy subjects. So, it appears there is a correlation with the pathogenesis and intense inflammatory damage to the joints of patients with RA. Thus, 8-OHdG might be a useful biomarker to monitor RA activity.

CONFLICT OF INTEREST

The authors declare that there is no actual or potential conflict of interest in relation to this article.

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Cost analysis of returned medicines at the outpatient pharmacy of a Malaysian state hospital

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ABSTRACT

Introduction: Returning unused medications to pharmacies is encouraged to reduce environmental pollution and safety hazards. However, this practice can impose financial losses on public health providers due to wasted drug supplies. This study aimed to quantify the costs of returned medicines at a Malaysian state hospital outpatient pharmacy and to characterise the returned items by therapeutic class and procurement category.

Materials and Methods: This was a prevalence-based, bottom-up cost-analysis study of all solid medicines at the outpatient pharmacy of Hospital Tuanku Fauziah from May to October 2023. Returned items (tablets/capsules) were collected, identified by WHO Anatomical Therapeutic Chemical (ATC) class and hospital's Always Better Control (ABC) inventory group, and recorded. Acquisition costs were obtained from hospital procurement records, and retail values were estimated using the Malaysian Consumer Price Guide. Disposal cost was calculated based on the contracted waste service. Descriptive statistics were used to summarise quantities and costs.

Results: The total government acquisition cost for returned medicines was RM18,487, with a retail replacement value of RM101,300. The top five returned medicines by quantity were metformin (14.3%), atorvastatin (6.9%), calcium carbonate (5.3%), ferrous fumarate (3.8%) and trimetazidine MR (3.8%). The top three pharmacological groups returned were cardiovascular system (39.6%), alimentary/endocrine (31.7%), and blood and blood-forming organs (10.9%). Group A medicines, according to ABC analysis, constituted the highest return in both acquisition cost (66.8%) and quantity (34.1%). The median (IQR) acquisition and retail values of medicines returned per month were RM5,429 (8,010) and RM19,609 (12,027), respectively. The monthly disposal cost ranged RM22.32-55.80 (excluding transportation fees).

Conclusion: Returned medicines lead to significant financial losses from both medication wastage and disposal for public providers. Shorter refill durations, medication adherence support, deprescribing and controls on high-value ABC group A items could reduce wastage.

KEYWORDS:
Returned medicines, cost analysis, outpatients, pharmaceuticals

INTRODUCTION

Medicines return programmes aim to prevent environmental contamination and improper disposal of unused medicines, aligning with national sustainability strategies. In Malaysia, the Ministry of Health Malaysia launched the "Return Your Medicines" (RYM) programme in 2010, subsequently improvised to relaunch as MyMediSAFE in 2024, to route unused medicines back to health facilities for safe disposal; returned items are not reused to safeguard quality and safety.[1-2] Previous studies have attributed returns to factors such as non-adherence, therapy changes, oversupply, adverse effects and expiry.[3-5]

Given Malaysia's highly subsidised public healthcare, wastage can accumulate materially.[6] Co-payment models have been proposed as one lever to reduce unwarranted demand.[7] Hospital Tuanku Fauziah (HTF), a state hospital in Perlis, Malaysia, was granted RM22 million in 2023 to procure medicines, as reported by the logistic pharmacy. In a logistic pharmacy unit of a public hospital, "Always Better Control" (ABC) analysis is normally used to monitor inventory and categorise the medicines based on their cost allocation. Group A medicines have the highest annual usage, accounting for 10–20% of medicines ordered and allocated 70% of the total budget. Group B medicines represent moderate annual usage, accounting for 10–20% of medicines ordered and allocating 20% of the total budget. Meanwhile, group C medicines account for the lowest annual usage, comprising 60–80% of medicines ordered and allocating 10% of the total budget. Within hospital inventory control, ABC analysis prioritises high-value drugs; if many returns are group A, monetary losses are amplified.

Despite environmental benefits, returns entail economic loss from acquisition spending on unused stock and incremental disposal costs borne by public providers. Prior Malaysian reports[2,5] described wastage primarily using acquisition prices, with limited triangulation against retail pricing or inventory priority frameworks such as ABC analysis, and with variation across settings regarding drug groups most often returned. The present study addresses these gaps by providing, for the first time in the Malaysian setting, a simultaneous quantification of acquisition and retail costs of returned medicines, coupled with World Health Organisation (WHO) Anatomical Therapeutic Chemical (ATC) and ABC inventory stratification to identify high-value waste items.

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This dual–perspective analysis allows direct comparison of the financial impact on the public provider and the broader societal replacement cost.

MATERIALS AND METHODS

A prevalence-based, bottom-up cost analysis was performed at the outpatient pharmacy of HTF. The bottom-up costing approach was employed as the individual returned items were counted and valued using unit acquisition cost (AC) and estimated retail price (RP). The analysis covered medicines returned by patients/caregivers at the pharmacy counter from May to October 2023. Returned solid oral dosage forms (tablets/capsules) dispensed by the outpatient pharmacy were included, while items without labels or originating from other facilities; non-tablet/capsule dosage forms were excluded. Non–solid dosage forms and unlabelled items were excluded because only tablets/capsules could be reliably identified and quantified against procurement records, and items without labels could not be verified for origin or safety, in line with standard return programme protocols.

Returned medicines were collected in a designated bin, identified and recorded. Items were classified by WHO ATC pharmacological grouping and by the ABC inventory group according to local procurement categorisation. AC was obtained as unit prices from hospital pharmacy procurement records, reflecting the direct public provider loss. RP was as mapped from the Malaysian Consumer Price Guide[7], reflecting private sector replacement value to communicate the broader market-equivalent value of wasted medicines. A simple sensitivity analysis was also applied to the RP estimate by varying unit prices by ±10% to gauge the robustness of the total RP. AC was not subjected to sensitivity analysis because it was obtained from hospital procurement records. Disposal cost was the per-kilogram rate quoted by the hospital support services contractor; recorded monthly ranges were calculated from observed weights of returns.

Descriptive statistics summarised volumes, AC and RP totals and medians, distributions by ATC classification and ABC grouping, and top medicines by quantity and value. No imputation or inferential tests were conducted. The study was purely descriptive because the objective was to quantify and characterise the return load without hypothesis testing. Ethical approval was obtained from the Medical Research & Ethics Committee, MOHM (NMRR ID-22-01404-D4Q) before the study was conducted.

RESULTS

A total of 124,435 tablets/capsules were returned to the outpatient pharmacy. The calculated AC was about RM 18,486.61, which translated into a RP of RM 101,300.00. Sensitivity analysis varying the RP guide values by ±10% produced a total RP of RM91,170-111,430. The median (IQR)AC and RP of medicines returned per month of RM5,428.85 (8,010.35) and RM19,607.71 (12,026.78), respectively.

The top five medicines returned by quantity were metformin (14.3%), atorvastatin (6.9%), calcium carbonate (5.3%), ferrous fumarate (3.8%) and trimetazidine MR (modified release) (3.8%). However, trimetazidine MR was the most returned in terms of the AC, which is around RM1,351.00, followed by metformin (RM1,344.53) and atorvastatin (RM1,070.12). By pharmacological patterns (ATC), cardiovascular medicines constituted the largest share of returned items by quantity (≈40%), followed by alimentary tract and metabolism/endocrine (≈32%), then blood and blood-forming organs (≈11%). Other groups (nervous system, musculoskeletal, respiratory, others) contributed smaller proportions (Figure 1).

According to ABC analysis, RM2,275,083.96 was spent in 2023 for medicines expenditure. The AC of medicines returned from May to October 2023 were 0.8% of the total expenditure in 2023.

The top ten medicines accounted for RM7,951.94, approximately 43.0% of total AC (Table I). The highest cost based on AC was trimetazidine 35mg MR. Pantoprazole 40mg was the most expensive in terms of RP. However, neither medicines were not the most returned in terms of quantity, but was metformin 500mg. While metformin accounted for the largest share of returned units, trimetazidine MR, as a higher–cost cardiac drug, generated the greatest acquisition cost, highlighting the importance of examining both volume and value.

The majority of medicines returned by quantity (Figure 1) and five out of the top ten (Table I) by AC were cardiovascular agents. Pantoprazole was found to be the highest RP replacement among medicines returned.

ABC analysis revealed that group A medicines constituted the in the highest total returned AC (66.8%) and a proportionally high item-return (34.1%) (Table II). Group A comprised

Table I: Top ten medicines returned by acquisition cost

Tablet	Quantity (Tab/Cap)	AC (RM)/Tab	Total AC (RM)	RP (RM)/Tab	Total RP (RM)
Trimetazidine 35mg MR (I)	4,475	0.30	1,351.00	1.62	7,249.50
Metformin 500mg (G)	17,041	0.08	1,344.53	0.16	2,726.56
Atorvastatin 20mg (G)	8,238	0.13	1,070.12	0.93	7,661.34
Ferrous Fumarate 200mg (G)	4,493	0.21	943.53	0.56	2,516.08
Clozapine 100mg (I)	754	0.91	687.20	3.75	2,827.50
Metoprolol Tartrate 100mg (G)	3,294	0.18	582.05	0.39	1,284.66
Pantoprazole 40mg (G)	3,003	0.19	557.66	3.4	10,210.20
Fenofibrate 145mg (I)	839	0.58	485.86	4.41	3,699.99
Calcitriol 0.25mcg (G)	1,837	0.26	477.44	1.58	2,902.46
Prazosin 2mg (G)	2,564	0.18	452.55	0.54	1,384.56

AC: Acquisition cost, RP: Retail price

Table II: ABC grouping based on total medicines returned

Group	Number of item	Percentage of item returned (%)	Total AC (RM)	Percentage of AC (%)
A	43	34.1	12,349.06	66.8
B	34	26.6	4,418.30	23.9
C	49	38.3	1,719.25	9.3
Total	126	100	18,486.61	100

AC: Acquisition cost

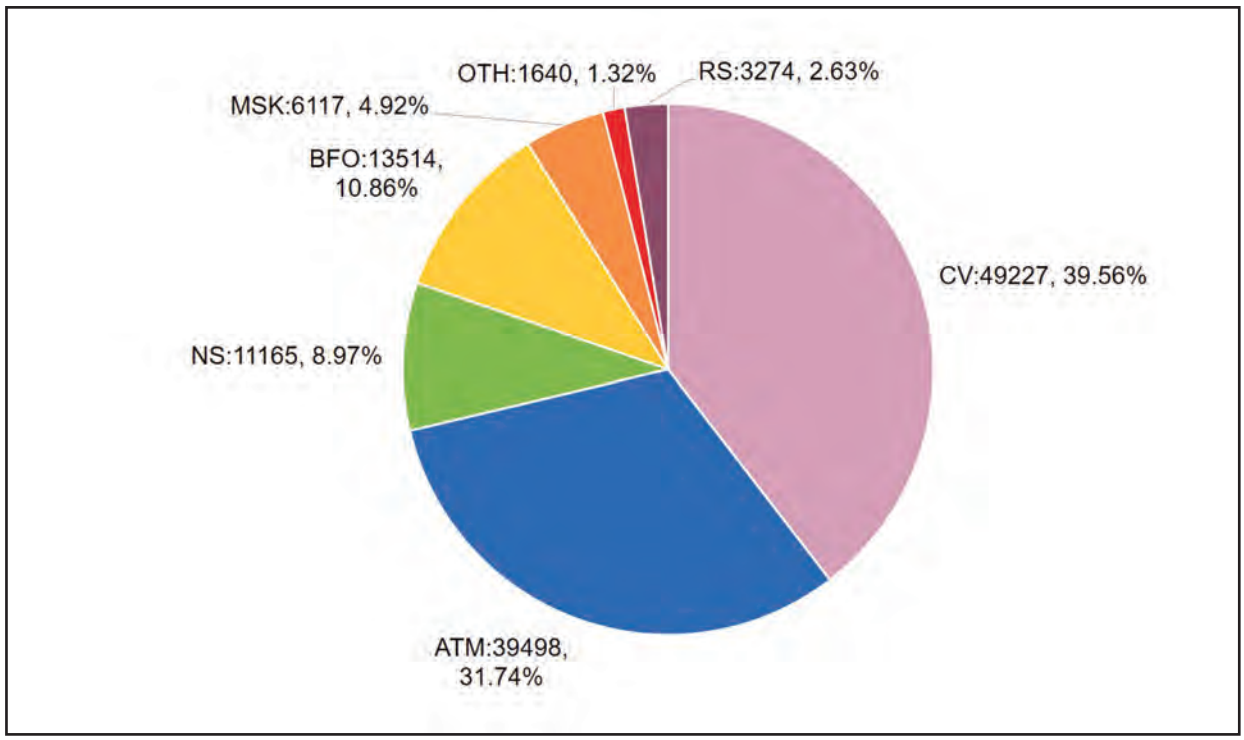

Fig. 1: Distribution of medicines returned by WHO ATC classification, expressed as percentage of total quantity (tablets/capsules)
Abbreviations: CV, cardiovascular system; ATM, alimentary tract and metabolism; BFO, blood and blood-forming organs; NS, nervous system; MSK, musculoskeletal system; RS, respiratory system; OTH, others.

expensive medicines that were highly prescribed by physicians. However, the types of medicine returned from group A were significantly higher and resembled group C. To illustrate the potential savings from targeted interventions, a 50% reduction in the wastage of group A items over the same six-month period would yield an estimated acquisition-cost saving of approximately RM6,175, or RM12,350 annualised. Even modest prevention among high-cost, high-volume group A drugs could therefore materially reduce financial losses.

At RM2.79/kg and ~2–5kg/week, the estimated disposal cost was RM22–56/month (excluding transport and packaging fees).

DISCUSSION

This study quantified the financial burden of outpatient medication returns in a Malaysian state hospital and profiled the returned items by therapeutic class and ABC inventory category. Three empirical patterns emerged: (1) cardiovascular and endocrine agents dominated returns by quantity (≈72% combined), reflecting the high prevalence of chronic diseases in our catchment population; (2) high-value (ABC group A) items, though representing only 34.1% of returned quantity, accounted for two-thirds (66.8%) of acquisition cost, indicating concentrated monetary loss among high-value inventory; and (3) the median RP (RM19,609/month) exceeded AC (RM5,429/month) by nearly four-fold, highlighting the broader societal opportunity cost beyond immediate budget impact. These patterns align with international reports wherein chronic-disease medicines comprise the largest share of unused or returned drugs, including studies from Oman and Italy.[8-9] Local experience at a Malaysian teaching hospital similarly documented substantial return volumes and costs.[5]

Expressing wastage in both AC and the estimated RP served different stakeholders. AC reflects the immediate budgetary loss to the public provider. RP, while not paid by our patients, approximates a market replacement value that is more intuitive to the public and can therefore help communicate the opportunity cost of returns. In Malaysia's highly subsidised context, even small percentages of wastage can

translate into meaningful absolute losses at system scale, reinforcing the need for stewardship.[6] Proposals such as minimal co-payments have been discussed nationally as one lever to reduce unwarranted demand; any exploration of such measures would require careful equity safeguards.[7]

The concentration of wastage among group A inventory items is operationally important. ABC analysis is designed to focus managerial control on the few, high-value items that consume most of the budget; finding that these same items constitute two-thirds of returned costs suggests an efficiency gap that targeted interventions could close. Practical levers supported by evidence on medication waste include shorter initial refill intervals (e.g., 2-4 weeks) for high-cost chronic therapies to test tolerance and adherence before issuing longer supplies; pharmacist-led medication reviews at refills; and structured deprescribing when risk–benefit turns unfavourable.[12-13] Education to avoid stockpiling and to improve disposal behaviours complements these changes.[1-2]

Specific therapeutic patterns in our data merit attention. Pantoprazole 40 mg generated the highest aggregate RP despite modest quantities returned, reflecting its high unit price and frequent gastroprotective prescribing in multimorbid patients. In our setting, proton-pump inhibitors (PPIs) were among the most commonly prescribed potentially inappropriate medications in older outpatients, indicating a priority area for medication review and deprescribing to reduce both clinical risk and waste.[11] Conversely, metformin 500 mg was the single most returned item by count, consistent with the large prevalent population with type 2 diabetes and the chronic, long-term nature of therapy. While our design did not capture patient-level reasons, previously described drivers: confusion, adverse effects, and regimen changes, likely apply.[3-5] Addressing these requires clearer counselling, regimen simplification where appropriate, and early follow-up after initiation to adjust therapy before large supplies accrue.[12-13]

Disposal costs in our study were modest relative to the value of the medicines themselves, yet they represent a recurring operational outlay and an environmental responsibility. Safe return and disposal programmes remain essential to protect public and environmental health, and continued public education on correct return practices is warranted.[1-2] Ultimately, preventing avoidable returns upstream will deliver the greatest gains by reducing both wastage and disposal costs.[12-13]

For the most–returned group A cardiovascular and endocrine drugs, short initial supplies and pharmacist–led adherence checks could directly reduce the oversupply. At the facility level, a pragmatic bundle could include: (i) default shorter initial supplies for ABC group A drugs and for patients newly started on long-term therapy; (ii) pharmacist-delivered adherence checks and medication reviews at each repeat; (iii) targeted deprescribing audits for medicines frequently returned (e.g. PPIs in older adults); and (iv) dashboards that track returns and costs by ABC group and ATC class to guide feedback to prescribers.[12-13]

Recent international evidence further supports interpreting medicine returns as a health-system stewardship issue rather than only a disposal activity. The Organisation for Economic Co-operation and Development (OECD) has highlighted unused or expired medicines as a source of environmental risk, public health risk and wasted healthcare resources and recommends combined strategies involving waste prevention, separate collection or take-back systems, public awareness and clear financing or governance arrangements.[14] Similarly, a 2024 systematic review of unused medicine take-back programmes across 15 countries found that better-performing programmes were characterised by accessible collection points, regular collection schedules, clear programme ownership and legislation defining financial responsibilities.[15] The same review reported that returned medicines commonly involved the nervous system, cardiovascular system, alimentary tract and metabolism groups,[15] which is broadly consistent with the therapeutic pattern observed in the present study. At the system level, sustained public messaging on the MyMediSAFE programme and patient engagement around not stockpiling medicines may curb returns, particularly for high-cost ABC group A chronic-disease medicines. Any consideration of cost-sharing as a demand-management tool should be evaluated prospectively for impact on access and equity.[7]

The study's strengths include bottom-up costing of all returned solid oral medications over six months, linkage to ABC groups, and expression of waste in both AC and RP to address different audiences. This study is not without its limitations. The single–centre design limits generalisability, although HTF is a typical state hospital serving a predominantly rural population, suggesting relevance to similar settings. The six–month period precludes assessment of seasonal variation in return patterns. Exclusion of non–tablet/capsule dosage forms and unlabelled items almost certainly leads to an underestimation of total medication wastage; future studies should capture all dosage forms.

We also did not apply VEN categorisation alongside ABC, which could further inform prioritisation. These constraints likely bias our estimates towards under-counting total wastage and limit causal inference. We were unable to relate returned quantities to per–product dispensing volumes because full utilisation data were unavailable at the drug–specific level; consequently, return rates could not be expressed as a proportion of dispensed medicines, limiting the assessment of relative wastage for individual agents.

While our design did not capture patient–level reasons, the same factors commonly reported in the literature,3-5 including confusion, adverse effects and regimen changes, are likely contributors to the high volumes of metformin and cardiovascular returns observed. Additionally, only medicines returned through formal pharmacy channels were captured, so informal disposal or stockpiling at home was missed, potentially biasing the cost estimates downward.

Multi-centre, year-round surveillance capturing patient-reported reasons for returns would better characterise drivers and seasonal effects. Embedding and evaluating targeted

interventions (shorter initial refills, pharmacist review, deprescribing prompts) using quality-improvement or stepped-wedge designs could quantify reductions in returns, particularly among ABC group A items. Adding ABC-VEN mapping could help align stewardship with clinical criticality.

CONCLUSION

Medication returns in this public hospital setting represent a substantial and quantifiable financial loss, driven primarily by the wastage of high-value, high-priority medicines prescribed for chronic diseases. The significant margin between the government's acquisition cost and the societal retail value highlights the full economic impact of this preventable loss. Developing patient education tools, particularly for high-return therapeutic classes (cardiovascular, endocrine) and ABC group A items, could communicate the societal value of medications, foster patient stewardship and support the sustainability of healthcare resources.

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ORIGINAL ARTICLE

Effectiveness of pursed lips breathing using a pinwheel on oxygenation status in children with pneumonia

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ABSTRACT

Introduction: Pneumonia is one of the causes of child death in the world. One of the non-pharmacological therapies given to overcome the impact of pneumonia in children is Pursed Lips Breathing (PLB) exercises. PLB is given to help overcome the ineffectiveness of airway clearance in patients with pneumonia by increasing the development of the alveoli in each lung lobe so that it can induce a normal breathing pattern and the child becomes more relaxed. The purpose of this study was to determine the effectiveness of PLB using pinwheel game on oxygenation status in children with pneumonia.

Materials and Methods: This study is a quantitative study using a quasi-experimental design using a pretest and posttest approach with control group design. This study consisted of two groups, namely the intervention group given PLB blowing a pinwheel with a penguin game, while the control group was given LPS. The study was conducted at Reksodiwiryo Army Hospital Padang with 15 respondents in the intervention group and 15 in the control group. Data analysis was carried out using a pooled t-test and paired t-test.

Results: The effectiveness of PLB using a pinwheel on oxygenation status in children with pneumonia found in this study can be used as evidence-based practice in treating children with pneumonia.

Conclusion: PLB can be used as an independent nursing intervention that can be implemented in hospitals.

KEYWORDS:
Children, Games, PLB, Respiratory Rate, Oxygen Saturation

INTRODUCTION

Children with pneumonia who come to the hospital will have an impact on the child's physical and psychological well-being. Psychologically, children will feel anxious due to the impact of hospitalization that can be experienced by children because they face stressors around the hospital environment. Feelings that are often experienced by children when being treated in the hospital are feeling anxious, angry, afraid, unfamiliar environment, separated from parents, lack of information, loss of freedom and loss of independence.[1]

The impact of children with pneumonia will experience oedema in the pulmonary alveoli which can provide opportunities for organisms and cause pneumonia. The inflammatory process in the lungs occurs in the tissue and lung capacity decreases, the bronchial narrows and mucus production increases.[2] This condition increases the resistance of the respiratory tract and decreases the expiratory volume of breathing. This can result in hypoxemia which is a complication of pneumonia that can cause death. Hypoxemia can be prevented by monitoring and evaluating oxygen administration. To maximize breathing in children with pneumonia, breathing exercises can be done using Pursed Lips Breathing (PLB) to train the lungs to do diaphragmatic breathing. Doing PLB can increase the residual capacity of the lungs during expiration after inspiration.[3] The PLB technique is used to activate the lungs, to increase alveolar pressure in each lobe of the lung so that it can increase air circulation during expiration and support improved gas exchange in the tissue. Doing PLB must be adjusted to the child's abilities.[4]

Hospitalized pneumonia patients often experience respiratory distress characterized by rapid breathing, chest retraction, nasal flaring and accompanied by stridor.[5] Both pharmacological and non-pharmacological therapies are given to help pneumonia patients, one of the non-pharmacological therapies given is PLB exercises. PLB is given to help overcome the ineffectiveness of airway hygiene in patients with pneumonia by increasing the development of the alveoli in each lobe of the lung so that alveolar pressure increases and can help push secretions into the airway during expiration and can induce normal breathing patterns.[6]

PLB exercises can also be performed on patients with severe airway obstruction, by opposing the lips during expiration, the respiratory pressure in the chest is maintained, preventing respiratory failure and collapse, during PLB the airways are open during expiration and will increase further, reducing shortness of breath and reducing the respiratory rate.[7] Modification of PLB using a pinwheel is effective in preschool children in reducing respiratory rate and increasing oxygen saturation in children with respiratory system problems.[8] Breathing exercises with PLB have stages that can help induce slow breathing patterns, improve oxygen transport, help patients control breathing and also train respiratory muscles, can also increase the exchange of O2 and CO2 gases that occur in the blood capillaries, which is caused by inflammation of the alveoli filled with fluid that makes it difficult for the body to get oxygen so that gas exchange cannot be carried out optimally, the accumulation

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of fluid between the capillaries and alveoli increases the distance that must be traveled by oxygen and carbon dioxide.

MATERIALS AND METHODS

This type of research is quantitative with a quasi-experimental design using a pre- and post-test with control group design approach. This study consists of an intervention group and a control group. The location of the study was at the Reksodiwiryo Army Hospital Padang from June to November 2023.

The population of this study were children with pneumonia who were treated at Reksodiwiryo Army Hospital Padang Hospital. The sampling technique used was probability sampling with consecutive sampling technique. The inclusion criteria in this study were children aged over 3 years with a diagnosis of pneumonia and willing to be respondents, while the exclusion criteria were children with a diagnosis of pneumonia but had other complications such as muscle weakness and children with labioschisis or labiopalatoschisis. The intervention group performed PLB for 3 cycles with 10 times for 2 minutes each cycle with an inspiration to expiration ratio of 1:2. The control group received standard intervention in the hospital. This study involved 15 people for each group with a total sample of 30 children. Ethical clearance was issued by the Ethical Committee of University of Perintis Indonesia No. 552/KEPK.F1/ETIK/2023.

Data analysis used univariate and bivariate analysis. Univariate analysis in this study was used to determine respiratory rate and oxygen saturation values. Bivariate analysis was conducted to determine the effect of PLB on oxygenation status in children with pneumonia. The bivariate test used in this study was a paired t-test to determine the mean respiratory rate and oxygen saturation.

RESULTS

Based on Table I, it shows that the average respiratory rate before PLB blowing a pinwheel in the intervention group was 41.33 times/minute and in the control group 40.93 times/minute. After PLB blowing a pinwheel in the intervention group was 27.73 times/minute and in the control group 36.60 times/minute. The average oxygen saturation before PLB blow the wheel in the intervention group was 93% and in the control group 92%. After PLB blow the wheel in the intervention group was 97.07% and in the control group 94.93%.

Based on table II, it shows that there is an effect of PLB intervention using a pinwheel on the respiratory rate in children with pneumonia with a p-value < 0.001 and there is an effect of PLB intervention using a pinwheel on oxygen saturation in children with pneumonia with a p-value < 0.001 at Reksodiwiryo Army Hospital Padang.

Table I: Mean respiratory rate and oxygen saturation before and after PLB blowing a pinwheel in children with pneumonia at Reksodiwiryo Army Hospital Padang (n=30)

Group	Mean ± SD	CI 95%
Respiratory Rate		
Intervention		
Before	41.33 ± 7.835	36.99 – 45.67
After	27.73 ± 5.750	24.55 – 30.92
Control		
Before	40.93 ± 6.670	37.24 – 44.63
After	36.60 ± 6.379	33.07 – 40.13
Oxygen Saturation		
Intervention		
Before	93 ± 3.873	90.86 – 95.14
After	97.07 ± 2.463	95.70 – 98.43
Control		
Before	92.40 ± 3.814	90.29 – 94.51
After	94.93 ± 2.120	93.76 – 96.11

Standard deviation (SD), confidence interval (CI)

Table II: Differences in respiratory rate and oxygen saturation before and after PLB Blowing a pinwheel in children with pneumonia at Reksodiwiryo Army Hospital Padang (n=30)

Variables	Intervention			p-value	Control			p-value
	Mean	SD	95%CI		Mean	SD	95%CI	
Respiratory Rate								
Before	41.33	7.835	11.021 ; 16.179	< 0.001*	40.93	6.670	3.382 ; 5.285	< 0.001*
After	27.73	5.750			36.60	6.379		
Oxygen Saturation								
Before	93	3.873	-5.014 ; -3.120	< 0.001*	92.40	3.814	-3.677 ; -1.389	< 0.001*
After	97.07	2.463			94.93	2.120		

Standard deviation (SD), confidence interval (CI) *Significant at p<0.05

DISCUSSION

Average Respiratory Rate and Oxygen Saturation Before PLB Blowing a Pinwheel in Children with Pneumonia

The results of the study showed that the average respiratory rate before PLB was performed in the intervention group was 41.33 times/minute and in the control group 40.93 times/minute. The average oxygen saturation before PLB was performed in the intervention group was 93 times/minute and in the control group 92 times/minute. This is in line with a study conducted by Arisa on the application of PLB therapy in children with pneumonia, data was obtained that the child's respiratory rate had a mean value of 37 and oxygen saturation of 93%. The respiratory rate is included in the fast category and the oxygen saturation in children is abnormal.[9]

Based on the results of respiratory rate measurements in this study, it was found that respondents with rapid breathing frequency and oxygenation status were included in the abnormal category. One of the factors that affects respiratory rate is body temperature, especially in feverish conditions. Fever will increase the need for oxygen for tissues and as a result carbon dioxide will increase. The body will try to adapt to the increase in carbon dioxide by increasing the depth and speed of breathing. In patients with pneumonia, obstruction of the upper or lower airways was found which can limit the delivery of inhaled oxygen to the alveoli.[10] If the concentration of inhaled oxygen decreases, the capacity of the blood oxygen content will also decrease. This is because in patients with pneumonia there is lung inflammation which has an impact on the disruption of oxygen fulfillment.[6]

Based on research conducted by Sadat stated that before the application of PLB on An. A and An. M, the results of oxygen saturation measurements were 95% and 93%.[3] Another study conducted by Muliasari and Indrawati regarding the application of PLB obtained results before the application with an average in the intervention group before being given PLB was 28 times/minute and a standard deviation of 6.088 and a standard error of 1.435.[11]

Mean Respiratory Rate and Oxygen Saturation After PLB Blowing a Pinwheel in Children with Pneumonia

The results of the study showed that the average respiratory rate after PLB with a pinwheel in the intervention group was 27.73 times/minute and in the control group 36.60 times/minute. The average oxygen saturation after PLB with a pinwheel in the intervention group was 97.07% and in the control group 94.93%. The results of the study showed that after PLB with a pinwheel, the average respiratory rate was 28.17% and oxygen saturation was 97.50%. This study agrees with the study conducted by Arisa et al., which explained that after the application of PLB, it showed that the respiratory rate was included in the fast category and oxygen saturation was included in the normal category. Measurement of oxygenation status was carried out after the provision of PLB intervention using pulse oximetry to measure oxygen saturation and calculate the respiratory rate manually.[10]

This is in line with the research of Devia which states that PLB is a breathing exercise in the form of breathing or inspiration through the nose for 2-3 seconds followed by slow expiration through the mouth for at least 2 inspirations (4-6 seconds) which is carried out for 30 minutes with a tolerance of 5 minutes of rest for 3 times (5 interventions, 5-minute rest interval, continued 5 minutes to 2 and 5 minutes of rest interval, then 5 minutes to 3 and rest/finish time for 5 minutes) then oxygen saturation is measured using a pulse oximeter.[12]

Another study conducted by Indrawati et. al showed that the average respiratory rate in the intervention group after being given PLB by blowing a pinwheel was 26.11 times/minute with a standard deviation of 5.487.[11] This is in accordance with the study conducted by Azizah et al. where the PLB action was given for 3 days, each day carried out 2 times of exercise in the morning and evening, and each exercise was done for 10 minutes.[10]

The application of PLB blowing a pinwheel is part of the breathing exercises needed for patients who experience disorders of the respiratory system, because PLB has a good effect on the respiratory system, including increasing ventilation, releasing air trapped in the lungs, keeping the airways open longer and reducing the work of breathing, prolonging the exhalation time which then slows down the breathing frequency, and introducing new air into the lungs, eliminating shortness of breath and increasing relaxation.

Physiologically, the PLB technique blowing a pinwheel can improve the flexibility of the chest cavity and diaphragm and train the expiratory muscles and increase airway pressure during expiration and this exercise can also induce breathing patterns, especially breathing frequency, into slow and shallow breathing and is done for 5-10 minutes in the morning.[13]

The Effect of PLB Blowing a Pinwheel on Respiratory Rate and Oxygen Saturation in Children with Pneumonia

The results of the study showed that there was an effect of PLB intervention blowing a pinwheel on the respiratory rate in children with pneumonia with a p-value < 0.001 and there was an effect of PLB intervention blowing a pinwheel on oxygen saturation in children with pneumonia with a p-value < 0.001 at Reksodiwiryo Army Hospital Padang. PLB is breathing through the lips using a pinwheel toy that can help train respiratory muscles, slow expiration, prevent small airway collapse, and control the speed and depth of breathing.[6] PLB exercises blowing a pinwheel are useful for improving ventilation and increasing the work of the abdominal and thoracic muscles.

Research conducted by Anggreini explained that the average oxygen saturation results in respondents before being given PLB intervention were 92.93% and after being given the intervention the average oxygen saturation value became 97.87%. The mean difference in oxygen saturation before and after being given PLB intervention was -4.94. These results show that the average oxygen saturation after being given the intervention was higher than before being given the intervention.[12] Another study by Arisa also explained that there was an effect of giving PLB on changes in oxygenation status in toddlers with pneumonia with a p-value < 0.001 and

there was a significant effect on children's airway clearance with a p-value < 0.001.[10]

PLB is also one of the easiest techniques to reduce shortness of breath. The same study also showed that the application of PLB in children with pneumonia can significantly affect the respiratory rate and oxygen saturation. Changes in respiratory rate and oxygen saturation are not only influenced by PLB. There are several things that can affect the oxygenation status of children with pneumonia, one of which is chest physiotherapy, positioning, oxygenation therapy and collaboration in administering drugs. This can affect changes in respiratory rate and oxygen saturation in children with pneumonia. So that the PLB intervention can be used as a supporting therapy which is also an independent nursing intervention that can be implemented with other therapies according to the interventions prepared by nurses in dealing with toddlers with pneumonia.

In addition, PLB is one of the easiest techniques to reduce shortness of breath. This technique is an easy way to reduce the frequency of breathing so that breathing becomes more effective. This technique can help to produce a lot of air into the lungs and reduce the energy expended when breathing. PLB can also increase alveolar pressure in each lobe of the lung so that it can increase air flow during expiration. Increased air flow during expiration will evacuate secretions out of the airways. This action is one of the efforts that can increase oxygenation because it can increase ventilation, free air trapped in the lungs, reduce the work of breathing, prolong exhalation which can slow down the frequency of breathing.[8]

CONCLUSION

The application of PLB using the windmill game is effective in improving oxygenation status in children with pneumonia. PLB pinwheel in this study is an implication of the application of nursing intervention classification and is also an independent nursing action. This can be used as a follow-up plan for hospitals conducting research to be applied by nurses in the pediatric inpatient room to be applied to children with pneumonia.

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ORIGINAL ARTICLE

Chronic kidney disease in type 2 diabetes: Identifying key risk factors from Johor national diabetes registry study

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ABSTRACT

Introduction: Chronic kidney disease (CKD) is a common and important complication among patients with, contributing to substantial morbidity and adverse clinical outcomes. This study aimed to determine the factors associated with CKD among patients with T2DM in Johor, Malaysia.

Materials and Methods: This was a registry-based cross-sectional study using secondary data from the Malaysian National Diabetes Registry (NDR). The study included patients with T2DM captured in the Johor NDR during the 2020-2021 audit cycle. CKD status was determined by calculating the estimated glomerular filtration rate (eGFR) using the CKD Epidemiology Collaboration (CKD-EPI) formula based on serum creatinine and relevant patient variables extracted from the registry. Patients were operationally classified as having CKD if the available registry-derived eGFR was <60 mL/min/1.73 m². Sociodemographic, clinical, biochemical, diabetes-related complication, and medication-related variables were analysed. Univariate analysis was performed using Chi-square test or Fisher's exact test, and variables with p<0.05 were entered into multivariable logistic regression to identify factors independently associated with CKD among patients with T2DM.

Results: A total of 10,117 patients with T2DM were included, of whom 2,387 (23.6%) had CKD. Factors independently associated with CKD were age ≥60 years (aOR: 2.97, 95% CI: 2.60, 3.38), hypertension (aOR: 1.37, 95% CI: 1.10, 1.70), diabetes duration >10 years (aOR: 1.84, 95% CI: 1.58, 2.14), abnormal triglyceride (aOR: 1.59, 95% CI: 1.42, 1.79), abnormal high-density lipoprotein (HDL) (aOR: 1.26, 95% CI: 1.13, 1.40), diabetic retinopathy (aOR: 1.22, 95% CI: 1.06, 1.40), cerebrovascular disease (aOR: 1.40, 95% CI: 1.06, 1.85), and diabetic foot ulcer (aOR: 2.40, 95% CI: 1.68, 3.41). Medication-related associations were observed but should be interpreted cautiously because of potential confounding by indication and reverse causation.

Conclusion: CKD affected nearly one-quarter of patients with T2DM in this Johor registry-based study. Older age, hypertension, longer diabetes duration, lipid abnormalities, diabetic retinopathy, cerebrovascular disease, and diabetic foot ulcer were independently associated with CKD. These findings provide useful real-world evidence to support earlier risk identification and future development of a locally derived CKD risk prediction model among Malaysian patients with T2DM.

KEYWORDS:
Type 2 Diabetes Mellitus, Chronic Kidney Disease, Diabetic Kidney Disease, National Diabetes Registry

INTRODUCTION

Type 2 diabetes mellitus (T2DM) remains a major global public health problem and is a well-recognised cause of chronic vascular and renal complications. In Malaysia, diabetes continues to impose a substantial burden with 15.6% of Malaysian adults having diabetes.[1] Among patients with T2DM, chronic kidney disease is clinically important because it is associated with increased morbidity, mortality, cardiovascular complications and healthcare utilisation.[2]

Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function, which present for at least three months.[3] In Malaysian clinical practice, patients are classified as having CKD when the estimated glomerular filtration rate (eGFR) is below 60 mL/min/1.73 m² for a minimum of three months.[4] Among individuals with T2DM, CKD is of particular importance because chronic hyperglycaemia promotes renal injury through interrelated metabolic and hemodynamic disturbances, together with inflammation and oxidative stress, which collectively accelerate structural and functional decline.[5]

The National Diabetes Registry (NDR) of Malaysia provides a valuable source of real-world clinical data, particularly from public primary care clinics, allowing evaluation of chronic disease patterns, complications and treatment practices in routine care settings.[6] Since its establishment in 2009, NDR reports have captured heterogeneity across states in patient characteristics and diabetes care performance, indicating that regional differences in demographic composition and clinical outcomes. Thus, underscoring the relevance of state-specific analyses.

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Therefore, this study aimed to determine factors associated with CKD among patients with T2DM in Johor using data from the NDR. Identifying these factors will provide the foundation for future development of a locally derived predictive model for CKD risk among Malaysian patients with T2DM. This analysis represents an early step toward identifying reliable, evidence-based predictors for inclusion in a future risk prediction tool tailored to the clinical and demographic context of Malaysia. This study aligns with the United Nations Sustainable Development Goal 3 (SDG 3) by addressing the burden of non-communicable diseases (NCDs), particularly type 2 diabetes and CKD. By identifying risk factors with CKD, it supports prevention and early intervention strategies. The findings also complement the 13th Malaysia Plan, which emphasizes strengthening NCD management, promoting data-driven healthcare, and improving early detection to enhance health outcomes in Malaysia.

MATERIALS AND METHODS

Study design and data source

This was a registry-based cross-sectional study using secondary data from the NDR. The NDR of Johor captures standardised information such as patient demographics, clinical characteristics, biochemical profile, medication use and diabetes-related complications from public healthcare facilities across Johor state of Malaysia.

Study population and eligibility criteria

The study population comprised patients with T2DM recorded in the Malaysian NDR under Johor state during the 2020–2021 audit period. Patients were eligible for inclusion if they had a documented diagnosis of T2DM and were registered in the NDR. Cases were excluded if they had missing serum creatinine data, as serum creatinine was required to calculate eGFR using the CKD-EPI formula (Chronic Kidney Disease Epidemiology Collaboration) for determination of CKD status. Repeated or overlapping records referring to the same individual in the annual audited registry list were also excluded.

Outcome variable

The dependent variable in this study was CKD. For this registry-based cross-sectional analysis, CKD status was operationally determined using the eGFR calculated from serum creatinine values and other relevant variables available in the NDR audit dataset. The eGFR was calculated using the CKD-EPI equation. Patients with an eGFR <60 mL/min/1.73 m² were classified as having CKD, whereas those with an eGFR ≥60 mL/min/1.73 m² were classified as not having CKD.[4] Although the clinical diagnosis of CKD conventionally requires evidence of persistent kidney abnormality for at least three months, longitudinal data were unavailable to confirm the persistence of reduced eGFR in the analysed registry.

Independent variables

The independent variables included sociodemographic, anthropometric measurements, clinical characteristic, biochemical, diabetes-related complications, and medication-related factors available in the registry.

Sociodemographic variables comprised age, sex, ethnicity, and smoking status. Clinical characteristics included duration of diabetes, body mass index (BMI), mean arterial pressure (MAP), hypertension, and dyslipidaemia. Biochemical parameters included glycated hemoglobin (HbA1c), total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol. Diabetes-related complications recorded in the registry included retinopathy, cerebrovascular disease, diabetic foot ulcer and ischaemic heart disease.

Medication-related variables included use of oral hypoglycaemic agents such as metformin, sulfonylureas, alpha-glucosidase inhibitors, meglitinides, and glitazones; insulin; antihypertensive medications such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), beta blockers, calcium channel blockers, diuretics, alpha blockers, and centrally acting agents; lipid-lowering agents such as statins and fibrates; and antiplatelet agents such as acetylsalicylic acid and ticlopidine.

In this study, all variables were categorised into categorical formats to facilitate descriptive and inferential analyses. For binary variables, the reference or normal category was generally coded as 0, while the abnormal or risk category was coded as 1. Continuous variables, including anthropometric and biochemical parameters, were categorised based on established guideline thresholds or clinically meaningful cut-off points before analysis.

Data management

Data cleaning was performed prior to analysis. Duplicate and overlapping records were removed, and records with missing serum creatinine values were excluded because CKD status could not be determined without serum creatinine-derived eGFR. Serum creatinine values were extracted from the registry and used to calculate eGFR for each patient. CKD status was then derived from the calculated eGFR values. As all independent variables were analysed in categorical format, missing categorical covariate values were handled using the imputation approach adopted from a previous registry-based study.[7] Binary variables were coded numerically, with reference or normal categories generally coded as 0 and abnormal or risk categories coded as 1. Missing values were estimated on this numeric scale. Imputed values greater than 0.5 were subsequently recorded as 1, while imputed values less than 0.5 were recoded as 0. All data were anonymized prior to analysis.

Statistical analysis

Data were analysed using IBM SPSS software version 30. A two-tailed approach was applied, and a p-value <0.05 was considered statistically significant. As all study variables were categorical, descriptive results were presented as frequencies and percentages. Univariate analysis was performed to examine the association between each independent variable and CKD status using Chi-square test or Fisher's exact test, as appropriate, based on expected cell counts.

Variables with p-value less than 0.05 in the univariate analysis were subsequently entered into the multivariable logistic regression model to determine factors independently associated with CKD among patients with T2DM. Adjusted

odds ratios (aORs) with 95% confidence intervals (95% CI) were reported. Collinearity among variables was assessed using variance inflation factors. Model fit and performance were assessed using the Omnibus test of model coefficients, Hosmer–Lemeshow goodness-of-fit test, Cox and Snell R^2, Nagelkerke R^2, classification accuracy, and the area under the receiver operating characteristic (ROC) curve. Sensitivity analyses were not performed in this study.

Ethical approval

Ethical approval for this study was obtained from the Medical Research Ethics Committee, Ministry of Health Malaysia (NMRR ID-25-03586-8SK (IIR)) and the Research Ethics Committee, UiTM (REC/01/2026 (PG/EX/8)).

RESULTS

A total of 14,747 Johor NDR records from the 2020–2021 audit dataset was initially screened. After removal of duplicate or overlapping records (n=3,584) and records with missing serum creatinine values (n=1,046), 10,117 patients with T2DM were included in the final analysis. The extent of missingness for other study variables ranged from 5.7% to 20.0%. Of the 10,117 patients with T2DM included in the final analysis, 2,387 patients had CKD, giving an overall prevalence of 23.6% (95% CI: 22.8, 24.4), while 7,730 patients did not have CKD (76.4%; 95% CI: 75.6, 77.2).

The baseline characteristics of the study population are presented in Table I. Most patients were aged 60 years and above (61.7%), female (60.9%), Malay (69.8%), and non-smokers (94.4%). In terms of anthropometric profile, 86.5% had increased waist circumference, while 46.0% were obese and 31.4% were overweight. A high proportion had hypertension (86.5%) and dyslipidaemia (84.8%) as comorbidities. With regard to diabetes duration, approximately one-third had lived with diabetes for more than 10 years. Poor glycaemic control was observed in 40.6% of patients. Abnormal triglyceride, HDL, and LDL levels were present in 34.6%, 40.6%, and 51.9% of patients, respectively. In addition, diabetic complications such as retinopathy, cerebrovascular disease, diabetic foot ulcer, and ischaemic heart disease were also recorded in a proportion of the study population. Metformin, statins, ACE inhibitors, and calcium channel blockers were among the most commonly used medications.

Univariate analysis demonstrated that multiple variables across sociodemographic, anthropometric measurement, clinical characteristic, biochemical, diabetes-related complication, and medication-related domains were significantly associated with CKD among patients with T2DM, as presented in Table II. Significant associations were observed for age group (p<0.001), ethnicity (p<0.001), body mass index (p<0.001), hypertension (p<0.001), dyslipidaemia (p<0.001), duration of diabetes (p<0.001), mean arterial pressure (p<0.001), HbA1c classification (p=0.011), total cholesterol (p=0.049), triglyceride (p<0.001), HDL (p<0.001) and LDL (p<0.001). In addition, diabetes-related complications, including diabetic retinopathy (p<0.001), cerebrovascular disease (p<0.001), diabetic foot ulcer (p<0.001), and ischaemic heart disease (p<0.001), were significantly associated with CKD. Several medication-related variables also showed significant associations with CKD status, namely metformin (p<0.001), sulfonylurea (p<0.001), insulin (p<0.001), aspirin (p<0.001), ticlopidine (p=0.041), ACE inhibitors (p<0.001), angiotensin receptor blockers (p<0.001), beta blockers (p<0.001), calcium channel blockers (p<0.001), diuretics (p<0.001), alpha blockers (p<0.01) statins (p=0.016), and fibrates (p=0.027). In contrast, gender, smoking status, waist circumference, alpha-glucosidase inhibitor use, meglitinides, glitazones, and centrally acting antihypertensives were not significantly associated with the presence of CKD in the univariate analysis.

The multivariable logistic regression analysis results are presented in Table III, and the adjusted effects of statistically significant factors are illustrated in Figure 1. After adjustment for confounders, several factors remained independently associated with CKD among patients with T2DM. Older age was a strong predictor, with patients aged 60 years and above having nearly three times the odds of CKD compared with those aged below 60 years (aOR 2.97, 95% CI: 2.60–3.38, p<0.001). Hypertension was also independently associated with CKD (aOR 1.37, 95% CI: 1.10–1.70, p=0.006). Patients with diabetes duration of more than 10 years had higher odds of CKD compared with those with diabetes duration of less than 5 years (aOR 1.84, 95% CI: 1.58–2.14, p<0.001), whereas duration of 5–10 years was not statistically significant.

Among biochemical variables, abnormal triglyceride level (aOR 1.59, 95% CI: 1.42–1.79, p<0.001) and abnormal HDL level (aOR 1.26, 95% CI: 1.13–1.40, p<0.001) remained independently associated with CKD. Poor HbA1c control showed an inverse association with CKD (aOR 0.70, 95% CI: 0.61–0.81, p<0.001), while intermediate HbA1c control was not significant. Complication-related factors independently associated with CKD were diabetic retinopathy (aOR 1.22, 95% CI: 1.06–1.40, p=0.005), cerebrovascular disease (aOR 1.40, 95% CI: 1.06–1.85, p=0.019), and diabetic foot ulcer (aOR 2.40, 95% CI: 1.68–3.41, p<0.001). Ischaemic heart disease did not remain statistically significant in the final model.

Several medication-related variables also remained associated with CKD in the adjusted model. Nonuse of insulin was associated with higher odds of CKD among T2DM patients (aOR 1.55, 95% CI: 1.36–1.76, p<0.001), as were nonuse of angiotensin receptor blockers (aOR 1.23, 95% CI: 1.01–1.50, p=0.042), beta blockers (aOR 1.61, 95% CI: 1.44–1.80, p<0.001), calcium channel blockers (aOR 1.23, 95% CI: 1.09–1.39, p<0.01), diuretics (aOR 1.49, 95% CI: 1.32–1.69, p<0.001), and alpha blockers (aOR 2.25, 95% CI: 1.86–2.72, p<0.001). In contrast, nonuse of metformin (aOR 0.20, 95% CI: 0.17–0.22, p<0.001) and nonuse of ACE inhibitors (aOR 0.88, 95% CI: 0.79–0.99, p=0.029) showed inverse associations with CKD.

A forest plot of statistically significant factors associated with chronic kidney disease among patients with T2DM in Johor, Malaysia is presented in Figure 1. The figure shows adjusted odds ratios and 95% confidence intervals derived from the final multivariable logistic regression model.

Table I: Characteristics of patients with type 2 diabetes mellitus registered in the National Diabetes Registry of Johor, Malaysia (N=10,117)

Variables	Frequency, n (%)
Sociodemographic characteristics	
Age, years:	
<60	3871 (38.3%)
≥60	6246 (61.7%)
Gender:	
Female	6162 (60.9%)
Male	3955 (39.1%)
Ethnicity:	
Malay	7059 (69.8%)
Chinese	2112 (20.9%)
Indian	893 (8.8%)
Others	53 (0.5%)
Smoking status:	
Yes	564 (5.6%)
No	9553 (94.4%)
Anthropometric measurements	
Waist circumference, cm	
> 90cm in men, > 80cm in women	8756 (86.5%)
< 90cm in men, < 80cm in women	1361 (13.5%)
BMI, kg/m2	
Normal	2136 (21.1%)
Overweight	3175 (31.4%)
Obese	4657 (46.0%)
Underweight	149 (1.5%)
Clinical characteristics	
Hypertension status:	
Present	8750 (86.5%)
Absent	1367 (13.5%)
Dyslipidaemia status:	
Present	8580 (84.8%)
Absent	1537 (15.2%)
Duration of diabetes, years	
< 5	2997 (29.6%)
5 – 10	3922 (38.8%)
> 10	3198 (31.6%)
Mean Arterial Pressure, mm Hg	
Between 65 – 100	5889 (58.2%)
Less than 65, more than 100	4228 (41.8%)
Biochemical profile	
HbA1c classifications	
Good control	3965 (39.2%)
Intermediate control	2040 (20.2%)
Poor control	4112 (40.6%)
Total Cholesterol, mmol/l	
< 4.5mmol/l	4371 (43.2%)
> 4.5mmol/l	5746 (56.8%)
Triglyceride, mmol/l	
< 1.7mmol/l	6620 (65.4%)
> 1.7mmol/l	3497 (34.6%)
HDL, mmol/l	
<1.0 mmol/l (Male), <1.2 mmol/l (Female)	4112 (40.6%)
>1.0 mmol/l (Male), >1.2 mmol/l (Female)	6005 (59.4%)
LDL, mmol/l	
<2.6 mmol/l	4871 (48.1%)
>2.6 mmol/l	5246 (51.9%)
Complications	
Diabetic Retinopathy	
Present	1535 (15.2%)
Absent	8582 (84.8%)
Cerebrovascular	
Present	297 (2.9%)
Absent	9820 (97.1%)
Diabetic Foot Ulcer (DFU)	
Present	179 (1.8%)
Absent	9938 (98.2%)

Table I: Characteristics of patients with type 2 diabetes mellitus registered in the National Diabetes Registry of Johor, Malaysia (N=10,117)

Variables	Frequency, n (%)
Ischaemic Heart Disease (IHD)	
Present	1054 (10.4%)
Absent	9063 (89.6%)
Medications	
Metformin	
Use	8467 (83.7%)
Nonuse	1650 (16.3%)
Sulfonylurea	
Use	4265 (42.2%)
Nonuse	5852 (57.8%)
Alpha-glucosidase Inhibitor	
Use	75 (0.7%)
Nonuse	10042 (99.3%)
Meglitinides	
Use	21 (0.2%)
Nonuse	10096 (99.8%)
Glitazones	
Use	86 (0.9%)
Nonuse	10031 (99.1%)
Insulin	
Use	3278 (32.4%)
Nonuse	6839 (67.6%)
Acetylsalicylic Acid (Aspirin)	
Use	2195 (21.7%)
Nonuse	7922 (78.3%)
Ticlopidine	
Use	37 (0.4%)
Nonuse	10080 (99.6%)
ACE Inhibitors	
Use	5234 (51.7%)
Nonuse	4883 (48.3%)
Angiotensin Receptor Blocker (ARB)	
Use	716 (7.1%)
Nonuse	9401 (92.9%)
Beta Blockers	
Use	2819 (27.9%)
Nonuse	7298 (72.1%)
Calcium Channel Blockers (CCB)	
Use	6431 (63.6%)
Nonuse	3686 (36.4%)
Diuretics	
Use	1927 (19.0%)
Nonuse	8190 (81.0%)
Alpha Blockers	
Use	648 (6.4%)
Nonuse	9469 (93.6%)
Centrally Acting Antihypertensives	
Use	13 (0.1%)
Nonuse	10104 (99.9%)
Statins	
Use	8810 (87.1%)
Nonuse	1307 (12.9%)
Fibrates	
Use	158 (1.6%)
Nonuse	9959 (98.4%)

Notes: BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table II: Univariate analysis of factors associated with chronic kidney disease among patients with type 2 diabetes mellitus in Johor, Malaysia (N=10117)

Variables	CKD		χ2 (df)	p-value
	Absent (n=7730) n (%)	Present (n=2387) n (%)		
Sociodemographic characteristics				
Age, year:				
<60	3424 (88.5%)	447 (11.5%)	504.742 (1)	<0.001*
≥60	4306 (68.9%)	1940 (31.1%)		
Gender:				
Female	4745 (77.0%)	1417 (23.0%)	3.129 (1)	0.077
Male	2985 (75.5%)	970 (24.5%)		
Ethnicity:				
Malay	5294 (75.0%)	1765 (25.0%)	32.670 (3)	<0.001*
Chinese	1654 (78.3%)	458 (21.7%)		
Indian	739 (82.8%)	154 (17.2%)		
Others	43 (81.1%)	10 (18.9%)		
Smoking status:				
Yes	435 (77.1%)	129 (22.9%)	0.173 (1)	0.678
No	7295 (76.4%)	2258 (23.6%)		
Anthropometric measurements				
Waist circumference, cm				
> 90cm in men, > 80cm in women	6695 (76.5%)	2061 (23.5%)	0.112 (1)	0.737
< 90cm in men, < 80cm in women	1035 (76.0%)	326 (24.0%)		
BMI, kg/m2				
Normal	1547 (72.4%)	589 (27.6%)	29.926 (3)	<0.001*
Overweight	2429 (76.5%)	746 (23.5%)		
Obese	3647 (78.3%)	1010 (21.7%)		
Underweight	107 (71.8%)	42 (28.2%)		
Clinical characteristics				
Hypertension status:				
Present	6501 (74.3%)	2249 (25.7%)	159.763 (1)	<0.001*
Absent	1229 (89.9%)	138 (10.1%)		
Dyslipidaemia status:				
Present	6482 (75.5%)	2098 (24.5%)	23.077 (1)	<0.001*
Absent				
1248 (81.2%)	289 (18.8%)			
Duration of diabetes, years				
< 5	2553 (85.2%)	444 (14.8%)	365.398 (2)	<0.001*
5 – 10	3093 (78.9%)	829 (21.1%)		
> 10	2084 (65.2%)	1114 (34.8%)		
Mean Arterial Pressure, mm Hg				
Between 65 – 100	4412 (74.9%)	1477 (25.1%)	17.278 (1)	<0.001*
Less than 65, more than 100	3318 (78.5%)	910 (21.5%)		
Biochemical profile				
HbA1c classifications				
Good control	2973 (75.0%)	992 (25.0%)	9.041 (2)	0.011*
Intermediate control	1557 (76.3%)	483 (23.7%)		
Poor control	3200 (77.8%)	912 (22.2%)		
Total Cholesterol, mmol/l				
< 4.5mmol/l	3298 (75.5%)	1073 (24.5%)	3.887 (1)	0.049*
> 4.5mmol/l	4432 (77.1%)	1314 (22.9%)		
Triglyceride, mmol/l				
< 1.7mmol/l	5213 (78.7%)	1407 (21.3%)	58.181 (1)	<0.001*
> 1.7mmol/l	2517 (72.0%)	980 (28.0%)		
HDL, mmol/l				
< 1.0 mmol/l (Male), <1.2 mmol/l (Female)	3018 (73.4%)	1094 (26.6%)	34.843 (1)	<0.001*
> 1.0 mmol/l (Male), >1.2 mmol/l (Female)	4712 (87.6%)	1293 (21.5%)		
LDL, mmol/l				
< 2.6 mmol/l	3649 (74.9%)	1222 (25.1%)	11.620 (1)	<0.001*
> 2.6 mmol/l	4081(77.8%)	1165 (22.2%)		
Complications				
Diabetic Retinopathy				
Present	1014 (66.1%)	521 (33.9%)	107.475 (1)	<0.001*
Absent	6716 (78.3%)	1866 (21.7%)		
Cerebrovascular				
Present	189 (63.6%)	108 (36.4%)	27.678 (1)	<0.001*
Absent	7541 (76.8%)	2279 (23.2%)		

Table II: Univariate analysis of factors associated with chronic kidney disease among patients with type 2 diabetes mellitus in Johor, Malaysia (N=10117)

Variables	CKD		χ2 (df)	p-value
	Absent (n=7730) n (%)	Present (n=2387) n (%)		
Diabetic Foot Ulcer (DFU)				
Present	93 (52.0%)	86 (48.0%)	60.431 (1)	<0.001*
Absent	7637 (76.8%)	2301 (23.2%)		
Ischaemic Heart Disease (IHD)				
Present	701 (66.5%)	353 (33.5%)	63.936 (1)	<0.001*
Absent	7029 (77.6%)	2034 (22.4%)		
Medications				
Metformin				
Use	7028 (83.0%)	1439 (17.0%)	1253.911 (1)	<0.001*
Nonuse	702 (42.5%)	948 (57.5%)		
Sulfonylurea				
Use	3465 (81.2%)	800 (18.8%)	95.680 (1)	<0.001*
Nonuse	4265 (72.9%)	1587 (27.1%)		
Alpha-glucosidase Inhibitor				
Use	62 (82.7%)	13 (17.3%)	1.643 (1)	0.200
Nonuse	7668 (76.4%)	2374 (23.6%)		
Meglitinides				
Use	17 (81.0%)	4 (19.0%)	0.241 (1)	0.623
Nonuse	7713 (76.4%)	2383 (23.6%)		
Glitazone				
Use	70 (81.4%)	16 (18.6%)	1.198 (1)	0.274
Nonuse	7660 (76.4%)	2371 (23.6%)		
Insulin				
Use	2184 (66.6%)	1094 (33.4%)	257.290 (1)	<0.001*
Nonuse	5546 (81.1%)	1293 (18.9%)		
Acetylsalicylic Acid (Aspirin)				
Use	1507 (68.7%)	688 (31.3%)	93.369 (1)	<0.001*
Nonuse	6223 (78.6%)	1699 (21.4%)		
Ticlopidine				
Use	23 (62.2%)	14 (37.8%)	4.179 (1)	0.041*
Nonuse	7707 (76.5%)	2373 (23.5%)		
ACE Inhibitors				
Use	4089 (78.1%)	1145 (21.9%)	17.750 (1)	<0.001*
Nonuse	3641 (74.6%)	1242 (25.4%)		
Angiotensin Receptor Blocker (ARB)				
Use	483 (67.5%)	233 (32.5%)	34.222 (1)	<0.001*
Nonuse	7247 (77.1%)	2154 (22.9%)		
Beta Blockers				
Use	1834 (65.1%)	985 (34.9%)	279.136 (1)	<0.001*
Nonuse	5896 (80.8%)	1402 (19.2%)		
Calcium Channel Blockers (CCB)				
Use	4708 (73.2%)	1723 (26.8%)	100.148 (1)	<0.001*
Nonuse	6200 (82.0%)	664 (18.0%)		
Diuretics				
Use	1238 (64.2%)	689 (35.8%)	195.284 (1)	<0.001*
Nonuse	6492 (79.3%)	1698 (20.7%)		
Alpha Blockers				
Use	308 (47.5%)	340 (52.5%)	320.217 (1)	<0.001*
Nonuse	7422 (78.4%)	2047 (21.6%)		
Centrally Acting Antihypertensives				
Use	9 (69.2%)	4 (30.8%)	0.372 (1)	0.542
Nonuse	7721 (76.4%)	2383 (23.6%)		
Statins				
Use	6697 (76.0%)	2113 (24.0%)	5.758 (1)	0.016*
Nonuse	1033 (79.0%)	274 (21.0%)		
Fibrates				
Use	109 (69.0%)	49 (31.0%)	4.900 (1)	0.027*
Nonuse	7621 (76.5%)	2338 (23.5%)		

*Statistically significant at α=0.05 , Statistical analysis: Chi-Square test, Fisher's Exact Test
Notes: BMI, body mass index; CKD, Chronic kidney disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein

Table III: Multivariable analysis of factors associated with chronic kidney disease among patients with type 2 diabetes mellitus in Johor, Malaysia (N = 10,117)

Variables	B (SE)[b]	Wald (df)[b]	p-value[b]	aOR[b]	95% CI (Lower, Upper)
Age:					
Age ≥60 years	1.087 (0.067)	260.043 (1)	<0.001*	2.97	2.60, 3.38
Age <60 years	REF				
Ethnicity					
Chinese	-0.420 (0.402)	1.095 (1)	0.295	0.66	0.30, 1.44
Indian	-0.625 (0.409)	2.330 (1)	0.127	0.54	0.24, 1.19
Malay	-0.125 (0.397)	0.099 (1)	0.753	0.88	0.41, 1.92
Others	REF				
BMI					
Overweight	-0.017 (0.074)	0.055 (1)	0.815	0.98	0.85, 1.14
Obese	-0.116 (0.072)	2.640 (1)	0.104	0.89	0.77, 1.02
Underweight	0.232 (0.207)	1.252 (1)	0.263	1.26	0.84, 1.89
Normal	REF				
Hypertension					
Present	0.311 (0.112)	7.702 (1)	0.006*	1.37	1.10, 1.70
Absent	REF				
Dyslipidaemia					
Present	0.075 (0.081)	0.851 (1)	0.356	1.08	0.92, 1.26
Absent	REF				
Duration of diabetes, years					
5 –10	0.122 (0.073)	2.773 (1)	0.096	1.13	0.98, 1.30
>10	0.607 (0.077)	61.962 (1)	<0.001*	1.84	1.58, 2.14
<5	REF				
Mean Arterial Pressure, mmHg					
65 - 100	-0.105 (0.056)	3.510 (1)	0.061	0.90	0.81, 1.01
<65, >100	REF				
HbA1c classification					
Good control	REF				
Intermediate control	-0.095 (0.074)	1.621 (1)	0.203	0.91	0.79, 1.05
Poor control	-0.353 (0.071)	24.958 (1)	<0.001*	0.70	0.61, 0.81
Total Cholesterol, mmol/L					
> 4.5 mmol/L	0.070 (0.083)	0.703 (1)	0.402	1.07	0.91, 1.26
≤ 4.5 mmol/L	REF				
HDL					
<1.0 mmol/l (Male), <1.2 mmol/l (Female)	0.228 (0.056)	16.653 (1)	<0.001*	1.26	1.13, 1.40
>1.0 mmol/l (Male), >1.2 mmol/l (Female)	REF				
LDL					
> 2.6 mmol/L	-0.054 (0.055)	0.967 (1)	0.325	0.95	0.85, 1.06
≤ 2.6 mmol/L	REF				
Triglyceride, mmol/l					
> 1.7mmol/l	0.466 (0.058)	63.863 (1)	<0.001*	1.59	1.42, 1.79
< 1.7mmol/l	REF				
Diabetic Retinopathy					
Present	0.199 (0.071)	7.856 (1)	0.005*	1.22	1.06, 1.40
Absent	REF				
Cerebrovascular disease					
Present	0.335 (0.143)	5.464 (1)	0.019*	1.40	1.06, 1.85
Absent	REF				
Diabetic Foot Ulcer (DFU)					
Present	0.874 (0.180)	23.533 (1)	<0.001*	2.40	1.68, 3.41
Absent	REF				
Ischaemic Heart Disease (IHD)					
Present	0.154 (0.081)	3.647 (1)	0.056	1.17	1.00, 1.37
Absent	REF				
Metformin					
Nonuse	-1.633 (0.065)	623.577 (1)	<0.001*	0.20	0.17, 0.22
Use	REF				
Sulfonylurea					
Nonuse	-0.024 (0.063)	0.149 (1)	0.699	0.98	0.86, 1.10
Use	REF				
Insulin					
Nonuse	–0.436 (0.066)	43.324 (1)	<0.001*	1.55	1.36, 1.76
Use	REF				
Acetylsalicylic acid					
Nonuse	0.085 (0.066)	1.672 (1)	0.196	1.09	0.96, 1.24
Use	REF				

Table III: Multivariable analysis of factors associated with chronic kidney disease among patients with type 2 diabetes mellitus in Johor, Malaysia (N = 10,117)

Variables	B (SE)[b]	Wald (df)[b]	p-value[b]	aOR[b]	95% CI (Lower, Upper)
Ticlopedine					
Nonuse	-0.193 (0.398)	0.236 (1)	0.627	0.82	0.38, 1.80
Use REF					
ACE Inhibitors					
Nonuse	–0.127 (0.058)	4.742 (1)	0.029*	0.88	0.78, 0.99
Use	REF				
Beta Blocker					
Nonuse	0.475 (0.058)	67.132 (1)	<0.001*	1.61	1.44, 1.80
Use REF					
ARB					
Nonuse	0.205 (0.101)	4.143 (1)	0.042*	1.23	1.01, 1.50
Use	REF				
Diuretics					
Nonuse	0.401 (0.064)	39.068 (1)	0.001*	1.49	1.32, 1.69
Use	REF				
Calcium Channel Blocker					
Nonuse	0.205 (0.062)	10.833 (1)	<0.001*	1.23	1.09, 1.39
Use	REF				
Alpha-Blockers					
Nonuse	0.809 (0.097)	70.092 (1)	<0.001*	2.25	1.86, 2.72
Use	REF				
Statins					
Nonuse	-0.004 (0.094)	0.002 (1)	0.965	1.00	0.83, 1.20
Use	REF				
Fibrates					
Nonuse	0.210 (0.103)	0.190 (1)	0.590	1.063	0.853, 1.327
Use	REF				

Notes: aOR = Adjusted Odds Ratio, REF = reference, *Statistically significant at α=0.05, bStatistical analysis: Multiple Binary Logistic Regression Test, Method: Backward LR, Omnibus test of the model coefficient was significant, P < 0.001 and the model was valid, P = 0.157 for the Hosmer and Lemeshow test. The overall correct percentage based on the classification table was 81.2%, and the coefficient of determination was 20.2%. No multicollinearity among the variables was detected in the final model. No influential outlier (Cook's influential statistic). The area under the Receiver Operating Characteristic (ROC) curve was 79.1%.
BMI: Body mass index; DM: Diabetes mellitus; HDL: High-density lipoprotein; LDL: Low-density lipoprotein

The final model of multivariable logistic regression was statistically significant overall (Omnibus test: χ^2=2281.028, df=23, p<0.001). The model demonstrated acceptable fit, with a non-significant Hosmer–Lemeshow goodness-of-fit test (p=0.157). The explained variance was 20.2% according to Cox and Snell R^2 and 30.4% according to Nagelkerke R^2. The model correctly classified 81.2% of cases, with acceptable discriminative ability of 0.791 (95% CI: 0.780–0.801, p<0.001).

DISCUSSION

In this study, the prevalence of CKD among patients with T2DM registered in the National Diabetes Registry of Johor was 23.6% (95%CI: 22.8%, 24.4%). The prevalence in this study is close to the Thailand Primary care study by Jitraknatee et al., which reported 24.4%.[8] Conversely, the Kedah-based study in Malaysia by Mohd Zuki et al., reported higher CKD prevalence among T2DM (38.6%).[9] This underscores how regional variations in population risk profiles and data collection can yield markedly different estimates even within the same country.[10] The observed differences in international and regional prevalence estimates are explained by substantial heterogeneity in CKD definition underlying study populations, and sources of data. In addition, registry-based prevalence estimates may vary depending on audit completeness, biochemical availability, and the proportion of patients with long-standing diabetes.

Several factors were found to be significantly associated with CKD in the multivariable analysis. Older age was one of the strongest factors independently associated with CKD in this study, with patients aged 60 years and above having almost three times the odds of CKD compared with those aged below 60 years. This finding is consistent with a 12-year retrospective cohort study reported that advancing age independently increased the risk of developing CKD among patients with T2DM.[11] In addition, a systematic review by Fenta et al., also reported older age as consistent predictor for CKD across included studies.[12] Biologically, advancing age is associated with nephron loss, vascular stiffening, leading to susceptibility to microvascular and macrovascular injury, all of which may accelerate renal decline in patient with diabetes.[13-14] The association between advancing age and CKD among people with T2DM is robust across multiple study designs and populations, reinforcing the view that older age functions as both a biological risk factor and a marker of cumulative disease exposure.[15-16]

Hypertension remained independently associated with CKD among patients with T2DM in the final model. Recent studies have similarly shown that hypertension is an independent predictor of CKD in people with T2DM. For example, Abdullah et al., found that poor blood pressure control had significantly higher odds of CKD (AOR = 2.63, 95% CI 1.48–4.68) among patients with T2DM.[17] Another study in tertiary hospital identified concomitant hypertension as important

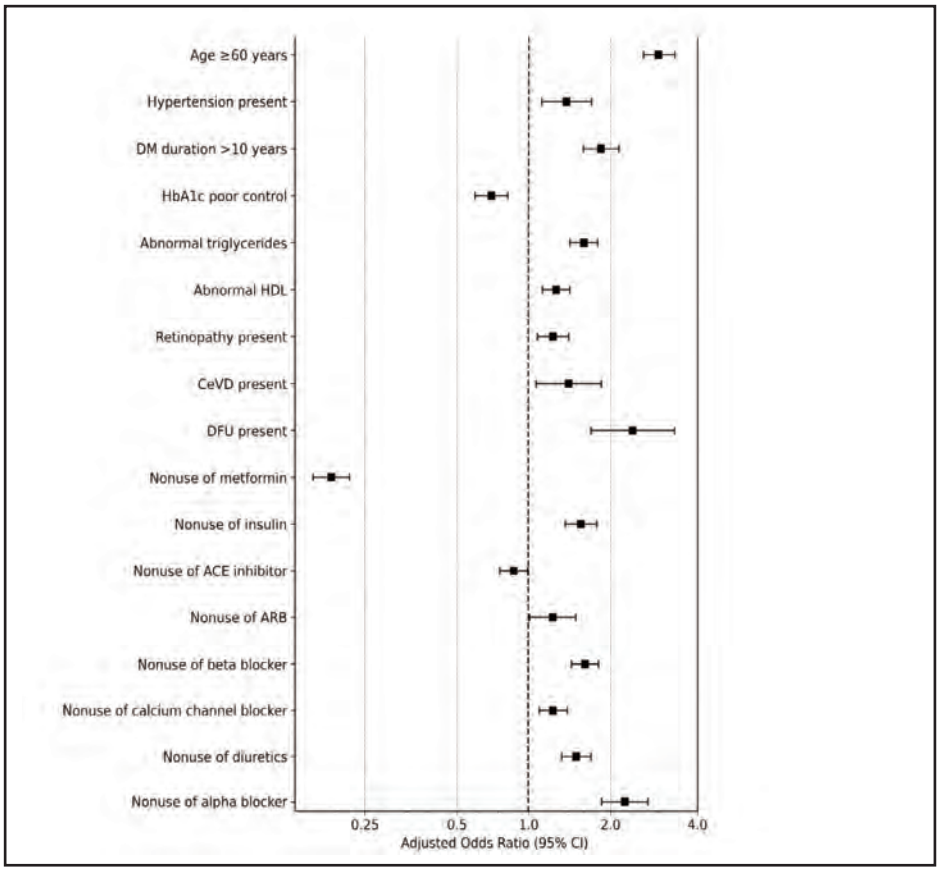

Fig. 1: Forest plot of statistically significant factors associated with chronic kidney disease among patients with type 2 diabetes mellitus in Johor

risk factor of CKD among diabetes patients.[18] It is also concordant with current KDIGO guidance, which emphasizes diabetes and hypertension as the dominant drivers of CKD progression worldwide.[19] The association is clinically plausible because elevated systemic and intraglomerular pressure contributes to glomerular injury, endothelial dysfunction, increased glomerular permeability, albumin leakage, and ultimately progressive nephron loss.[20] In patients with T2DM, the coexistence of hyperglycaemia and hypertension likely produces synergistic renal damage, making blood pressure control central to CKD prevention and progression delay.

Longer duration of diabetes was independently associated with CKD in this study, particularly among patients with diabetes duration exceeding 10 years. This finding is consistent with recent literature conducted in a large nationwide study in China.[21] Similarly, a local study found that longer diabetes duration more than 10 years had higher odd (AOR = 1.27, 95% CI 1.21–1.33) of CKD among patients with T2DM.[10] This association is biologically plausible because longer disease duration reflects prolonged cumulative exposure to hyperglycaemia, oxidative stress, and progressive microvascular injury over time.[22] Additionally, a longer duration of diabetes may indicate prolonged exposure to coexisting risk factors including hypertension which may collectively contribute to the progression of kidney injury.

This study also found that abnormal triglyceride and abnormal high-density lipoprotein (HDL) levels were significantly associated with CKD among patients with T2DM. This finding is supported by recent literature showing that triglyceride-related metabolic abnormalities are positively associated with albuminuria and CKD in patients with T2DM.[23] In addition, higher HDL has been reported to be associated with a lower incidence of CKD progression in patients with T2DM, reflecting that reduced HDL may contribute to worsening renal outcome.[24] Lipid abnormalities may contribute to renal injury through lipotoxicity, oxidative stress, endothelial dysfunction and inflammation, thus promote progressive kidney injury and fibrosis.[25] Collectively, these findings highlight the important role of dyslipidaemia within the broader metabolic environment associated with chronic kidney disease among diabetes patients.

In this study, the inverse association was found between poor HbA1c control and CKD among patients with T2DM. This contrasts with the broader literature that usually places poor glycaemic control among the major drivers of diabetic kidney disease. Thus, the inverse relationship warrants cautious interpretation. The paradoxical finding has been reported and recent consensus literature stated that HbA1c tends to underestimate true plasma glucose in advanced CKD when compared with continuous glucose monitoring, further supporting the possibility of reverse association in cross-sectional studies.[26] The cross-sectional design prevents

assessment of temporality in which glycaemic control measured at the time of registry assessment may not reflect long-term glycaemic exposure preceding CKD development. In addition, Tang et al., demonstrated that carbamylation and anaemia modify the association between HbA1c and renal outcome in patients with diabetes, supporting the view that HbA1c should be interpreted carefully in this population.[27] These factors affect HbA1c levels independently of true plasma glucose concentrations and may lead to underestimation of glycaemic exposure in patients with more advanced renal impairment.

Diabetic retinopathy was significantly associated with CKD among patients with T2DM in the present study. The finding is consistent with previous literature which reported that diabetic retinopathy associated with an increase prevalence of CKD among patients T2DM.[14] A study in China found that increasing retinopathy severity corresponding to more severe glomerular lesions.[28] This association is clinically plausible because diabetic retinopathy and diabetic kidney disease are both microvascular complications that share common pathogenic pathways, including chronic hyperglycaemia, endothelial dysfunction, inflammation and progressive microvascular damage affecting both retinal and renal circulation.

The association of cerebrovascular disease and increased risk of CKD in this study is consistent with existing cohort study of adult T2DM.[29] The American Heart Association highlighted the close bidirectional relationship between CKD and cerebrovascular disease, including shared risk factors and worse outcomes when both conditions coexist.[30] In this study, Diabetic foot ulcer (DFU) showed as one of the strongest associations with CKD. This finding is parallel with recent literature, which highlighted that individual with diabetes-related foot disease have a substantially greater burden of CKD and poorer cardio-renal outcome than those without foot complications.[31-32] This relationship is clinically relevant as both share common mechanisms, including microvascular injury, chronic inflammation and impaired healing, thus, leading to both renal and foot complications.[33]

Medication-related findings in this study should be interpreted cautiously because medication use in routine clinical care is not randomly assigned. Prescribing decisions for glucose-lowering and antihypertensive medications are commonly influenced by kidney function, albuminuria, blood pressure control, cardiovascular comorbidities, disease severity, contraindications and clinician judgement. Therefore, the observed medication-related associations may reflect underlying clinical status and treatment patterns rather than independent causal effects on CKD.

With regard to glucose-lowering medication, nonuse of metformin was associated with lower odds of CKD in patients with T2DM, should be interpreted cautiously. Metformin prescribing is strongly influenced by renal function, and its use is commonly reduced or withheld as kidney function declines. Thus, the lower odds observed among patients with nonuse of metformin may reflect reverse causation, confounding by contraindication, or treatment channeling rather than true beneficial effect of avoiding metformin.[22] A recent study in Hong Kong, showed the opposite pattern, with metformin usage associated with lower risk of major adverse kidney events and overt diabetic nephropathy.[34] The present study found that nonuse of insulin was associated with higher odds of CKD among patients with T2DM. The evidence indicates that insulin is often necessary in T2DM because of progressive beta-cell failure, thus, appropriate insulin therapy can slow CKD progression by achieving better glycaemic control.[35]

The nonuse of antihypertensive medication classes, namely angiotensin receptor blocker (ARB), beta blockers, calcium channel blocker (CCB), alpha blockers and diuretics, were associated with higher odds of CKD among patients with T2DM. The clinical rationale for this association is supported for ARBs, as current diabetes and CKD guideline consistently recommend ARBs or ACE inhibitors as first-line antihypertensive therapy in patients with diabetes due to its renal protective effects.[3] The other antihypertensive agents are commonly used as add-on therapy when blood pressure is not adequately controlled.[36] Therefore, the observed higher odds of CKD among nonusers of these medications reflects the importance of adequate antihypertensive treatment.[37] A paradoxical inverse association was observed for nonuse of ACE inhibitors, which may reflect confounding by indication and reverse causation. Thus, it is unlikely to reflect true biological protective effects. Plausible explanation, whereby patients with more severe renal disease, albuminuria and hypertension are preferentially prescribed ACE inhibitors, causing ACE inhibitors use to appear associated with CKD in observational analyses.[22,38] This confounding by indication commonly seen in pharmacoepidemiology, where treatment allocation is influenced by patient's baseline prognosis and disease severity.[39-40]

This study has several strengths. Firstly, it used a relatively large registry-based sample of patients with T2DM from public primary care clinics in Johor, which enhances the relevance of the findings to routine clinical practice. Secondly, the study utilised real-world data from the National Diabetes Registry, allowing assessment of multiple sociodemographic, clinical, biochemical, complication-related, and medication-related factors within a single population. Thirdly, the use of routinely collected variables increases the practical value of the findings, particularly as an early step toward identifying candidate predictors for future CKD risk prediction model development in Malaysian patients with T2DM.

LIMITATIONS

However, several limitations should be acknowledged. As this was a cross-sectional study based on registry data, causal relationships cannot be established. The use of secondary data may also be subject to missing information, recording errors, and possible misclassification of some variables. In addition, CKD status was determined using the eGFR calculated from the single serum creatinine value available for each patient in the registry dataset. As repeated serum creatinine measurements were unavailable, persistence of reduced eGFR for at least three months could not be verified. This may have resulted in misclassification, particularly

among patients with transient reductions in kidney function, and may have overestimated CKD prevalence or influenced the observed associations. Medication-related findings should also be interpreted with caution. Because medication use was assessed cross-sectionally, the temporal relationship between prescribing and CKD status could not be established. Therefore, the observed medication-related associations may be affected by confounding by indication, confounding by contraindication, treatment channelling and reverse causation. Finally, as the study was based on patients receiving care in public primary care facilities in Johor, the findings may not be fully generalisable to private healthcare settings.

CONCLUSION

CKD affected nearly one-quarter of patients with T2DM in this Johor registry-based study. Older age, hypertension, longer diabetes duration, lipid abnormalities, diabetic retinopathy, cerebrovascular disease, and diabetic foot ulcer were independently associated with CKD. These findings highlight the multifactorial nature of CKD in T2DM and provide real-world evidence that may support earlier risk identification, improved clinical management, and future development of a locally derived CKD risk prediction model among Malaysian patients with T2DM.

CONFLICT OF INTEREST

The authors declared no conflict of interest in this study.

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Determinants of quality of life among older adults with recurrent diabetic foot ulcers

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ABSTRACT

Introduction: Diabetic foot ulcers (DFUs) are a serious complication of diabetes mellitus. DFUs have a profound impact on patients' health-related quality of life (HRQoL). This study aimed to evaluate age-related variations in HRQoL and to identify factors associated with physical and mental health among patients with recurrent DFUs.

Materials and Methods: A cross-sectional study was conducted among 245 patients with type 2 diabetes mellitus. HRQoL was measured using the Indonesian version of the SF-36, whereas depression, diabetes distress, and self-care adherence were evaluated using the Beck Depression Inventory II (BDI-II), the Diabetes Distress Scale-17 (DDS-17), and the Summary of Diabetes Self-Care Activities (SDSCA), respectively. Data were analysed using bivariate tests and multivariate linear regression.

Results: Older adults (≥60 years) had significantly lower physical functioning and general health scores ($p < 0.05$). Depression ($\beta = -0.48$, $p < 0.001$) and diabetes distress ($\beta = -0.25$, $p = 0.003$) were independent predictors of poorer physical HRQoL, whereas higher self-care adherence improved HRQoL ($\beta = 0.18$, $p = 0.014$). Age was not a significant factor after adjustment. Physical HRQoL is poorer among older adults with recurrent DFUs, primarily mediated by psychosocial distress.

Conclusion: Our findings demonstrated that psychosocial conditions, especially depression and diabetes-related distress, significantly contribute to poor HRQoL. There is a relationship between depression, distress, and poor quality of life. Moreover, depression and distress independently predicted lower physical QoL, and better self-care is a predictor of QoL. Integrated management addressing psychological well-being and self-care behaviours may enhance the overall patient outcomes.

KEYWORDS:

Diabetic foot ulcer, quality of life, depression, diabetes distress, self-care adherence

INTRODUCTION

Diabetic foot ulcers (DFUs) are a serious complication of diabetes mellitus, often leading to infection, hospitalization, amputation, and even death.[1-2] Globally, about 19–34% of people with diabetes will develop DFUs in their lifetime.[1] Even after healing, DFUs tend to recur. Approximately 42% of patients experience recurrence within one year, and up to 65% within five years.[1] DFUs impose a staggering burden, significantly increasing healthcare costs, and are associated with a 5-year mortality rate of 50–70%, rivalling or exceeding that of many cancers.[1] In Indonesia, the incidence of recurrent DFUs is also high, estimated at around 13.30%-33.30% in one year.[3] According to data, there is a need for effective prevention and management strategies. Beyond clinical outcomes, DFUs have a profound impact on patients' health-related quality of life (HRQoL). Studies have consistently shown that patients with active or healed DFUs have markedly lower HRQoL than diabetic patients without foot ulcers.[2,4-7] The chronic wounds, pain, reduced mobility, and threat of amputation associated with DFUs can lead to physical limitations, psychological distress, social isolation, and financial hardship, all of which degrade quality of life (QoL).[6]

The patient's age may play a crucial role in the QoL impact of DFUs. Older adults tend to have more comorbidities, poorer circulation and wound healing, and greater loss of physical function, potentially leading to a worse physical HRQoL.[6] Younger adults, in contrast, may have better baseline physical function but could experience significant psychological and social consequences from DFUs during their prime working years. International studies have reported mixed findings on age-related differences. For example, a cross-sectional study in Greece found that older patients with DFUs (≥ 60 years) had significantly poorer physical function and energy or fatigue scores than younger patients.[2] Similarly, a study in Saudi Arabia identified older age (along with female sex, lower education, and income) as a predictor of worse HRQoL in patients with DFUs.[6] These suggest that older people with DFUs are especially vulnerable to QoL. However, other studies have reported no apparent age-related differences. A recent study in Indonesia reported uniformly low QoL among recurrent DFUs patients and no significant QoL gap between older and younger groups.[7] Given these discrepancies, further investigation is needed, particularly in the Indonesian context, where the literature is scant.

Apart from age, various physical, psychological, and social factors can influence HRQoL in patients with DFUs. Prior studies indicate that greater disease severity (e.g., larger or

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higher-grade ulcers and more complications) correlates with worse QoL.[6] However, some findings suggest that wound severity is not always a determinant of QoL.[7] Metabolic control and diabetes duration have been linked to poor QoL.[6] Psychosocial factors such as depression and diabetes-related distress are highly prevalent among people with DFUs. Depression affects nearly half of DFUs patients in some reports, and its presence significantly impairs QoL.[8] Anxiety and low psychological resilience have also been associated with a poor HRQoL.[6]

On the other hand, positive health behaviour and self-care may buffer QoL. Patients who adhere to foot care, diet, and exercise recommendations tend to report better physical and daily functioning.[9] Social support and socioeconomic status can also impact outcomes, whereas low income or lack of family support might exacerbate stress and reduce access to proper wound care.[6,8] However, these factors have not been well studied in Indonesian DFUs patients. Most research on diabetic foot has focused on clinical and wound outcomes, with little attention to patient-centered outcomes such as QoL and psychosocial determinants. Therefore, this study aims to evaluate age-related variations in HRQoL and identify factors associated with physical and mental health among patients with recurrent DFUs.

MATERIALS AND METHODS

Study Design and Participants

We conducted a cross-sectional study that adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Setting

Patients with type 2 diabetes mellitus (T2DM) registered at the rural clinic, PKU Muhammadiyah Pontianak, West Kalimantan, Indonesia, between March and September 2025, were recruited for this study.

Study Participants

A total of 316 participants were recruited using a consecutive sampling. The study population included individuals 18 years or older with T2DM. Inclusion criteria were a history of at least one prior DFUs that had healed, followed by a current foot ulcer at the exact location, and the ability to understand and complete the questionnaires (either independently or with minimal assistance). The required sample size was calculated using G*Power software to compare mean HRQoL scores between younger and older adults with recurrent DFUs. The calculation assumed a medium effect size (Cohen's d = 0.50) based on previous studies investigating quality of life differences among patients with DFUs. A two-tailed significance level (α) of 0.05, statistical power of 80% (1–β = 0.80).[10] To compensate for an anticipated 15% nonresponse or incomplete questionnaire rate. We excluded patients with conditions such as end-stage renal disease, malignancy, severe cognitive impairment or dementia, or primary disabling neurological, critically ill, or those who had undergone emergency amputation. As a result, 245 patients with recurrent DFUs met the inclusion criteria (Figure 1).

Observational Data

We collected data on participants' demographics, clinical characteristics, and QoL through interviews and chart reviews. Demographic data included age, sex, educational level, employment status, and monthly income. Clinical data included duration of diabetes, comorbid conditions (hypertension, heart disease, kidney disease, etc.), diabetes complications, and the number of previous DFUs episodes. We assessed the current characteristics of ulcers using the Wagner classification and infection severity grading,[11] which were determined by the wound care specialist. Infection severity was evaluated using the site, ischemia, neuropathy, bacterial infection, and depth (SINBAD) or IDSA criteria (mild, moderate, and severe infection), as documented in the medical records.[11-12]

We used two complementary questionnaires to measure HRQoL. Firstly, the Short Form-36 Health Survey (SF-36) assesses eight domains: Physical functioning (PF), role physical (RP) limitations, bodily pain (BP), general health (GH) perceptions, vitality (VT), social functioning (SF), role emotional (RE) limitations, and mental health (MH). Several studies have demonstrated that SF-36 has high validity and reliability.[13-14] We administered the validated Indonesian version of the SF-36 through interviews.[15] For the analysis, we considered domain scores individually, whereas scores for each domain ranged from 0 to 100. Secondly, we utilized the physical component summary (PCS) and mental component summary (MCS), which are standardized summary measures derived from the SF-36 Health Survey that assess overall physical and mental health-related quality of life, respectively. PCS primarily reflects PF, RP, BP, and GH, whereas MCS primarily reflects MH, RE, SF, and VT. Both summary scores are standardized using norm-based scoring (mean=50, SD=10), with higher scores indicating better health status and quality of life. [16–18]

We also used other psychosocial measures. Firstly, the Diabetes Distress Scale-17 (DDS-17) was used to measure diabetes-related emotional distress. This 17-item questionnaire yielded a total distress score (range: 17–102, with higher scores indicating greater distress) and subscale scores for emotional burden, physician-related distress, regimen-related distress, and interpersonal distress. Diabetes distress refers to frustration, worry, and burnout associated explicitly with managing diabetes and its complications.[19] Cronbach's alpha for this scale ranged from 0.78 to 0.83.[19] Secondly, the Beck Depression Inventory II (BDI-II) is a 21-item self-report scale widely used to screen for depression in medical populations. The BDI-II scores range from 0 to 63, with higher scores indicating more severe depressive symptomatology (commonly categorized as minimal, mild, moderate, or severe depression). This scale has been validated in multiple countries, with a Cronbach's alpha ranging from 0.86 to 0.93.[20–22] The Cronbach's alpha for the Indonesian version of the BDI-II ranged from 0.74 to 0.81.[23] Finally, we measured patient self-care behaviour using the Summary of Diabetes Self-Care Activities (SDSCA) questionnaire. The SDSCA inquired about the frequency of performing various diabetes self-management tasks (such as diet control, blood glucose monitoring, foot hygiene and inspection, and exercise) in the past week.[24] This questionnaire has been

widely used in other studies.[25-27] We used a modified version that focused on foot care and general adherence; for example, patients reported how many days per week they checked their feet, washed their feet, wore appropriate footwear, followed dietary recommendations, and exercised for at least 30 minutes.[24] An overall self-care adherence score (0–7 days) was derived by averaging the items, with higher values indicating better adherence to the recommended self-care practices. A study showed that Cronbach's alpha for the Indonesian version of the SDSCA was 0.72.[28]

Ethical Considerations

The study was approved on March 5, 2025, by the Institute of Technology and Health of Muhammadiyah West Kalimantan Committee (number: 15/II). I.AU/KET.ETIK/III/2025.

Data Analysis

IBM SPSS Statistics (version 22.0) was used for data analysis. First, we performed descriptive statistics to summarize the demographic and clinical characteristics of the data. Continuous data were expressed as mean and standard deviation if normally distributed, or as median and interquartile range if skewed. Categorical data are summarized as frequencies and percentages. We assessed the normality of continuous data with the Kolmogorov–Smirnov test. For bivariate comparisons between the younger and older age groups, we used independent sample t-tests for continuous variables and chi-square tests for categorical variables. To evaluate the associations between potentially related factors and HRQoL, we used Pearson correlation analyses. We examined correlations between HRQoL scores (SF-36 summaries and DFS-SF total score) and key continuous predictors, including age, diabetes duration, DDS-17, BDI-II, and SDSCA self-care scores. In addition, Spearman's rank correlation was used for ordinal or non-normal variables (e.g., Wagner ulcer grade and income level). Finally, we built a multivariable linear regression model to identify the independent factors associated with overall HRQoL. We chose the SF-36. PCS score as the dependent variable for this regression, as our primary interest was in differences in physical quality of life by age, and because the PCS provides a composite of the physical health domains. We included age group (younger vs. older), sex, diabetes duration, number of diabetes complications, DDS-17, BDI-II, and SDSCA score as the initial predictor variables based on theoretical relevance and bivariate results. Using a stepwise backward elimination approach (removing factors with $p>0.10$ sequentially), we arrived at a final model that retained the significant predictors. We checked assumptions of linearity, normal residuals, and multicollinearity in this regression. A two-sided $p<0.05$ was considered statistically significant for all analyses. The results are presented with corresponding 95% confidence intervals (CI) or p-values. For subgroup analyses, the patients were stratified into two groups: younger adults (18–59 years) and older adults (≥ 60 years), as categorized by the Indonesian Ministry of Health.

RESULTS

Participant Characteristics

A total of 245 patients with recurrent DFUs were analysed. Table I presents the demographic and clinical characteristics stratified by age group. Older adult patients had a longer duration of diabetes ($p<0.001$), had hypertension comorbidity ($p<0.001$), and had a Wagner grade greater than 3 than younger adult patients ($p=0.04$). However, younger adult patients were not currently working ($p<0.001$), and the wound presented with moderate to severe infection compared to older adult patients ($p=0.003$). There were no differences between the groups in education, low income, number of prior DFUs episodes, SDSCA, DDS-17, BDI-II, and moderate to severe depression score. The following analysis adjusted for these demographic and clinical characteristics.

HRQoL

HRQoL was markedly impaired in both age groups, as expected in the recurrent DFUs population, but older adults showed significantly lower scores on several SF-36 domains. Table II displays that the PCS score was significantly lower in older patients compared to younger patients ($p=0.002$). In the PF, RP, and GH domains, significant differences were observed due to physical problems ($p<0.001$, $p=0.005$, and $p=0.04$), respectively. However, in contrast to the MCS score, there was no significant difference between younger and older.

Table III, as expected, showed that diabetes-related psychosocial factors had the strongest correlations with QoL. Higher depressive symptom scores were strongly correlated with a worse overall HRQoL. For instance, the BDI-II score had a significant negative correlation with the SF-36 PCS ($r=-0.56$, $p<0.001$). Similarly, diabetes distress (DDS-17 score) was inversely correlated with HRQoL ($r=-0.42$, $p<0.001$), as measured by PCS. The SDSCA overall score correlated modestly with the SF-36 PCS ($r=0.29$, $p<0.001$). Among the clinical variables, longer diabetes duration was significantly associated with lower SF-36 GH ($r=-0.30$, $p<0.001$). Ulcer severity showed a weak negative correlation with SF-36 PF ($r=-0.15$, $p=0.02$). Age was correlated with lower SF-36 PF ($r=-0.26$, $p<0.001$), but not significantly with MH or DFS-SF scores, reinforcing that age is primarily linked to physical aspects of QoL.

Independently associated factor of HRQoL in younger and older adults

Table IV shows that the BDI-II depression score emerged as the strongest independently associated factor with worse PCS (standardized $\beta=-0.48$, $p<0.001$). Diabetes distress was the next most significant independently associated factor ($\beta=-0.25$, $p=0.003$), indicating that emotional distress specific to diabetes also independently contributed to poorer physical QoL. Self-care adherence had a positive, independent effect ($\beta=0.18$, $p=0.014$), indicating that better self-care was associated with higher PCS scores after controlling for mood factors and demographics. Notably, age group (older vs. younger) was not a significant predictor of PCS in the multivariate model ($p=0.27$) once depression, distress, and self-care were considered. This implies that the bivariate age differences in physical QoL observed earlier may be primarily explained by the higher burden of psychosocial issues and longer disease duration in older patients rather than age. Consistent with this, adding diabetes duration to the model (which was correlated with age) attenuated the age effect. In

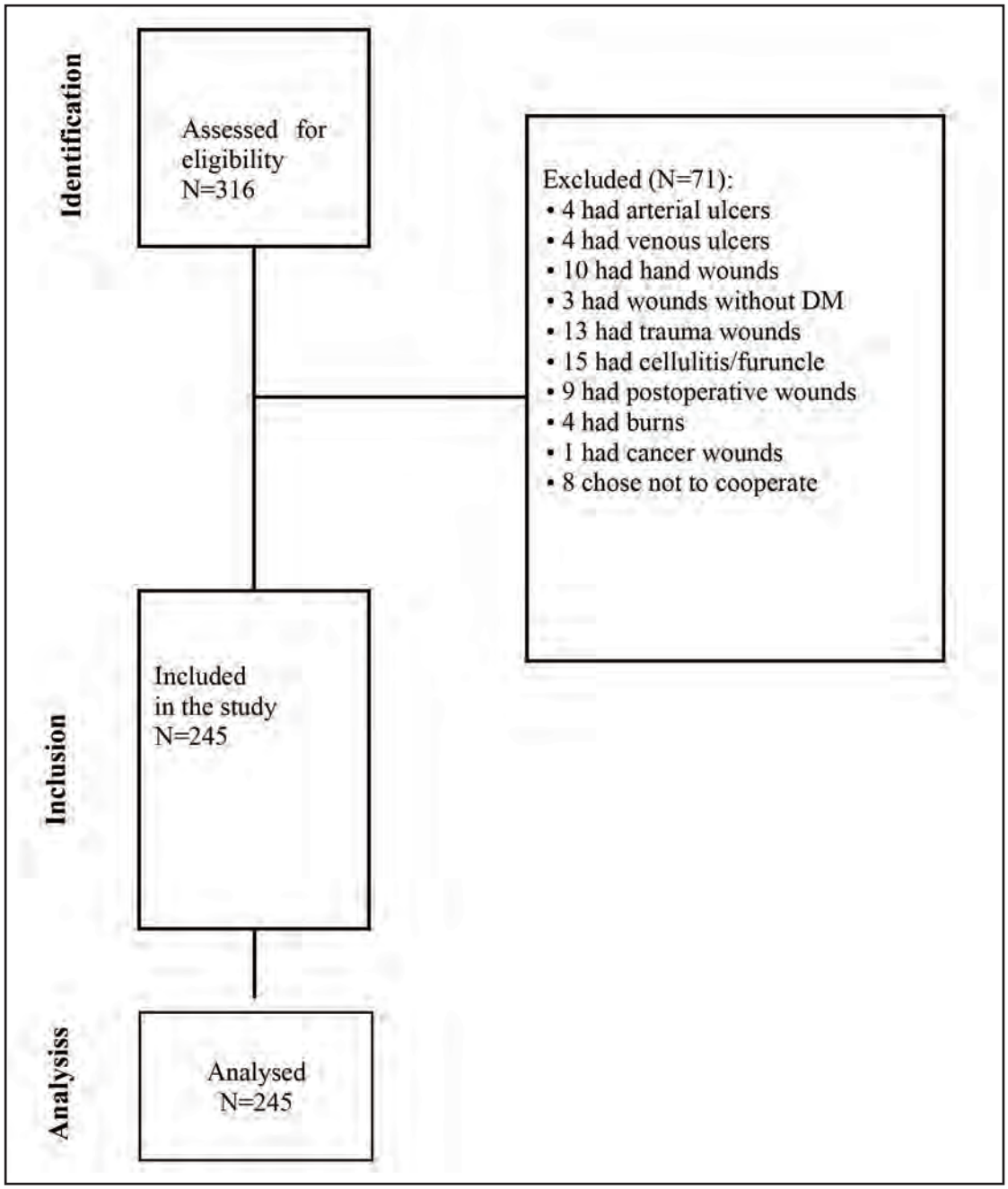

Fig. 1: Strengthening the reporting of observational studies in epidemiology: flow chart of the participant enrolment process

the final model, diabetes duration itself was not significant (p=0.12), nor was the comorbidity count or ulcer severity (these variables were removed in the stepwise elimination process due to p>0.2). Although diabetes complications and ulcer severity demonstrated significant associations with physical HRQoL in the univariate analyses, these associations were attenuated after adjustment for depression, diabetes distress, self-care adherence, age, and diabetes duration. Consequently, they did not remain independently associated factors in the final multivariable model and were excluded during the backward stepwise selection procedure. The model explained approximately 42% of the variance in PCS (adjusted R^2=0.42, F=36.8, p<0.001).

DISCUSSION

To the best of our knowledge, this is the first study of Indonesian patients with recurrent DFUs to compare patients across different age groups. In this study, we found that depression and distress scores, both in adult younger and adult older, were independently associated with lower physical QoL. Our study found that older patients had a

Table I: Demographic and clinical characteristics of participants by age group (n=245)

Characteristics	Total (N=245)	Younger Adults (18–59 yrs, n=150)	Older Adults (≥60 yrs, n=95)	p-value (Younger vs Older)
Age, mean (SD), years	57.4 (10.2)	50.8 (6.7)	67.4 (5.3)	< 0.001**
Male sex, n (%)	152 (62.0%)	90 (60.0%)	62 (65.3%)	0.40
Duration of diabetes, mean (SD), yrs	10.9 (8.2)	8.6 (6.5)	14.2 (9.1)	< 0.001**
≥1 Diabetes complications (cardiovascular disease or nephropathy), n (%)	146 (59.6%)	68 (45.3%)	78 (82.1%)	< 0.001**
Hypertension comorbidity, n (%)	142 (58.0%)	72 (48.0%)	70 (73.7%)	< 0.001**
Education: ≥College, n (%)	52 (21.2%)	52 (21.3%)	20 (21.1%)	0.98
Low income (<minimum wage=IDR 3.024.820), n (%)	133 (54.3%)	81 (54.0%)	52 (54.7%)	0.90
Currently not working, n (%)	198 (80.8%)	110 (73.3%)	88 (92.6%)	< 0.001**
Number of prior DFU episodes, median [range]	1 [1–3]	1 [1–3]	1 [1–3]	0.72
Wagner ulcer grade ≥ 3, n (%)	75 (30.6%)	36 (24.0%)	39 (41.1%)	0.04 *
Moderate/severe infection, n (%)	112 (45.7%)	57 (38.0%)	55 (57.9%)	0.003**
SDSCA self-care score (0–7), mean (SD)	4.2 (1.5)	4.3 (1.5)	4.0 (1.6)	0.09
DDS-17 diabetes distress, mean (SD)	40.2 (12.5)	39.0 (12.0)	42.1 (13.1)	0.08
BDI-II depression score, mean (SD)	18.0 (11.3)	17.5 (10.8)	18.8 (12.0)	0.36
Moderate-to-severe depression (BDI ≥20), n (%)	53 (21.6%)	27 (18.0%)	26 (27.4%)	0.10

Values are mean (SD) or n (%) unless otherwise indicated, p-values by independent t-test for means, or chi-square test for proportions (except DFU episodes by Mann–Whitney U test). Statistical significance was set at $p < 0.05$. Abbreviations: SD = standard deviation; DFU = diabetic foot ulcer; SDSCA = Summary of Diabetes Self-Care Activities (weekly frequency of recommended behaviors); DDS-17 = 17-item Diabetes Distress Scale; BDI-II = Beck Depression Inventory-II. Significance: p<0.05, marked with*; p<0.01, marked with**.

Table II: SF-36 Health-related quality of life domain scores by age group (n=245)

SF-36 Domain	Younger (18–59 yrs) Mean (SD)	Older (≥60 yrs) Mean (SD)	p-value
Physical Functioning (PF)	64.3 (21.5)	52.0 (22.7)	< 0.001**
Role Physical (RP)	35.3 (41.0)	21.8 (35.7)	0.005**
Bodily Pain (BP)	50.9 (24.6)	51.2 (25.4)	0.95
General Health (GH)	50.2 (19.8)	44.5 (17.6)	0.04 *
Vitality (Energy) (VT)	53.5 (20.4)	47.0 (21.9)	0.06
Social Functioning (SF)	52.1 (23.3)	48.3 (24.5)	0.30
Role Emotional (RE)	37.8 (44.0)	34.1 (45.3)	0.58
Mental Health (MH)	60.8 (18.9)	59.4 (19.5)	0.67
Physical Component Summary (PCS)	38.0 (9.5)	34.1 (8.9)	0.002**
Mental Component Summary (MCS)	40.8 (11.7)	41.1 (12.4)	0.88

The SF-36 domain scores ranged from 0 (worst) to 100 (best). Higher scores indicate a better health status in that domain. PCS and MCS are composite scores normalized to a population mean of ~50 (SD = 10). Significant differences (independent t-tests) are shown in bold font. Older adults had significantly lower scores in the physical domains (PF, RP, GH) and PCS, whereas no significant age differences were observed in the mental and social domains.

Table III: Correlation of Selected Factors with Health-Related Quality of Life Measures

Predictor Variables	SF-36 PCS (Physical Component)	SF-36 MCS (Mental Component)
Age (years)	–0.26 **	–0.04
Diabetes duration (years)	–0.33 **	–0.08
No. of diabetes complications	–0.28 **	–0.10
Wagner ulcer grade	–0.15 *	–0.05
SDSCA self-care score	+0.29 **	+0.14 *
DDS-17 diabetes distress score	–0.42 **	–0.37 **
BDI-II depression score	–0.56 **	–0.45 **
Age group (older=1, younger=0)	–0.22 **	–0.01

Values are Pearson's correlation coefficient (r). p<0.05 = *; p<0.01 = **. A positive r indicates that a higher predictor is associated with a higher (better) QoL score, and a negative r indicates that a higher predictor is associated with a worse QoL. For the categorical "Age group," point-biserial correlation is shown. The BDI-II and DDS-17 showed strong negative correlations with both generic and ulcer-specific QoL.

Table IV: Multivariate linear regression predicting physical HRQoL (SF-36 PCS)

Predictor (Independent Variable)	Unstandardized B (SE)	Standardized β	t value	p-value
BDI-II Depression score (per 10 pts)	–3.21 (0.50)	–0.48	–6.43	<0.001**
DDS-17 Distress score (per 10 pts)	–1.45 (0.47)	–0.25	–3.05	0.003**
SDSCA Self-care (per 1 day increase)	+0.98 (0.39)	+0.18	+2.49	0.014*
Age group (Older vs Younger)	–1.18 (1.06)	–0.06	–1.10	0.27
Diabetes duration (years)	–0.08 (0.05)	–0.10	–1.57	0.12
Adjusted R^2=0.422; F=36.8 and p < 0.001				

The dependent variable was the SF-36 Physical Component Summary (PCS) score. The table shows the final model after the stepwise selection. B (SE) = unstandardized coefficient with standard error. Sex, number of complications, and ulcer severity were not included in the final model (p > 0.10). Higher depression and distress scores independently predicted lower physical QoL, whereas better self-care predicted a higher QoL. Age and diabetes duration were not significant after controlling for other factors.

lower PCS score than younger patients. Our findings are similar to those of Sari et al., although our study included patients with recurrent DFUs.[29] The PCS score is lower, which may be because in Indonesia, older adults experience a decrease in physical and role function following a wound. Thus, a program to increase PCS not only in diabetic older adults but also in patients with DFUs, particularly those with recurrent disease.

Interestingly, in the present study, there was no difference in the MCS of younger and older adult patients. The result is similar to those of Sari et al.[29] This can be explained by the fact that all participants experienced depression and distress. Depression and distress are likely attributable to the prolonged duration of diabetes mellitus, diabetes complications, Hypertension comorbidity, Wagner ulcer grade, and infection.

Our study found a negative correlation between PCS and age, diabetes duration, diabetes complications, Wagner ulcer grade, DDS, and BDI in both younger and older adult patients. Interestingly, DDS and BDI have a high correlation with physical decline, resulting in poor quality of life in people with DFUs, older and younger. These results are in line with previous research, which stated that depression causes a decrease in QoL.[30] Meanwhile, the wound healing process will be disrupted due to stress, anxiety, and depression.[31] We also found a negative correlation between MCS with DDS and BDI. This is in line with the results of previous studies that reported that there was a negative association between MCS and depression and depression in people with chronic illnesses.[32] Therefore, the intervention approach carried out for management in DFUs sufferers is not only physical but also mental or psychological. Additionally, a positive correlation was found between PCS, MCS, and SDSCA. This finding is consistent with previous studies showing that poor diet management (a component of the SDSCA) is associated with lower MCS.[33] However, in other studies, it was reported that there was no association between SDSCA and PCS.[17] This difference may be due to differences in the characteristics of sufferers and Indonesian culture.

In the present study, we found depression and distress were independently associated with lower physical QoL. These results are similar to previous studies that depression and anxiety are independently associated factors of poor QoL.[34–36] Moreover, our findings show that better self-care is a predictor of QoL.[37] Although the sample in this study was of patients with heart failure, we assumed that the condition and response of heart failure disease and DFUs were the same as those of chronic diseases.

Although diabetes complications and ulcer severity were significantly associated with poorer physical quality of life in the univariate analyses, they were not retained in the final multivariable model. This finding suggests that their apparent effects may be partly mediated or shared with psychosocial factors, particularly depression and diabetes-related distress, which demonstrated stronger independent associations with HRQoL. In patients with recurrent DFUs, psychological burden may represent a more proximal determinant of perceived QoL than clinical severity alone.

Clinical and Public Health Implications

Our findings provide a comprehensive approach for managing DFUs. Multidisciplinary foot care teams should ideally include not only podiatrists and wound care specialists, but also diabetes educators, mental health professionals, and social workers.

LIMITATIONS

This study had several limitations. Firstly, the cross-sectional design does not allow researchers to determine a causal relationship between depression and HRQoL. Although depression was found to be significantly associated with lower QoL, the direction of this relationship remains uncertain. While depression may contribute to decreased QoL, poor QoL due to complications of DFUs may also increase depressive symptoms. Therefore, longitudinal studies are needed to clarify this causal relationship. Secondly, although several important demographic and clinical variables were included in the analysis, residual confounding remains possible. Factors such as ulcer duration, wound severity progression, pain intensity, glycemic variability, treatment adherence, and psychosocial support were not measured and may have influenced HRQoL outcomes. Consequently, the findings should be interpreted with caution, and future studies should include these variables to further elucidate their contribution to QoL outcomes. Lastly, our sample was drawn from a single center, which might limit the generalizability of our results. Additionally, our study focused on patients with recurrent ulcers; thus, the findings might differ from those of patients with first-time ulcers or more acute cases. Recurrent DFUs patients likely have more experience and potentially different coping mechanisms, which could affect their reporting of QoL.

CONCLUSION

This study provides evidence that psychosocial well-being and self-care should be considered as important components in the comprehensive management of diabetic foot. These findings indicate that improving only QoL for patients with recurrent DFUs is not just about wound care but also about psychological screening, diabetes self-management support, and multidisciplinary care. The integration of these components into clinical practice can contribute to more patient-centered care and better long-term outcomes. Future longitudinal and intervention studies are needed to establish causal relationships and evaluate the effectiveness of integrated management strategies.

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Outcomes and patterns of management of metastatic/recurrent cervical carcinoma in Malaysia: A single institutional observational cohort study

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ABSTRACT

Introduction: Cervical cancer is the fourth most common malignancy in women. Approximately 15% of the patients have metastatic disease. The Malaysian National Cancer Registry (MNCR) 2017-2021 reported that over the five-year period, there were 2654 new cases. 47.1% of the patients presented with late stages (stages 3 and 4), slightly higher compared to 41% in the MNCR 2012-2016 report. There were no standard approaches to the management of metastatic/recurrent cervical cancer. Therefore, this study aimed to determine the survival outcomes of patients with metastatic/recurrent cervical cancer and to evaluate the clinicopathological factors based on demographic and tumour characteristics that may affect survival outcomes. Besides that, we would like to outline the management patterns in this cohort of patients.

Materials and Methods: This was a retrospective observational cohort study looking at the 35 patients diagnosed with metastatic/recurrent cervical cancer at the Department of Clinical Oncology, Universiti Malaya Medical Centre (UMMC) over the five-year period from 1st of January 2016 until 31st of December 2020. Data were obtained from the electronic medical record. The Kruskal-Wallis H and Mann-Whitney U non-parametric tests, Spearman correlation, and Kaplan-Meier survival analysis were conducted to analyse the survival outcomes and clinicopathological factors that may affect the survival outcomes in the form of progression-free survival (PFS) and overall survival (OS). Descriptive analysis was used to describe the prevalence of metastatic/recurrent cervical cancer and the patterns of management.

Results: Out of the total 94 cervical cancer patients registered at the Department of Clinical Oncology, UMMC, 37.2% had metastatic/recurrent disease. Survival analysis demonstrated that median PFS and OS for metastatic/recurrent cervical cancer were six and 12 months, respectively, which were consistent with the global populations. Nonparametric multivariate tests and survival analysis showed that the presence of metastatic disease at less common sites had worse survival. Most of the patients received active oncological treatments, i.e., chemotherapy, radiotherapy or combinations of both.

Conclusion: This study showed that a significant portion of the patients were diagnosed at a late stage, with poor survival outcomes, indicating the necessity for enhanced initiatives in the screening and education programmes to increase awareness of early diagnosis and detection, hence improving survival outcomes of cervical cancer patients.

KEYWORDS:
Cervical cancer, metastatic cervical cancer, recurrent cervical cancer, survival outcomes

INTRODUCTION

Carcinoma of the cervix is one of the most common malignancies in the world. According to the Global Cancer (GLOBOCAN) 2022 report, an estimated 661,021 cervical cancer cases were reported globally, currently ranked the fourth most common cause of cancer-related mortality among women, with 348,189 deaths.[1] In addition, the symptoms, particularly pelvic pain and per-vaginal bleeding, can result in significant morbidities for the patients, leading to hospitalisation, blood transfusion, reduced performance status, and ultimately affecting their quality of life.

The Papanicolaou (PAP) smear screening programme has significantly contributed to early detection of cervical cancer, particularly in developed countries. However, it remains a challenge in developing countries, as we still observe higher incidence and mortality rates. Developed or wealthier countries such as New Zealand, Canada, and Saudi Arabia showed that their mortality from cervical cancer was seven times lower compared to poorer countries such as Sub-Saharan Africa, which reported 18 times higher mortality rates.[2]

The high mortality from cervical cancer is primarily due to the late diagnosis at the advanced stage. About 13% of the patients presented with metastatic disease worldwide.[3] Despite the small percentage, studies showed that five-year survival rates dropped from 91.5% for localised disease to only 16.5% for metastatic disease.[3]

The radical treatment for localised disease would consist of either surgical resection, including lymphadenectomy, and/or radiation therapy with or without chemotherapy, depending on the staging.[4] However, in metastatic/recurrent disease, the best treatment modalities are still an ongoing dilemma. Therefore, it is interesting to study current evidence and updates on the management of metastatic/recurrent cervical cancer.

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MATERIALS AND METHODS

This was a retrospective single-centre study conducted at Universiti Malaya Medical Centre (UMMC), a tertiary oncology referral centre in Malaysia. Patients diagnosed with metastatic/recurrent cervical carcinoma, either de novo metastatic disease or recurrent disease not amenable to curative treatment, who were registered and treated at the Department of Clinical Oncology between 1 January 2016 and 31 December 2020 were included. All histological subtypes were eligible. Patients who received only radiotherapy at UMMC but continued systemic treatment and follow-up at other centres were excluded.

Patients were identified through departmental registry records. Demographic, clinicopathological, and treatment-related data were extracted from electronic medical records using a standardised proforma. Survival status and dates of death were obtained from the Malaysian National Institute of Health registry using national identification numbers.

The primary outcomes were progression-free survival (PFS) and overall survival (OS), defined as the time from diagnosis of metastatic or recurrent disease to disease progression or death, and to death from any cause, respectively. Demographic factors (age, ethnicity, performance status, and comorbidities), tumour characteristics (disease status at diagnosis, histology, and metastatic sites), and first-line treatment modalities were analysed.

Descriptive statistics were used to summarise patient characteristics, treatment patterns, and prevalence of metastatic/recurrent cervical carcinoma. Normality of survival data was assessed using the Shapiro–Wilk test. As PFS and OS were not normally distributed, non-parametric tests were applied. The Mann–Whitney U test and Kruskal–Wallis H test were used to evaluate differences in survival outcomes across clinicopathological variables. Kaplan–Meier survival analysis was performed for survival estimation, and Spearman's rho was used to assess correlations between survival outcomes and clinical variables. A p-value < 0.05 was considered statistically significant. The data cut-off date was 1st of June 2025.

Ethics approval was obtained from the Medical Research Ethics Committee (MREC ID: 202315-11924). Individual informed consent was waived due to the retrospective nature of the study.

RESULTS

Prevalence of metastatic cervical carcinoma

During the period from 1st of January 2016 until 31st of December 2020, a total of 94 cervical cancer patients were registered at the Department of Clinical Oncology, UMMC. Out of this, 35 patients (37.2%) were found to have metastatic or recurrent diseases that were not amenable to curative treatment.

Demographic factors

In this study, the age of the patients was grouped based on the MNCR as a guide. The distribution of patients revealed significant prevalence among middle-aged individuals. 60.2% of the patients were observed to be in the age group between 40 and 64 years old.

Ethnicity played a notable role in the distribution of metastatic/recurrent cervical carcinoma within the study population. The Chinese ethnic group represented the majority of the patients, accounting for 68.6% of the sample, followed by the Malay group with 25.7% and the Indian group with 5.7%.

Eastern Cooperative Oncology Group (ECOG) performance status scoring was used to determine patients' performance status. 94.4% of the patients had good performance status with an ECOG score of less than 2.

The prevalence of comorbidities in this cohort of patients revealed that most of the patients did not have existing medical illnesses. Among those with comorbidities, hypertension (HPT) was the most common chronic illness (a total of 28.5%), followed by hypercholesterolaemia (HCT) (a total of 14.3%) and diabetes mellitus (DM) (a total of 11.4%). 11.4% of patients had multiple comorbidities. Table I showed the descriptive analysis for the demographic factors and tumour characteristics.

Tumour characteristics

As shown in Table I, the distribution of cancer status at initial diagnosis indicated that most of the patients (68.6%) developed metastatic or recurrent disease as a progression from previously diagnosed and treated early-stage cervical carcinoma. In contrast, only 31.4% of patients were diagnosed with de novo metastatic cervical carcinoma.

The histological subtypes of cervical carcinoma in this study demonstrated that 68.6% of cases were SCC, followed by adenocarcinoma, which accounted for 28.6% of the sample. Only one patient had a rarer neuroendocrine subtype.

For the metastatic sites' analysis, more than 50% of the patients reported metastasis at a single site, and 48.6% of the patients had metastases at multiple sites. The data showed that nodal and local recurrence were the main disease burdens in the majority of the patients, with 45.7% and 37.1% of the patients had nodal and local recurrence, respectively. Nevertheless, lung was the most common site for visceral metastases.

Overall survival outcomes

The progression-free survival (PFS), defined as the time from the diagnosis of metastatic or recurrent diseases to the disease progression or death, whichever came first, had a median value of six months with an interquartile range (IQR) of 6.5 months. On the other hand, overall survival (OS), defined as the time from the diagnosis of metastatic or recurrent diseases to the death of the patients from any cause, had a median survival of 12 months with an IQR of 11.5 months. Two patients had not progressed and were still alive at the time of data cut-off analysis.

In addition, the Spearman's rho correlation coefficients were calculated to assess the relationships between PFS and OS. The correlation between PFS and OS was found to be

Table I: Descriptive analysis for demographic factors and tumour characteristics

Factors	Group	N (35)	Percentage (%)
Age	20-24	1	2.9
	30-34	3	8.5
	35-39	1	2.9
	40-49	6	17.2
	50-54	1	2.9
	55-59	8	22.9
	60-64	6	17.2
	65-69	3	8.5
	70-74	3	8.5
	75+	3	8.5
Ethnicity	Malay	9	25.7
	Chinese	24	68.6
	Indian	2	5.7
ECOG	0	22	62.9
	1	11	31.5
	2	1	2.8
	3	1	2.8
Comorbidities*	No	21	60.0
	HPT	6	17.1
	DM	2	5.7
	HCT	1	2.9
	CKD	1	2.9
	HPT+HCT	2	5.7
	HPT+HCT+DM	2	5.7
Tumour characteristics			
Cancer status at initial diagnosis	Localised disease	24	68.6
	Metastatic disease	11	31.4
Histology subtype	SCC	24	68.6
	Adenocarcinoma	10	28.6
	Neuroendocrine	1	2.8
Number of metastatic/recurrence sites	1	18	51.4
	2	16	45.7
	3	1	2.9
Metastatic/recurrence site			
Lung	Yes	9	25.7
	No	26	74.3
Liver	Yes	3	8.6
	No	32	91.4
Bone	Yes	7	20.0
	No	28	80.0
Local recurrence	Yes	13	37.1
	No	22	62.9
Nodal	Yes	16	45.7
	No	19	54.3
Others	Yes	4	11.4
	No	31	88.6

* HPT-hypertension, DM-diabetes mellitus, HCT - hypercholestrolaemia, CKD-chronic kidney disease

statistically significant with a moderate positive correlation ($r=0.630$, $p<0.01$). This indicated that a patient who experienced a longer PFS tended to have a longer OS.

Effects of demographic factors on survival outcomes

The Kruskal-Wallis H non-parametric test revealed a statistically significant difference in progression-free survival across different age groups, with a p-value of 0.026. The median PFS varied with patients aged 60-64 years showing a much higher median of 35.50 months, while younger patients showed median PFS ranging from two to six months. Therefore, Spearman's rho correlation analysis was conducted. The correlation between PFS and age was moderate and positive ($r=0.469$, $p<0.01$); hence, this relationship was also statistically significant. These results suggested that age may play a role in the rate of disease progression, with older patients experiencing slower progression compared to younger patients. However, the effects of different age groups were not statistically different for overall survival with a p-value of 0.158.

The Kruskal-Wallis H test also demonstrated no statistically significant differences affecting both PFS and OS between the groups in terms of ethnicity, performance status, and comorbidities, as shown in Table II. The p-values were above the threshold level of 0.05.

Effects of tumour characteristics on survival outcomes

The Mann-Whitney U non-parametric test (Table III) revealed no significant differences in PFS or OS among patients with metastases at common sites such as the lung, liver, bone, lymph nodes, or with local recurrence. However,

Table II: Kruskal-Wallis H non-parametric test for survival outcomes by demographic factors and tumour characteristics

Factors	Group	Progression free survival						Overall survival				
		N	Median	IQR	Mean Rank	Kruskal-Wallis H	p-value	Median	IQR	Mean Rank	Kruskal-Wallis H	p-value
Demographic factors												
Age	20-24	1	5.00		10	20.33	0.026*	11.00		13.00	14.34	0.158
	30-34	3	4.00	3	6.83			11.00	22	15.67		
	35-39	1	6.00		16.5			15.00		20.50		
	40-49	6	6.00	2.5	14.67			12.00	17	17.67		
	50-54	1	2.00		4			2.00		3.00		
	55-59	8	6.00	2.25	15.44			8.50	9	10.88		
	60-64	6	35.50	62.5	31.83			36.00	48	28.83		
	65-69	3	16.00	12	28.17			20.00	29	23.33		
	70-74	3	7.00	8	17.25			23.00	8	27.50		
	75+	3	8.00	7	20.17			12.00	13	16.00		
Ethnicity	Malay	9	5.00	16.5	16.44	1.18	0.554	9.00	24.75	14.56	1.17	0.558
	Chinese	24	6.00	5.5	19.32			13.00	9.5	18.69		
	Indian	2	20.00	35	24			11.00	22.75	15.00		
ECOG	0	22	6.00	8.25	18.65	0.946	0.814	11.00	12.5	15.83	1.97	0.579
	1	11	6.00	6	19.09			15.00	11	19.91		
	2	1	6.00		16.50			12.00		17.50		
	3	1	12.00		29.00			19.00		26.00		
Comorbidities	No	21	5.50	3	13.52	12.756	0.078	11.00	9.25	14.5	6.42	0.378
	HPT	6	16.00	17	26.6			18.00	28.5	22.5		
	DM	2	6.50	4.25	18.75			33.00	39.5	21.75		
	HCT	1	8.00		23			9.00		10.5		
	CKD	1	12.00		28			19.00		26		
	HPT+HCT	2	6.00	5	16.5			15.00		21.5		
	HPT+HCT+DM	2	9.00		25.5			21.00		28		
Tumour characteristics												
FIGO stage at initial diagnosis	Early stages (Recurrences)	24	6.00	3.75	17.46	3.12	0.21	11.50	6.5	16.14	2.20	0.333
	Metastatic disease at presentation	11	6.00	3	20.18			16.50	37.75	18.70		
Histology subtype	Adenocarcinoma	10	6.00	6	17.32	0.48	0.788	17.50	18.5	21.90	3.13	0.209
	Neuroendocrine	1	6.00		16.5			15.00		21.50		
	SCC	24	7.00	9	19.84			12.00	12	15.41		
Number of metastatic sites	1	18	8.00	7	19.42	0.73	0.694	12.00	13	16.92	2.00	0.368
	2	16	6.00	9	19.06			12.00	16	19.03		
	3	1	5.00		10			5.00		5.00		

* Significant, p<0.05

Table III: Mann-Whitney U non-parametric test for survival outcomes by different metastatic sites

Metastatic site	Progression free survival								Overall survival					
	Group	N	Median	IQR	Mean Rank	Sum of Ranks	Mann-Whitney U	p-value	Median	IQR	Mean Rank	Sum of Ranks	Mann-Whitney U	p-value
Lung	Yes	9	6.00	3.00	17.90	179.00	124.00	0.705	11.00	4.50	15.28	137.50	92.50	0.434
	No	26	6.00	7.00	19.41	524.00			14.00	6.50	18.30	457.50		
Liver	Yes	3	5.00	46.00	15.75	63.00	53.00	0.522	21.00	35.25	24.88	99.50	30.50	0.114
	No	32	6.00	5.50	19.39	640.00			12.00	6.25	16.52	495.50		
Bone	Yes	7	6.00	23.75	18.88	151.00	115.00	0.97	11.00	4.00	16.36	114.50	86.50	0.733
	No	28	6.00	5.50	19.03	552.00			12.00	8.00	17.80	480.50		
Local recurrence	Yes	13	7.50	4.75	19.82	277.50	149.50	0.717	14.00	6.25	17.68	247.50	137.50	0.93
	No	22	6.00	6.00	18.50	425.50			12.00	6.00	17.38	347.50		
Nodal	Yes	16	6.00	8.50	20.59	350.00	143.00	0.407	14.50	14.75	20.04	280.50	104.50	0.213
	No	19	6.50	2.50	17.65	353.00			11.50	6.00	15.73	314.50		
Others	Yes	4	4.00	1.50	7.63	30.50	20.50	0.025*	7.50	6.50	10.25	41.00	31.00	0.121
	No	31	7.00	5.50	20.38	672.50			12.00	8.25	18.47	554.00		

*Significant, p<0.05

Table IV: Patterns of management in metastatic/recurrent cervical carcinoma

Patterns of management		N (35)	Percentage (%)
Treatment Modalities			
Radiotherapy	Yes	20	57.1
	No	15	42.9
Chemotherapy	Yes	24	68.6
	No	11	31.4
Surgery	Yes	4	11.4
	No	31	88.6
Patterns			
Best supportive care		6	17.1
Chemotherapy alone		8	22.8
Chemotherapy followed by radical RT		8	22.8
Chemotherapy followed by palliative RT		2	5.7
Radical RT alone		3	8.6
Palliative RT alone		1	2.9
Radical RT then chemotherapy		2	5.7
Palliative RT then chemotherapy		1	2.9
Surgery alone		1	2.9
Surgery followed by chemotherapy		3	8.6

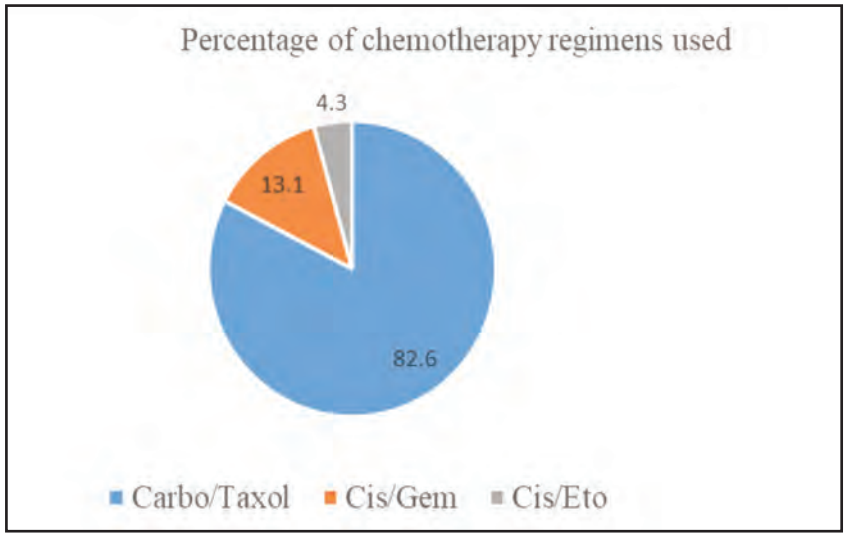

Fig. 1: Percentage of chemotherapy regimens used

metastases at less common sites (other sites) were associated with significantly shorter PFS. Patients with metastases at these sites had a median PFS of four months, compared to seven months for those without, with a p-value of 0.025. This difference, however, was not statistically significant for OS.

Nevertheless, the Kruskal-Wallis H non-parametric test showed no statistical differences between the groups in terms of cancer status at initial diagnosis, histology subtypes, and number of metastatic sites for both PFS and OS, as demonstrated in Table II.

Kaplan-Meier survival estimates for metastatic disease at other sites

As explained previously, metastatic sites were grouped based on the common sites of metastasis which were lung, liver, bone, nodal, and local recurrence. However, metastasis at the less common sites were separated as one group and there were four patients in this group. Out of these four patients, two had metastasis at adrenal glands, one patient had both peritoneal and adrenal metastases, and another one patient had peritoneal metastasis. This group of patients showed significant effect statistically in PFS by Mann-Whitney U test, hence we further conducted Kaplan-Meier survival analysis.

The patients with metastatic disease showed median PFS of four months (95% CI: 0.61 to 7.39 months) while the patients without presence of metastatic disease at these sites showed PFS of six months (95% CI: 4.5 to 7.49 months). The Log-Rank (Mantel-Cox) test yielded a Chi-square statistic of 8.14 with a p-value of 0.004 indicating a statistically significant difference in survival times between the groups. This result indicates that cervical carcinoma with metastasis at less common sites such as peritoneal and adrenals had poorer outcomes. The Kaplan-Meier survival estimates was also conducted for overall survival. However, although median OS for patients with metastasis at other sites was only four months compared to 12 months for patients who did not have the metastasis, they were not statistically significant with a p-value of 0.062.

Patterns of management

Table IV demonstrates the descriptive analysis of management of the patients with metastatic/recurrent cervical carcinoma in Department of Clinical Oncology, UMMC. The most commonly employed treatment modality was palliative chemotherapy, administered to 68.6% of the patients, followed by radiation therapy, which was used in 57.1% of the patients. A small number of the patients had debulking surgeries. 17.1% of the patients were treated conservatively with best supportive care.

Almost half of the patients (45.7%) had combination of treatment modalities as their first line management, either chemotherapy followed by radiotherapy (RT), radiotherapy followed by chemotherapy, or surgery followed by chemotherapy. One patient had surgery alone as she passed away shortly after the surgery. Four patients had radiotherapy alone mainly due to patients' refusal for chemotherapy.

For patients who had chemotherapy, combination of carboplatin-paclitaxel (carbo/taxol) was the most commonly used regimen, followed by gemcitabine-cisplatin (cis/gem). 1 patient with neuroendocrine carcinoma had cisplatin-etoposide (cis/eto) regimen as illustrated in Figure 1.

DISCUSSION

This retrospective study aimed to evaluate the survival outcomes of the patients with metastatic/recurrent cervical carcinoma registered at the Department of Clinical Oncology, UMMC. In addition to that, the study aimed to analyse demographic and tumour characteristics that may influence the survival in this cohort of cancer patients as well as patterns of management practised.

This study reported that the median progression-free survival (PFS) for metastatic/recurrent cervical cancer was six months, while median overall survival (OS) was 12 months. These findings were consistent with previous studies, notably Bonomi et al., Moore et al. and Monk et al., where they reported PFS ranged from 3.9 to 6.9 months and median OS ranged from 9.9 to 12.87 months.[5-7] Our study also showed that there was a moderate positive correlation between the PFS and OS. Patients who had longer PFS tended to have longer OS and vice versa. Although PFS has yet to be established as a validated surrogate endpoint for OS, a meta-analysis by Yarza et al. suggested that PFS may serve as a potential surrogate endpoint depending on treatment strategies.[8] However, further prospective studies are required to confirm this association.

This study found that 37.2% of cervical cancer patients at this centre were diagnosed with metastatic/recurrent disease, either as de novo or recurrent cases. This incidence was significantly higher than both global reports (10–30%) and national data, where the MNCR reported only 21.7% of metastatic cervical cancer cases between 2017 and 2021.[3,9] However, this study had included the cases of recurrent diseases either at distant sites or local recurrences that were not amenable to curative treatment, hence were treated as per metastatic diseases. This had contributed to higher prevalence compared to national or global reports.

The demographic factors evaluated in this study were age, ethnicity, performance status by ECOG, and comorbidities. This study reported that the occurrence of metastatic/recurrent disease increased with increasing age, particularly after the age of 40 years old. This was consistent with the MNCR report, which also reported a marked increase in cervical cancer after the age of 40 years old.[9] More than 50% of the patients were of Chinese ethnicity, which again reflected the national registry, which reported that Chinese origin has a higher lifetime risk of cervical cancer compared to Malay or Indian races. No statistically significant differences in patients' survival were observed across the groups stratified by performance status, and comorbidities.

Tumour characteristics evaluated in this study included cancer status at initial diagnosis, histological subtypes, and metastatic sites (both location and number of sites involved). The analysis found no statistically significant association between initial cancer status and patients' survival. However, local recurrence and nodal metastases were prevalent within these patients' cohort. These findings emphasised the importance of management in early-stage cervical cancer to reduce the risk of recurrence, hence survival.

Squamous cell carcinoma (SCC) was the most common histological subtype in this cohort 68.6%, followed by adenocarcinoma 28.6%. One patient was diagnosed with neuroendocrine carcinoma. These findings were consistent with global epidemiological trends.[4] Although many studies reported that adenocarcinoma demonstrated poorer survival outcomes compared to the SCC subtype in the overall population of cervical cancer patients, comparisons in metastatic/recurrent settings were scarce.[10] Nevertheless, the findings of the present study, which demonstrated no significant difference in survival outcomes between SCC and adenocarcinoma subtypes, were consistent with those of the NRG Oncology/Gynaecologic Oncology Group study led by Seamon et al., which reported comparable outcomes in patients with metastatic cervical carcinoma between the groups.[11]

Human papillomavirus (HPV) infection is recognised as the primary risk factor in the epidemiology of cervical cancer.[2] However, HPV association was not studied in this survey, as it was not a standard practice for HPV reporting in our centre. Hence, the analysis may have led to misinterpretation.

The majority of patients in this cohort demonstrated local and nodal recurrence, emphasising the importance of timely and optimal management during the early stages of disease. However, among visceral metastases, lung was the most commonly affected site, followed by bone and liver involvement. This pattern was consistent with findings from a large population-based study by Zhou et al., which reported lung metastases in 37.9% of 1,347 patients.[12] Similarly, most patients in the current study presented with metastases confined to a single site.

Distant metastases at sites other than nodal regions, local recurrence, lung, bone, or liver were associated with significantly worse survival outcomes. This suggested that metastases to fewer common sites, such as the peritoneum and adrenal glands, may be associated with more aggressive diseases and poorer prognoses, although evidence was scarce due to their rarity. However, the number of metastatic sites did not have a significant impact on survival.

This study demonstrated a variety of management approaches for metastatic cervical carcinoma, including best supportive care, chemotherapy alone, chemotherapy followed by radical radiotherapy, chemotherapy followed by palliative radiotherapy, radical radiotherapy alone, palliative radiotherapy alone, radical radiotherapy followed by chemotherapy, palliative radiotherapy followed by chemotherapy, surgery alone, and surgery followed by radiotherapy.

Although the optimal management of metastatic/recurrent cervical carcinoma remained debated, many studies and clinical guidelines recommended initiating systemic treatment.[4] This was consistent with our findings, where chemotherapy alone or in combination with other modalities were the most frequently used treatment modalities, together accounting for 68.6% of the patients in this cohort.

Historically, single-agent intravenous cisplatin was the most commonly used chemotherapy for metastatic cervical carcinoma. However, in this study, all patients who received chemotherapy were treated with doublet regimens. Carboplatin-paclitaxel was the most frequently administered combination, while cisplatin-gemcitabine and cisplatin-etoposide were used in a minority of cases. This practice was concordant with international guidelines, supported by landmark trials demonstrating improved survival outcomes with doublet regimens.[6-7] Since 2015, Kitagawa and colleagues reported the non-inferiority of carboplatin-paclitaxel compared to cisplatin-paclitaxel, with the added benefit of better quality of life.[13] Although bevacizumab and immunotherapy had been shown to improve outcomes in metastatic cervical cancer, none of the patients in this cohort received these agents, likely due to financial constraints, as bevacizumab and immunotherapy were not reimbursed by standard government funding in Malaysia.[14-16]

The main limitation of this study was its small sample size and retrospective nature. Hence, there were risks of inaccuracy in data reporting, which may affect the analysis. Although UMMC is one of the few cancer centres in Malaysia, due to the sudden Coronavirus-19 pandemic that hit the country in 2019-2021, accessibility was restricted. The management of the patients was also affected; as national healthcare efforts were directed towards addressing the pandemic. Besides that, the accessibility and affordability of the newer agents, particularly bevacizumab, had also improved over the past few years due to the availability of a generic version of bevacizumab, which may demonstrate better results and outcomes. Therefore, future researches should include multicentre studies, as they may provide more robust data and allow for a more comprehensive evaluation of treatment effects and their tolerability in relation to survival outcomes.

In addition, this study only looked at the first-line systemic therapies. Therefore, further studies are needed to evaluate the effects of subsequent therapies in survival of metastatic/recurrent cervical cancer.

CONCLUSION

The median progression-free survival of six months and median overall survival of 12 months were consistent with global survival statistics, hence suggesting that local treatment practices were comparable to the international standards.

The data also indicated that middle-aged women represented the most affected demographic, emphasising the need for targeted cancer screening, education, and prevention programmes to enhance awareness and promote early detection within this population. Additionally, this study demonstrated that the majority of metastatic/recurrent cervical cancer cases developed as a progression from early-stage disease. This emphasised the importance of optimal management during radical treatment, particularly ensuring timely initiation of therapy and access to oncological services.

The management of metastatic/recurrent cervical cancer in Malaysia was consistent with international recommendations and studies. However, none of the patients in this cohort had received newer therapeutic agents such as bevacizumab or pembrolizumab, which may have prolonged their survival outcomes. Therefore, efforts and support to enhance accessibility to these newer therapies should be improved at the national level for better outcomes.

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Prevalence and associated factors of single pill combination therapy among people with hypertension in a tertiary hospital

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ABSTRACT

Introduction: Effective management of hypertension often requires pharmacological intervention, which can involve either single pill combination therapy (SPC) or multiple pill combination therapy (MPC). However, the choice between SPC and MPC can be influenced by patient demographics, clinical characteristics, comorbid conditions and physician preferences. This study was aimed at exploring the prevalence of SPC versus MPC usage among people with hypertension in a tertiary hospital and its associated factors.

Materials and Methods: A cross-sectional study using a validated questionnaire was conducted among the hypertensive patients aged 18 years and on antihypertensive medication(s) for at least six months attending various speciality clinics at Hospital Sultan Abdul Aziz Shah, Selangor.

Results: The prevalence of patients using SPC was 27.9% (78/280). In univariate analysis, factors that were found to be associated with the use of SPC were presence of diabetes mellitus (p < 0.001), presence of chronic kidney disease (p = 0.033), physician's own preference for SPC (p = 0.027) and duration of hypertension (p = 0.003). The independent factors associated with SPC use was the presence of chronic kidney disease, physician's own preference for SPC and absence of diabetes mellitus (p < 0.05).

Conclusion: The use of SPC is only 27.9%. The independent factors associated with SPC use was the presence of chronic kidney disease, physician's own preference for SPC and absence of diabetes mellitus. Hence, this study's findings can be applied by healthcare providers who should consider these factors when prescribing hypertension treatments. Tailoring the treatment plan to the individual patient's needs and circumstances can enhance adherence and efficacy.

KEYWORDS:
Single pill combination therapy (SPC), Multiple pill combination therapy (MPC), Prevalence, Factors, Malaysia

INTRODUCTION

Hypertension is defined by the World Health Organization (WHO) as high or elevated blood pressure, and is a medical condition characterised by consistently heightened pressure within the blood vessels. According to Carey et al., in their review published in JAMA, primary drug treatment for hypertension typically involves using a thiazide or thiazide-like diuretic, like hydrochlorothiazide or chlorthalidone, an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker, such as enalapril or candesartan, along with a calcium channel blocker like amlodipine.[1] These drugs can be given as a single pill combination or multiple pill combination. Single pill combination or fixed dose combination therapy (SPC) contains two or more different medications of various doses in a single pill.[2] Example with include innovator drug such as Twynsta® which contains variable doses of telmisartan and amlodipine in a single pill. Multiple pill combination (MPC) therapy is defined as the specific use of two or more drugs for a chronic condition in an individual.[3] Examples will include innovator drugs such as Micardis® (which contains telmisartan) and Norvasc® (which contains amlodipine).

International hypertension guidelines increasingly recommend SPC therapy as the preferred initial pharmacological treatment for most patients with hypertension who require more than one antihypertensive agent. The WHO 2021 Hypertension Guideline recommends initiating treatment with combination therapy, preferably as an SPC, because it improves medication adherence, treatment persistence, and blood pressure control compared with free-drug combinations.[4] The guideline also highlights that combining antihypertensive agents from complementary drug classes at lower doses provides greater blood pressure reduction while reducing dose-dependent adverse effects.[4]

Similarly, the 2024 European Society of Cardiology (ESC) Guidelines for the management of elevated blood pressure and hypertension recommend that most patients with hypertension should begin treatment with a low-dose two-drug combination, preferably as a single-pill combination.[5-6]

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The guideline emphasizes that SPC therapy achieves more rapid blood pressure control, improves long-term adherence and persistence, and reduces therapeutic inertia. The recommended first-line combinations include an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) combined with either a calcium channel blocker (CCB) or a thiazide/thiazide-like diuretic. These recommendations are particularly relevant for patients with diabetes mellitus and chronic kidney disease, who frequently require combination therapy to achieve stricter blood pressure targets and reduce cardiovascular and renal complications.[5-6]

The decision to focus on people with hypertension in tertiary hospitals in this study was because people with hypertension may need to consume a lot of medicine which can lead to patient compliance and mistakes in taking the medication. Understanding the factors associated with the choice between SPC and MPC is vital for optimising treatment adherence, patient outcomes, and healthcare resource utilisation.

This study was aimed at determining the prevalence and associated factors of multiple pill combination versus single pill combination therapies among people with hypertension in a tertiary hospital. The result of this study will provide information on the currently prescribed patterns of managing hypertensive conditions in a tertiary hospital. The findings stand to optimise patient outcomes and contribute to the refinement of current medical practices in tertiary healthcare settings. In addition, this research can help healthcare professionals optimise hypertension therapy strategies.

MATERIALS AND METHODS

A cross-sectional study was conducted at the family medicine, general and subspecialties internal medicine clinics at Hospital Sultan Abdul Aziz Shah (HSAAS), Selangor, from December 2023 to June 2024. The study included people with hypertension who had been on antihypertensive medication for at least six months and were able to understand Malay or English language. Patients with cognitive impairment or acute psychiatric illness were excluded. Systematic random sampling was used for participants selection, and a validated self-administered questionnaire was employed to collect sociodemographic, lifestyle and clinical data. The systematic random sampling procedure over the one-month data collection involves setting a fixed time or participant interval and picking a random starting point to ensure every participant has an equal chance of being selected.

Sample size calculation was based on the number of total patients with hypertension expected to be seen in the study site over the study period which was 600 patients. Using the Raosoft® sample size calculator, the estimated required sample size will be 280 participants, after accounting for 20% possible non respondents.

Upon giving consent, the participants were then provided with a questionnaire to answer. The estimated time to answer the questionnaire was approximately 5 to 10 minutes. This validated questionnaire consisted of three sections as above. The languages used in the questionnaire are English and Malay. Validation process of the questionnaires involved both content validation and face validation. Content validation was done with an expert panel of two primary care physicians, two geriatricians and on biostatistician. Face validation was done with 30 adults (about 10% of the estimated sample size, accounting for additional 20% non-respondent) who attended the clinic. Changes recommended during the content and face validation were incorporated into the final version of the questionnaire. The Cronbach's alpha of the relevant sections in the questionnaire ranged from 0.82- 0.88, therefore indicating good reliability. Pilot testing was done prior to actual data collection to enable the study to be conducted with minimal disruptions to the clinic operations.

One of variable used was Physician preference, which means the specific choices a doctor makes regarding either advocating SPC or MPC. However, the final choice of the type of medication used may still be subjected to availability and additional cost. For the dependant variable, participant classified as SPC user may also include those that are on additional antihypertensive agents as long as they are using SPC antihypertensive therapy.

IBM Statistical Package for Social Science (SPSS) software version 29.0 was used for statistical analysis. Descriptive data was described as frequency and percentages. Chi-square or Fisher's exact test was used in the univariate analysis to analyse the categorical independent variables. For multivariate analysis, multiple logistic regression analysis was used. Independent variables with a p-value of <0.25 from univariate analysis was included into final multiple logistic regression analysis to determine the independent factors associated with SPC use. The statistical significance was accepted at p-value of <0.05. Patient confidentiality was maintained by labelling questionnaires with identification numbers instead of personal information. Ethical approval was obtained from the Universiti Putra Malaysia Ethical Committee (JKEUPM). The study ensured ethical standards by obtaining informed consent from participants and safeguarding data through secure storage and restricted access. The potential benefits and risks of participation were explained to the patients, and assistance was provided to vulnerable participants in completing the questionnaires.

RESULTS

The response rate was 100%. In this study, the prevalence of people with hypertension that used SPC therapy was 27.9% (78/280), while 72.1% of the participants used MPC therapy. Table I shows the socio-demographic, lifestyle and clinical characteristic of the participants. The majority of the participants were male (55.5%), unemployed (mainly retirees) (42.3%), and of Malay ethnicity (75.2%), with a significant proportion falling within the age range of above 60 years old (83.9%). Most of the participants are married (83.2%) and have attained tertiary education (71.6%). Household income distribution shows that 58.4% of the participant earn between RM4,850 and RM10,970 (i.e. falling into M40 category). Additionally, a large majority of participants have never consumed alcohol (91.2%) or

Table I: Descriptive analysis for demographic factors and tumour characteristics

Factors	Group	N (35)	Percentage (%)
Age	20-24	1	2.9
	30-34	3	8.5
	35-39	1	2.9
	40-49	6	17.2
	50-54	1	2.9
	55-59	8	22.9
	60-64	6	17.2
	65-69	3	8.5
	70-74	3	8.5
	75+	3	8.5
Ethnicity	Malay	9	25.7
	Chinese	24	68.6
	Indian	2	5.7
ECOG	0	22	62.9
	1	11	31.5
	2	1	2.8
	3	1	2.8
Comorbidities*	No	21	60.0
	HPT	6	17.1
	DM	2	5.7
	HCT	1	2.9
	CKD	1	2.9
	HPT+HCT	2	5.7
	HPT+HCT+DM	2	5.7
Tumour characteristics			
Cancer status at initial diagnosis	Localised disease	24	68.6
	Metastatic disease	11	31.4
Histology subtype	SCC	24	68.6
	Adenocarcinoma	10	28.6
	Neuroendocrine	1	2.8
Number of metastatic/recurrence sites	1	18	51.4
	2	16	45.7
	3	1	2.9
Metastatic/recurrence site			
Lung	Yes	9	25.7
	No	26	74.3
Liver	Yes	3	8.6
	No	32	91.4
Bone	Yes	7	20.0
	No	28	80.0
Local recurrence	Yes	13	37.1
	No	22	62.9
Nodal	Yes	16	45.7
	No	19	54.3
Others	Yes	4	11.4
	No	31	88.6

* HPT-hypertension, DM-diabetes mellitus, HCT - hypercholestrolaemia, CKD-chronic kidney disease

smoked (72.3%). Dyslipidaemia was noted among 67.2% of participants, while 51.8% of participants had diabetes mellitus. Majority of the patients do not have chronic kidney disease (91.1%). Majority of participants had normal body weight (58.5%). The cost of medication is uncertain for a significant portion (87.2%) of participants, and physician preferences are varied, with (54.7%) unsure of their own preference regarding the use of MPC and SPC. Hypertension duration also varies, with the majority of the participants diagnosed with hypertension for >5 to 10 years (67.9%). These socio-demographic characteristics provide a comprehensive understanding of the patient population being studied, allowing for a detailed analysis of factors associated with the use of SPC and MPC therapies among people with hypertension.

Table II shows the association between various sociodemographic factors, lifestyle and clinical characteristics with the intake of single pill combination (SPC) or multiple pill combination (MPC) antihypertensive medications (univariate analysis) among the participants of this study. Chi-square test (or Fischer Exact test) and corresponding p-values were utilised to assess the significance of these associations. Results indicate that gender, ethnicity, marital status, highest level of education, household income, alcohol consumption, smoking habit, dyslipidaemia, and obesity do not exhibit significant associations with medication choice (had a p-value > 0.05). It was noted that the presence or absence of diabetes mellitus, chronic kidney disease and the duration of hypertension showed an association with medication intake, either SPC or MPC therapy ($p<0.05$). Participants with diabetes mellitus were less likely to be on

Table I: Socio-demographic, lifestyle and clinical characteristic of the participants (N=280)

Variable	Frequency (%)
Gender	
Male	154 (55.5)
Female	126 (44.5)
Occupation	
Government workers	98 (35.0)
Private workers	19 (6.6)
Self-employment	45 (16.1)
Unemployed/retirees	118 (42.3)
Ethnicity	
Malay	211 (75.2)
Chinese	29 (10.2)
Indian	40 (14.6)
Age (years)	
18 - < 40 years	8 (2.9)
40 - < 60 years	37 (13.1)
> 60 years	235 (83.9)
Marital status	
Single	21 (7.5)
Married	233 (83.2)
Widowed	26 (9.3)
Highest level of education	
None	8 (2.9)
Primary	8 (2.9)
Secondary	63 (22.6)
Tertiary	201 (71.6)
Household income	
< RM4,850 (B40)	43 (15.3)
RM4,850 - RM10,970 (M40)	164 (58.4)
> RM10,970 (T20)	73 (26.3)
Alcohol consumption	
Currently consume	1 (0.4)
Previously consume	24 (8.0)
Never consume	255 (91.2)
Smoking habit	
Currently smoking	10 (3.6)
Previously smoking	68 (24.1)
Never smoking	202 (72.3)
Dyslipidaemia	
No	92 (32.8)
Yes	188 (67.2)
Body mass index	
Underweight	14 (5.0)
Normal weight	164 (58.5)
Overweight	94 (33.5)
Obese	8 (3.0)
Chronic kidney disease	
No	255 (91.1)
Yes	25 (8.9)
Diabetes mellitus	
Absent	135 (48.2)
Present	145 (51.8)
Cost of SPC/MPC	
Yes	20 (7.1)
No	16 (5.7)
Unsure	217 (87.2)
Physician preferences	
MPC	26 (9.5)
SPC	9 (3.0)
No preferences mentioned	92 (32.8)
Unsure	153 (54.7)
Duration of hypertension	
< 1 year	6 (2.2)
1 - 5 years	20 (7.3)
>5 - 10 years	190 (67.9)
> 10 years	64 (22.6)

Table II: Association between the sociodemographic factors, lifestyle and clinical characteristics with the intake of single pill combination (SPC) and multiple pill combination (MPC) among the participants (N=280)

Variables	MPC n (%)	SPC n (%)	Chi Square, X2	p-value
Gender				
Male	116 (75.0)	38 (25.0)	0.257	0.612
Female	99 (78.7)	27 (21.3)		
Occupation				
Government workers	79 (80.7)	19 (19.3)	3.337	0.343
Private workers	11 (57.9)	8 (42.1)		
Self-employment	37 (82.2)	8 (17.8)		
Unemployed	87 (73.7)	31 (27.3)		
Ethnicity				
Malay	162 (76.8)	49 (23.2)	1.079*	0.583*
Chinese	24 (82.8)	5 (17.2)		
Indian	28 (70.0)	12 (30.0)		
Age range				
18 - < 40 years	4 (50.0)	4 (50.0)	3.292*	0.141*
40 - < 60 years	25 (67.7)	12 (32.3)		
> 60 years	186 (79.1)	49 (20.9)		
Marital status				
Single	17 (81.0)	4 (19.0)	0.639*	0.784*
Married	180 (77.3)	53 (22.7)		
Widowed	18 (69.2)	8 (30.8)		
Highest level of education				
None	8 (100.0)	0 (0.0)	1.544*	0.705*
Primary	8 (100.0)	0 (0.0)		
Secondary	47 (74.6)	16 (25.4)		
Tertiary	152 (75.6)	49 (24.4)		
Household income				
< RM4,850	35 (81.4)	8 (18.6)	4.438	0.116
RM4,850 - RM10,970	134 (81.7)	30 (18.3)		
> RM10,970	47 (64.4)	26 (35.6)		
Alcohol consumption				
Currently consume	0 (0.0)	1 (100.0)	3.081*	0.266*
Previously consume	18 (75.0)	6 (25.0)		
Never consume	198 (77.6)	57 (22.4)		
Smoking habit				
Currently smoking	6 (60.0)	4 (40.0)	1.123*	0.683*
Previously smoking	54 (79.4)	14 (20.6)		
Never smoking	155 (76.7)	47 (23.2)		
Dyslipidaemia				
Absent	72 (78.3)	20 (21.7)	0.048	0.835
Present	143 (76.1)	45 (23.9)		
Body mass index				
Underweight	10 (71.4)	4 (28.6)	1.697*	0.681*
Normal weight	131 (79.9)	33 (20.1)		
Overweight	67 (71.3)	27 (28.7)		
Obese	6 (75.0)	2 (25.0)		
Chronic kidney disease				
Absent	202 (79.2)	53 (20.8)	-	0.033*
Present	12 (48.0)	13 (52.0)		
Diabetes mellitus				
Absent	82 (60.7)	53 (39.3)	18.294	<0.001
Present	133 (91.7)	12 (8.3)		
Cost of MPC/SPC				
Yes	12 (60.0)	8 (40.0)	2.613	0.278
No	14 (87.5)	2 (12.5)		
Unsure	170 (78.3)	47 (21.7)		
Physician preferences				
MPC	24 (92.3)	2 (7.7)	6.517	0.072
SPC	2 (22.2)	7 (77.8)		
No preferences mentioned	72 (78.3)	20 (21.7)		
Unsure	116 (75.8)	37 (24.2)		
Duration of hypertension				
< 1 year	2 (33.3)	4 (66.7)	12.230*	0.003*
1 - 5 years	8 (40.0)	12 (60.0)		
>5 - 10 years	159 (83.7)	31 (16.3)		
> 10 years	45 (70.3)	19 (29.7)		

(*) = Fisher's Exact Test

Table III: Factors associated with the use of single pill combination (SPC) of antihypertensives (N=280)

Variables	Odds Ratio	95 % Confidence Interval	p-value
Age range			
18 - < 40 years	Reference	Reference	Reference
40 - < 60 years	4.017	0.028 - 568.197	0.582
> 60 years	1.735	0.232 - 12.952	0.591
Household income			
< RM4,850	Reference	Reference	Reference
RM4,850 - RM10,970	4.563	0.541 - 38.457	0.163
> RM10,970	8.362	0.921 - 75.949	0.059
Chronic kidney disease			
No	Reference	Reference	Reference
Yes	6.908	1.526 - 31.274	0.012
Diabetes mellitus			
No	Reference	Reference	Reference
Yes	0.145	0.043 - 0.493	0.002
Physician preferences			
MPC	Reference	Reference	Reference
SPC	185.883	4.499 - 7680.442	0.006
No preferences mentioned	5.837	0.377 - 90.322	0.207
Not sure	10.098	0.720 - 141.545	0.086
Duration of hypertension			
< 1 year	6.662	0.183 - 242.570	0.301
1 - 5 years	4.059	0.312 - 52.845	0.285
6 - 10 years	0.538	0.168 - 1.724	0.297
> 10 years	Reference	Reference	Reference

SPC therapy compared to MPC therapy ($p < 0.001$), similar with participants with chronic kidney disease ($p = 0.033$). In addition, there was a significant association between the duration of hypertension and the type of therapy. Patients with a longer duration of hypertension (>5-10 years or more) were less likely to be on SPC therapy compared to those with a shorter duration (p=0.003). These findings underscore the complexity of factors influencing medication selection in hypertension management, highlighting the importance of personalised approaches in clinical practice. In univariate analysis, factors that were found to be associated with the use of SPC were presence or absence of Diabetes Mellitus ($p<0.001$), presence or absence of chronic kidney disease (p=0.033) and duration of hypertension (p=0.003).

Variables that had a p-value of <0.25 in Table II were entered into multiple logistic regression analysis to determine the independent factors associated with SPC use. The assumptions underlying multivariable logistic regression were evaluated before model fitting. Model calibration was assessed using the Hosmer–Lemeshow goodness-of-fit test, multicollinearity was examined using variance inflation factors (VIFs), and model discrimination was evaluated using the area under the receiver operating characteristic (ROC) curve (AUC). The logistic regression model is highly reliable, accurate, and ready for use, as every diagnostic test score falls comfortably within the ideal range. The Hosmer-Lemeshow test indicates a good fit (p=0.16), the area under the ROC curve shows excellent discrimination (AUC=0.87), and the highest Variance Inflation Factor (VIF=3.2) confirms no significant multicollinearity.

Table III shows the independent factors associated with SPC use among the participants of this study. The independent factors associated with SPC use were assessed using odds ratios (OR), 95% confidence intervals (CI), and p-values. The presence of chronic kidney disease was significantly associated with the use of SPC therapy. Patients with chronic kidney disease were 6.90 times more likely to use SPC as compared to those without chronic kidney disease (95% CI: 1.526 -31.274, p=0.012). The presence of diabetes mellitus was also significantly associated with a lower likelihood of using SPC therapy. Patients with diabetes were 0.15 times less likely to use SPC therapy compared to those without diabetes (95% CI: 0.043 -0.493, p=0.002). Physician preference for SPC significantly influenced the use of SPC therapy. Participants whose physicians preferred SPC were 186.00 times more likely to use SPC therapy compared to those whose physicians preferred multiple pill combination (MPC) therapy (95% CI: 4.499 - 7680.442, p = 0.006). On checking, the goodness-of-fit assessment was good and there was no missing data.

DISCUSSION

In this study, the prevalence of participants using SPC was 27.9% (78/280). This is much less than a similar study done among people with hypertension in China a few years earlier.[7] The difference in this finding maybe related to different demographic used and the fact that most SPC therapy used in Malysia mainly involved innovator drugs and may involve additional cost, as compared to widely available and cheaper generic drugs.

Independent factors associated with SPC use was the presence of chronic kidney disease, physician's own preference for SPC and absence of diabetes mellitus ($p<0.05$). Chronic kidney disease (CKD) was found to significantly influence therapy type in both univariate (p=0.033) and multivariate (p=0.012) analyses in this study. This finding is consistent with previous research suggesting that SPC therapy may benefit CKD patients by improving adherence and potentially enhancing blood pressure control.[8] CKD patients often manage complex

medication regimens, and simplifying antihypertensive therapy with SPCs could improve compliance and outcomes. However, other studies have shown mixed results, with some advocating for MPC therapy to better address the specific needs and complications of CKD.[9] Differences in sample size, patient demographics, or healthcare practices across studies may contribute to these varying findings.

The study found that diabetes mellitus was significantly associated with the use of MPC therapy over SPC therapy (p <0.001). This finding is supported by previous research, which suggests that diabetic patients often require more aggressive treatment regimens involving multiple antihypertensive agents due to the complex nature of diabetes.[10] This similarity in findings underscores the practice of tailoring hypertension treatment to meet the specific needs of patients with diabetes, particularly those at higher cardiovascular risk and with stricter blood pressure targets.

Patients with CKD and diabetes are strongly associated with SPC therapy due to the need to hit specific clinical targets, and efforts to reduce pill burden. Certain SPCs are formulated with lower doses of individual medications. By using two drugs at lower doses rather than one drug at a maximum dose, physicians can effectively target disease pathways (e.g., lowering blood pressure) while minimizing the adverse side effects associated with high single-drug doses.[11-12]

Physician's own preference for SPC also influence the use of SPC therapy. Research often noted physician-driven decisions were based on guidelines and patient adherence.[13] Physician preferences played a significant role, with higher recommendations for SPC usage when physicians advocated for it, emphasising their influence in treatment decisions. Despite SPC therapy's potential benefits in improving adherence and reducing pill burden, its adoption is influenced by clinical complexities and physician practices, suggesting a balanced approach to hypertension treatment. Physicians generally show a strong preference for SPC therapy due to its proven benefits in improving patient adherence to medication, reducing pill burden, and achieving better and more rapid blood pressure control.[14-17] Physician preference for SPC also may be affected by guidelines across various specialities such as endocrinology and nephrology, availability, creatine clearance and costs.[4-5] This can further be exacerbated by clinical inertia, i.e. the failure to initiate or intensify therapy when treatment goals are not being met.[18] However, the very large odds ratio for physician preference (OR 185.9; 95% CI 4.5-7680.4) remains difficult to interpret and should be acknowledged as likely reflecting sparse data or model instability rather than just representing a strong association.

LIMITATIONS

This study had a few limitations. A limitation of this study was that this was a cross-sectional study, thereby limiting the causality relationship. While statistical methods can adjust for confounders, cross-sectional studies are limited in their ability to control for all potential confounding variables, which can influence the observed associations. Another limitation of this study was that it was conducted in a single centre and therefore limiting the external validity, generalizability and introducing possible selection bias to the wider hypertensive population. Additional limitations in this study may also include recall bias, self-report bias, residual confounding and the lack of medication adherence assessment. It is to be noted that several clinically relevant factors were included in the logistic regression model as the p-values were > 0.25. The authors acknowledge that they may be important confounding factors and may affect the conclusion of the study. Therefore, results of this study should be interpreted with caution.

Despite these limitations, this is one of the first few studies to look at data on usage of SPC therapy among people with hypertension in Malaysia and had a quite significant number of participants. Therefore, this study may still hold some value to promote the use of SPC therapy among people with hypertension and stimulate future multi-centre research into this interesting subject matter.

CONCLUSION

This study demonstrates that the prevalence of patients using single pill therapy was 27.9% (78/280). For future research and clinical practice, this study identifies prescribing patterns and associated factors that may inform future prospective studies and help in selecting patients for SPC therapy. Future research can also recruit more centres to get a more accurate nationwide data on the prevalence of SPC therapy and associated factors. Thus, a message that can be conveyed from this study is healthcare providers should consider these factors when prescribing hypertension treatments.

CONFLICT OF THE INTERESTS

The authors declare no conflict of interests.

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Potential utility of cell-free deoxyribonucleic acid for detection of early-stage resectable non-small cell lung cancer

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ABSTRACT

Introduction: Cell-free DNA (cfDNA) has emerged as a promising non-invasive biomarker for cancer detection, including non-small cell lung cancer (NSCLC). While these approaches have demonstrated high diagnostic accuracy in controlled settings, their performance in real-world clinical populations remains uncertain. This study aimed to evaluate the diagnostic performance of a plasma cfDNA assay for early-stage NSCLC detection and to explore its association with clinicopathological parameters.

Materials and Methods: This was a single-center, cross-sectional study involving 61 patients with radiologically suspected lung lesions, of whom 52 were confirmed NSCLC. Plasma samples were analyzed using a shallow genome-wide sequencing-based cfDNA assay incorporating fragmentomic and copy number features. cfDNA results were compared against histopathological diagnosis to determine sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Associations between cfDNA detection and clinical variables were evaluated using appropriate statistical tests.

Results: The cfDNA assay demonstrated a sensitivity of 75% and a PPV of 84.8% with a specificity of 22.2% and NPV of 13.3%. cfDNA detection rates increased with advancing disease stage, although a relatively high sensitivity was observed even in stage I disease (79.4%). No statistically significant associations were found between cfDNA positivity and conventional markers of tumour burden, including tumour size, serum carcinoembryonic antigen, and SUVmax.

Conclusion: The cfDNA assay evaluated in this study demonstrated limited clinical utility as a standalone screening tool due to its low specificity and NPV in a real-world early-stage NSCLC population. Future efforts should focus on improving assay specificity through the incorporation of multi-omic tumour-specific biomarkers and validation that includes early-stage lung cancer cases and benign pulmonary conditions.

KEYWORDS:
cfDNA, early diagnosis, screening, non-small-cell lung cancer (NSCLC), lung cancer detection

INTRODUCTION

Lung cancer remains a leading cause of cancer-related mortality worldwide due to a preponderance of late-stage diagnosis in a majority of cases. Early diagnosis is critical, as curative-intent therapy and prognosis are largely stage-dependent. Low-dose computed tomography (LDCT) screening creates an impactful stage-shift with a reduction in lung cancer-specific mortality but is hampered by cost, false positives and accessibility issues. Presently, tissue biopsy is the gold standard for diagnosis however procedures are invasive and subjective due to spatial and temporal tumour heterogeneity. Yield may also be insufficient for molecular profiling resulting in concurrent or repeated sampling with additional risk and cost to the patient.

Liquid biopsy approaches enable minimally invasive detection of tumour-derived genetic and epigenetic alterations on cell-free DNA (cfDNA) and have potential applications in early diagnosis, disease monitoring and treatment stratification.[1] Multi-cancer early detection (MCED) and single-cancer early detection (SCED) strategies are emerging approaches aimed at improving cancer diagnosis at earlier, more treatable stages through more minimally invasive analysis of cfDNA. MCED assays use cfDNA-based fragmentation patterns, methylation signatures, or mutation profiles to detect signals from multiple tumour types in a single blood test.[2-4] In contrast, SCED approaches focus on detecting a single cancer type with higher sensitivity for a specific disease. In lung cancer, cfDNA-based SCED strategies include targeted mutation panels and methylation or fragmentomic-based classifiers designed specifically for early-stage lung cancer detection. These lung-specific cfDNA assays may complement LDCT, helping to reduce false-positive rates and improve diagnostic confidence in screening settings.

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To date, there is a paucity of data regarding the role of cfDNA for primary diagnosis or risk stratification of indeterminate pulmonary nodules (IPN), a small focal lung lesion identified on imaging that may represent a precursor of lung cancer but cannot be definitively classified as benign or malignant at initial detection, which requires further evaluation. Much of the current literature focuses on postoperative monitoring for molecular residual disease (MRD), response to therapy including surgery, and relapse prediction.[5-7] It is believed that the low tumour burden and reduced DNA shedding in early-stage disease limits its sensitivity for detection. However, efforts incorporating ultra-deep sequencing methodology or a multi-modal approach coupled with machine learning classification models may have the potential to enhance the detection of early lung cancers.

We conducted a prospective, observational, cross-sectional, real-world evidence study to evaluate the diagnostic performance of a commercially available cfDNA assay for the screening and diagnosis of early-stage non-small cell lung cancer (NSCLC) in predominantly asymptomatic individuals who presented with suspicious lung pathology on imaging, suggestive of potentially resectable disease.

MATERIALS AND METHODS

Patient recruitment and clinical procedures

From January 2025 to February 2026, we enrolled 61 patients from Sunway Medical Centre referred for surgical evaluation and further management of suspicious lung nodules on PET-CT imaging suggestive of possible early-stage lung cancer. Some patients had a pre-operative tissue biopsy confirming NSCLC or benign pathology. Serum carcinoembryonic antigen (CEA), a common lung cancer biomarker, was measured for most patients pre-operatively. Patients underwent PET-CT imaging to determine the clinical stage, tumour size as well as F-18 fluorodeoxyglucose (FDG)-based metabolic activity of the tumour using maximum standardized uptake value (SUVmax) measurement. All eligible patients underwent surgical resection after appropriate staging, with baseline cfDNA testing performed pre-surgically. Histopathological examination of the resected specimen was performed in all cases.

Blood collection, cfDNA extraction and next-generation sequencing

A 10ml peripheral blood draw was obtained from each patient on the evening before the operation, using a commercially available SCED assay named SPOT-MAS Lung (Gene Solutions).[2] Plasma was separated through a two-step centrifugation process, followed by cfDNA extraction. The extracted and purified cfDNA was then subjected to next-generation sequencing (NGS) using the DNBSEQ-G400 system (MGI) with shallow sequencing coverage (0.5x), integrating fragmentomic, nucleosome footprinting, copy number alterations (CNAs), and 4-mer end motif analyses, according to the manufacturer's protocol.[8]

Statistical analyses

Diagnostic performance of the cfDNA assay was evaluated using histopathological findings as the reference standard. Statistical analyses were performed using 2 × 2 contingency tables comparing cfDNA results with corresponding histopathology outcomes. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall diagnostic accuracy were calculated to determine the performance of the cfDNA assay in detecting cancer. Sensitivity was defined as the proportion of histopathologically confirmed positive cases correctly identified by cfDNA analysis, whereas specificity represented the proportion of histopathologically negative cases correctly classified as negative by cfDNA testing. PPV and NPV were calculated to assess the probability that positive and negative cfDNA results reflected the true disease status, respectively. Diagnostic accuracy was defined as the proportion of correctly classified cases among all evaluated samples. Sensitivity was also calculated according to the clinical stage of the cancers.

Continuous variables, including CEA level, tumour size, and SUVmax were summarized using the median and interquartile range (IQR). The associations between cfDNA status and these clinicopathological parameters were evaluated using the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables, as appropriate. For subgroup analyses, predefined cut-off values were applied to dichotomize variables: CEA level (≥5 ng/mL vs. <5 ng/mL), tumour size (≥3 cm vs. <3 cm), and SUVmax (≥5 vs. <5). The association between categorized variables and cfDNA positivity was further assessed using Fisher's exact test. A two-tailed p-value of <0.05 was considered statistically significant. Statistical analyses were performed using GraphPad PRISM version 10.6 (GraphPad Software, San Diego, CA, USA).

Ethics approval

This study was approved by the Sunway Medical Centre Independent Research Ethics Committee (SREC) with the approval number 044/2025/IND/ER.

RESULTS

Patient cohort and diagnostic classification

61 patients were enrolled in this study. Mean patient age was 60 years with a majority being female (63.9%), of Chinese ethnicity (68.9%) and never smokers (70.5%). 52 patients had pathological confirmation of a NSCLC, and 9 patients had non-NSCLC conditions such as granulomatous inflammation, tuberculosis, carcinoid tumours, focal pneumonia, and lymphocytic infiltrations.

Overall Diagnostic Performance of cfDNA

The cfDNA results were evaluated against histopathological examination as the reference standard using a disease confusion matrix to assess diagnostic performance (Table I). The comparison quantified concordance between cfDNA-based classification and tissue histopathology, enabling calculation of sensitivity, specificity, and overall diagnostic accuracy.

Based on the confusion matrix, the analysis revealed that the tested assay demonstrated a sensitivity of 75%, specificity of 22.2%, positive predictive value (PPV) of 84.8%, and negative predictive value (NPV) of 13.3%, with an overall accuracy of 67.2% (Table II).

Table I: Disease Confusion Matrix

	NSCLC (HPE +)	Non-NSCLC (HPE -)	Total
cfDNA positive	39 (True Positive)	7 (False Positive)	46
cfDNA negative	13 (False Negative)	2 (True Negative)	15
Total	52	9	61

NSCLC= Non-small cell lung cancer, HPE= histopathology examination

Table II: Overall diagnostic performance of cfDNA

Metric	Value (%)
Sensitivity	75
Specificity	22.2
Positive Predictive Value (PPV)	84.8
Negative Predictive Value (NPV)	13.3
Accuracy	67.2

Table III: cfDNA Sensitivity by Clinical Stage

Clinical Stage	True Positive (TP)	False Negative (FN)	Sensitivity (%)
Stage I	27	7	79.4
IA	22	4	84.6
IB	5	3	62.5
Stage II	5	5	50
IIA	0	3	0
IIB	5	2	71.4
Stage III	7	1	87.5
IIIA	5	1	83.3
IIIB	2	0	100

Table IV: Association of cfDNA Results with Clinical and Imaging Parameters

Variable	Overall Median (IQR)	cfDNA+ (n=40) Median (IQR)	cfDNA- (n=13) Median (IQR)	p-value (Mann-Whitney)	Cut-off value	cfDNA+ n (%)	cfDNA- n (%)	p-value (Fisher)
CEA (ng/mL) (n= 49)	2.6 (1.8-8.2)	2.7 (1.75- 8.35)	2.3 (1.9- 5.6)	0.9421	≥5ng/mL	36 (73.5)	13 (26.5)	> 0.999
Tumor size(cm) (n= 52)	2.7 (2.2- 3.9)	2.7 (2.2- 3.9)	2.7 (2.1- 4.2)	0.8984	≥3cm	39 (75)	13 (25)	> 0.999
SUVmax (n= 49)	6.6 (2.85- 9.99)	7.06 (2.85- 10.14)	6.58 (4.29- 8.94)	0.7437	≥5	37 (75.5)	12 (24.5)	0.7434

IQR= Interquartile range

Table V: cfDNA Results in Non-NSCLC Patients

Diagnosis	Number	cfDNA Positive	cfDNA Negative
Granulomatous inflammation/ tuberculosis (TB)	3	3	0
Carcinoid tumour	2	1	1
No granuloma, atypical cells or malignancy	2	1	1
Focal pneumonia	1	1	0
Lymphocytic infiltration	1	1	0
Total	9	7	2

cfDNA sensitivity by clinical stage

To further stratify the cfDNA detection results, we analyzed the sensitivity by clinical stage as determined pre-operatively using imaging (Table III). The results demonstrated that the sensitivity for stage I disease remains relatively high, given the high representation of these cases.

Association of cfDNA Results with Selected Clinical Parameters in NSCLC Patients

Tumour size was recorded in all 52 NSCLC patients while baseline serum CEA levels and FDG-PET SUVmax uptake values were available in only 49 patients. Median CEA levels did not differ significantly between groups (2.7 vs 2.3 ng/mL, $p = 0.942$), and the proportion of patients with elevated CEA (≥5 ng/mL) was similar ($p > 0.999$). Likewise, tumour size was comparable (median 2.7 vs 2.7 cm, $p = 0.898$), with no

difference in the proportion of tumours ≥3 cm (p>0.999). SUVmax values showed no significant variation between cfDNA-positive and cfDNA-negative groups (median 7.06 vs 6.58, p=0.744), and categorization by SUVmax ≥5 was not associated with cfDNA status (p=0.743). Overall, these findings indicate that cfDNA positivity was not associated with the tested clinical parameters in this cohort (Table IV).

cfDNA results in non-NSCLC patients

cfDNA results for the nine non-NSCLC patients are summarized in Table V. A high proportion of non-NSCLC cases tested cfDNA positive, including all three cases of pulmonary tuberculosis, contributing to the low overall specificity of the assay. False positive findings were observed across various benign conditions.

Association of cfDNA findings with genomic mutations detected in NSCLC patients

Forty-eight of the 52 NSCLC patients had genomic tumor mutational sequencing analysis using a targeted panel, of whom 36 were cfDNA positive and 12 were cfDNA negative. Among patients who underwent NGS testing, the most frequently identified mutations were EGFR (n=27), TP53 (n=15), KRAS (n=6), and ALK (n=3), with several other mutations detected at low frequency (results not shown). A subset of the patients (n=6) had no detectable mutations. Categorical analyses performed using predefined thresholds demonstrated no significant association between cfDNA positivity and the presence of an oncogenic mutation (Fisher's exact test, p=0.563).

DISCUSSION

The diagnostic usage of cfDNA is relatively new and its use in the detection of early-stage NSCLC is still limited. cfDNA appears to be effective for predicting relapse risk and pre-operative positivity is associated with a reduced recurrence-free survival. The presence of postoperative cfDNA, reflecting MRD, is strongly associated with subsequent disease recurrence.[9-11] The performance of cfDNA in early lung cancer detection is influenced by the methods used for its analysis. Several approaches can improve detection sensitivity. Mutation-based detection remains the most conventional method and involves identifying tumour-specific genetic alterations in circulating DNA. However, it requires adequate cfDNA and is therefore limited in early-stage disease due to reduced tumour burden and less DNA shedding. Methylation-based approaches offer a promising alternative that focuses on epigenetic modifications of DNA rather than changes in the DNA sequence. For example, a plasma DNA methylation–based ctDNA assay developed by Liang et al distinguished malignant from benign pulmonary nodules with 79.5% sensitivity and 85.2% specificity in plasma (93.2% specificity in healthy controls), while demonstrating strong performance for early-stage disease (75.0% in stage IA and 85.7% in stage IB), supported by tissue-level accuracy of 92.7% sensitivity and 92.8% specificity.[12] Similarly, Zhao et al developed a multiplex digital methylation-specific PCR platform that improved the detection of low cfDNA levels and had superior performance compared to standard assays.[13] These findings suggest methylation-based approaches may help overcome the limitations of mutation-based methods, particularly in early-stage disease where detectable cfDNA levels are low.

In addition to methylation-based approaches, alternative methods such as fragmentomics can improve cfDNA detection. Fragmentomics analyse patterns in cfDNA fragmentation rather than specific DNA changes. Mathios et al combined fragmentation analysis with clinical risk factors, CEA levels and CT imaging to accurately detect 94% of patients with cancer across various stages and subtypes, including 91% of stage I or II disease.[14] Using whole-genome sequencing to profile cfDNA fragmentomics, the machine learning model developed by another research group achieved exceptionally high accuracy for early lung cancer detection across validation cohorts, while maintaining strong performance at low sequencing depth and demonstrating 83.2% sensitivity for stage I disease and 85.0% for tumors <1 cm.[15]

Our real-world evidence study is the first in Malaysia to evaluate the diagnostic performance of a commercially available plasma cfDNA assay for the detection of early-stage NSCLC in a cohort of mostly asymptomatic individuals who presented with an incidental or screening-detected lung nodule suggestive of a possible underlying early-stage resectable NSCLC. Some patients had histological confirmation of lung cancer pre-surgery, from a CT-guided percutaneous biopsy. We explored the association of baseline cfDNA positivity with clinicopathological parameters and tumour genomic profiles. Our findings demonstrated that the assay had reasonable sensitivity (75%) and a relatively high positive predictive value (PPV) (84.8%) for moderate detection of NSCLC in largely asymptomatic individuals with indeterminate visible pathology on a PET-CT imaging. Hence the assay may help personalize surveillance scan intervals, lower the threshold for confirmatory tissue biopsy or proceed with upfront surgical resection after appropriate staging. However, the low specificity (22.2%) and negative predictive value (NPV) (13.3%) mean a negative cfDNA result could not reliably exclude an underlying lung cancer and thus is presently not suitable as a standalone screening modality or a substitute for physician acumen based on clinical risk profiling and morphology of the lung nodule. The low specificity we observed may be attributable to the detection of non-tumour-derived cfDNA, particularly in patients with inflammatory or infectious pulmonary conditions which can contribute to background genomic noise and false-positive signals. Interestingly, there was no significant association of cfDNA results with clinical parameters such as baseline CEA, tumour size, metabolic SUVmax uptake on FDG-PET imaging, and tumour mutation signatures.

The detection of cfDNA in our study utilized a multimodal cfDNA assay with shallow sequencing coverage which combines fragmentomic, nucleosome, end-motif, and copy number alteration analyses.[8] This assay has a previously reported sensitivity of 94% and 90% in the discovery and validation cohorts respectively, with a specificity of 92% for both. These reported values differ significantly from the results of our real-world patient cohort, and this discrepancy may be due to the varied characteristics of the lung cancer patients in their study compared to ours. In terms of disease

stage, only 6% and 6.8% of their discovery and validation cohorts respectively comprised early-stage (stage I, II) patients.[8] In contrast, our study involved patients with potentially resectable NSCLC, with a majority (83%) having early-stage disease. Furthermore, no staging information was available for 58.6% and 46.6% of lung cancer patients in their discovery and validation cohorts respectively. This lack of accurate staging data and their low proportion of early-stage NSCLC patients in both their training and validation cohorts, may have hindered the accuracy of the advanced machine learning models used in this assay to detect early-stage NSCLC. Additionally, the non-lung cancer cases used as a control in the study by Nguyen et al were all healthy individuals, which differs largely from our patient cohort who had visible lung pathology, including benign lung conditions.[8] The assay does not detect NSCLC or lung cancer-specific markers solely, but rather cfDNA fragmentation patterns, copy number alterations, nucleosome positioning, and genome-wide cfDNA signatures, all surrogates or indirect signals of abnormal cellular processes, and not tumour-specific signals or mutations. Besides malignant tumours, cfDNA may be released in benign conditions through various cellular mechanisms including apoptosis, necrosis, autophagy and phagocytosis[16] and therefore may be detected with granulomatous inflammation,[17-18] tuberculosis,[19-20] focal pneumonia,[21-22] and carcinoid tumours.[23] Hence, the markedly low specificity we observed is likely attributable to the inclusion of patients with non-malignant but biologically active pulmonary conditions. Unlike healthy controls, these conditions are characterized by increased cellular turnover, inflammation, and tissue injury, all of which can lead to the release of cell-free DNA with altered fragmentation patterns and genomic features that may overlap with those observed in malignancy. Consequently, the assay may erroneously misclassify such cases, contributing to the high false-positive rate and low specificity we observed.

Our study highlights a key limitation of cfDNA-based assays when applied in clinically heterogeneous populations, where distinguishing malignancy from inflammatory or benign conditions is inherently more challenging than in case-control settings involving healthy individuals. Our study population reflects a more heterogeneous, real-world cohort of patients who often present with an IPN, including many with benign pulmonary diseases that can confound cfDNA detection. In countries like Malaysia, with a high prevalence of inflammatory or infectious lung diseases, existing cfDNA-based assays may lack critical specificity and require further refinement with more diverse training and validation datasets to generate more accurate and discriminatory ensemble machine learning models. Our findings reiterate the importance of external validation in diverse patient populations prior to clinical implementation of any assay for population-based screening and detection of early-stage NSCLC.

When stratified by clinical stage, we observed cfDNA detection rates generally increased with advancing disease stage, consistent with published data suggesting that tumour burden influences cfDNA shedding, either through apoptosis, necrosis, or active secretion. Notably, the sensitivity observed in stage I disease (79.4%) remained relatively high, encouragingly indicating that cfDNA may still be detectable in a subset of early-stage patients despite lower tumour burden. However, the variability in detection rates, particularly in stage II disease, is likely due to our small sample size, and the results should be interpreted with caution. Interestingly, we found no significant association between cfDNA positivity and conventional markers of tumour burden, such as serum CEA levels, tumour size, and FDG-PET SUVmax values. These findings contrast with the expectation that larger or more metabolically active tumours would release greater quantities of cfDNA. A previous study demonstrated a significant association between cfDNA shedding and tumour size and volume in surgically resected oncogenic-driven NSCLC.[24] Our results suggests that cfDNA release is not solely dependent on tumour burden but rather a complex, multifactorial process influenced by tumour biology, including cellular turnover, necrosis, apoptosis, and vascular invasion. Tumours can exhibit biological heterogeneity; wherein certain tumours exhibit low cfDNA shedding despite substantial size or metabolic activity.[25] Tumours with high proliferative rates or increased apoptotic and necrotic activity may release greater amounts of DNA into the circulation, independent of size. Conversely, small tumours with aggressive biological behavior may shed detectable ctDNA, whilst others are non-shedders.[26] Tumour location, vascular access, and host-related factors such as cfDNA clearance mechanisms may further influence circulating ctDNA levels.[27] Taken together, these findings highlight that ctDNA is not simply a surrogate of tumour burden but reflects the tumour biology and microenvironment.

With respect to genomic profiling, tumour sequencing revealed a spectrum of mutations, most commonly involving EGFR, TP53, and KRAS. However, overall mutation burden was not significantly associated with cfDNA detection. This lack of association may be explained by discordance between tumour tissue and plasma cfDNA, as not all tumour-derived mutations are shed into the bloodstream at detectable levels. Additionally, technical limitations, including assay sensitivity and detection thresholds, may contribute to this discrepancy. Given the complexity of cfDNA biology, tissue-based genomic alterations may not be easily extrapolated to plasma-based detection.

LIMITATIONS

The strength of our study is the heterogeneous clinical cohort, which included patients with both NSCLC and various benign pulmonary conditions, reflecting real-world settings. Furthermore, we correlated the diagnostic performance of the cfDNA assay with critical clinical, molecular, and imaging features, and importantly, using the gold-standard histopathological tissue confirmation as a reference standard, in all cases. Study limitations include the relatively small sample size and single-center study design.

CONCLUSION

cfDNA offers a promising non-invasive approach for early cancer detection, however our findings suggest limited utility of this particular cfDNA assay presently, as a screening or

diagnostic tool for detection of early-stage NSCLC as the low specificity and NPV, means a negative result cannot reliably exclude an underlying malignancy. Given the relatively high PPV, a positive result may guide decision making with regards to thresholds for a continued 'wait and watch' approach, confirmatory tissue biopsy or upfront surgical resection after appropriate staging. The high false positive rate however limits its standalone diagnostic applicability. The low specificity and NPV suggest that the assay is currently not suitable as a standalone screening modality and should not replace clinical judgement. The false negatives observed in 13 NSCLC patients were a particular concern as clinician reliance on the biomarker result might have prompted a conservative approach with possible interim disease progression.

cfDNA detection appears to capture a complex and distinct aspect of tumour biology, and its clinical utility will depend on continued advancements in assay design and a deeper understanding of its underlying biological determinants. Future efforts should focus on improving assay specificity, potentially through the incorporation of more tumour-specific biomarkers, refinement of bioinformatic filtering strategies, and integration with other diagnostic modalities such as imaging or protein biomarkers. Diverse training and validation patient cohorts incorporating both more early-stage lung cancer cases as well as benign pulmonary conditions are likely to enhance the diagnostic performance of future iterations of the assay to facilitate impactful real-world use.

CONFLICT OF THE INTERESTS

The authors have no conflicts of interest to disclose.

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ORIGINAL ARTICLE

Prevalence and determinants of antimicrobial resistance in pneumonia among adult patients in Hospital Shah Alam, Malaysia

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ABSTRACT

Introduction: Antimicrobial resistance (AMR) continues to threaten our healthcare system. Unnecessary antibiotic use contributes to the development of AMR infections in hospitalized pneumonia patients. This study was conducted to determine the prevalence of AMR and its associated factors in pneumonia among adult patients treated in-patient in a hospital.

Materials and Methods: A cross-sectional study was conducted using data extracted from the hospital's electronic medical records. Patients aged 18 years or older admitted to the hospital from 1st January 2018 to 31st December 31 2023, discharged with a diagnosis of pneumonia were included in the study population.

Results: A total of 300 eligible samples were selected using universal sampling. The analysis revealed a prevalence of AMR of 15.7% (95% CI: 11.5, 19.8). Multivariable analysis using multiple logistic regression showed that patients' age (OR = 1.03; 95% CI: 1.01, 1.05), Indian and other ethnicities (OR = 2.24; 95% CI: 1.05, 4.77), length of stay (OR = 1.05; 95% CI: 1.01, 1.08) and invasive procedures (OR = 3.65; 95% CI: 1.71, 7.82) were significantly associated with AMR.

Conclusion: The findings from our study highlighted a considerable burden of AMR among pneumonia patients in a Malaysian tertiary hospital. Thus, there is a need for targeted infection control strategies and antimicrobial stewardship, especially among high-risk groups. Strengthening surveillance and justified antibiotic use is crucial to fight the rising threat of AMR in Malaysia.

KEYWORDS:
Antimicrobial resistance, pneumonia, hospital, antibiotic, Malaysia

INTRODUCTION

Antimicrobial resistance (AMR) is defined as the capacity of microorganisms to resist the effects of antimicrobial agents that were previously effective in treating infections.[1] Globally, AMR was associated with an estimated 4.7 million deaths in 2021, with approximately one-quarter directly attributable to bacterial resistance.[2] The economic burden is also substantial with projected global capital losses from AMR-related mortality estimated at USD 300 billion to USD 1 trillion by 2050.[3] In Malaysia, surveillance data had demonstrated increasing antibiotic resistance among clinically important pathogens, including *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, which are associated with serious infections such as pneumonia, sepsis and urinary tract infections.[4-5]

Pneumonia is a common infection requiring hospitalisation and is particularly relevant to AMR because of its substantial antibiotic exposure. Studies have reported high resistance rates among bacterial pathogens causing pneumonia with up to 100% resistance to certain antibiotics such as ampicillin.[6-7] The COVID-19 pandemic also further contributed to AMR through increased empirical antibiotic use for suspected bacterial infections.[8] AMR in pneumonia is therefore concerning because it can compromise treatment effectiveness and increase healthcare costs.[9]

However, AMR surveillance and research remain limited in many low- and middle-income countries, including Malaysia, where relatively few studies have examined AMR specifically among adult pneumonia patients.[10] This evidence gap is important in the context of Malaysia's healthcare system, whereby AMR has been recognised as an emerging threat. The Malaysia Health White Paper identifies the re-emergence of communicable diseases as being partly attributable to AMR.[11]

Therefore, the limited local evidence on AMR among adult pneumonia patients together with the increasing burden of AMR highlights the need for further investigation. Determining the prevalence and associated factors of AMR in this population may provide locally relevant evidence to improve antibiotic prescribing and strengthen antimicrobial stewardship while supporting national efforts to address AMR. Therefore, this study was conducted to determine the prevalence and associated factors of AMR in pneumonia among adult patients treated in-patient in a hospital.

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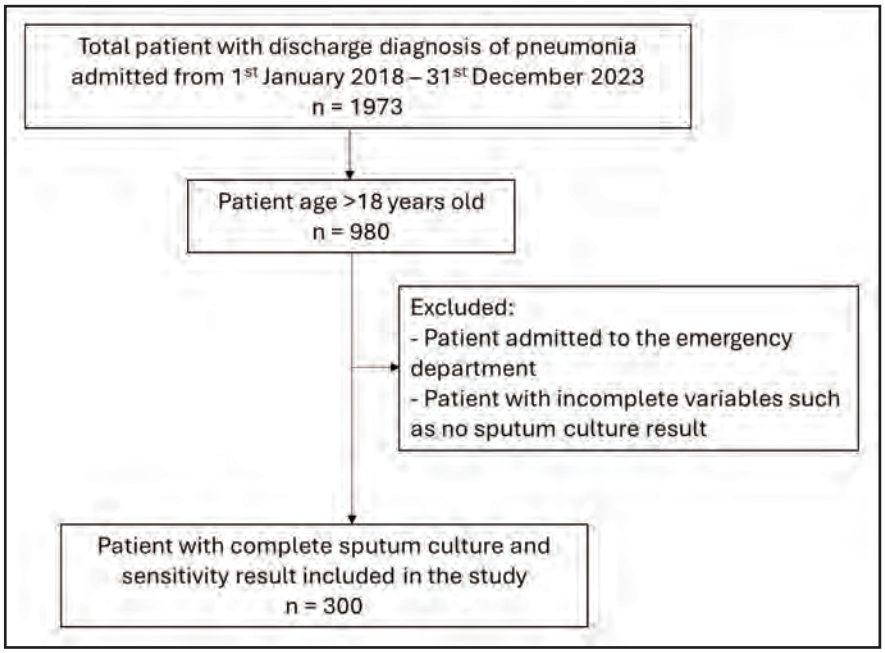

Fig. 1: Data extraction flowchart

MATERIALS AND METHODS

Study settings

Petaling district in Selangor provides an important setting for local investigation because of its rapid population growth, from approximately 360,000 in 1980 to 2.3 million in 2023.[12] Hospital Shah Alam is the only publicly funded tertiary hospital in this district and also receiving referrals from surrounding hospitals and health clinics. In 2022, the incidence of extended-spectrum beta-lactamase (ESBL) *Klebsiella pneumoniae* infection at Hospital Shah Alam was estimated at 0.22 per 100 admissions, approaching the Ministry of Health Malaysia indicator of ≤0.3 per 100 admissions.[13-14] Antimicrobial susceptibility testing in this hospital was conducted according to Clinical & Laboratory Standards Institute (CLSI) standards.

Study design

This cross-sectional study was conducted using data extracted from the Hospital Shah Alam's electronic medical records (EMR). The study was done between October 2024 and June 2025 involving secondary data analysis of patients admitted to the hospital between 1st January 2018 and 31st December 2023. The inclusion criteria consist of patients aged 18 years and above who were admitted within the specified timeframe and discharged with a diagnosis of pneumonia identified based on administrative ICD-10 discharge coding (ICD-10: J18.9). Patients discharged from the emergency department with a diagnosis of pneumonia for outpatient treatment and those without sputum culture results were excluded from the study.

Sample size calculation

The sample size was estimated using online sample size calculator based on the prevalence of AMR in pneumonia patients reported by Purba et. al.[7,15] Using a prevalence of 22%, an estimated population of 2000 patients, a 95% confidence interval level and 80% power, the required sample size was 234 samples. After adjusting for 20% missing data rate, the minimum required sample size was 292. Universal sampling method was used to select the sample for the study.

Statistical analysis

AMR status as the outcome in this study was operationally defined as positive (coded as 1) if the organism identified from the culture was resistant to at least one class of antibiotics, including the intermediate susceptibility. All univariate and multivariable analyses were conducted using SPSS version 29. To maintain confidentiality, patient identifiers were removed and only study identification numbers were used. The data extraction flowchart is described in Figure 1. Missing data were handled using multiple imputation. The prevalence and its 95% confidence interval (95% CI) were calculated using the formula:

$$\text{Prevalence} = \frac{\text{(No. of AMR positive sample)}}{\text{(Total adult pneumonia patient in the sample)}} \times 100\%$$

$$95\%\ \text{CI} = z \times \sqrt{\frac{p(1-p)}{n}}$$

For the determination of factors associated with AMR, data were analysed using simple logistic regression and Fisher's exact test. Subsequently, variables with a p-value<0.25 were included in the multivariable analysis using multiple logistic regression.[16] The crosstabulation of organisms isolated and antibiotic class resistance was presented by frequency and percentage.

Ethical approval

The study's ethical approval was obtained from the Malaysian Research Ethics Committee (MREC) with reference number: NMRR ID-25-00243-CVW. Exemption from the faculty ethics review was obtained from Universiti Teknologi MARA Faculty Ethics Review Committee (FERC) with reference number: 100 - FPR (PT.9/19) (FERC-EX-25-06).

Table I: Characteristics of study sample by AMR status

Characteristics	AMR (n = 47)	Non-AMR (n = 253)	Total (n = 300)
Age (years), mean (SD)	58.79 (17.061)	53.26 (18.270)	54.13 (18.17)
Gender, n (%)			
Male	22 (46.8)	118 (46.6)	140 (46.7)
Female	25 (53.2)	135 (53.4)	160 (53.3)
Ethnicity, n (%)			
Malay	26 (55.3)	184 (72.7)	210 (70.0)
Chinese	3 (6.4)	20 (7.9)	23 (7.7)
Indian & others	18 (38.3)	49 (19.4)	53 (22.3)
Citizenship, n (%)			
Malaysian	47 (100.0)	241 (95.3)	288 (96.0)
Non-Malaysian	0 (0.0)	12 (4.7)	12 (4.0)
Diabetes mellitus, n (%)			
Yes	17 (36.2)	103 (40.7)	120 (40.0)
No	30 (63.8)	150 (59.3)	180 (60.0)
Hypertension, n (%)			
Yes	29 (61.7)	127 (50.2)	156 (52.0)
No	18 (38.3)	126 (49.8)	144 (48.0)
Chronic Kidney Disease, n (%)			
Yes	5 (10.6)	31 (12.3)	36 (12.0)
No	42 (89.4)	222 (87.7)	264 (88.0)
Coronary Heart Disease, n (%)			
Yes	7 (14.9)	41 (16.2)	48 (16.0)
No	40 (85.1)	212 (83.8)	252 (84.0)
Smoking status, n (%)			
Yes	14 (29.8)	76 (30.0)	90 (30.0)
No	33 (70.2)	177 (70.0)	210 (70.0)
Length of stay (days), mean (SD)	17.53 (21.612)	7.65 (7.002)	9.20 (11.23)
ICU admission, n (%)			
Yes	23 (48.9)	51 (20.2)	74 (24.7)
No	24 (51.1)	202 (79.8)	226 (75.3)
Prior antibiotic use, n (%)			
Yes	9 (19.1)	24 (9.5)	33 (11.0)
No	38 (80.9)	229 (90.5)	267 (89.0)
Prior admission <30 days, n (%)			
Yes	8 (17.0)	27 (10.7)	35 (11.7)
No	39 (83.0)	226 (89.3)	265 (88.3)
Prior history of pneumonia, n (%)			
Yes	7 (14.9)	18 (7.1)	25 (8.3)
No	40 (85.1)	235 (92.9)	275 (91.7)
History of HAI, n (%)			
Yes	2 (4.3)	7 (2.8)	9 (3.0)
No	45 (95.7)	246 (97.2)	291 (97.0)
Invasive procedures, n (%)			
Yes	28 (59.6)	55 (21.7)	83 (27.7)
No	19 (40.4)	198 (78.3)	217 (72.3)

RESULTS

Out of 1,973 pneumonia admissions assessed, 980 met the age criteria and a total of 300 samples were found to be eligible for final analysis in the study (Figure 1). The characteristics of the samples are presented in Table I. The prevalence of AMR in pneumonia among patients in this study was 15.7% (95% CI: 11.5, 19.8). The mean age of patients was 54.13 years (SD: 18.17), with a slightly balanced proportion of males and females. Most patients in this study were of Malay ethnicity and Malaysian citizens.

Univariate analyses of the factors examined in this study identified a few statistically significant variables with p-value<0.25 (Table II). Variables included in the multivariable analysis were patients' age, ethnicity, presence of hypertension comorbidity, length of stay, ICU admission, prior antibiotic use, prior admission, prior history of pneumonia and invasive procedures. When multiple logistic regression analysis was used to build the prediction model, only patients' age, ethnicity, length of stay, and invasive procedures were found to be statistically significant at p-value<0.05 (Table III). The Receiver Operating Characteristic (ROC) curve shows acceptable prediction with Area Under Curve (AUC) of 0.771 (95% CI: 0.696, 0.845).

A total of 68 positive patient samples were identified, and among them, the majority of isolated organisms were K. pneumoniae (50.0%), followed by *P. aeruginosa* (23.5%) and *A. baumannii* (7.4%). Resistance to penicillin was highest in number in pneumonia cases with *K. pneumoniae* (47.8%), while resistance to penicillin combined with beta-lactamase inhibitors was highest in *P. aeruginosa* infections (37.5%). *A. baumannii* showed resistance rates of 20% to the carbapenem group, penicillin combined with beta-lactamase inhibitors and cephalosporins. The crosstabulation between antibiotic resistance class and the organism is presented in Table IV.

Table II: Univariate analysis of factors associated with AMR

Variables	Crude OR (95% CI)[a]	p-value
Age (years), mean ± SD	1.02 (0.99, 1.04)	0.057*
Gender, n (%)		
Male	1.01 (0.54, 1.88)	0.983
Female	ref	
Ethnicity, n (%)		
Malay	ref	
Chinese	1.06 (0.30, 3.82)	0.927
Indian & others	2.60 (1.32, 5.12)	0.006*
Citizenship, n (%)		
Malaysian	1.20 (1.14, 1.26)[b]	0.225
Non-Malaysian		
Diabetes mellitus, n (%)		
Yes	0.83 (0.43, 1.67)	0.560
No	ref	
Hypertension, n (%)		
Yes	1.60 (0.85, 3.02)	0.149*
No	ref	
Chronic Kidney Disease, n (%)		
Yes	0.85 (0.31, 2.32)	0.755
No	ref	
Coronary Heart Disease, n (%)		
Yes	0.91 (0.38, 2.16)	0.822
No	ref	
Smoking status, n (%)		
Yes	0.99 (0.50, 1.95)	0.972
No	ref	
Length of stay (days), mean ± SD	1.07 (1.04, 1.10)	<0.001*
ICU admission, n (%)		
Yes	3.80 (1.98, 7.27)	<0.001*
No	ref	
Prior antibiotic use, n (%)		
Yes	2.26 (0.98, 5.23)	0.057*
No	ref	
Prior admission <30 days, n (%)		
Yes	1.72 (0.73, 4.05)	0.217
No	ref	
Prior history of pneumonia, n (%)		
Yes	2.29 (0.90, 5.82)	0.083*
No	ref	
History of HAI, n (%)		
Yes	1.56 (0.31, 7.76)	0.586
No	ref	
Invasive procedures, n (%)		
Yes	5.31 (2.76, 10.21)	<0.001*
No	ref	

[a]Univariate analysis done using simple logistic regression unless specified otherwise. OR: Odds Ratio. CI: Confidence Interval.
[b]Analysed using Fisher's Exact Test.
*Variables significant at P-value<0.25 were included into the multivariable analysis.

Table III: Multivariable analysis

	Adjusted ORa (95% CI)	Wald (df)	p-value*
Age (years)	1.03 (1.01, 1.05)	6.79 (1)	0.009
Ethnicity			
Malay	ref		
Chinese	0.75 (0.18, 3.06)	0.16 (1)	0.688
Indian & others	2.24 (1.05, 4.77)	4.38 (1)	0.036
Length of stay (days)	1.05 (1.01, 1.08)	6.99 (1)	0.008
Invasive procedures	3.65 (1.71, 7.82)	11.15 (1)	<0.001

[a]Multivariable analysis done using multiple logistic regression. Backward Likelihood Ratio method was used. Multicollinearity checked where Variable Inflation Factor (VIF) for all factors were less than 2. Final model Hosmer-Lemeshow goodness-of-fit test was not significant (p-value: 0.96). Cox & Snell adjusted R2: 0.143. No influential outliers were detected. p-values for interactions between variables were not significant.
*Statistically significant at p-value<0.05.

Table IV: Crosstabulation of antibiotic class resistance and cultured organisms

Antibiotic Organism	Amino glycoside, n (%)	Sulpho namide*, n (%)	Carba penem, n (%)	Cepha losporin, n (%)	Cephal osporin +β-lactam ase inhibitor**, n (%)	Fluroq uinolone, n (%)	Fusi dane***, n (%)	Macro lide, n (%)	Peni cillin, n (%)	Peni cillin +β-lactam ase inhibitor****, n (%)	Total
K. pneumonia	3 (4.5)	3 (4.5)	1 (1.5)	8 (11.9)	2 (3)	5 (7.5)	0 (0)	0 (0)	32 (47.8)	13 (19.4)	67
A. baumannii	2 (10)	0 (0)	4 (20)	4 (20)	2 (10)	3 (15)	0 (0)	0 (0)	1 (5)	4 (20)	20
E. coli	1 (10)	1 (10)	0 (0)	2 (20)	1 (10)	1 (10)	0 (0)	0 (0)	2 (20)	2 (20)	10
Acinetobacter sp.	0 (0)	0 (0)	2 (25)	2 (25)	2 (25)	0 (0)	0 (0)	0 (0)	1 (12.5)	1 (12.5)	8
P. aeruginosa	1 (12.5)	0 (0)	1 (12.5)	2 (25)	0 (0)	0 (0)	0 (0)	0 (0)	1 (12.5)	3 (37.5)	8
S. aureus	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (25)	2 (25)	4 (50)	0 (0)	8
Enterobacter sp.	0 (0)	0 (0)	0 (0)	1 (33.3)	0 (0)	0 (0)	0 (0)	0 (0)	1 (33.3)	1 (33.3)	3

*Sulphonamide class: sulfamethoxazole/trimethoprim.
**Cephalosporin+β-lactamase inhibitor class: cefoperazone/sulbactam
***Fusidane class: fusidic acid
****Penicillin+β-lactamase inhibitor class: amoxicillin/clavulanic acid, ampicillin/sulbactam and piperacillin/tazobactam.

DISCUSSION

The prevalence of AMR found in this study was substantially higher compared to a study in the United States, which estimated AMR prevalence of 1.4%.[17] Fortunately, our results showed a lower burden compared to a study in Ethiopia, which revealed a staggering AMR prevalence of 50%.[6] This finding aligns with evidence in the literature indicating that the burden of AMR is related to the country's income level.[2,18-19]

Through the multivariable regression analysis, our study found that patients' age has a positive association with the AMR (OR=1.03; 95% CI: 1.01, 1.05). This result corroborates the findings of recent studies, indicating that older age groups have increased odds of AMR.[6,20] As patients' age increases, their comorbidities may significantly contribute to the development of AMR. Therefore, clinicians should consider patients' age when selecting an appropriate antibiotic treatment.

Interestingly, this study found that Indian and other ethnicities were significantly associated with AMR compared to Malay ethnicity (OR=2.24; 95% CI: 1.05, 4.77). A prior study by Haque et al. showed that ethnicity influences knowledge and beliefs about antibiotic prescriptions, while a study by Hassali et al. found that ethnicity was associated with the level of antibiotic practice.[21-22] Both studies suggested possible hypothesis that the association could also be attributed to differences in health beliefs and cultural perceptions among various ethnicities.

Additionally, the duration of patient admission was found to be statistically significant with the AMR (OR = 1.05; 95% CI: 1.01, 1.08). This finding is consistent with previous reports indicating that the length of patient stay is an essential predictor of AMR.[23-24] Besides AMR, the duration of patient stay also contributes to the overall cost of healthcare.[25] However, because total length of stay was evaluated cross-sectionally, prolonged stays could be both a cause and a consequence of AMR infection. Nevertheless, regularly evaluating whether continued hospitalization is needed is essential to avoid unnecessary admissions when appropriate.

Meanwhile, the presence of invasive procedures performed on the patient was found to be a significant predictor of AMR (OR=3.65; 95% CI: 1.71, 7.82). This result also corresponds with previous literature.[26-27] Patients who underwent invasive procedures such as mechanical ventilation, central line insertion and catheterization could be at higher risk of AMR. For example, procedures like mechanical ventilation can predispose patients to ventilator-associated pneumonia. Similarly, patient catheterisation carries a higher risk of catheter-related bloodstream infections (CRBSI), which may lead to the development of resistant infections.

This study also found that the majority of *K. pneumoniae*-positive sputum cultures are resistant to the Penicillin antibiotic class, similar to findings reported in the literature.[8,17,28] This could be due to the prevalent genetic mutations of *K. pneumoniae* bacteria, such as production of β-lactamases, plasmid-mediated resistance and low outer membrane permeability.[29-31] According to a recent report by the World Health Organization, there is an increase in the detection of hypervirulent *K. pneumoniae* bacteria in patients' clinical samples.[32] Meanwhile, a study in Nigeria found that 86.7% of *K. pneumoniae* isolates from their samples were multidrug-resistant organisms.[33] Conversely, a study in the United States reported that 37.7% of *S. pneumoniae* isolates were associated with AMR, with the greatest resistance observed against macrolide antibiotic class.[19]

However, this study was unable to show statistically significant results for a few factors, unlike what previous research had suggested. Intensive care unit admission, prior antibiotic use and prior history of pneumonia showed borderline significance in the univariate analysis but did not remain significant in the final multivariable analysis. Although the exact reason is unclear, this could be due to the relatively small sample size in this study compared to other studies in the literature. For example, a retrospective analysis study involving 2899 patients found that ICU admission was significantly associated with multi-drug resistant infection.[34]

Several limitations are acknowledged in this study. Firstly, being a single-centre study, the findings may have limited

generalisability to other hospitals. Secondly, selection bias is possible due to the exclusion of patients with incomplete data. Furthermore, the study does not differentiate between sporadic and outbreak cases of pneumonia, community or hospital acquired pneumonia and healthcare worker-related factors, such as prescribing patterns, are not considered due to limitations in the data source. Additionally, the cross-sectional nature of the study restricts the ability to establish causality between the study variables. Future longitudinal research should be considered to overcome this study's limitations.

CONCLUSION

This study revealed a high rate of AMR in hospitalised adult pneumonia cases. Implementing targeted infection control and antimicrobial stewardship is urgently essential to lessen AMR impact. Since developing new antibiotics is time-consuming and resource-intensive, improving local surveillance and promoting the proper use of current antibiotics are vital in tackling this escalating issue in Malaysia. Addressing this "silent" pandemic requires coordinated action throughout the healthcare system to maintain antibiotic effectiveness for future generations.

CONFLICT OF INTEREST

None declared.

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Tuberculosis treatment success and its determinants among healthcare workers with tuberculosis in Selangor: A retrospective cross-sectional study

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ABSTRACT

Introduction: Tuberculosis (TB) remains a major occupational risk for healthcare workers (HCWs), who face higher exposure and potential challenges in achieving optimal treatment outcomes. Despite extensive national TB control strategies in Malaysia, evidence on treatment success and its determinants among HCWs is limited. This study aimed to determine the proportion of TB treatment success and identify associated factors among HCWs with active TB in Selangor from 2014 to 2023 using the National Tuberculosis Registry (NTBR) system.

Materials and Methods: A retrospective cross-sectional study was conducted using registry data from NTBR involving all HCWs diagnosed with active TB and registered in Selangor between 2014 and 2023. Universal sampling was applied to include all eligible cases with complete data. Variables were extracted across sociodemographic, occupational, sociocultural, and clinical domains. TB treatment success was defined as "cured" or "treatment completed", while unsuccessful outcomes included death, treatment failure, and not evaluated. Data were cleaned, de-identified, and analysed using SPSS version 29. Simple logistic regression identified variables with p<0.25 for inclusion in multiple logistic regression Adjusted odds ratios (AOR) and 95% confidence intervals (CI) were reported. Model diagnostics included the Hosmer–Lemeshow test, ROC (Receiver Operating Characteristic) analysis, multicollinearity checks, interaction terms, and Cook's distance.

Results: A total of 313 HCWs with active TB were included. The TB treatment success rate was 86.9%, with 51.5% cured and 48.5% completing treatment. In multivariable analysis, three factors remained significantly associated with treatment success. HCWs aged <34 years had higher odds of treatment success (AOR=5.071; 95% CI: 2.009–12.801). Conversely, doctors (AOR=0.024; 95% CI: 0.003–0.218) and supporting staff (AOR=0.366; 95% CI: 0.143–0.936) showed significantly lower success compared to paramedics. Advanced chest X-ray (CXR) findings demonstrated strong positive associations: moderate (AOR=14.686; 95% CI: 5.873 – 36.724) and far advanced disease (AOR=10.783; 95% CI: 1.909–60.904). Commonly reported risk factors such as HIV, diabetes, smoking, BCG (Bacillus Calmette-Guérin) status, and comorbidities were not significantly associated. Model performance was robust (ROC: 88.3%; Hosmer–Lemeshow p=0.858).

Conclusion: TB treatment is successful among HCWs in Selangor (86.9%), which is near to the WHO (World Health Organization) End TB Strategy. The odds of treatment success were much higher among younger HCWs, whereas doctors and other supporting staff reported had lower adjusted odds in comparison with paramedics. Moderate and far advanced CXR findings at diagnosis were independently associated with higher treatment success; however, this finding should be interpreted cautiously because of the small number of far advanced cases and the possibility of estimate instability and residual confounding. Conventional risk factors like human immunodeficiency virus infection, diabetes mellitus, smoking, and BCG status were found not associated significantly and may be due to the small subgroups and the nature of this registry data limitation. These conclusions indicate the fact that occupational role and clinical presentation are significant factors defining TB treatment outcomes among HCWs. Role-specific and targeted adherence support enhanced psychosocial interventions, and better NTBR data coverage can further improve the outcome of treatment and support the TB control in the Malaysian healthcare labour force.

KEYWORDS:
Tuberculosis, healthcare workers, treatment outcomes

INTRODUCTION

Tuberculosis (TB) remains a critical global public health challenge, ranking among the top ten causes of death worldwide. Despite significant efforts and strategic goals by the World Health Organization (WHO) under "End-TB Strategy", which aims for a TB treatment success rate of more than 90% by 2025, global targets are not yet being met.[1] In 2024, the Western Pacific region achieved only a 74% treatment success rate, while the global average was reported to be 75%.[2] In Malaysia, the number of reported TB cases rose to 26,781 in 2023, up from 21,727 in 2021 with Selangor accounts for an estimated 20-22% of total TB cases in Malaysia.[3] A similar proportion is observed for cases among healthcare workers (HCWs). This high concentration of cases

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in Selangor presents a significant public health challenge at the regional level; therefore, low-level treatment success may impair productivity and increase the burden on the country's health system.

HCWs face approximately three times higher risk of TB compared to the general population due to its occupational hazards.[4] While HCWs are expected to achieve higher treatment success rates, evidence from existing studies is inconsistent. Some global papers report high success rates, even up to 100%,[5] while others show rates between 57.9% and 84.0%.[6] This variability highlights an important knowledge gap in understanding the specific factors and hinders the development of effective strategies to improve treatment success.

Based on literature review, some studies on sociodemographic factors indicate that males and older age groups are associated with lower TB treatment success.[7] Other factors, like lower education levels and foreign nationalities, have also been linked to less favourable outcomes. Similar impact is also seen on human immunodeficiency virus (HIV) co-infection, alcohol consumption and smoking habits.[8-10] Workplace exposure in certain specialities and duration of employment may link to chronic stress and long working hours, potentially leading to lower success rates. Doctors might also tend to self-treat or adjust their regimens, contributing to inconsistent adherence. Furthermore, TB-related stigma may negatively affect treatment completion.[11-12] Clinical factors such as HIV co-infection and diabetes mellitus (DM) can prolong TB treatment, while other chronic diseases show no significant influence after adjustment.[10,13] The severity of the disease, often assessed by Chest X-ray (CXR) findings, as well as the history of previous TB and BCG (Bacillus Calmette-Guérin) vaccination status, are also considered contributing factors to the treatment outcome.[14]

Therefore, by understanding the determinants will provide evidence-based recommendations to the Ministry of Health (MOH) at both the state and national levels, enabling more targeted interventions, efficient resource allocation, and a tailored support system; and it will also support Malaysia's commitment to the global "End-TB Strategy". To achieve these aims, this study pursues two specific objectives: to describe the proportion and characteristics of TB as well as identify the determinants for TB treatment success among HCWs with TB in Selangor from 2014 to 2023.

MATERIALS AND METHODS

Study Design and Sample Size Calculation

A retrospective cross-sectional study using secondary data from the National Tuberculosis Registry (NTBR) was conducted. Treatment outcomes were assessed at a single point of analysis without considering changes over time, and information from the registry was analyzed prior to treatment completion. This study involved HCWs who were diagnosed with active TB and subsequently registered in Selangor during 2014 to 2023. The study population only involved HCWs working in government healthcare facilities in Selangor who had a confirmed diagnosis of active TB and had a final TB treatment outcome documented in the NTBR. Cases with ongoing treatment or a subsequent change in diagnosis were excluded.

As TB case registration within the NTBR is primarily based on the patient's residential address, HCWs working in Selangor but residing outside the state may not be comprehensively captured within the Selangor registry. The study was limited to HCWs who resided in Selangor and were accessed and managed by the Selangor NTBR system to ensure consistency in the ascertainment of cases and the accurate collection of treatment outcome data.

HCWs were defined as individuals engaged in activities primarily intended to improve health, including doctors, nurses, midwives, public health professionals, laboratory personnel, health technicians, support staff, and other occupations involved in health-related services.[15] Detailed sample size calculation was carried out based on a previously published paper that reported the success rate of 81.7% and 84.0% by using Open-epi software (single proportion formula), alpha 0.05 and power of 80%. With accounting for a conventional 20% attrition rate, the minimum sample size is set at 177. However, a universal sampling approach was used, where all eligible healthcare workers with complete data in the NTBR registry during the study period were included.

Data Collection and Management

The NTBR system is a web-based database designed to capture comprehensive information on disease surveillance, treatment, contact tracing, and reporting. It captures details on case notifications, investigation findings, treatment regimens and subsequent follow-up care, including treatment outcomes.[16] Treatment outcomes were determined based on the final treatment outcome recorded in the NTBR upon completion of the treatment episode. According to the Malaysian clinical practice guidelines (CPG) for TB, standard treatment duration is generally six months for drug-susceptible TB, although treatment duration may be extended depending on clinical response, disease severity, or other medical indications. The outcome recorded in the NTBR was used to determine the success or failure of treatment in this study.

All variables relevant to the study objectives were clearly defined. Age was categorised into <34 years and ≥34 years based on the median age of the study population to achieve balanced group sizes and facilitate logistic regression analysis. The "TB treatment success" is defined as the combination of two specific outcomes: 'cured' or 'treatment completed' at the end of the treatment period. According to the Malaysia CPG Management of TB (4th Edition) 2021, 'cured' is define when "a patient with bacteriologically confirmed TB at the beginning of treatment who is smear- or culture-negative in the final month of treatment and at least one before that". Conversely, 'completed treatment' applied to "a TB patient who completed treatment without evidence of failure but with no record to show that sputum smear or culture results in the final month of treatment and at least one previous occasion is negative, either because tests are not done or because results are unavailable."

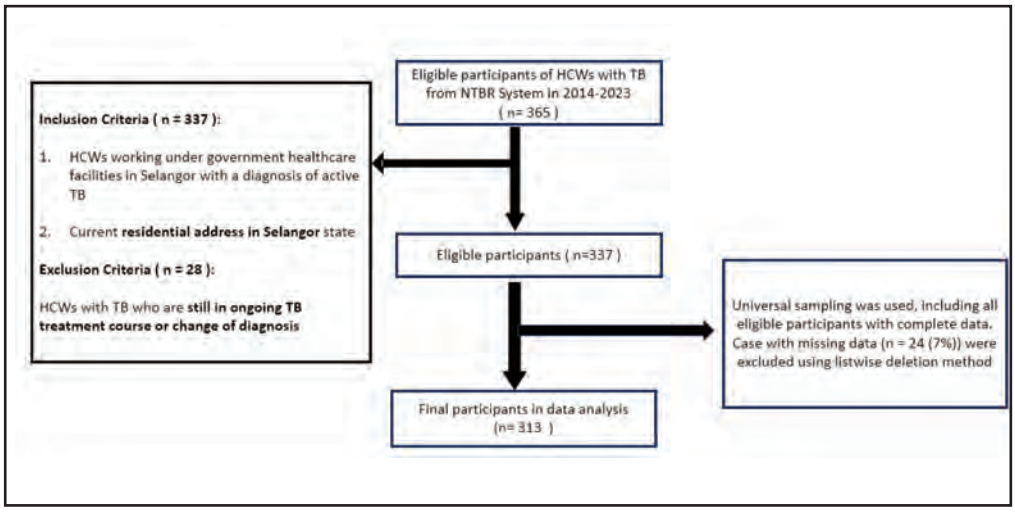

Fig. 1: Flow chart of data extraction and sample size selection

The "unsuccessful TB treatment" is encapsulated within a range of undesirable outcomes, such as died, treatment failed, loss to follow-up, transferred out or not evaluated. According to the same guideline, died defines as "a TB patient who dies for any reason before starting or during the course of treatment". 'Treatment failed' define as" a TB patient whose sputum smear or culture is positive at month 5 or later during treatment" while 'loss to follow up' define as "a TB patient who does not start treatment or whose treatment is interrupted for two consecutive months or more". Cases were also deemed unsuccessful if they were "transferred out" to another unit with an unknown outcome, "not evaluated" means no assigned outcome, including transfers to other countries or cases with unknown outcomes, and "change of diagnosis" where the initial TB diagnosis was later found to be incorrect. Although loss to follow-up and transferred-out cases were included in the predefined outcome definition, no such cases were identified among HCWs in the final analytical dataset. Our independent variables were systematically grouped for comprehensive analysis (Tables I and II). Certain aspects, like social support, cultural beliefs, stigma and treatment acceptance, were not included in the study due to limitations in data availability within the registry.

In a collaborative effort, data management protocols were rigorously followed to ensure the integrity and security of the information obtained. The data collection process was supervised by relevant personnel and were de-identified before being copied to an external hard disk. The data were later stored online with backup storage, and all digital data in Google Drive and Excel were password protected. During data cleaning, all variables were screened for duplication and assessed for completeness. A total of 337 eligible healthcare workers were identified in the NTBR, of whom 24 (7.1%) had incomplete data and were excluded using listwise deletion before statistical analysis. Given the relatively small proportion of missing data, complete-case analysis using listwise deletion was considered appropriate. The data extraction and sample selection process are presented in Figure 1.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 29. A value of $p<0.05$ was considered statistically significant with $\alpha = 0.05$ in the final statistical analysis. Results were analysed based on descriptive statistics, including frequencies and percentages, to determine the proportion of TB treatment success. The Simple Logistic Regression (SLogR) was used to determine crude outcome by taking into consideration of significant level, p-value < 0.25. Simple logistic regression with p-value <0.25 was used to screen variables to reduce overfitting of the model, and only the variables that passed the screening were added to the multiple logistic regression model. The model diagnostics such as multicollinearity, interaction terms, goodness of fit, and influential observations were carried out to assess model stability. The events-per-variable (EPV) ratio was not formally assessed during model development. Nevertheless, model stability was evaluated using multiple diagnostic procedures, including assessment of multicollinearity, interaction terms, Hosmer–Lemeshow goodness-of-fit, ROC analysis, and Cook's distance, all of which demonstrated acceptable model performance.

These findings were later proceeded to Multiple Logistic Regression (MLogR) to determine the association by controlling for potential confounders (p-value <0.05). Model fitness was checked using the Hosmer-Lemeshow goodness-of-fit. Receiver Operating Characteristic (ROC) curve were calculated to evaluate the discriminatory power and predictive capability of the model to achieve the observed outcome. The Cox & Snell is used to show how well the model explains differences of the outcomes. Another model diagnostic test is by checking the multicollinearity among independent variables by using the Variance Inflation Factor (VIF). We also checked for potential interaction among variables; and no statistically significant interactions were found, suggesting that the variables acted independently in the model. Influential outliers, which could disproportionately affect the regression results, were identified and assessed using Cook's influential statistics.

Table I: Result descriptive analysis proportion and characteristic of TB treatment success among HCWs in Selangor from 2014 to 2023 (N = 313)

Variables			N (%)
Sociodemographic Factors			
Age (in years)		< 34 years old	204 (65.2%)
		≥ 34 years old	109 (34.8%)
Gender		Male	79 (25.5%)
		Female	234 (74.8%)
Nationality		Malaysian	313 (100.0%)
Ethnicity		Malay	251 (80.2%)
		Chinese	18 (5.8%)
		Indian	32 (10.2%)
		Others	12 (3.8%)
Education Level		Secondary	118 (37.7%)
		Tertiary	195 (62.3%)
Monthly Personal Income		< RM 3365	159 (50.8%)
		> RM 3365	154 (49.2%)
Socio-cultural Factors			
High Risk Behaviour	Smoking	Yes	33 (10.5%)
		No	280 (89.5%)
	Alcohol	Yes	4 (1.3%)
		No	309 (98.7%)
	History of Drug Use	Yes	0 (0.0%)
		No	313 (100.0%)
Occupation Factor			
Job Role		Doctor	78 (24.9%)
		Paramedics	113 (36.1%)
		Supporting Staff	122 (39.0%)
Type of Facilities		Hospital	255 (81.5%)
		Primary Health Clinic	58 (18.5%)
Department of Work		General Medicine Department	83 (26.5%)
		Emergency Department	31 (9.9%)
		Outpatient	64 (20.4%)
		Others	135 (43.1%)
Duration of Service		< 36 months	166 (53.0%)
		> 36 months	147 (47.0%)
Clinical Factor			
Co-morbidity	Diabetes Mellitus	Yes	16 (5.1%)
		No	297 (94.9%)
	Hypertension	Yes	19 (6.1%)
		No	294 (93.9%)
	Chronic Lung Disease	Yes	0 (0.0%)
		No	313 (100.0%)
	HIV Status	Positive	3 (1.0%)
		Negative	310 (99.0%)
Types of TB		Pulmonary TB	230 (73.5%)
		Extrapulmonary TB	83 (26.5%)
History of TB		Yes	10 (3.2%)
		No	303 (96.8%)
	Sputum Pre-Treatment	Positive	169 (54.0%)
		Negative	144 (46.0%)
Chest X-ray Pre-Treatment		No Lesion	74 (23.6%)
		Minimal	167 (53.4%)
		Moderate Advanced	63 (20.1%)
		Far Advanced	9 (2.9%)
BCG Vaccination		Yes	310 (99.0%)
		No	3 (1.0%)

Ethical Approval

The study received full ethical approval from the Research Ethics Committee of Universiti Teknologi MARA (UiTM) through its Faculty Ethics Review Committee (FERC). All necessary approvals were secured from the National Medical Research Register (NMRR) and the Medical Research and Ethics Committee (MREC) of the Ministry of Health Malaysia, formally identified by the NMRR ID-25-00516-NRM (IID). JKNS has granted permission to utilise their data from the NTBR System for the purposes of this study.

RESULTS

Both analytical methods were employed to understand the descriptive characteristics and proportion of this cohort and the key determinants influencing treatment success among HCWs (Table I). A total of 140 cases (51.5%) were classified as "cured", while the remaining 48.5% achieved "treatment completed" status. Unfortunately, 41 cases (13.1%) of the studied group were categorised as "unsuccess TB treatment" outcomes, where six cases were reported as death in the system, while the remainder were classified as treatment

Table II: Analyses of factors associated with TB treatment success among HCWs in Selangor from 2014 to 2023 (N = 313)

Variables		COR	p-value	AOR	p-value
Sociodemographic Factors					
Age	< 34 years old	3.947 (1.988, 7.837)	0.152*	5.071 (2.009, 12.801)	0.001**
(in years)	≥ 34 years old	1	Ref	1	Ref
Gender	Male	1.499 (0.710, 2.959)	0.308		
	Female	1	ref		
Ethnicity	Malay	1	ref		
	Chinese	0.363 (0.047, 2.815)	0.332		
	Indian	1.143 (0.413, 3.166)	0.797		
	Others	0.000	0.999		
Education Level	Secondary	1	Ref		
	Tertiary	1.509 (0.779, 2.925)	0.223*		
Monthly Personal	< RM 3365	1	Ref		
Income	> RM 3365	1.228 (0.636, 2.372)	0.541		
Socio-cultural Factors					
High Risk Behaviour					
Smoking	Yes	1	Ref		
	No	3.492 (1.521, 8.027)	0.003*		
Alcohol Consumption	Yes	1	Ref		
	No	2.242 (0.277, 22.079)	0.489		
Occupation Factor					
Job Role	Doctor	0.064 (0.008, 0.491)	0.008*	0.024 (0.003, 0.218)	0.001**
	Paramedics	1	Ref	1	Ref
	Supporting Staff	1.010 (0.507, 2.010)	0.978	0.366 (0.143, 0.936)	0.036**
Type of Facilities	Hospital	2.291 (0.783, 6.705)	0.130*		
	Primary Health Clinic	1	Ref		
Department of Work	General Medicine Department	1	Ref		
	Emergency Department	1.005 (0.249, 4.057)	0.995		
	Outpatient	1.339 (0.474, 3.787)	0.582		
	Others	1.825 (0.772, 4.314)	0.170*		
Duration of Service	< 36 months	1	Ref		
	> 36 months	2.163 (1.097, 4.265)	0.026*		
Clinical Factor					
Co-morbidity					
Diabetes Mellitus	Yes	6.016 (2.104, 17.198)	0.001*		
	No	1	Ref		
Hypertension	Yes	1	Ref		
	No	5.752 (2.159, 15.327)	0.001*		
HIV Status	Positive	1	Ref		
	Negative	3.375 (0.299, 38.081)	0.325		
Types of TB	Pulmonary TB	1.329 (0.605, 2.917)	0.478		
	Extrapulmonary TB	1	Ref		
History of TB	Yes	1	Ref		
	No	1.692 (0.347, 8.262)	0.515		
Sputum Pre-Treatment	Positive	2.001 (0.994, 4.028)	0.052*		
	Negative	1	Ref		
Chest X-ray	No Lesion	< 0.001 (0.00)	0.997	0.000	0.997
Pre-Treatment	Minimal	1	Ref	1	Ref
	Moderate Advanced	9.077 (4.193, 19.649)	<0.001*	14.686 (5.873, 36.724)	<0.001**
	Far Advanced	6.458 (1.434, 29.095)	0.015*	10.783 (1.909, 60.904)	0.007**
BCG Vaccination	Yes	< 0.001 (0.00)	0.999		
	No	1	Ref		

Note:
N, total number of units in the sample; p value based on chi-squared test or Fishers exact test for categorical variables; *Significant factor in simple logistic regression analysis (p-value <0.25). **Significant determinant included in the final model (p-value <0.05).
BCG: Bacillus Calmette- Guérin, CI: confidence interval, HIV: human immunodeficiency virus, COR: crude odds ratio, AOR: adjusted odds ratio.
***ROC was 88.3%; Hosmer-Lemeshow goodness-of-fit = 0.858, Cox & Snell = 0.264.
****No multicollinearity, Cook's influential statistic shows no influential outliers.

failures. There were no "loss to follow-up" or "transferred out" cases among these HCWs.

By looking under the sociodemographic factors, the majority of HCWs diagnosed with TB were below 34 years old (65.2%) and predominantly female (74.8%). The educational attainment within the studied cohort was considered high, as most HCWs had achieved a tertiary education level (62.3%). Most participants claimed they did not smoke (89.5%) or consume alcohol (98.7%). Significantly, no participants reported a history of drug use (0.0%). Most affected job roles were among supporting staff (39.0%) which comprises lab personnel, cleaners, administrative, assistant environmental health officer (PPKP), public health assistant (PKA) and health care assistant (PPK); followed by paramedics (36.1%) and doctors (24.9%). The majority of HCWs reported working in a hospital setting (81.5%) compared to 18.5% working at primary health care facilities. A slightly majority (53.0%) of the HCWs reported less than 36 months of working experience in the healthcare sector.

Only a small percentage reported being diagnosed with chronic illness; diabetes mellitus (5.1%), hypertension (6.1%) and HIV (1.0%). A history of previous or recurrent TB was found to be uncommon (only 3.2%), and 99.0% claimed to have received BCG vaccination. Sputum results upon TB diagnosis were found almost evenly split between positive (54.0%) and negative (46.0%).

By using the SLogR method, several factors show statistically significance which indicates a potential association before adjustment. After analysing using the MLogR model, only three variables were found to be statistically significant (Table II). HCWs age less than 34 years old had significantly higher odds of TB treatment success (AOR=5.071, (95% CI: 2.009–12.801) compared to the higher age group. Doctors (AOR=0.024, 95% CI: 0.003–0.218) and supporting staff (AOR=0.366, 95% CI: 0.143–0.936) show significantly lower odds compared to paramedics. As for the CXR, those presented with moderate (AOR=14.686, 95% CI: 5.873–36.724) and far advanced (AOR=10.783, 95% CI: 1.909–60.904) CXR changes upon diagnosis had significantly higher odds of TB treatment success compared to those with minimal changes group.

DISCUSSION

With the findings of 86.9% treatment success rate, Selangor is brought closer to the WHO "End-TB Strategy" target of 90% by 2025. This figure is slightly higher compared to other studies by Uchimura et al. involving HCWs in Japan and from Cardos et al. from Brazil, which both reported at 80.0% success rate.[17,22] Another study by Pleszewski et al. reported 84.0% of TB treatment success rate.[18]

From Table I, most HCWs diagnosed with TB were predominantly female (74.8%). A paper by Lee et al. shows risk factors of TB among HCWs, including nursing professionals, due to its job requiring direct and extended contact with patients.[18-19] Since this profession is usually female dominated, might indirectly lead to a higher number of exposures compared to males. Regarding education level, one might assume that individuals with higher education have a lower risk of infection due to their better knowledge. However, in real healthcare settings, particularly concerning TB cases, the situation is often the opposite. Professions with a tertiary education level, such as doctors, nurses and medical assistants, generally have the most direct and prolonged contact with patients compared to supporting staff, thereby posing a higher risk of occupational TB exposure. This is supported by a paper by Tudor et al. which shows HCWs who spent more time working with patients had twice the odds of developing TB.[20]

In Table II, several significant determinants show a p-value <0.05 which indicates a significant association with the outcome. HCWs aged less than 34 years old show 5 times odds (AOR=5.071, 95% CI: 2.009–12.801) of having better treatment outcomes compared to older ages. This aligns with some literature indicating older age has lower TB treatment success rate.[13,21-22] Doctors (AOR = 0.024, 95% CI: 0.003 - 0.218) and supporting staff (AOR = 0.366, 95% CI: 0.143 - 0.936) both show a significantly lower odds of treatment success compared to paramedics. The findings for doctors might be surprising, as they were expected to have better treatment outcome due to their knowledge and access to healthcare. This may be explained by long working hours and chronic stress, as high stress levels are known to reduce treatment adherence, leading to low success rate.[23-24] Other possibilities include treatment interruptions caused by busy schedules or the tendency to self-treat or self-adjust treatment,[25] believing they know better compared to treating physicians. A paper by Nezenega et al. mentioned perceived stigma and discrimination towards the disease itself may lead to delay in diagnosis and compromise treatment adherence, reducing treatment success rate.[26-27] As for the supporting staff, the lower odds may be due to low health literacy as they don't perceive themselves as frontliners and underestimate risk of contracting TB as mentioned by Engelbrecht et al.[28] Similarly to doctors, they may also experience stigma or fear of being terminated, leading them to hide their illness or avoid regular follow-up, which will affect their outcomes. Unfortunately, all these factors were not studied in this research due to insufficient data availability.

In addition, those who had moderate (AOR=14.686, 95% CI: 5.873–36.724) and far advanced (AOR=10.783, 95% CI: 1.909–60.904) CXR findings at diagnosis had significantly higher odds of treatment success than those who had minimal CXR changes. This finding should be interpreted cautiously, as it is not consistent with the conventional expectation that more severe disease is associated with poorer treatment outcomes. Relatively small sample size of HCWs in far advanced disease (n=9) may have contributed to the wide confidence intervals observed and estimate instability. Furthermore, this association may have been influenced by other unmeasured factors, or by differences in clinical management, in residual confounding, or in disease classification. The reasons for this could not be fully explored as the NTBR does not collect detailed data on treatment adherence, intensity of treatment follow-up or changes in disease severity during treatment. Therefore, this finding should not be interpreted as evidence of a true clinical association between more severe radiographic disease and

better treatment outcomes. Rather, it may reflect estimate instability resulting from the small number of far advanced cases, residual confounding, or other unmeasured factors. Further studies with larger sample sizes are required to confirm this association.

Several variables that were commonly discussed and highlighted in other TB-related literature, however, were found to be statistically insignificant in our study. This includes HIV co-infections, DM, smoking habits and BCG vaccination status.[31-33] These insignificant findings might be due to the relatively small number of cases among the study population, which limited the statistical power to detect associations. Additionally, the unique characteristics of our study population and the potential role of confounding may have influenced these results.

One of the strengths is the utilisation of a comprehensive and reliable 10-year period of data obtained from the NTBR system from 2014 to 2023. This large, real-world dataset enables extensive analysis and provides strong statistical power to study the determinants of TB treatment outcome. The use of universal sampling indicates less data bias and leads to good representativeness of the actual situation in Selangor. Furthermore, the findings from this study may establish a new baseline, offering supplementary insights for the MOH and the Selangor State Health Department, particularly due to the scarcity of published research concerning the healthcare worker population in Malaysia. This study addresses the current gap and may be further investigated in future study.

LIMITATIONS

Although this study demonstrates several strengths, it is not without limitations. By using cross-sectional study design, we can only identify association, but unable to establish cause-effect relationship or measure incidence. Therefore, future researchers should consider conducting a longitudinal study to explore the causal relationship between occupational factors and socio-cultural factors towards TB treatment outcome over time. Full reliance on the NTBR data registry means we missed certain potentially associated factors that are not routinely captured in the systems such as psychosocial factors, adherence behaviours, stigma even cultures. Although only 24 records (7.1%) were excluded because of missing data, the use of listwise deletion may have introduced selection bias if the missingness was not completely random. In the future, the relevant unit should emphasize on improvement of data quality in the system to ensure the accuracy and completeness of recorded variables to minimise missing data. However, another drawback is the small number of patients in some groups, including those with HIV infection (n=3), diabetes mellitus (n=16), and those with far advanced CXR findings (n=9). These low numbers may have caused imprecise estimates, broad confidence intervals and decreased statistical power to detect significant associations. Another limitation of the system is that it is self-reported, which may result in recall error or under-reporting. The use of the Selangor NTBR database also introduces a potential source of selection bias. Healthcare workers who work in Selangor but live outside the state may not have been captured if their case was registered in another state's registry, as registration in the NTBR is mostly based on place of residence. The same applies to HCWs who reside in Selangor but work outside of the state and to whom investigations in the workplace may have been incomplete and not adequately documented. Therefore, the results may not reflect the entire HCWs population in Selangor especially for those who cross state lines to work. Future studies utilising the national NTBR database would provide a more comprehensive assessment of TB treatment outcomes among HCWs regardless of their state of residence.

Despite ongoing programs to improve TB treatment outcome among HCWs, one cannot deny the potential negative impact of mental health status on the TB treatment adherence. In the future, the MOH may consider prioritising and ensuring sufficient resource allocation, especially mental health support, as one of the elements in improving treatment outcomes. Since, from the study, doctors and supporting staff has lower odds-on treatment outcome, the management may consider role-specific intervention to improve the results in future.

CONCLUSION

High TB treatment success rate was found among HCWs in Selangor (86.9%) nearing to WHO's "End-TB Strategy" target. Younger age and advanced CXR upon diagnosis were found positively associated with better outcomes, while doctors and supporting staff show a contrary effect. Common risk factors such as HIV, smoking, diabetes and BCG were found to be non-significant in this study. Future research should consider conducting longitudinal studies to establish causal relationships by including additional socio-cultural and occupational factors. Several recommendations have also been suggested, such as strengthening mental health support for HCWs; implementing job-based targeted interventions; and improving data quality and completeness in the NTBR system, including capturing data on psychosocial, cultural influences and adherence-related factors. Hopefully by integrating these recommendations, Malaysia will be able to enhance its TB control and management efforts, as well as promoting a healthier and more effective healthcare workforce.

CONFLICT OF INTEREST

There are no conflicts of interest.

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Diagnostic accuracy of procalcitonin for identifying paediatric sepsis: A retrospective study in a Malaysian tertiary hospital

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ABSTRACT

Introduction: Early diagnosis of paediatric sepsis remains challenging because clinical manifestations are non-specific and microbiological culture results are often delayed. Procalcitonin (PCT) has emerged as a promising biomarker for bacterial infection; however, its diagnostic performance varies across patient populations and clinical settings. This study evaluated the diagnostic accuracy of serum PCT for identifying paediatric sepsis in a Malaysian tertiary referral hospital.

Materials and Methods: A retrospective descriptive study was conducted at Hospital Sultanah Nur Zahirah, Terengganu, Malaysia, between June 2022 and June 2024. Children aged 1 month to 18 years who underwent serum PCT testing for suspected infection were included. Paediatric sepsis was classified according to the 2005 International Paediatric Sepsis Consensus Conference criteria, supported by microbiologically confirmed infection or a Phoenix Sepsis Score ≥2 in culture-negative cases. Serum PCT, C-reactive protein (CRP), and total white cell count (TWC) obtained at initial presentation were analysed. Diagnostic performance was evaluated using receiver operating characteristic (ROC) curve analysis, sensitivity, specificity, predictive values, likelihood ratios, and diagnostic odds ratio.

Results: A total of 242 children were included, of whom 129 (53.3%) were classified as having sepsis. Median PCT concentrations were significantly higher in the sepsis group than in the non-sepsis group (1.940 vs. 0.240 ng/mL; p < 0.0001). At a cut-off value of 0.5 ng/mL, PCT demonstrated a sensitivity of 76.0%, specificity of 73.5%, positive predictive value of 76.6%, negative predictive value of 72.8%, positive likelihood ratio of 2.86, negative likelihood ratio of 0.33, and diagnostic odds ratio of 8.75. ROC analysis showed moderate diagnostic accuracy with an area under the curve of 0.747 (95% confidence interval: 0.692–0.802). PCT demonstrated a moderate positive correlation with CRP (Spearman's r = 0.546) but no significant correlation with TWC.

Conclusion: Serum PCT demonstrated moderate diagnostic accuracy for identifying paediatric sepsis and may serve as a useful adjunctive biomarker for the early evaluation of children with suspected sepsis. However, PCT should be interpreted alongside clinical assessment and microbiological investigations rather than used as a standalone diagnostic test.

KEYWORDS:
Procalcitonin, Sepsis, Child, Biomarkers, Diagnosis, Sensitivity and Specificity, Paediatrics, Malaysia

INTRODUCTION

Sepsis is a clinical syndrome resulting from a dysregulated host response to infection and remains a significant cause of morbidity and mortality, particularly in the paediatric population.[1-2] Despite its clinical importance, the definition of paediatric sepsis remains a subject of ongoing debate and lacks consensus. Currently, a positive microbial culture remains the reference standard for confirming infection; however, obtaining culture results often requires several days. As outcomes in paediatric sepsis are highly time-dependent, delays in diagnosis may postpone timely treatment. Therefore, there is a critical need for reliable diagnostic biomarkers that enable earlier recognition and intervention.

Procalcitonin (PCT) is a 116-amino acid peptide with a molecular weight of approximately 14.5 kDa, encoded by the Calcitonin 1 (CALC-1) gene located on chromosome 11. It has emerged as a promising biomarker for bacterial sepsis because of its favourable kinetic profile compared with other inflammatory markers routinely used in clinical practice. Serum PCT concentration begin to rise within 2 to 4 hours following bacterial infection, peak at approximately 6 to 24 hours, and have a biological half-life of approximately 24 hours, allowing level to decline rapidly with resolution of infection or effective antimicrobial therapy. In contrast, C-reactive protein (CRP) typically begins to increase after 6 to 12 hours, reaches peak concentrations at 36 to 50 hours, and remains elevated for several days because of its continued hepatic synthesis during the inflammatory response, despite

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having biological half-life of approximately 19 hours. Total white cell count (TWC) may increase within a few hours of infection but demonstrates considerable biological variability and limited specificity, as it can be influenced by numerous non-infection condition, including physiological stress, corticosteroid therapy, and haematological disorders.[3–5] These differences in biomarker kinetics suggest that PCT may provide earlier and more specific evidence of bacterial infection than CRP or TWC.

Although globally PCT has been extensively evaluated as a biomarker for bacterial sepsis, variability in diagnostic performance across different patient populations and clinical settings makes it difficult to extrapolate evidence directly to routine paediatric practice. Consequently, validation in local real-world populations remains essential to determine its diagnostic utility within specific epidemiological and healthcare contexts.

Existing Malaysian studies have evaluated the diagnostic performance of PCT in neonatal sepsis, postoperative sepsis in paediatric cardiac surgery and infected adult diabetic foot ulcers.[6–8] However, evidence regarding its diagnostic performance in non-neonatal paediatric sepsis remains scarce. Although neonates represent the paediatric age group at greatest risk of sepsis, neonatal sepsis differs substantially from sepsis beyond the neonatal period in terms of immune system maturity, pathogen distribution, clinical presentation, and the interpretation of inflammatory biomarkers. Therefore, findings from neonatal studies cannot be directly applied to older children.

In current Malaysian practice, the diagnosis of paediatric sepsis continues to rely primarily on clinical assessment, conventional inflammatory markers, and microbiological investigations. Although blood culture remains the reference standard for confirming bloodstream infection, its clinical utility is limited by delayed turnaround time and suboptimal sensitivity, while CRP lacks specificity for bacterial infection. Therefore, this study evaluated the diagnostic accuracy of PCT in Malaysian children with suspected sepsis presenting to a tertiary referral hospital, with the aim of providing locally relevant evidence to support its appropriate use in routine paediatric practice.

MATERIALS AND METHODS

This retrospective descriptive study was conducted at Hospital Sultanah Nur Zahirah (HSNZ), Terengganu, Malaysia, a tertiary referral hospital, between June 2022 and June 2024. Children aged 1 month to 18 years who underwent serum PCT testing for suspected infection at Hospital Sultanah Nur Zahirah between June 2022 and June 2024 were eligible for inclusion. Patients with incomplete medical records or missing key laboratory investigations, including PCT, CRP, or TWC count, were excluded from the study.

Demographic, clinical, and laboratory data were retrospectively retrieved from the hospital electronic medical records and laboratory information system. Demographic variable included age. Clinical data included the presence of Systemic Inflammatory Response Syndrome (SIRS) criteria, suspected or confirmed infection, microbiological culture results, and the Phoenix Sepsis Score where applicable. Laboratory data included serum PCT, CRP and TWC count measured at the initial presentation. Microbial culture results from blood, cerebrospinal fluid, urine, or other normally sterile body sites were obtained from the culture collected closest to the PCT request during the same hospital admission.

Paediatric sepsis was classified according to the 2005 International Paediatric Sepsis Consensus Conference (IPSCC) criteria 9, defined as the presence of SIRS criteria with suspected or confirmed infection. According to the IPSCC criteria, SIRS was defined as the presence of at least two of four clinical criteria (abnormal temperature, heart rate, respiratory rate, or leukocyte count), one of which had to be abnormal temperature or leukocyte count, with age-specific thresholds applied.

Confirmed infection was established by the isolation of a pathogenic microorganism from blood, cerebrospinal fluid, urine, or another normally sterile body site. As microbiological cultures may be negative despite true infection, patients with clinically suspected infection and negative culture results were further evaluated using the Phoenix Sepsis Score 1. A Phoenix Sepsis Score of ≥2 was considered supportive of sepsis-associated organ dysfunction. Accordingly, patients who fulfilled the IPSCC criteria and had either microbiologically confirmed infection or clinically suspected infection with a Phoenix Sepsis Score ≥2 were classified as having sepsis. Patients who did not meet these criteria were classified as non-sepsis. The classification algorithm used in this study is illustrated in Figure 1

The diagnostic interpretation of PCT levels is based on established clinical guidelines and studies. A PCT level of 0.5 ng/mL is widely recognised as a critical threshold in distinguishing bacterial infection and possible sepsis from other non-bacterial causes of inflammation. Levels below 0.5 ng/mL are generally considered to indicate a low likelihood of systemic bacterial infection. Meanwhile, levels above 0.5 ng/mL suggest a higher probability of bacterial sepsis, warranting further clinical evaluation or initiation of antimicrobial therapy.[10-11]

The sample size was calculated based on Buderer's formula. Previous regional studies suggested an expected sensitivity of 83.3% and specificity of 56.3%[12] for PCT in identifying sepsis. The prevalence of paediatric sepsis in similar tertiary care settings was estimated at 52%.[13] A confidence level of 95% (Z=1.96) and a precision of ±10% were selected to ensure an acceptable margin of error for both estimates. The final minimum sample size was set at 197 patients, including 102 with sepsis and 95 without.

Serum PCT concentrations were measured using the UniCel DxI 800 Access Immunoassay System (Beckman Coulter, Brea, CA, USA), employing a sequential two-step chemiluminescent immunoenzymatic (sandwich) assay. The assay has an analytical measuring range of 0.01–100 ng/mL. Calibration was performed using manufacturer-provided calibrators in accordance with the manufacturer's

recommendations. Internal quality control (IQC) was performed daily using commercially available quality control materials at two concentration levels. The laboratory also participated in the Randox International Quality Assessment Scheme (RIQAS) for PCT throughout the study period, demonstrating satisfactory performance.

Serum CRP concentrations were measured using the AU680 Clinical Chemistry Analyser(Beckman Coulter, Brea, CA, USA) by an immunoturbidimetric latex assay calibrated according to the International Federation of Clinical Chemistry (IFCC) recommendations. Routine calibration and daily IQC were performed in accordance with the manufacturer's recommendations. The laboratory also participated in the RIQAS for CRP, achieving acceptable external quality assessment performance throughout the study period.

TWC counts were determined using the Sysmex XN-Series 5-Part Differential Haematology Analyser (Sysmex Corporation, Kobe, Japan) as part of the routine full blood count analysis. Internal quality control and routine analyser maintenance were performed according to the manufacturer's recommendations and the laboratory's quality management system.

Microbiological investigations, including aerobic and anaerobic blood culture and antimicrobial susceptibility testing were performed according to established laboratory protocols. All laboratory analyses were conducted in accordance with the manufacturers' instructions, the laboratory's quality management system, and standard operating procedures.

Microsoft Excel for Microsoft 365 (Microsoft Corporation, Redmond, WA, USA) was used for initial data collection, cleaning, and to identify missing values prior to statistical analysis. Data distribution was assessed using visual inspection and the Shapiro-Wilk normality test. As the numerical data were not normally distributed, continuous variables including PCT, CRP and WBC were summarised as medians with Interquartile Ranges (IQR) and compared between groups using the Mann-Whitney U test. The Hodges-Lehmann estimator was used to quantify the median difference (location shift) between groups, along with corresponding 95% Confidence Intervals (CI). A two-tailed p-value of <0.05 was considered statistically significant.

Diagnostic test parameters, including sensitivity, specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV), Receiver Operating Characteristic (ROC) curves, and Area Under the Curve (AUC), were evaluated using Analyse-it software (Analyse-it Software Ltd, Leeds, UK), an Excel-based statistical add-in. CIs for diagnostic metrics were calculated using methods integrated within the software.

Correlation between PCT and other laboratory parameters was assessed using Spearman's rank correlation coefficient (r), due to the non-normal distribution of data. Correlation strength was interpreted as follows: r < 0.3 (weak), 0.3-0.7 (moderate), and > 0.7 (strong), with 95% CIs reported for each correlation coefficient.

RESULTS

Patient Characteristics

A total of 242 paediatric patients were included in the analysis. Among them, 129 (53.31%) were diagnosed with sepsis, and 113 (46.67%) were non-sepsis.

As summarised in Table I, both PCT and CRP levels were significantly elevated in patients with sepsis compared to those without. The median PCT level was 1.940 ng/mL (IQR: 0.470-12.527) in the sepsis group and 0.240 ng/mL (IQR: 0.120-0.843) in the non-sepsis group. The Hodges-Lehmann location shift was 1.100 ng/mL (95 % CI: 0.680 to 1.930), indicating a significant difference (p<0.0001).

Similarly, CRP levels were higher in sepsis (median 19.10 mg/L, IQR: 6.63-68.77) than in non-sepsis (median 14.20 mg/L, IQR: 2.90-36.57), with a Hodges-Lehmann shift of 4.70 mg/L (95% CI: 0.70 to 9.60; p=0.0159). In contrast, there were no statistically significant differences in age (p = 0.110) or WBC (p=0.472) between the groups.

Spearman's correlation analysis (Table II) revealed a moderate positive correlation between PCT and CRP (r=0.546, 95% CI: 0.448 to 0.631), indicating that higher PCT values were associated with higher CRP levels.

In contrast, there was no significant correlation between PCT and WBC (r=0.052, 95% CI: –0.079 to 0.180), indicating that WBC was not strongly associated with PCT levels in this cohort.

The diagnostic performance of PCT at a cut-off value of 0.5 ng/mL was evaluated using a 2 × 2 contingency table (Table III). PCT correctly identified 98 true-positive and 83 true-negative cases, while 31 cases were classified as false negatives and 30 as false positives. ROC curve analysis demonstrated moderate diagnostic accuracy, with an area under the curve (AUC) of 0.747 (95% CI: 0.692–0.802) (Figure 2). The corresponding sensitivity, specificity, predictive values, likelihood ratios, diagnostic odds ratio, and Youden Index are presented in Table III.

DISCUSSION

The present study demonstrated that serum PCT has moderate diagnostic accuracy for identifying paediatric sepsis, with an AUC of 0.747, sensitivity of 76.0%, and specificity of 73.5%. The observed diagnostic performance is broadly consistent with previous paediatric and adult studies, which generally report moderate-to-good discriminatory ability for PCT in bacterial sepsis.

Although our AUC of 0.747 was lower than the pooled AUCs reported in the systematic reviews by Wacker et al. (0.85) and Chairaj et al. (0.84),[14-15] it was comparable to the pooled AUCs reported by Ghatak et al. (0.77) in adult emergency department populations and Omar et al. (0.76) in neonatal population.[7,16] These findings suggest that the diagnostic performance of PCT varies across clinical settings and patient populations, with differences likely reflecting variations in study populations, sepsis definitions, and methodology rather than limitations of PCT itself.

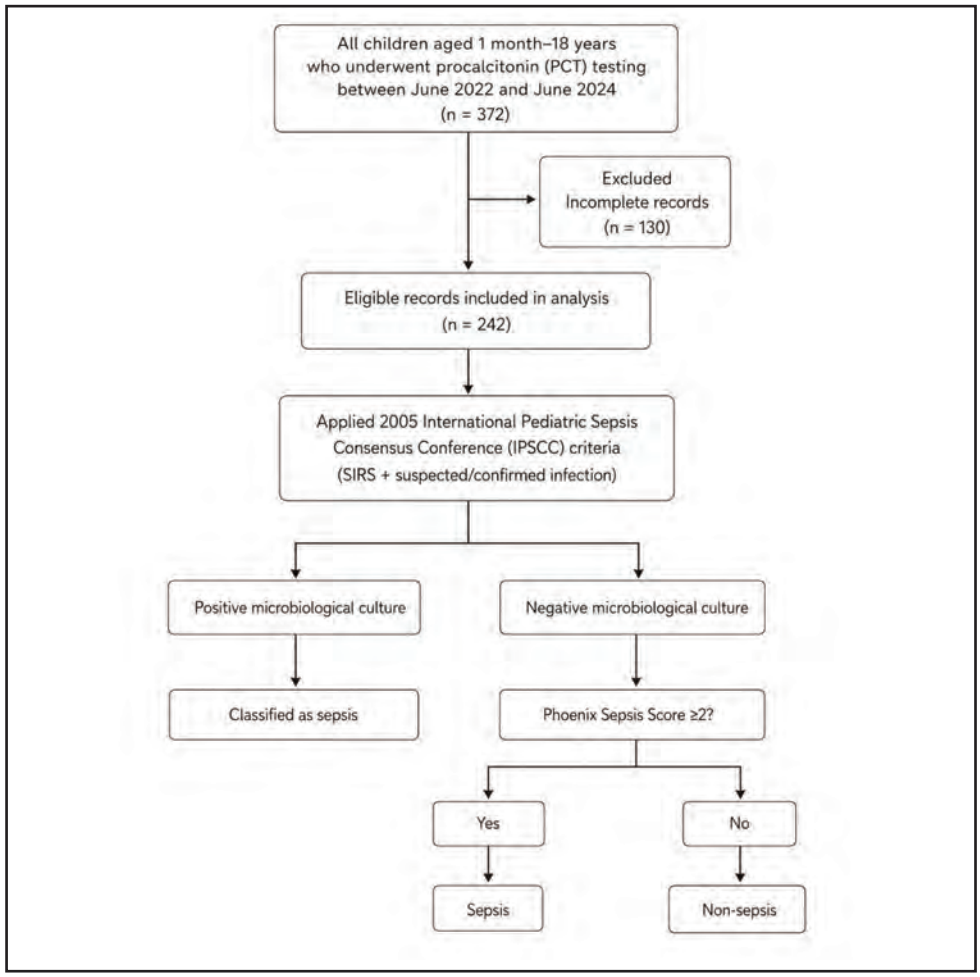

Fig. 1: Flowchart of patient selection and classification

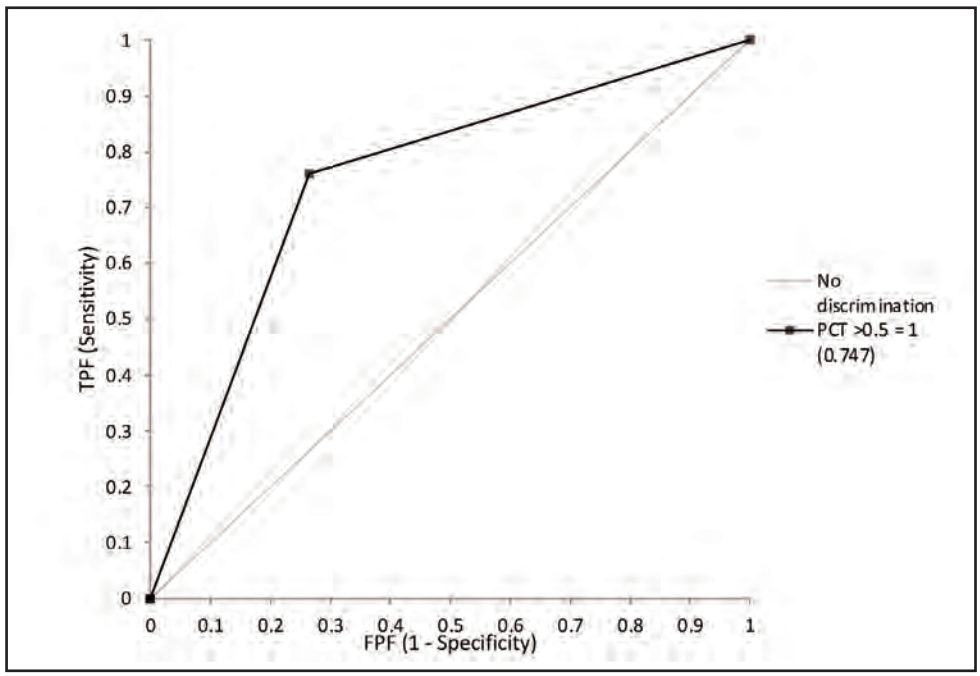

Fig. 2: Receiver Operating Characteristic (ROC) curve analysis

Table I: Comparison of laboratory findings between the sepsis and non-sepsis groups

Variables	Median (IQR)		Hodges-Lehmann Shift (95% CI)	p-value
	Sepsis	Non-sepsis		
PCT (ng/mL)	1.940 (0.470-12.527)	0.240 (0.120-0.843)	1.100 (0.680 to 1.930)	< 0.0001
CRP (mg/L)	19.10 (6.63-68.77)	14.20 (2.90-36.57)	4.70 (0.70 to 9.60)	0.0159
WBC ($\times 10^9$/L)	8.0 (2.0-49.0)	11.40 (7.37-17.57)	2.0 (0.0 to 5.0)	0.110

Table II: Spearman's correlation between PCT and selected laboratory parameters (n = 242)

Variable Pair	Spearman's (r)	95% Confidence Interval
PCT vs. CRP	0.546	0.448 to 0.631
PCT vs. TWC	0.052	–0.079 to 0.180

Table III: Diagnostic performance of procalcitonin in identifying paediatric sepsis

A. 2 x 2 Contingency table

Reference standard	PCT > 0.5 ng/mL (Positive)	PCT ≤ 0.5 ng/mL (Negative)	Total
Sepsis (yes)	98 (TP)	31(FN)	129
No Sepsis (No)	30 (FP)	83 (TN)	113
Total	128	114	242

B. Diagnostic performance indices

Parameter	Estimate (95% CI)
Sensitivity	75.97% (67.91–82.52)
Specificity	73.45% (64.64–80.72)
Positive predictive value	76.56% (68.52–83.06)
Negative predictive value	72.81% (64.00–80.13)
Positive likelihood ratio (LR+)	2.86 (2.07–3.95)
Negative likelihood ratio (LR–)	0.33 (0.24–0.45)
Diagnostic odds ratio	8.75 (4.89–15.64)
Youden's Index	0.494

Our study included a heterogeneous real-world paediatric population with diverse infection sources, disease severity, and underlying clinical conditions, whereas many previous studies evaluated more homogeneous cohorts, such as children admitted to paediatric intensive care units or adult in emergency department. Furthermore, differences in reference standards may also have contributed to variability across studies. While many contemporary adult studies have adopted organ dysfunction-based definitions, such as the Sequential Organ Failure Assessment (SOFA) or quick Sequential Organ Failure Assessment (qSOFA), these tools have not been validated for routine use in children. Accordingly, our study classified patients using the 2005 IPSCC criteria, which remain widely applied in paediatric sepsis research and were appropriate for this retrospective cohort.

The moderate sensitivity and specificity observed in this study may also reflect the occurrence of false-negative and false-positive PCT results in routine clinical practice. False-negative results may occur when blood samples are collected early in the course of infection before sufficient PCT production has occurred, in patients with localized bacterial infections, or in immunocompromised individuals with attenuated inflammatory responses. Previous antibiotic exposure before specimen collection may also reduce bacterial burden and culture positivity, potentially influencing both sepsis classification and circulating PCT concentrations. Conversely, false-positive PCT elevations have been reported in non-infectious inflammatory conditions, including major trauma, surgery, and severe systemic inflammation. Collectively, these factors may have reduced the observed sensitivity, specificity, and overall diagnostic performance of PCT in our retrospective cohort.

Although PCT demonstrated moderate overall diagnostic accuracy, the likelihood ratios (LR+ 2.86 and LR– 0.33) indicate that positive and negative test results produce only modest changes in the probability of sepsis. Similar likelihood ratios reported by Ghatak et al. (LR+ 2.80 and LR– 0.42) support this finding. 16 Therefore, PCT should be interpreted as an adjunct to clinical assessment and microbiological investigations rather than as a stand-alone diagnostic test.

We observed a moderate positive correlation between PCT and CRP, suggesting that both biomarkers increase in response to systemic inflammation during bacterial infection.

Although previous paediatric studies have primarily compared the diagnostic performance of PCT and CRP rather than their correlation, both biomarkers are recognised indicator of the host inflammatory response.[17] Despite this association, PCT is considered more specific for bacterial infection because its production is directly stimulated by bacterial endotoxins and pro-inflammatory cytokines, whereas CRP is a non-specific acute-phase reactant that may be elevated in a broader range of infectious and non-infectious inflammatory conditions. These findings support the use of PCT as a complementary biomarker alongside CRP, rather than as a replacement, in the diagnostic evaluation of paediatric sepsis.[18-19]

In contrast, no significant correlation was observed between PCT and TWC count. This finding is consistent with previous studies demonstrating that leukocyte counts are influenced by age, physiological stress, viral infections, and immune status, thereby limiting their specificity for bacterial infection.[5] Compared with conventional haematological indices, PCT appears to provide more specific information regarding bacterial infection and systemic inflammatory responses.

These findings have practical implications for paediatric sepsis management in Malaysia. As microbiological culture results typically require 24 to 72 hours and blood cultures may yield false-negative results, clinicians often initiate empirical antimicrobial therapy based on clinical suspicion. In this context, PCT may assist in the early recognition and risk stratification of children with suspected sepsis while awaiting microbiological confirmation, particularly in tertiary hospitals where rapid PCT testing is available. Nevertheless, PCT should be interpreted alongside clinical assessment and microbiological investigations rather than used as a standalone diagnostic test.

Despite its potential clinical utility, routine PCT testing remains largely confined to tertiary and selected secondary hospitals in Malaysia because of cost considerations and limited laboratory infrastructure. Consequently, clinicians in many district hospitals continue to rely primarily on CRP and TWC count despite their lower specificity for bacterial infection. In such settings, point-of-care (POC) PCT testing may represent a practical alternative, as previous studies have demonstrated good analytical agreement with central laboratory assays and shorter turnaround times, thereby facilitating earlier clinical decision-making in emergency and critical care settings.[20]

Beyond its diagnostic utility, previous studies have demonstrated that PCT-guided algorithms can support antimicrobial stewardship by reducing unnecessary antibiotic exposure and treatment duration. Although these outcomes were not evaluated in the present study, the moderate diagnostic performance observed suggests that PCT may contribute to more informed clinical decision-making when used alongside clinical assessment and other laboratory investigations.

Several emerging biomarkers, including presepsin and interleukin-6 (IL-6), have shown promising diagnostic performance for early sepsis detection. Nevertheless, these biomarkers require further validation in paediatric populations and are currently less accessible in routine clinical practice.[21-22] Compared with these novel biomarkers, PCT remains more widely available and better established, although its moderate diagnostic performance observed in the present study suggests that future research should evaluate whether multimarker approaches can further improve diagnostic accuracy in Malaysian children.

The strengths of this study include the use of real-world data from a Malaysian tertiary referral hospital, a sample size exceeding the calculated minimum requirement, and standardised laboratory analyses performed within an ISO 15189-accredited laboratory. Furthermore, inclusion of both culture-positive and culture-negative patients better reflects routine clinical practice and enhances the applicability of the findings to similar healthcare settings.

Nevertheless, several limitations should be acknowledged. The retrospective design limited control over important confounding factors, including prior antibiotic exposure, timing of biomarker measurement, patient comorbidities, and heterogeneity of infection sources, all of which may have influenced PCT concentrations and reduced the observed diagnostic performance. The use of the 2005 International Paediatric Sepsis Consensus Conference criteria together with microbiological findings and the Phoenix Sepsis Score for culture-negative cases may also have introduced classification bias. In addition, only the first PCT measurement obtained at presentation was analysed, whereas serial measurements may provide greater diagnostic and prognostic value.

CONCLUSION

Overall, the present study provides local evidence supporting the clinical utility of serum PCT as an adjunctive biomarker for the early evaluation of suspected paediatric sepsis. Despite demonstrating only moderate diagnostic accuracy, PCT may support clinical decision-making when interpreted in conjunction with clinical assessment and other laboratory findings. These findings highlight the potential role of PCT in routine paediatric sepsis evaluation while underscoring the need for larger prospective multicentre studies using contemporary paediatric sepsis definitions and the evaluation of combined biomarker models to further validate its diagnostic performance and optimise its clinical application.

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ORIGINAL ARTICLE

The barriers to colorectal cancer screening tests among adults attending Seremban health clinic in Negeri Sembilan, Malaysia

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ABSTRACT

Introduction: Colorectal cancer (CRC) is the second most common cancer in Malaysia, with most cases diagnosed at late stages, leading to poor survival. Stool-based screening methods, like the immunological faecal occult blood test (iFOBT), can reduce CRC mortality, but national uptake remains below 3%. This study explores barriers to CRC screening and their association with sociodemographic factors among adults aged 50 and above attending Seremban Health Clinic.

Materials and Methods: A cross-sectional study was conducted in March 2025 at Seremban Health Clinic, Negeri Sembilan, involving 400 adults aged 50 and above. Participants were selected through purposive sampling and completed a self-administered questionnaire adapted from the Scottish Bowel Screening Programme. Data analysis was performed using IBM SPSS version 28.0, with statistical methods including multiple linear regression.

Results: The most frequently reported barriers included low self-efficacy, unfamiliarity with screening procedures, emotional concerns, and negative perceptions of screening. Age, gender, education level, employment status, and previous experience on cancer screening were found to have significant associations with barriers to cancer screening. Respondent's belief in early detection, a sense of health responsibility, and encouragement from healthcare providers and family were identified as facilitators to cancer screening. Prior screening experience was linked to fewer barriers.

Conclusion: Findings indicate the need for targeted interventions to improve awareness, confidence, and attitudes toward screening.

KEYWORDS:
Barriers, Colorectal cancer, Screening, Malaysia

INTRODUCTION

Colorectal cancer (CRC) is the second most common cancer in Malaysia represented for 14.1% of all newly diagnosed cancer cases from 2017 to 2021, increasing from 13.5% between 2012 and 2016.[1-2] In Malaysia, which is multiethnic country CRC is a great burden as most CRC patients are detected at a late stage such as stage 4 or 5, with a 5-year relative survival rate lower than that of developed Asian countries.[3] Moreover, due to a lack of cancer awareness and other barriers to screening, nearly 80% of cancer patients requested treatment when they were already in the late stages.[4-5]

Stool-based tests, such as the guaiac Faecal Occult Blood Test (gFOBT) and the immunological faecal occult blood test (iFOBT), are suggested for CRC screening in asymptomatic individuals. It has been suggested that iFOBT screening could reduce CRC mortality by as much as 70%.6 In 2014, the Ministry of Health (MOH) launched a nationwide CRC screening program utilising iFOBT kits. This screening is available at public health clinics through an opportunistic approach. It is currently offered to all asymptomatic males and females aged 50 to 75 who visit the clinics. Patients receive a stool container and are asked to return a stool sample to the health clinic for analysis at the laboratory. Patients who receive positive results are referred to the nearest public hospital for a colonoscopy.[6]

Since its introduction, there has been a gradual increase in screening rates; however, the CRC screening uptake in the target population is still less than 3%, which is at a sub-optimal level. [7-8]

A cross-sectional study in 44 health clinics in West Malaysia found extremely low knowledge and attitude towards CRC screening in the moderate risk group.[4] In addition, research by Yusoff et al. in 2012 found that only 7% of almost 2000 healthy respondents knew about CRC screening.[9] The main barriers to screening participation identified were embarrassment and anxiety, reflecting psychological obstacles.[9] Another study done in Malaysia's Klang Valley found low awareness of CRC among urban Malaysians, with many unable to recall its warning signs.[10]

A key outcome from another Malaysian study showed increased public awareness of the significance of CRC

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screening, where 91.3% of respondents agreed that screening tests can detect cancer early, while 86.3% agreed that late detection leads to a lower survival rate.[11]

Moreover, some recent research conducted in Al-Baha, Saudi Arabia, and Southern Italy showed low adherence to and awareness of CRC screening. 20.3% of Italians were aware of all screening tests, and 29.2% had completed FOBT; education and medical advice were important contributing factors. 49.7% of Al-Baha residents were aware that CRC could be identified early, but only 2.8% had undergone screening, indicating the necessity for focused education.[12-13]

Prior studies reveal persistently low CRC screening rates nationwide, with an uptake below 3% among the target population. Factors such as fear, embarrassment, lack of awareness, and inadequate health counselling have consistently contributed to low participation rates in CRC screening.[9,14] Recent qualitative studies have identified specific barriers and facilitators, such as trust in healthcare providers and the need for culturally adapted screening instructions, suggesting that enhanced education and trust-building measures could play vital roles in increasing screening uptake.[6,8] In addition, recent behavioural research on CRC screening has highlighted the importance of self-efficacy, perceived benefits of screening, social support, and culturally appropriate communication in influencing screening participation.[6,8]

To better understand the factors influencing CRC screening participation, behavioral science frameworks have increasingly been used to examine screening uptake. The Integrated Screening Action Model (I-SAM) is a screening-specific framework that recognizes screening behavior as being influenced by multiple interacting factors, including self-efficacy, beliefs about screening effectiveness, practical and emotional barriers, social influences, and existing health conditions.[15] By categorizing barriers and facilitators into distinct behavioral domains, I-SAM provides a structured approach for understanding determinants of screening participation and identifying potential targets for intervention. As the questionnaire used in this study was developed based on the I-SAM framework, this model was adopted to guide the assessment and interpretation of barriers and facilitators to CRC screening.

Despite these insights, there remains a need for a localized understanding of how socio-demographic factors impact screening barriers. The objectives of this study also aim to provide a comprehensive understanding of barriers to access CRC screening, specifically adults attending Seremban Health Clinic.

MATERIALS AND METHODS

This cross-sectional study was conducted at Seremban Health Clinic in March 2025 among Adults (aged 50 and above) who attended Seremban health clinic, Malaysia. Our exclusion criteria include people below the age of 50, non-Malaysians, population diagnosed with colorectal cancer, mental illnesses, or who are blind, deaf, and/or dumb, and medical doctors were excluded from the study. The questionnaire was adapted from a survey used in a cross-sectional study conducted among the participants of the Scottish Bowel Screening Programme in 2022.1[5]

Simple random sampling was used for data collection. The population size for adults aged 50 and above in Seremban is approximately 138,000 as of 2023.[16] Based on a rate of 70.9% of urban respondents with awareness of at least one CRC symptom,10 and a 95% confidence level, the sample size required was 317 using the OpenEpi calculator. Considering an 80% response rate, the modified sample size was 317 / 0.80 = 396.25 (~ 397). Therefore, a total of 400 individuals were targeted.

We used purposive sampling to recruit the required number of individuals who presented for CRC screening at Seremban Clinic. Eligible respondents were approached consecutively and invited to participate until the target sample of 400 was reached. Recruitment occurred during routine clinic hours over the study period, with refusals and reasons recorded and replaced by the next eligible patient.

Questionnaire validation

The questionnaire was adapted from the previous study.15 The questionnaire was culturally adapted to ensure clarity and relevance in the Malaysian context. It was translated into Malay, English, and Tamil using a forward–backward translation procedure. Forward translations were carried out by bilingual experts, followed by back-translation into the original language by independent translators. Any discrepancies were reviewed and resolved to ensure equivalence in meaning across all versions. Face validity was assessed through expert review and pilot testing among 30 respondents to confirm the clarity and appropriateness of the items. Internal consistency reliability, assessed from the pilot study, showed strong reliability for the barrier items (Cronbach's alpha=0.918).

Statistical Analysis

Statistical analysis was done using IBM SPSS version 28.0. Responses to each barrier item were measured using a 5-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree). Barrier items were grouped into seven thematic domains according to the Integrated Screening Action Model (I-SAM) as done by the questionnaire's developer.[15] For barriers, the domains comprised low self-efficacy, low perceived screening test efficacy, practical barriers, emotional barriers, fatalism, lack of social support, and comorbidities. For each domain, a mean domain score was calculated by averaging the scores of all items within that domain, with higher scores indicating stronger perceived barriers. Multiple linear regression analyses were performed to identify sociodemographic predictors for each barrier domain. Statistical significance was set at $p<0.05$ for all tests.

Ethical considerations

The Ministry of Health Malaysia (MOH) has provided ethical approval for this study on 31 December 2024 with NMRR ID-24-02972-LNE. All personal information provided by participants was kept strictly confidential, and patient identities were anonymized in the final report. Informed consent was obtained from all participants prior to data

Table I: Barrier's domains based on mean Likert scores

Barrier Domain	Mean	Standard deviation
Low self-efficacy	2.914	1.047
Low perceived screening test efficacy	2.509	0.894
Practical barriers	2.385	0.833
Emotional barriers	2.305	0.857
Fatalism	2.297	0.903
Lack of social support	1.991	0.624
Comorbidities	1.938	0.736

collection. The research was carried out in accordance with the principles outlined in the Declaration of Helsinki.

RESULTS

In this study, a total of 400 participants completed the questionnaire. Most participants involved in this study ranged between 60-69 years of age and were females. The predominant ethnicity was Chinese (45.8%), followed by Indians (39.3%), preceding Malays (14.5%). More than half of them had completed secondary education and were retired at the time. For those who had undergone screening previously, government hospitals have been the choice of institution. Although around 85% of the participants had not undergone screening tests for colorectal cancer previously, it is evident that the majority believed the screening test to be easy and were willing to undergo the test if deemed required. The primary reasons for refusing CRC screening were shown in Figure 1, ranked from highest to lowest mean score of individual questionnaire item. The main reasons reported by the respondents were being unsure about where to get the test (3.030±1.228), unfamiliarity with the test (2.760±1.208), being worried about the test results (2.840±1.391), being unsure how to take the stool sample (2.760±1.208), perceiving that the test was not necessary (2.72±1.306), anxiety about screening (2.690±1.328), and insufficient stuff to test (2.680±1.087).

Barriers were further categorized into 8 thematic domains according to I-SAM, as shown in Table I. The strongest barrier category to CRC screening was low self-efficacy, followed by low perceived screening test efficacy and practical barriers. The lowest-scoring barrier domains lack of social support and comorbidities.

Multiple linear regression analyses were performed to examine the association between sociodemographic factors and different domains of barriers to CRC screening in Tables II and III. Overall, the sociodemographic variables accounted for 6% to 16% of the variation observed across the different CRC screening barrier domains. The assumptions of multiple linear regression were assessed before interpreting the model. The normality of the regression residuals was assessed using the Shapiro–Wilk test and normal P–P plot. Although the Shapiro–Wilk test was statistically significant ($p<0.001$), indicating some deviation from normality, the points on the normal P–P plot closely followed the diagonal line, suggesting that the deviation was not substantial. The independence of residuals was assessed using the Durbin–Watson statistic, which ranged from 1.20 to 1.40 across the different barrier domains. Given the cross-sectional study design, with one observation contributed by each participant, independence was primarily supported by the study design. Homoscedasticity was assessed by examining a scatterplot of standardized residuals against standardized predicted values. Multicollinearity was assessed using tolerance and variance inflation factor (VIF) values; all predictors had tolerance values >0.20 and VIF values <5, indicating no evidence of problematic multicollinearity.

The Enter method was used, whereby sociodemographic variables (age, gender, ethnicity, education, employment, previous cancer screening) identified a priori were entered into the regression model simultaneously. Variables were selected based on their relevance to CRC screening behaviour and barriers, rather than on statistical significance during variable selection.

For each categorical variable, one category was designated as the reference category, and the remaining categories were compared with this reference category. The reference categories were selected based on their conceptual relevance. Female was used as the reference category for sex, while primary education was used for education, Indian for ethnicity, unemployed for employment status, and no previous experience for history of cancer screening. Age was entered into the model as a continuous variable, with a median age of 65 years (IQR=14 years).

The findings showed that comorbidities were not significantly associated with any of the barrier domains. Gender emerged as a significant predictor for all barrier domains except perceived screening test efficacy.

Compared with females, males reported significantly lower practical barrier scores (B=-0.199, p=0.021), emotional barrier scores ($B = -0.257$, $p < 0.001$), low self-efficacy scores (B=-0.407, $p<0.001$), fatalism scores (B=-0.312, p=0.001), and perceived lack of social support scores (B=-0.165, p=0.011). These findings indicate that females experienced greater practical and emotional barriers, lower self-efficacy, higher levels of fatalism, and a greater perceived lack of social support toward CRC screening than males.

Previous cancer screening experience was significantly associated with lower barrier scores across several domains. Participants who had undergone cancer screening previously reported lower practical barriers (B=-0.039, p=0.001), lower levels of low self-efficacy (B=-0.889, $p<0.001$), lower fatalistic beliefs (B=-0.304, p=0.014), lower perceived barriers related to screening test efficacy (B=-0.469, $p<0.001$), and lower perceived lack of social support (B=-0.228, p=0.008)

Table II: Sociodemographic factors associated with practical, emotional barriers, and low self-efficacy

Variable	Practical barriers			Emotional barriers			Low self-efficacy		
	B(95% CI)	ß	p-value	B(95% CI)	ß	p-value	B(95% CI)	ß	p-value
Constant	4.103[3.251,4.955]	-	<0.001	4.100[3.244,4.956]		<0.001	5.088[4.065,6.110]		<0.001
Age	-0.013[-0.023, -0.004]	-0.144	0.006*	-0.010[-0.020, -0.001]	-0.109	0.032*	-0.006[-0.018,0.005]	-0.055	0.228
Gender	-0.199[-0.368,-0.030]	-0.119	0.021*	-0.257[-0.611, -0.271]	-0.257	<0.001**	-0.407[-0.609,-0.206]	-0.194	<0.001**
Ethnicity	0.053[-0.064,0.170]	0.044	0.373	0.910[-0.027,0.209]	0.073	0.13	0.113[-0.028,0.253]	0.074	0.115
Education	-0.062[-0.183,0.060]	-0.051	0.318	-0.130[-0.252, -0.007]	-0.104	0.038*	-0.099[-0.245,047]	-0.065	0.182
Employment	-0.041 [-0.186,0.104]	-0.029	0.583	-0.074[-0.219,0.720]	-0.051	0.321	-0.063[-0.237,0.110]	-0.036	0.473
Previous Cancer screening	-0.390[-0.613,-0.167]	-0.17	0.001**	-0.189[-0.414,0.35]	-0.08	0.098	-0.889[-1.157,-0.621]	-0.307	<0.001**
R square	0.075			0.117			0.159		
F statistic	5.293			8.605			12.244		
Df(regression,residual)	6,391			6,391			6,391		
Model p-value	<0.001			<0.001			<0.001		

*Significant at 0.05, ** significant at 0.01, B: unstandardized coefficient, ß: standardized coefficient, CI: confidence interval, P: probability, Df: Degree of freedom

Table III: Sociodemographic factors associated with fatalism, low perceived screening test efficacy, and lack of social support

Variable	Fatalism			Low perceived screening test efficacy			Lack of social support		
	B (95% CI)	ß	p-value	B(95% CI)	ß	p-value	B(95% CI)	ß	p-value
Constant	2.838[1.918,3.758]		<0.001	3.666[2.744,4.588]		<0.001	3.202[2.565,3.838]		<0.001
Age	0.009[-0.001,0.019]	0.09	0.082	-0.001[-0.012,0.009]	-0.014	0.787	-0.006[-0.013,0.001]	-0.084	0.108
Gender	-0.312[-0.495, -0.13]	-0.173	0.001**	0.038[-0.145,0.221]	0.021	0.684	-0.165[-0.291.-0.038]	-0.132	0.011*
Ethnicity	0.042[-0.084,0.169]	0.032	0.512	-0.045[-0.171,0.082]	-0.034	0.489	0.047[-0.041,0.134]	0.052	0.296
Education	-0.186[-0.317,0.055]	-0.141	0.006*	-0.013[-0.144,0.119]	-0.01	0.848	-0.082[-0.173,0.009]	-0.091	0.076
Employment	-0.008[-0.164,0.149]	-0.005	0.923	-0.225[-0.382,-0.069]	-0.151	0.005*	-0.119[-0.227,-0.011]	-0.114	0.032*
Previous Cancer screening	-0.304[-0.545,0.063]	-0.122	0.014*	-0.469[-0.711,-0.227]	-0.19	<0.001**	-0.228[-0.395,-0.061]	-0.133	0.008*
R square	0.081			0.061			0.076		
F statistic	5.774			4.254			5.328		
Df (regression,residual)	6,391			6,391			6,391		
Model p-value	<0.001			<0.001			<0.001		

*Significant at 0.05, ** significant at 0.01, B: unstandardized coefficient, ß: standardized coefficient, CI: confidence interval, P: probability, Df: Degree of freedom

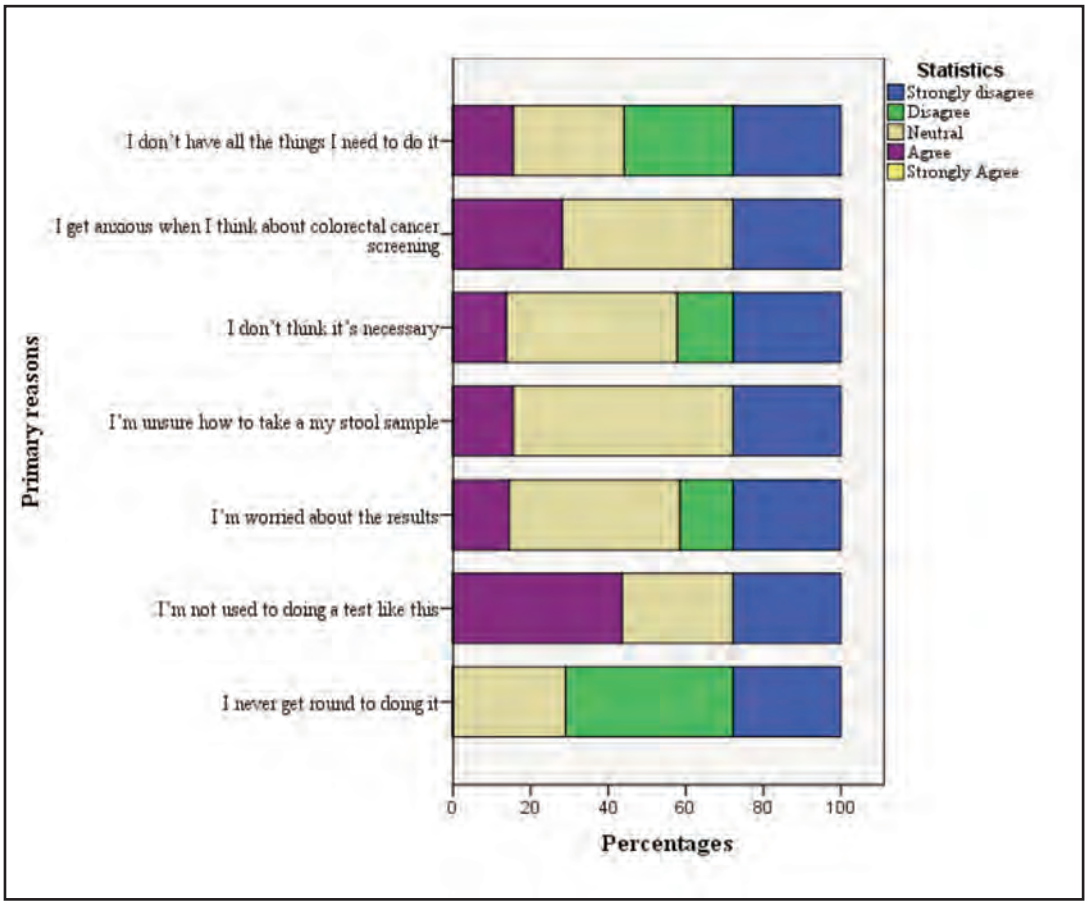

Fig. 1: Primary reasons for refusing CRC screening

compared with those who had never been screened. Previous screening experience was associated with greater familiarity and confidence regarding the screening process, less negative beliefs, greater perceived social support and fewer perceived barriers to CRC screening.

Age was a significant predictor of both practical barriers (B= -0.199, p=0.006) and emotional barriers (B=-0.013, p=0.006). These findings indicate that older participants perceived fewer practical and emotional barriers to CRC screening compared with younger participants.

Education was also significantly associated with emotional barriers (B=-0.130, p=0.038) and fatalism (B=-0.186, p=0.006). These findings suggest that higher education was associated with lower emotional barriers and lower fatalism, characteristics that have previously been linked with greater CRC screening participation.

Employment status was a significant predictor of perceived screening test efficacy (B=-0.225, p=0.005) and perceived lack of social support (B=-0.119, p=0.032). Compared with unemployed individuals, those who were employed or retired reported more favorable perceptions of screening effectiveness and perceived greater social support for CRC screening.

The findings suggest that being male, older age, higher educational attainment, employment, and previous cancer screening experience were associated with more favorable attitudes toward CRC screening and a greater likelihood of screening uptake.

DISCUSSION

This study highlighted those psychological and informational factors are more significant obstacles than logistical or systemic issues in undergoing CRC screening. Low self-efficacy emerged as the dominant barrier category, suggesting that individuals lack confidence in their ability to correctly perform or understand the CRC screening procedure. Additionally, a gap in understanding the importance of early detection underscores the importance of patient empowerment and education in public health strategies for CRC screening. These results align with previous research demonstrating that knowledge gaps, fear of results, and the belief that screening is unnecessary are critical determinants of CRC screening behaviour.[7] Therefore, addressing a patient's confidence in performing the screening test and the perceived value of the test may have a more profound impact on improving screening uptake than solely focusing on access or cost-related interventions.

There are several other deterrents beyond the seven categories identified by participants. Long waiting times can contribute

to the reluctance to participate, while logistical challenges like transportation and language barriers add another layer of difficulty. A study that explored the barriers to CRC screening in semi-rural Malaysia reported that the most common barriers to CRC screening at clinics were long waiting times and a lack of transport.[6] These findings are of considerable importance as they offer a comprehensive understanding of the factors that may hinder certain patients from accessing critical screening services. Addressing these barriers could help improve participation rates in CRC screening, which could lead to earlier detection and better health outcomes.

Fatalism, which is a belief system characterized by a perception that serious illnesses like colorectal cancer are predetermined or a natural part of aging, has been perceived significantly in the oldest age group (80 years and above). This sense of inevitability can diminish motivation to undergo the screening test.[17] Together with the complex interplay of factors such as the influence of cultural beliefs in healthcare and varying perceptions of illness that create ethnic disparities in screening barriers, a multifaceted and culturally sensitive approach to shift this perception and emphasize the value of preventive care is required while respecting their individual autonomy, life experiences, and cultural beliefs. This finding may be interpreted through the Health Belief Model (HBM), which suggests that individuals are more likely to engage in preventive health behaviours when they perceive themselves to be susceptible to a disease, recognise its potential severity, and believe that screening can provide meaningful benefits. Recent studies have demonstrated significant associations between HBM constructs, fatalistic beliefs, and CRC screening behaviours, including among Malaysian populations.[18-19] Fatalistic beliefs may reduce perceived benefits and self-efficacy, leading individuals to view screening as unnecessary or ineffective. Therefore, culturally sensitive educational interventions that emphasise the preventable and treatable nature of CRC when detected early may help address these misconceptions. Educational interventions based on HBM principles have been shown to improve CRC screening behaviours.[19] Engagement of community leaders, religious leaders, and culturally tailored health promotion activities may further enhance acceptance of CRC screening across diverse populations.[6,19]

The doctor-patient relationship may also play an important role in improving CRC screening uptake. In the Malaysian healthcare setting, patients often rely heavily on healthcare providers when making decisions regarding preventive health measures. Consequently, recommendations from doctors may serve as an important cue to action and help overcome uncertainty, misconceptions, and low confidence regarding screening.[8,18] Opportunistic counselling and proactive recommendations for iFOBT during clinic visits may therefore represent practical strategies for increasing participation in CRC screening programmes.

The findings indicated that male gender, older age, higher educational attainment, employment, and a previous history of cancer screening were associated with lower barriers and a greater likelihood of CRC screening uptake.

Public health narratives that have historically focused more on female-specific cancers, such as breast and reproductive cancers, might lead to comparatively lower awareness of other cancers among women, or the perceived burden of undergoing multiple screening tests may discourage them from participating in low-prioritized cancer screening.[20] Although the current study found that male gender was associated with a greater likelihood of CRC screening uptake, more than half of male patients continue to present to healthcare facilities at a late stage of the disease. Despite CRC being one of the most common cancers among Malaysian men, awareness and participation in screening remain suboptimal. This suggests that while men in the study reported fewer barriers to screening, overall awareness and timely screening uptake among the broader male population may still be inadequate.[21]

Furthermore, individuals with lower educational attainment and consequently lower health literacy, as well as unemployed individuals, may have limited access to health information, support systems, and preventive healthcare services. As a result, they may have fewer opportunities to attend regular medical check-ups, receive vaccinations, or participate in cancer screening programmes. Research suggests that people who are not working may also have lower health literacy and less engagement with healthcare systems, which can affect their confidence in navigating screening processes.[22] Thus, community-based education, peer support groups, and personalized reminders should be used to improve screening rates in these groups.

Employment status may influence attitudes toward screening and access to supportive social networks that facilitate screening participation. In Malaysia, government employees, particularly those aged 40 years and above, may have greater access to CRC screening through annual health check-ups provided at government health facilities.[23] Similarly, retirees from lower-income households (B40 group) may be eligible for subsidized or free health screening programmes under government healthcare initiatives.[24] These opportunities may increase awareness of CRC screening and reduce barriers to participation.

Notably, people who had done the screening test before reported fewer barriers overall. This finding is consistent with a study among the Saudi population, where participants who had not undergone any previous CRC screening reported more barriers compared to those who had previously screened.[13] Participants with previous screening experience also reported greater confidence in their ability to complete the test and were less worried about the results or the process. Therefore, based on previous evidence, providing clear information and adequate support when individuals are first invited to participate in CRC screening may help improve their screening experience and encourage future participation. While the present study focused on barriers related to participation in CRC screening, the effectiveness of screening programmes also depends on timely diagnostic follow-up after a positive screening result. Barriers such as limited colonoscopy availability, prolonged waiting times, and incomplete follow-up may affect the overall effectiveness of CRC screening programmes, particularly in opportunistic

public sector settings. These factors were beyond the scope of the present study and warrant further investigation in future research evaluating the entire CRC screening pathway.

The significance of perceived test efficacy in shaping health behaviour is emphasised in our study, in line with earlier research that emphasises the part perceived benefits play in screening uptake.[25] Internal motivation and expectations of favourable results are also important factors that influence CRC screening participation.[25]

The process of identifying these barriers among clinic-attending patients was predicated on the assumption that they were aware of the availability of screening tests and knew where to access them. Implementing a more proactive strategy, such as establishing information booths or using visual content on social media platforms, may be more effective in increasing awareness and promoting screening uptake among the older population. The fundamental challenge underpinning the effort to enhance CRC screening uptake by the targeted population is the widespread lack of awareness about the risk factors of CRC and the fact that it can remain asymptomatic until advanced stages. In Malaysia, March is designated as "CRC Awareness Month" to implement focused and coordinated educational campaigns, aligned with the national strategic plan, aimed at increasing public awareness and encouraging early screening. There is limited research on colorectal cancer screening in Malaysia, so the findings from this study offer important insights that could help improve screening rates across various population groups. This, in turn, supports national initiatives aimed at lowering colorectal cancer mortality.

LIMITATIONS

Since this is a cross-sectional study, the results cannot establish cause-and-effect relationships, nor can they track changes in behavior over time. In addition, this study was conducted at a single health clinic in Seremban. Participants were recruited exclusively from clinic attendees, who may be more health-conscious and more engaged with healthcare services than the general population. The use of purposive sampling and a single-centre study design may limit the generalizability of the findings to the broader population. In addition, the study may underestimate barriers experienced by individuals who are less likely to access or attend healthcare facilities.

CONCLUSION

This study highlights that psychological and informational barrier, such as fear, low confidence, and lack of knowledge, are the primary obstacles to CRC screening among adults aged 50 and above attending Seremban Health Clinic. The findings underscore the importance of proactive and sustained efforts to increase awareness, correct misconceptions, and normalize CRC screening as a routine part of preventive healthcare. Ultimately, fostering a culture of early detection through informed and confident participation is essential in reducing the burden of colorectal cancer in Malaysia.

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ORIGINAL ARTICLE

Medical negligence adjudication in Malaysia: A retrospective analysis of law cases in 2025

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ABSTRACT

Introduction: Medical negligence litigation in Malaysia is rising, making judicial decisions vital for defining contemporary duties of care and clinical governance. This study presents a retrospective document-based analysis of medicolegal cases adjudicated in 2025 to systematically identify and categorise the core clinical and systemic issues driving liability.

Materials and Methods: A retrospective document search was conducted on reported Malaysian medical negligence judgments published between January 1 and December 31, 2025, across the LexisNexis and Current Law Journal databases. From 51 initial records, 22 non-relevant disputes were excluded, yielding 29 clinically relevant medicolegal cases for analysis. A descriptive, quantitative and demographic profiling of the dataset was conducted to map the structural landscape of the litigation. To systematically analyse the evolving standards of medical accountability and clinical governance in Malaysia, a retrospective, document-based thematic analysis using a structured three-stage qualitative coding framework was conducted.

Results: Litigation was heavily concentrated in the High Court (22 cases), clustered in urban centres, and dominated by public hospitals (15 cases). Surgical domains were the most frequently litigated: Orthopaedics (10 cases), Obstetrics & Gynaecology (8 cases), and Other Surgical Specialities (6 cases). The qualitative analysis synthesised five dominant areas of judicial scrutiny: 1) Negligence in Timely Intervention and Diagnosis, 2) Breach of Informed Consent and Patient Autonomy, 3) Medical Records and Documentation Evidence, 4) Systemic Liability, and 5) Legal and Procedural Issues. Liability was consistently driven by critical delays in time-sensitive interventions, such as emergency Caesarean sections resulting in severe birth injuries and delayed vascular treatment leading to limb loss. Diagnostic failures, including the inability to order essential radiological investigations or misdiagnosing acute conditions like Deep Vein Thrombosis and fatal septic shock, were also key findings. Furthermore, the judiciary showed a consistent judicial emphasis on protecting patient autonomy, penalising doctors for insufficient disclosure of material risks and failure to advise on alternative treatments. Judicial severity was notably demonstrated against healthcare professionals operating beyond their credentialed boundaries, confirming that practice must strictly adhere to regulatory standards. A significant trend identified is the increased focus on corporate accountability, with hospitals being held corporately liable under the principle of non-delegable duty for systemic failures. Inadequate referral systems and a lack of qualified standby personnel led to hospital liability even where individual treating doctors were absolved of direct clinical negligence. Additionally, the integrity of medical records proved pivotal, as issues of tampering, fabrication, and post-incident insertion of notes were treated as severe aggravating factors that profoundly undermined the defence's credibility.

Conclusion: The 2025 retrospective case law analysis indicates that the Malaysian medicolegal environment is evolving toward a standard of total accountability. The courts demand strict adherence to clinical best practices, respect for patient autonomy, robust institutional systems, and honest professional conduct. For healthcare professionals and institutions, mitigating legal risk now necessitates not just technical competence, but also absolute integrity in documentation and unwavering professional transparency.

KEYWORDS:
Negligence, malpractice, jurisprudence, clinical governance, informed consent

INTRODUCTION

Medical negligence claims are of serious global concern in Malaysia, increasing pressure on healthcare providers to maintain high standards of care.[1-2] Judicial decisions serve as vital markers that define duties of care, clinical governance, and professional accountability. The legal landscape depends heavily on complex judicial tests, such as the transition from the traditional Bolam test to the Foo Fio Na standard and relies fundamentally on expert evidence.[2-3] Systematic analysis of recent outcomes is therefore essential for risk management, legal reform, and professional education.

The historical evolution of Malaysian medical negligence jurisprudence began with Chin Keow v Kerajaan Malaysia.[4] Over subsequent decades, claims have steadily increased due to heightened public awareness of patient rights, expanding medical specialisation, and growing healthcare complexity.

Historically, judicial assessment was grounded in the Bolam principle, which defines negligence as a failure to act in accordance with the standards of reasonably competent

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medical men at the time.[5] This benchmark recognises that medicine is not an exact science. Similarly, Hunter v Hanley clarified that negligence only arises when a clinician exhibits a failure that "no doctor of ordinary skill would be guilty of acting with ordinary care".[6] The law demands conduct consistent with a reasonably competent practitioner, not perfection.

This reluctance to equate adverse outcomes with negligence is reflected in the Malaysian case of Payremalu Veerappan v Dr Amarjeet Kaur & Ors.[7] Referencing M Shoba v Dr Mrs Rajakumari Unnithan case, the court emphasised that "a doctor is never presumed to be infallible" and negligence cannot be inferred merely because treatment goes wrong. A positive finding that the practitioner fell below ordinary standards is required. This principle is vital when analysing rare complications, high-risk surgeries, or rapidly evolving emergencies, demonstrating that Malaysian courts remain cautious against imposing retrospective perfectionism.

This paper undertakes a retrospective document-based analysis of Malaysian medical negligence cases adjudicated in 2025. The primary objective is to identify, synthesise, and categorise prevailing issues and judicial trends by examining clinical circumstances, legal debates, liability findings, and damages. This analysis provides a vital snapshot of the evolving medicolegal environment, offering essential insights for clinicians, administrators, and legal professionals to mitigate risk and ensure compliance with contemporary standards of care.

MATERIALS AND METHODS

To systematically examine the evolving standards of medical accountability and clinical governance in Malaysia, this study employed a retrospective document-based analysis, a rigorous qualitative method involving the systematic evaluation of textual records to develop empirical knowledge. A comprehensive electronic search was conducted across the LexisNexis and Current Law Journal (CLJ) databases, which house authoritative records from all levels of the Malaysian judiciary, using the explicit keyword phrase "medical negligence" OR "medical malpractice" OR "clinical negligence" for cases published or decided between January 1 and December 31, 2025. This initial search yielded 51 raw records, which were then subjected to a strict multi-stage screening process. Inclusion criteria required cases from any level of the Malaysian judiciary involving a patient against a healthcare practitioner or assistant across any delivery site, including public hospitals, private centres, and standalone clinics. Conversely, exclusion criteria eliminated non-medical negligence, purely commercial or employment disputes, road traffic accidents lacking central medical mismanagement, and out-of-court settlements. Following screening, 22 cases were excluded, resulting in a final sample of 29 cases. For each selected case, a structured data extraction protocol recorded baseline descriptive variables, including jurisdictional level, geographic registry distribution, healthcare sector, and the specific clinical speciality under scrutiny. The core textual data within the written judgments, comprising the judges' ratios decidendi, obiter dicta, cited expert testimonies, and established case facts, were then analysed.

First, open coding was conducted to isolate and label specific clinical failures and legal disputes. Next, axial coding cross-examined these raw codes, mapping their conceptual relationships and clustering them into broader categories based on shared clinical or legal vulnerabilities. Data analysis followed a thematic qualitative approach combining inductive coding with deductive categorisation. The initial coding framework was mapped deductively into established medicolegal and ethical domains (e.g., duty of care in intervention, informed consent, documentation, systemic liability, and procedural/legal issues). Using these standard ethical and legal frameworks ensured a rigorous, domain-appropriate analysis tailored to judicial case law review. Finally, selective coding integrated and refined these categories into five distinct, overarching thematic domains that encapsulate the primary drivers of contemporary Malaysian medicolegal liability. This comprehensive approach ensured the study's conclusions were grounded entirely in objective legal texts, providing a transparent, rigorous, and reproducible framework for evaluating modern healthcare accountability.

RESULTS

Demographic

The systematic database search identified 29 medical negligence cases in Malaysia meeting the inclusion criteria for 2025. A descriptive baseline profiling was performed to map out the structural and clinical characteristics of the litigation dataset. As comprehensively detailed in Table I, litigation was heavily concentrated within the High Court's jurisdiction (n = 22), with the remaining 5 in the Court of Appeal and another two in the Session Court, and geographically clustered in the major urban centres of the Klang Valley (Kuala Lumpur and Shah Alam) and Ipoh. Public sector hospitals accounted for more claims (n = 15), followed by private facilities (n = 13). The patient cohort primarily comprised adults, though key vulnerable populations, including newborns (n = 4) and children (n = 3), were represented. Surgical-based domains emerged as the most frequently litigated sectors, led by Orthopaedics (n = 10), Obstetrics & Gynaecology (n = 8), and Other Surgical Specialities (n = 6). Notably, several cases overlap; this frequently manifested as clinical boundary intersections between orthopaedics and other surgical subspecialties (spine and vascular surgery), and O&G and paediatrics specialities.

[Table I: Demographic and Legal Profile of Included Medical Negligence Judgments (N = 29)]

Key Thematic Findings

Thematic analysis of the 29 selected cases identified five major themes. Refer to Table II for case summary and details.

[Table II: Summary of 2025 Medical Negligence Cases in Malaysia according to Key Issues, Decisions, and Damages]

Under the first theme, Negligence in Timely Intervention and Diagnosis, delays in emergency intervention were prominently identified in obstetric and vascular management. Delayed emergency Caesarean sections resulting in severe birth injuries were litigated in A (a child...)[8] and Nitin Sharma[21], while vascular-related delays leading to

Table I: Demographic and legal profile of included medical negligence judgments (N = 29)

No.	Demographic	Classification	Frequency (n)	Case Citation
1	Judicial Jurisdiction	Session Court	2	35, 36
		High Court	22	8-29
		Court of Appeal	5	30-34
		Federal Court	0	-
2	Geographic Registry	Kuala Lumpur	5	8,11,16,21,25
		Shah Alam	5	14,15,23,24,27
		Ipoh	4	17, 18, 26, 31
		Seremban	2	12,23
		Georgetown	1	9
		Taiping	1	10
		Penang	1	19
		Alor Setar	1	20
		Kota Bahru	1	13
		Melaka	1	28
3	Health Sector	Public Hospital	15	8, 10, 12–14, 16, 17, 19–21, 23, 24, 26, 29, 32
		Private Hospital	10	19, 27, 28, 30, 31, 33, 34, 36
		Private Outpatient Clinics	3	9,22,35
		University Hospital	1	25
4	Patient Age Cohort	Adult	22	Remaining cases
		Child	4	8, 20, 21, 33
		Newborn	3	16, 29, 36
5	Main Speciality Involved	Orthopaedics	10	9, 12, 14, 17, 19, 23, 24, 27, 28, 34
		Obstetrics & Gynaecology	8	8, 11, 12, 20, 21, 25, 32, 33
		Other Surgical Specialities	6	10, 13, 15, 16, 19, 25
		Paediatrics	4	20, 21, 29, 36
		Emergency Medicine	1	30
		Otorhinolaryngology	1	31
		Anaesthesiology	1	14
		Ophthalmology	1	18
		General Practice	1	22
		Aesthetic Medicine	1	35
6	Specialty Distribution	Multidisciplinary Overlap	9	12, 14, 16, 17, 19, 20, 21, 25, 26
		Single Speciality Case	20	Remaining cases

*Note: Frequencies across clinical specialities exceed N = 29 due to multidisciplinary overlap in several cases.

ischemic gangrene and amputation were evaluated in Fairuz Fahmy[12] and Wee You Kheong.[28] Diagnostic failures were also recurring, such as the failure to perform radiological investigations for a spinal giant cell tumour in Daniel Lee Eng Wern,[9] alongside missed diagnoses of vascular injury in Wee You Kheong,[28] Deep Vein Thrombosis in Thavani a/p Kaliaperummal,[26] and septic shock in Zuasnita bt Baharudin.[29] Substandard perioperative management was further identified, including unmanaged postoperative ischemia resulting in amputation[14], negligent peripheral administration of inotropes,[16] and premature sinus surgery.[31] Conversely, Tan Sri Datuk Seri Mohd Hussein case saw no negligence found for a rare arthroscopic vascular complication.[34]

The second theme is Breach of Informed Consent and Patient Autonomy. Insufficient disclosure of material risks, alternatives, or conservative treatment pathways was scrutinised in Dr Chandran a/l Gnanappah,[31] Evelyn Sharmini,[11] and Tan Sri Datuk Seri Mohd Hussein,[34] whereas Siti Arbaiyah bt Umar[25] was dismissed due to adequate disclosure. This theme also captured practitioners operating beyond their credentialed scope, including a general practitioner using unapproved filler substances[35] and a gynaecologist performing bowel repair.[11]

The third theme is Medical Records and Documentation Evidence. Allegations of altered or post-incident inserted records arose in Loganathan a/l Thiagarajan[18] and Evelyn Sharmini,[11] while the suppression or total absence of evidence was noted in Nitin Sharma[21] and Muhammad Aiman bin Mohd Hisham.[20] Documentation and system-related deficiencies were similarly central to Nur Fuziatun bt Mohd Fadzli[33] and Mohammad Nabill Sajid.[19]

Systemic liability formed the fourth theme. Nur Fuziatun involved hospital liability stemming from inadequate referral networks and absent standby personnel.[33] Dr Chandran a/l Gnanappah[31] addressed corporate liability alongside indemnity against the doctor, and A (a child...)[8] scrutinised institutional compliance with Decision-to-Delivery Interval (DDI) guidelines.

The final theme encompassed legal and procedural issues. Claims were dismissed due to statutory limitation periods under the Public Authorities Protection Act 1948,[13] while contributory negligence was argued in Daniel Lee Eng Wern[9] and Bukit Tinggi Hospital.[30] Lastly, substantial aggravated and exemplary damages were awarded for egregious misconduct in Loganathan,[18] Thavani,[26] Hasmani,[14] and Rafianee.[35]

Table II: Summary of 2025 medical negligence cases in malaysia: Key issues, decisions, and damages

No	Case Name (Date of Judgment)	Date of incident	Summary of Case	Issues	Liability	Damages Awarded (RM)
1	A (a child suing through his mother and litigation representative, Noor Shahizan bt Ajmi) v Kerajaan Malaysia & Ors[8] (6 May 2025)	11 Feb 2010 (filed 11 Jan 2023)	Plaintiff suffered severe brain damage (cerebral palsy) due to a delay in performing an emergency caesarean section. The court found negligence in the delay.	The court held that the 30-minute decision-to-delivery interval is a guideline, not a strict rule, and is contingent on hospital feasibility. Aggravated damages were denied due to the plaintiff's 12-year delay in filing the suit, noting the defendants did not pursue a limitation defence. Lastly, the court determined the plaintiff's maximum life expectancy as 29 years, rejecting the claimed 44 years.	Yes (against D1, D3, D4).	RM2,286,490.00 (Total)(Includes Gen: RM300k, Special: RM458k, Future: RM1.47m).
2	Bukit Tinggi Hospital Sdn Bhd & Anor v Navin Sharma a/l Karam Chand[30] (23 September 2025)	13 May 2019	Appeal on quantum for a patient's death (septicaemia/ruptured cyst).	- contributory negligence of the patient (deceased) & husband in AOR discharge. - The appellants argued that the deceased's estate could not claim for aggravated damages as that was a claim that was personal to a 'living plaintiff'.	Yes (Liability upheld) 6.	RM173,000.00 (approx.)(Reduced from ~RM1.08m. P&S: RM50k, Special: ~RM33k, Costs: RM75k).
3	Daniel Lee Eng Wern v Aaron Lim Boon Keng[9] (19 February 2025)	19 & 26 February 2019, 3 & 13 December 2019 (Clinic visits), 11 Jan 2020 (fracture diagnosis), 14 Jan 2020 (tumour diagnosis)	An orthopaedic surgeon failed to order appropriate investigations for persistent back pain, delaying diagnosis of a giant cell tumour on the spine.	- Failure to conduct a proper physical examination on the patient's spine led to failure to diagnose the tumour after several visits to the clinic -There is no revision of the provisional diagnosis conducted by the Defendant on pt repeated visits & he failed to provide a conclusive diagnosis - the injuries suffered and/or losses incurred by the Plaintiff were caused by or substantially contributed to by the negligence of the Plaintiff himself (refusal for MRI & failure to come to appointments)	Yes (75% liable; 25% contrib. neg.).	RM126,204.23
4	Dato Dr Gengatharan @ Jeganathan s/o Venkatesan v Dr Shanker Sathappan & Anor[10] (25 December 2025)	19/12/2014 (First admission) 8/1/2015 (transfer hospital) 10/1/2015 (Fall incident)	Claim by the husband of a deceased patient alleging she died after falling off a hospital bed post-surgery. The court found no negligence in management.	The court examined whether the patient fell from her hospital bed due to the defendants' negligence. Additionally, the plaintiff alleged that IV Mannitol and Phenytoin were administered without proper consent, causing the confusion and disorientation that ultimately led to the fall	No (Dismissed).	Nil (Costs RM50k to each Defendant).
5	Dr Chandran a/l Gnanappah v Gan See Joe[31] (19 May 2025)	27 March 2014	The patient died after sinus surgery. The doctor proceeded prematurely without waiting for the antibiotics to work. The hospital was liable for a non-delegable duty.	-failure to provide informed consent prior to surgery(advice) & perform surgery which is not indicated at that time (failure to treat). -adjustment of indemnity between doctor and hospital.	Yes (D1 liable; D2 liable but indemnified).	~RM900,000+(Gen: RM100k, Loss of Contrib: RM288k, Special: RM143k, Aggravated: RM350k).
6	Dr Jerilee Mariam Khong & Ors v Yusnita bt Johari3[2] (30 July 2025)	11/11/2013 (referred to hospital) 12/12/2013 (admitted for delivery) High Court judgment (15/4/2021)	The plaintiff suffered severe and irreversible brain damage secondary to amniotic fluid embolism following an emergency Caesarean section.	The main issues determined in this case were whether the plaintiff's pre-existing health condition triggered the "Egg-Shell Skull" rule affecting the defendants' liability, and whether the trial court made factual errors in finding certain medical staff liable for negligence that materially contributed to the plaintiff's brain damage. The Court of Appeal upheld the liability of the hospital and specific medical staff while dismissing claims against several other doctors, and significantly reduced the overall quantum of damages awarded	Yes (D2, D3, D7-D17).	RM585,829.60 (approx.) (Gen: RM400k, Special: ~RM34k, Future care awards varied).

Table II: Summary of 2025 medical negligence cases in malaysia: Key issues, decisions, and damages

No	Case Name (Date of Judgment)	Date of incident	Summary of Case	Issues	Liability	Damages Awarded (RM)
7	Evelyn Sharmini a/p Mariasoosay Nathan v Dr Yogaraj Ramanathan & Anor1[1] (21 November 2025)	10 July 2018	Gynaecologist liable for bowel perforations during surgery and failure to advise on conservative options. Hospital not vicariously liable.	- failure to advise (informed consent) & treat (complications, bowel injuries) - D1 undertook bowel repair, though did not credential to perform it. - documentation of outpatient notes - appears to have been inserted later.	Yes	RM967,710.40(Gen: RM420k, Aggravated: RM50k, Future: RM121k, Costs: RM200k).
8	Fairuz Fahmy bin Harun lwn Sivanathan a/l Jeyaramu & Anor[12] (23 December 2025)	8 December 2017	Defendant in a road accident suit brought 3rd party proceedings against the hospital for the delay in vascular treatment leading to amputation.	- whether the delay in referring to the vascular hospital was intentional, leading to negligence.	No (3rd Party Claim dismissed).	Nil (against 3rd Party).
9	Hamzan bt Hamzah v Dr Ahmad Zul Fikri B Mohamad & Ors[13] (7 August 2025)	15 May 2021 (admit), 3 August 2022 (final treatment received), 2 August 2025 (cause of action ended)	Negligence claim struck out as time-barred under the Public Authorities Protection Act 1948.	- Plaintiff did not name any doctors in the suit -exceeded the limitation period of 36 months	No.	Nil.
10	Hasmani bin Tahir v Kerajaan Malaysia dan lain-lain[14] (20 December 2025)	22 January 2019 (Admission) 21 February 19 (plan for surgery), postponed to 4 Mac 19	Negligence leading to amputation of the right leg. Liability was found against the government and doctors. The court awarded exemplary damages.	- Whether the use of a tourniquet during surgery was according to the standard of care - Failure to advise: to explain complications of vascular injury - Failure to treat within golden hour (6 hours of ischaemic time)	Yes.	RM300,000 (General) + RM300,000 (Exemplary) + Special Damages.
11	Juwariyah bt Sal Hamid @ Ahmad v Dato' Dr Shahrudin bin Mohd Dun[15] (14 April 2025)	25 May 2017 (1st surgery) 7 June (2nd surgery)	Plaintiff claimed negligence for biliary stricture following gallbladder surgery.	Whether the defendant breached the standard of care by prioritising an ERCP over an MRCP and discharging the plaintiff without a post-stent removal cholangiogram or scheduled follow-ups, the court found that stricture was a known risk and that management was proper.	No (Dismissed).	Nil (Costs RM35k).
12	Krishnasamy a/l Jayaraman & Anor v Kementerian Kesihatan Malaysia & Ors[16] (7 November 2025)	14 Jan 2019	Assessment of damages for a minor who suffered multiple amputations due to the negligent administration of inotropes. Liability conceded.	The plaintiff alleged medical negligence involving highly inconsistent diagnoses and the improper administration of inotropes through a peripheral vein, which caused severe gangrene necessitating multiple amputations. Furthermore, a breach of confidentiality occurred when doctors openly discussed the patient's unconfirmed diagnosis with relatives.	Yes (Conceded).	RM7,400,883.19(Prosthetics, future care, Gen damages, etc.).
13	L/Kpl Naraayanan Nair a/l Subramaniam v Kerajaan Malaysia & Ors17 (9 January 2025)	13 Mac 2018 (Admission), 14 Oct 2021 (Admission of liability)	Assessment of damages for arm amputation. Liability admitted. The court awarded significant aggravated damages due to the conduct.	The assessment of various heads of damages following the defendants' admission of liability for medical negligence that resulted in the amputation of the plaintiff's left arm	Yes (Admitted).	~RM2,256,981(Gen: RM150k, Aggravated: RM200k, Prosthetics: ~RM1.8m).
14	Loganathan a/l Thiagarajan v Dr Lee Mun Toong18 (28 March 2025)	6 July 2011 (Admission), 7 July 2011 (Surgery)	Ophthalmologist negligent for failing to detect a foreign body in the eye. Aggravated damages were awarded due to the fabrication of records.	The court rejected the defendant's claim that the patient refused a CT scan, citing the absence of a signed waiver and contradictory nurses' notes. Significant discrepancies also emerged regarding the injury's mechanism, and a 3cm scleral tear was only documented post-operatively	Yes.	RM1,032,870.59(Gen: RM200k, Aggravated: RM500k, Future income: ~RM253k).

Table II: Summary of 2025 medical negligence cases in malaysia: Key issues, decisions, and damages

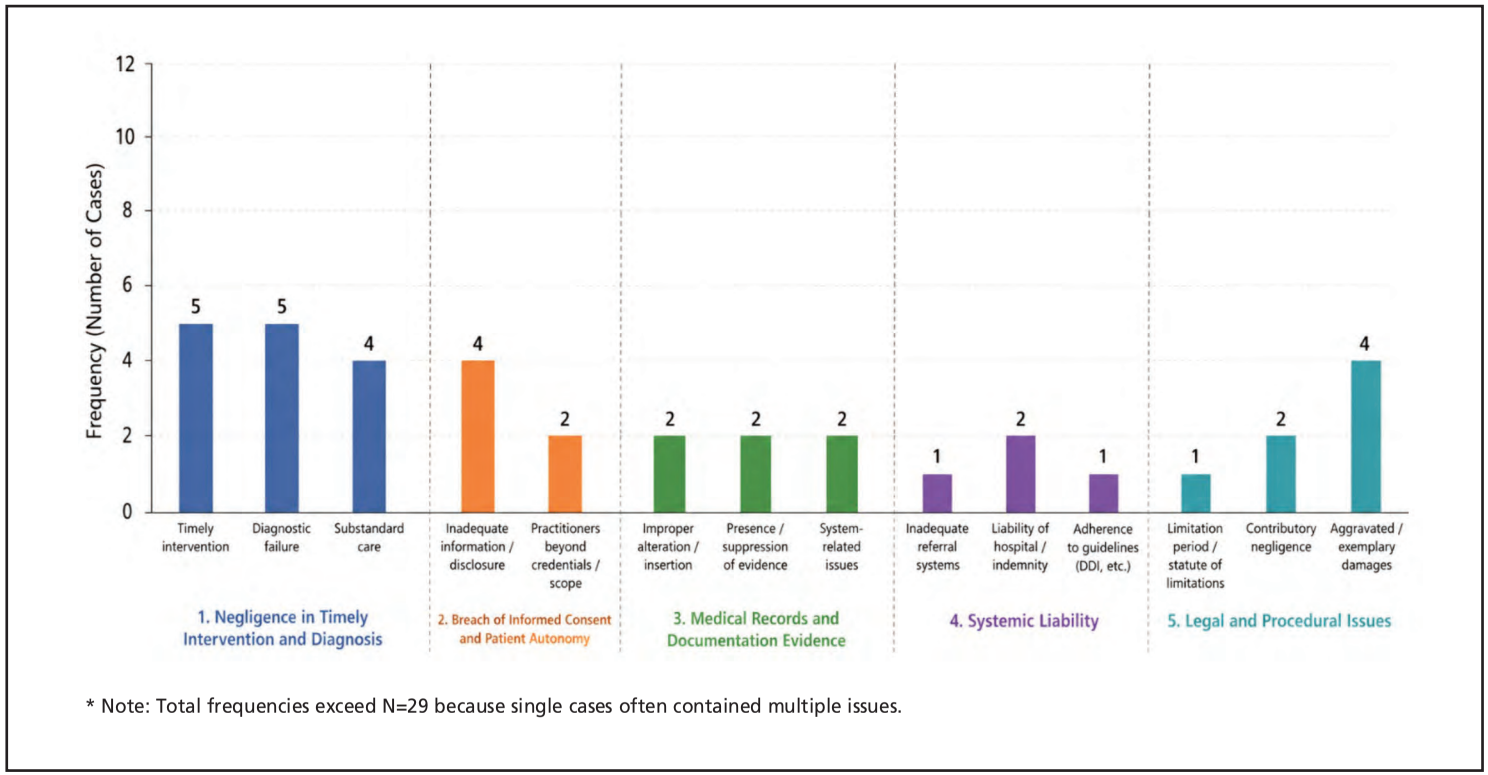
No	Case Name (Date of Judgment)	Date of incident	Summary of Case	Issues	Liability	Damages Awarded (RM)
15	Mohammad Nabill Sajid bin Mohammad Aslam Sajid v Government of Malaysia & Ors19 (22 April 2025)	11 July 2020 (Admission) 15 July 2020 (Surgery)	Claim for paralysis due to delayed spinal surgery dismissed. The court found the delay was to stabilise the patient and did not alter the outcome.	The plaintiff alleged a four-day delay in spinal decompression surgery caused his permanent paralysis. Conversely, the defendants maintained this delay was medically necessary to stabilise his severe lung and spine injuries safely. The treating specialist strongly denied claims that surgery was delayed for financial approvals, while the plaintiff further alleged incorrect documentation and refusal of neurosurgical treatment.	No (Dismissed).	Nil (Assessed at RM400k+ if liable).
16	Muhammad Aiman bin Mohd Hisham v Kerajaan Malaysia 20 (30 June 2025)	24/03/2009 (Admission), 20/03/2009 (Discharge at own risk), 31/3/2009 (Second presentation), 2/4/2009 (date of delivery)	Medical negligence suit involving a child suing through the mother.	The plaintiff failed to prove that the defendants' negligence caused the birth defect. The court highlighted alternative causes, including premature delivery, four episodes of antepartum haemorrhage, intra-uterine growth restriction, and the mother's consumption of traditional medicine. Furthermore, an adverse inference was drawn against the plaintiff for suppressing crucial prenatal records, including the "pink book."	No.	Nil (cost of RM 50,000)
17	Nitin Sharma s/o Ram Krishen v Kerajaan Malaysia & Ors 21 (3 June 2025)	31 Dec 2000 (First presented), 14 Jan 2001 (delivery date)	Plaintiff suffered cerebral palsy/Erb's palsy due to negligence at birth. Defendants failed to produce rebuttal expert evidence [66]67.	The 22-year-old plaintiff's high-risk pregnancy involved an unstable lie and cord prolapse risk. Despite recognising the need for an elective caesarean on 31 December, the defendants inexplicably delayed the delivery. Furthermore, the defendants failed to call the material treating doctors and the CT scan assessor.	Yes.	~RM5,684,991.98(Gen: RM450k, Aggravated: RM100k, Future Care: RM4m+, Costs: RM300k) 69.
18	Nur Fuziatun bt Mohd Fadzli v Gombak Medical Centre Sdn Bhd & Ors33 (12 November 2025)	17 June 2014 (delivery)	The court allowed an appeal against the hospital and Person in Charge regarding the non-delegable duty/system failure but dismissed the appeal against the delivering doctor.	The plaintiff alleged negligence in diagnosing fetal distress, performing a vacuum delivery, and lacking an adequate specialist referral system. The hospital and its person-in-charge were initially absolved because the treating doctor was found not liable. Key issues involved the person-in-charge's duty of care, delayed early-morning transfers, handwritten note discrepancies, and post-2016 specialist standby requirements	Yes.	Remitted to the High Court for assessment.
19	Punitha a/p Padathaly v Salam Alliance Sdn Bhd & Anor22 (24 November 2025)	22 June 2018 (clinic visit) 28 June 2018 (referral letter written)	Claim regarding a psychiatric referral letter issued without consent/exam. The application by the defendants to strike out the application is dismissed.	The plaintiff alleged professional negligence against the doctor for issuing a psychiatric referral letter diagnosing her with bipolar disorder without conducting any clinical examination or consultation. Furthermore, she claimed a breach of confidentiality and misuse of medical information when the doctor wrongfully disclosed this letter to her husband without her lawful authorisation.	To proceed to full trial.	To be decided.
20	Radha a/p Sekar v Pengarah Hospital Port Dickson23 (21 July 2025)	27 Nov 2017 (Admission), 14 December 2017 (Surgery for debridement)	Appeal against dismissal of the claim for the death of a patient. The High Court affirmed the lower court decision dismissing the claim.	The plaintiff failed to prove that the improper insertion of an IV drip caused the deceased's thrombophlebitis. The court found no negligent delay in the orthopaedic referral or surgical debridement, as appropriate antibiotic treatment had already commenced. Ultimately, the cause of death was sepsis with multiorgan failure exacerbated by pre-existing conditions.	No.	Nil (Costs RM10k).

Table II: Summary of 2025 medical negligence cases in malaysia: Key issues, decisions, and damages

No	Case Name (Date of Judgment)	Date of incident	Summary of Case	Issues	Liability	Damages Awarded (RM)
21	Rafianee bt A Razak v Dr Suffia Hany bt Mohamad Amin & Ors35 (29 July 2025)	26 Oct 2020 (contacted through phone), 28 October, 9 & 11 November 2020 (Surgery/procedure).	Breast filler procedure by a general practitioner using an unapproved product.	The plaintiff alleged negligence against the doctor for performing an aesthetic breast filler procedure without the mandatory Letter of Credentialing and Privileging. Furthermore, the injected filler was primarily composed of silicone, contrary to the consented 100% hyaluronic acid. Additionally, the clinic was operating illegally without the required Ministry of Health license under the applicable healthcare laws.	Yes.	~RM919,009.60(Gen: RM85k, Exemplary: RM800k, Special: RM34k).
22	Selvaraju a/l Ponniah v Pengarah Hospital Tengku Ampuan Rahimah & Ors24 (1 April 2025)	15 March 2018 (Admission), 25th March 2018 (Deceased)	Claim for death due to Fat Embolism. Alleged delay in surgery/implant application.	Whether the delay of surgery causes death (fat embolism), and whether the delay was due to the payment process for the implant.	No (Dismissed).	Nil (Costs RM10k).
23	Shahrul Izam bin Mat Desa v Dr Mohamad Shahbodin bin Sarik36 (3 March 2025)	1 April 2014	Suit regarding the death of a child from pneumonia.	Failure to prove that negligence was committed during the 4 days of treatment before transfer to the government hospital.	No (Dismissed).	Nil (Costs RM6,825).
24	Siti Arbaiyah bt Umar v UKM Kesihatan Sdn Bhd & Anor25 (13 August 2025)	31/10/2014 - first surgery 21/05/2015 - second surgery	Plaintiff alleged the surgeon failed to advise on an alternative surgical approach. The court found the plaintiff was properly advised and consented.	The plaintiff failed to prove a breach of the doctor's duty to advise on surgical risks. The court held the doctor adequately advised on the anterior approach, deemed the safest option, and reasonably relied on another specialist to advise the patient on the less common posterior approach.	No.	Nil (Costs RM38k).
25	Tan Sri Datuk Seri Mohd Hussein bin Abd Hamid v. Gleneagles Hospital (Kuala Lumpur) Sdn Bhd & Anor34 (20 June 2024)	27 December 2013 (the date the arthroscopic debridement surgery was performed)	The patient suffered a popliteal artery tear following an arthroscopic knee surgery.	Whether the surgeon was negligent in causing the popliteal artery injury during the arthroscopy and in failing to inform the patient of this specific material risk. Whether the private hospital was vicariously liable for the surgeon's negligence, and if the hospital owed and breached a non-delegable duty of care to the patient. Both the surgeon and the hospital were found liable, overturning the High Court's dismissal.	Yes (by 2-1 Court of Appeal majority).	To be assessed. The Court of Appeal remitted the case back to the High Court for the assessment of damages
26	Thavani a/p Kaliaperummal v Kerajaan Malaysia & Ors 26 (14 January 2025)	4 May 2018 (Accident), 5 July 2018 (Deceased)	Assessment of damages for death due to an undiagnosed deep-vein thrombosis.	Following the defendants' admission of liability, the primary issue determined was the assessment of various damages arising from the fatal misdiagnosis and mismanagement of the deceased's deep-vein thrombosis. The court examined whether the medical personnel's prolonged neglect warranted these compensations	Yes (Admitted).	~RM682,176.00(Gen: RM100k, Aggravated: RM500k, Dependency: RM45k).
27	Vasanthi a/p B Balakrisnan v Sunway Medical Centre Sdn Bhd 27 (23 May 2025)	27 Jan 2017	Plaintiff alleged negligence in wrist fracture surgery (implant placement). The court found treatment was within standard medical practice.	The plaintiff alleged the defendant operated only on her radius fracture and failed to disclose a concomitant ulna fracture, causing her persistent wrist pain. Ten months later, another hospital operated on the unhealed ulna. Ultimately, the court dismissed the suit, ruling that the plaintiff failed to prove the defendant was negligent in his treatment.	No (Dismissed).	Nil.

Table II: Summary of 2025 medical negligence cases in malaysia: Key issues, decisions, and damages

No	Case Name (Date of Judgment)	Date of incident	Summary of Case	Issues	Liability	Damages Awarded (RM)
28	Wee You Kheong v Hasbullah bin Azhar & Ors[28] (14 February 2025)	25 August 2015	Plaintiff suffered a severe leg injury in a road traffic accident (RTA). The 4th Defendant (Orthopaedic surgeon) was at the 3rd Defendant hospital.	The 1st and 2nd defendants were found liable for the road traffic accident, resulting in the dismissal of their third-party claim. However, the court ruled there was a break in the chain of causation regarding the plaintiff's leg amputation, attributing this specific injury entirely to the subsequent medical negligence of the 3rd and 4th defendants. It was concluded as a misdiagnosis of a vascular injury leading to compartment syndrome, causing a delay in treatment that resulted in ischemic gangrene and an above-knee amputation.	Yes (3rd & 4th Defendants liable for medical negligence; 1st & 2nd Defendants liable for the accident).	~RM782,917 (Includes Future Prosthetic: RM512k, General Damages: RM125k, Special Damages: ~RM135k). Plus ~RM101k against RTA defendants.
29	Zuasnita bt Baharudin & Anor v Government of Malaysia & Ors[29] (24 April 2025)	5 April 2018 (Admission), 21 May 2018 (Deceased)	Assessment for the death of a child (septic shock). The court awarded aggravated damages for prolonged suffering/neglect and a lack of urgency.	Delays in medical intervention: treatment administered was inadequate and lacked proper escalation to a specialist facility.	Yes.	RM822,180.00(Gen: RM300k, Aggravated: RM500k, Special: RM22k).



* Note: Total frequencies exceed N=29 because single cases often contained multiple issues.

Fig. 1: Frequency of medical negligence issues according to thematic categories in 29 selected cases

DISCUSSION

An important methodological observation is that the keyword "medical negligence" captures a broader range of healthcare disputes than direct clinical malpractice alone. Of 51 initially retrieved cases, 23 were excluded because they involved insurance disputes, employment conflicts, corporate litigation, product liability, and regulatory issues rather than negligent patient care. This demonstrates the value of using a broader search term initially to avoid prematurely excluding relevant medicolegal cases. The findings also illustrate how modern litigation extends beyond bedside care into wider issues involving healthcare systems, manufacturers, and medical technology. This is reflected in cases like Johnson & Johnson v Vijayakumar, which concerned liability from a defective medical implant, shifting focus to product safety and manufacturer responsibility.[37]

Continuing the analysis of administrative oversight, Ramani a/p Visvanathan involved a judicial review against the Malaysian Medical Council (MMC) regarding disciplinary proceedings, indicating that professional negligence can be contested through administrative law.[38] While these cases were excluded from the final clinical negligence analysis, their initial retrieval indicates that medicolegal risk encompasses commercial, administrative, and regulatory compliance, necessitating a holistic approach to risk management.

Surgical specialities such as orthopaedics, neurosurgery, vascular surgery, and O&G represented the most frequently litigated domains, a pattern consistent with international data. Steele et al. (2015), analysing United Kingdom National Health Service Litigation Authority (NHSLA) data, identified 617 neurosurgical claims, with 46% being successful, totalling a litigation burden of £67.4 million.[39] Similarly, Li et al. reported that orthopaedics and O&G accounted for 11.3% and 10.0% of malpractice claims in Chinese tertiary hospitals, respectively.[40] The present findings challenge the perception that O&G exclusively dominates disputes in Malaysian government hospitals. Although obstetric litigation remains prominent, the highest damages awarded in the 2025 cases were associated with surgical specialities due to the long-term financial implications of severe surgical injuries, particularly limb loss requiring lifelong prosthetic replacements and revisions.

The number of defendants differed remarkably between public and private hospital cases. For example, the Muhammad Aiman,[20] Nitin Sharma,[21] and Nur Fuziatun[33] public hospital cases involved more than 30 defendants, including house officers, medical officers, registrars, consultants, administrators, and government entities. This contrasts with private litigation, which commonly involves fewer individually named practitioners or specialist teams. This discrepancy reflects differing organisational structures. In public hospitals, patient management involves multiple clinical teams across different specialities and levels of seniority. Conversely, private hospital consultants often function under an "independent contractor" model. The increased number of defendants in public-sector litigation underscores the complexity of assigning accountability within highly layered systems. Many disputes arose from breakdowns in shared responsibility, supervision, escalation pathways, and institutional communication across multiple clinical tiers. While multidisciplinary management theoretically strengthens patient care, fragmented responsibility within large healthcare systems may create ambiguity in decision ownership and delay decisive intervention.

Negligence in Timely Intervention and Diagnosis

This observation is reflected in the broader thematic findings of the present study, where medical negligence litigation remained heavily centred on failures involving timely intervention, diagnostic judgment, and perioperative clinical management. Across multiple cases, liability frequently arose not merely from rare complications but from delays in escalation, inadequate reassessment, failure to investigate evolving symptoms, and breakdowns in clinical decision-making during time-sensitive situations. The courts consistently treated delays in intervention seriously where they resulted in irreversible neurological injury, limb loss, or death. The courts consistently treated delays in intervention seriously where they resulted in irreversible neurological injury, limb loss, or death.

A recurring pattern involved emergency and acute care settings where deterioration required urgent intervention within a limited therapeutic window. In obstetric litigation, delays in performing emergency Caesarean Sections in A (a child...)8 and Nitin Sharma[21] resulted in severe hypoxic injury and cerebral palsy. Similarly, in vascular and postoperative settings, the courts scrutinised whether clinicians acted promptly once signs of ischaemia, vascular compromise, or deterioration became apparent. Wee You Kheong illustrates the compounded consequences of delayed intervention and diagnostic error, where misdiagnosis of a vascular injury as compartment syndrome ultimately resulted in ischemic gangrene and above-knee amputation.[28] The analysis suggests that the judiciary increasingly recognises the practical importance of the "golden hour" principle in emergency medicine, namely the critical therapeutic window during which rapid assessment, diagnosis, escalation, and intervention are necessary to prevent irreversible physiological damage. In many acute conditions, such as fetal distress, vascular compromise, sepsis, ischemia, or major trauma, delays beyond this period may transform a potentially reversible condition into permanent disability, organ failure, limb loss, or death. Rather than viewing delay as a secondary issue, the findings demonstrate that courts increasingly regard failure to intervene within this critical period as a direct breach of the standard of care where earlier action could reasonably have altered the clinical outcome. The significance of the "golden hour" therefore lies not merely in speed alone, but in the expectation that healthcare systems and clinicians must recognise deterioration early, communicate effectively, escalate promptly, and initiate decisive management before the opportunity for meaningful recovery is lost.

The cases also demonstrate that diagnostic reasoning remains central to the professional duty of care. Several judgments involved failures to pursue appropriate investigations, reconsider provisional diagnoses, or

adequately interpret persistent clinical signs. In Daniel Lee Eng Wern,[9] the orthopaedic surgeon's failure to order radiological imaging despite repeated complaints of back pain delayed the diagnosis of a giant cell tumour of the spine. Similar issues arose in Thavani a/p Kaliaperummal[26] involving undiagnosed DVT, and Zuasnita bt Baharudin,[29] where septic shock was not recognised in time. Collectively, these cases indicate that courts increasingly view diagnosis as a continuous and dynamic clinical obligation rather than a single isolated event. Clinicians are expected not only to initiate treatment but also to continuously reassess the patient's evolving condition, revisit differential diagnoses, and escalate investigations when the clinical trajectory deviates from expectations.

The findings further suggest that contemporary negligence litigation increasingly scrutinises perioperative judgment and postoperative monitoring. In Hasmani bin Tahir,[14] failure to recognise and manage postoperative ischaemia within the accepted six-hour therapeutic window directly resulted in limb amputation. In Krishnasamy a/l Jayaraman, negligent administration of inotropes through a peripheral line caused multiple amputations in a minor.[16] Similarly, in Dr Chandran a/l Gnanappah, liability arose from proceeding with sinus surgery before adequate infection control had been achieved.[31] These cases demonstrate that courts are not merely examining technical procedural performance, but also evaluating the broader clinical judgment surrounding the timing, justification, and safety of surgical intervention and postoperative care.

At the same time, the findings demonstrate that Malaysian courts continue to distinguish between genuine negligence and recognised medical complications. In Tan Sri Datuk Seri Mohd Hussein, the Court of Appeal accepted expert evidence that the popliteal artery injury sustained during arthroscopy was an exceptionally rare avulsion injury that could occur despite the exercise of reasonable care and skill.[34] The court therefore rejected allegations that excessive force had been used and found no negligence in the diagnosis, surgical execution, or postoperative management, particularly given the prompt referral to vascular specialists once the complication was identified. The decision reinforces the principle that adverse outcomes alone do not establish negligence. Nevertheless, the surgeon was ultimately found liable for failure to adequately advise the patient regarding material risks, illustrating the judiciary's increasing separation between technical competence and the independent duty to secure informed patient autonomy.

Breach of Informed Consent and Patient Autonomy

The findings indicate a growing judicial emphasis on informed consent and patient autonomy within Malaysian medical negligence litigation. Liability increasingly extends beyond technical treatment errors to include failures in disclosure, counselling, and patient communication. Several cases demonstrate that courts now expect clinicians to provide patients with sufficient information regarding material risks, alternative treatments, and conservative management options before obtaining consent for intervention.

In Dr Chandran a/l Gnanappah, the lack of adequate informed consent was considered alongside the doctor's decision to proceed prematurely with surgery.[31] Similarly, in Evelyn Sharmini, the court criticised the failure to advise the patient regarding conservative management alternatives prior to surgery.[11] These cases suggest that courts increasingly regard disclosure obligations as part of the substantive standard of care rather than a purely administrative formality.

The Court of Appeal decision in Tan Sri Datuk Seri Mohd Hussein further illustrates the evolving judicial approach toward material risk disclosure.[34] The majority held that the surgeon failed to warn the patient about the specific risk of popliteal artery injury prior to arthroscopy, thereby depriving the patient of the opportunity to make a fully informed decision. However, the dissenting judgment by Azimah Omar demonstrates the continuing legal tension regarding the scope of disclosure obligations for exceptionally rare complications. Her Ladyship opined that the rare and unforeseeable vascular injury was not sufficiently material to require disclosure and further argued that such a warning would not have altered the patient's decision to proceed with surgery. The differing judicial approaches reflect the continuing evolution of Malaysian informed consent jurisprudence from traditional professional-centred disclosure toward a more autonomy-based standard.

The analysis also demonstrates that courts are prepared to reject informed consent claims where adequate counselling is established through evidence. In Siti Arbaiyah bt Umar, the court dismissed allegations that alternative approaches had not been discussed after finding that the doctor had adequately advised the patient regarding the selected surgical plan.[25] The contrasting outcomes across these cases suggest that liability in informed consent disputes frequently turns on the adequacy, materiality, and documentation of the advice provided rather than merely the occurrence of complications themselves.

Another significant issue identified involves practitioners operating beyond their credentials, training, or regulatory approval. In Rafianee bt A Razak v Dr Suffia Hany, a general practitioner performed breast filler procedures using unapproved substances, raising both credentialing and regulatory concerns.[35] Likewise, in Evelyn Sharmini, the defendant gynaecologist undertook bowel repair despite lacking the appropriate credentials to perform such procedures.[11] These findings indicate that courts increasingly view professional boundaries, credentialing, and regulatory compliance as integral components of the standard of care. Negligence, therefore, extends beyond technical incompetence to include undertaking procedures outside the practitioner's recognised expertise or authorised scope of practice.

Medical Records and Documentation Evidence

The findings demonstrate that medical records increasingly function not merely as clinical communication tools, but as central evidentiary instruments in medical negligence litigation. Across several cases, the integrity, completeness, and reliability of documentation significantly influenced judicial findings on credibility, liability, and damages.

Courts responded particularly severely to allegations involving altered or fabricated records. In Loganathan a/l Thiagarajan, the court awarded substantial aggravated damages after identifying serious concerns regarding tampering with medical records and inconsistencies in the defendant's account of events.[18] Similar concerns arose in Evelyn Sharmini, where outpatient notes appeared to have been retrospectively inserted.[11] These cases suggest that documentation irregularities are viewed not merely as administrative deficiencies, but as conduct affecting professional honesty and the integrity of the judicial process itself.

The findings also highlight the evidentiary significance of witness presentation and disclosure during litigation. In Nitin Sharma, the defence's failure to call relevant witnesses or rebuttal experts weakened its position regarding the delay in the emergency Caesarean Section.[21] Conversely, in Muhammad Aiman, although concerns were raised regarding withheld evidence, the claim nevertheless failed because causation was not established.[20] These contrasting outcomes indicate that deficiencies in documentation or evidentiary presentation alone do not automatically establish negligence unless they materially affect proof of breach or causation.

The analysis further suggests that documentation failures may also reflect broader systemic deficiencies within healthcare institutions. In Nur Fuziatun, issues relating to illegible handwriting formed part of the wider system failures identified by the court.[33] However, Mohammad Nabill Sajid demonstrates that flawed documentation does not invariably result in liability where the underlying clinical management remains justified, and causation cannot be established.[19] Overall, the findings indicate that courts increasingly regard accurate documentation as an essential component of professional accountability, continuity of care, and medicolegal defensibility.

Systemic Liability

The findings demonstrate an increasing judicial willingness to impose liability upon healthcare institutions in addition to individual clinicians. Modern medical negligence litigation in Malaysia increasingly examines failures involving systems of care, institutional preparedness, staffing arrangements, escalation pathways, and multidisciplinary coordination rather than focusing solely on isolated acts of individual negligence.

A central issue identified is the concept of non-delegable duty. In Nur Fuziatun, the hospital and Person in Charge were found liable because of system failures involving inadequate referral arrangements, lack of standby specialists, and insufficient intensive care support.[33] Importantly, liability arose despite the delivering doctor not being personally negligent. The case illustrates judicial recognition that hospitals owe independent corporate duties to ensure that appropriate systems, staffing, and facilities are available for safe patient care.

The relationship between institutional liability and individual practitioner negligence is further demonstrated in Dr Chandran a/l Gnanappah.[31] Although the hospital was held liable under a non-delegable duty, the court ultimately granted indemnity against the treating doctor because the primary negligence arose from his clinical decisions and inadequate informed consent process. This reflects the judiciary's attempt to balance institutional accountability with personal professional responsibility within modern healthcare systems.

The findings also demonstrate that courts continue to treat clinical guidelines as influential but non-binding standards. In A (a child...), the court clarified that the Decision-to-Delivery Interval (DDI) guideline for emergency Caesarean Sections was not a strict mandatory rule but a feasibility-dependent recommendation.[8] Nevertheless, liability was still imposed because the delay was not adequately justified under the circumstances. The decision illustrates that courts may permit flexibility in guideline application while still requiring clinicians and institutions to provide reasonable explanations for departures from accepted standards where adverse outcomes occur.

Legal and Procedural Issues

The findings additionally highlight several recurring procedural and legal issues influencing the outcome of medical negligence litigation, particularly limitation periods, contributory negligence, and punitive damages.

In Hamzan bt Hamzah, the claim was struck out after exceeding the limitation period prescribed under the Public Authorities Protection Act 1948, illustrating the procedural barriers faced by plaintiffs pursuing claims against government healthcare institutions.[13] The case demonstrates that even potentially arguable negligence claims may fail if statutory procedural requirements are not satisfied.

The findings also indicate that Malaysian courts remain willing to reduce liability where patient conduct contributed to the adverse outcome. In Daniel Lee Eng Wern, damages were reduced by 25% due to the plaintiff's refusal to undergo an imaging investigation and failure to attend follow-up appointments.[9] Similarly, Bukit Tinggi Hospital involved arguments relating to contributory negligence following an Against Own Risk (AOR) discharge.[30] These cases demonstrate that courts assess patient compliance and decision-making alongside professional duties when determining liability and quantum.

Finally, the analysis demonstrates a clear judicial willingness to impose substantial aggravated and exemplary damages in cases involving particularly serious professional misconduct. High aggravated damages were awarded in Loganathan a/l Thiagarajan,[18] Thavani a/p Kaliaperummal,[26] and Zuasnita bt Baharudin,[29] while exemplary damages featured prominently in Hasmani bin Tahir[14] and Rafianee bt A Razak.[35] These awards indicate that Malaysian courts increasingly utilise punitive damages not only to compensate plaintiffs, but also to condemn dishonest conduct, gross neglect, regulatory breaches, and serious departures from acceptable professional standards.

LIMITATIONS

This study has several limitations. First, relying solely on cases published in the LexisNexis and CLJ databases, retrieved using the keyword "medical negligence," inherently excludes undocumented decisions or cases catalogued under different legal terms. The sample size of 29 reflects only fully adjudicated cases published in law reports during the study period. It does not encompass the broader spectrum of medical negligence claims that were settled out of court, dismissed prior to full hearing, or managed internally through institutional or Ministry of Health grievance mechanisms. Consequently, these findings illustrate trends in judicial adjudication and legal reasoning rather than the absolute incidence or epidemiology of medical malpractice in Malaysia.

Second, restricting the analysis to the single calendar year of 2025 provides only a temporal snapshot; it reflects the year of judgment rather than the year in which the actual clinical incidents occurred, limiting real-time clinical trend analysis. Additionally, the lack of 2025 Federal Court cases leaves out recent authoritative interpretations from Malaysia's apex court.

Finally, focusing exclusively on reported judicial decisions introduces a selection bias toward high-severity, high-value, and complex litigations. The vast majority of medical errors, patient disputes, and complaints are resolved outside the formal judicial system through private negotiations, out-of-court settlements, alternative dispute resolution (ADR), or internal institutional disciplinary processes (such as by the MMC). Consequently, this study cannot analyse the frequency or nature of these lower-severity or pre-court disputes. The findings, therefore, represent the most severe legal precedents rather than the complete, everyday landscape of medical errors and healthcare disputes in Malaysia. Future research incorporating administrative data directly from hospitals and regulatory bodies is recommended to capture a comprehensive, system-wide picture. To establish broader longitudinal shifts in judicial attitudes toward patient rights, future studies should conduct multi-year comparative analyses of case law and integrate administrative data from health authorities and institutional risk management registries.

CONCLUSION

This study maps the contemporary 2025 Malaysian legal landscape of medical negligence, establishing a sophisticated judicial standard that demands technical proficiency, system resilience, and absolute integrity.

At the core of judicial scrutiny are critical delays in time-sensitive interventions and diagnostic failures regarding acute conditions. These issues represent primary drivers of liability when resulting in catastrophic harm. Furthermore, the judiciary showed a judicial emphasis on protecting patient autonomy and informed consent, penalising practitioners for inadequate risk disclosure, withholding information on conservative alternatives, and practising beyond credentialed or regulatory boundaries.

The most significant shift identified is the increased focus on hospital systemic liability and documentation integrity. Under the principle of non-delegable duty, hospitals face corporate liability for operational failures, such as inadequate referral networks or a lack of qualified standby personnel, even when individual doctors are absolved. Crucially, the integrity of medical records proved pivotal; issues of tampering, fabrication, or post-incident note insertions were treated as severe aggravating factors that profoundly undermined defence credibility.

In conclusion, the 2025 case law indicates an evolution toward total accountability. The courts demand adherence to clinical best practices, respect for patient autonomy, auditable institutional systems, and honest conduct. For healthcare professionals and institutions, preventing negligence requires strict clinical standards, but mitigating legal risk demands absolute transparency and documentation integrity.

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Handheld echocardiography for rural cardiac triage in primary care: A feasibility and diagnostic agreement study of a task-shifting model with remote cardiologist validation

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ABSTRACT

Introduction: Access to formal echocardiography is often delayed in geographically remote settings. This study evaluated the feasibility, image quality and diagnostic agreement of focused handheld echocardiography performed by a trained Family Medicine Specialist (FMS) in a rural Malaysian clinic with asynchronous cardiologist validation.

Materials and Methods: We conducted a retrospective observational study of 41 adult patients who underwent focused handheld echocardiography for dyspnoea or suspected cardiac symptoms at a rural primary care clinic in Sarawak, Malaysia, between 24 August 2025 and 5 February 2026. A trained FMS performed focused examinations during routine care. Stored images were reviewed asynchronously by a consultant cardiologist blinded to the FMS interpretation. We evaluated workflow feasibility, cardiologist-rated image quality and agreement for classification of left ventricular (LV) systolic function as normal or reduced.

Results: Forty-one patients were included (mean age 60.4±17.5 years; 51% male). Median scan duration was 8 minutes (range 3–14), and technical difficulties were reported in 19 examinations (46.3%). Nevertheless, all 41 stored studies contained sufficient images for cardiologist classification of LV systolic function. Endocardial border definition was rated good or fair in 87.8% of studies, whereas colour Doppler was frequently non-diagnostic. The FMS identified reduced LV systolic function in 13 patients (32%), compared with 10 patients (24%) by cardiologist review. Overall agreement was 82.9%, with Cohen's kappa 0.58. Sensitivity was 80.0%, specificity 83.9%, positive predictive value 61.5%, negative predictive value 92.9% and overall accuracy 82.9%.

Conclusion: In this rural primary care setting, focused handheld echocardiography performed by a trained FMS was feasible and showed moderate agreement with remote cardiologist interpretation for identifying reduced left ventricular systolic function. These findings support a hypothesis-generating service-delivery model in which handheld ultrasound may assist rural cardiac triage and referral prioritization, but larger multi-site studies are needed before practice-changing implementation can be recommended.

KEYWORDS:
Handheld echocardiography, Rural healthcare, Task shifting, Health service delivery, Cardiac triage

INTRODUCTION

Cardiovascular disease remains a major cause of morbidity and mortality, and timely access to cardiac imaging is central to the evaluation of symptoms such as dyspnoea, suspected heart failure, and structural heart disease.[1] Echocardiography is particularly valuable because it is non-invasive, portable relative to other imaging modalities, and capable of providing real-time assessment of cardiac structure and function.[2-3]

Despite its clinical importance, access to formal transthoracic echocardiography remains uneven. In rural and geographically isolated settings, echocardiography services are commonly concentrated in tertiary centres, creating delays in diagnosis and referral for patients who must travel long distances for specialist assessment. This access gap is especially relevant in Sarawak, where dispersed populations, difficult terrain, and long travel times can limit timely evaluation of patients presenting to primary care clinics with cardiopulmonary symptoms.[3-4]

Handheld cardiac ultrasound offers a potential service-delivery response to this problem. When used as focused cardiac ultrasound rather than comprehensive echocardiography, handheld devices may allow frontline clinicians to answer targeted clinical questions at the point of care, including whether left ventricular systolic function appears reduced or whether urgent escalation is needed. Prior studies have shown that handheld ultrasound can improve bedside cardiovascular assessment and that non-cardiologist clinicians, after focused training, may identify clinically important abnormalities with variable but sometimes acceptable accuracy.[5-12]

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Task-shifting models are particularly relevant in rural health systems, where workforce constraints and limited specialist availability require new approaches to diagnostic access. In low-resource settings, handheld echocardiography performed by non-cardiologists has been studied in screening and service-delivery roles, including rheumatic heart disease programmes and focused cardiac assessment pathways.[13-16] However, evidence from remote primary care settings remains limited, especially in Southeast Asia, and many published studies have been conducted in hospital-based or urban environments.[5-12]

Within our current practice context, rural patients with suspected cardiac disease are often assessed clinically and then referred onward for formal echocardiography if concern persists. This pathway can delay risk stratification, prolong uncertainty, and contribute to inefficient referral prioritization. We therefore implemented a focused handheld echocardiography workflow in a rural primary care clinic, supported by asynchronous cardiologist review of stored images. This approach was designed not to replace standard echocardiography, but to strengthen frontline triage in a setting where access is constrained.

This study aimed to evaluate the feasibility, image quality, and diagnostic agreement of this task-shifting model in rural Sarawak. We conceptualised the project as a hypothesis-generating implementation study: if focused handheld echocardiography can be integrated into rural primary care with acceptable performance, it may inform larger-scale research on equitable diagnostic access, rural referral systems, and service redesign.

MATERIALS AND METHODS

Study Design and Setting

This was a retrospective observational service-evaluation study of a task-shifting echocardiography workflow implemented at Klinik Kesihatan Sungai Asap, a rural primary care clinic in Sarawak, Malaysia, located approximately three hours from the nearest tertiary cardiac centre. All adult patients recorded as having undergone handheld echocardiography between 24 August 2025 and 5 February 2026 as part of routine care were included.

Training Programme

Prior to implementation of handheld echocardiography services at the clinic, a Family Medicine Specialist (FMS) underwent a structured two-week supervised echocardiography training programme at Sarawak Heart Centre, focusing on acquisition of standard parasternal and apical views, qualitative assessment of left ventricular (LV) systolic function, and recognition of major valvular abnormalities. The training programme was designed to provide competency-based acquisition of standard echocardiographic views and qualitative assessment of left ventricular systolic function, in line with recommendations for focused cardiac ultrasound training.[17]

Patient Recruitment

Adult patients presenting with dyspnoea or suspected cardiac symptoms who underwent handheld echocardiography as part of routine clinical care were included. All 41 recorded examinations during the study period were analysed, and no scanned patient was excluded. The total number of clinic attendees with these symptoms who were not selected for scanning was not captured; therefore, the proportion of all symptomatic attendees who underwent scanning could not be determined.

Echocardiography Protocol

Focused cardiac ultrasound examinations were performed using a wireless phased-array handheld ultrasound probe (VaveHealth, San Jose, CA, USA). Standard views included parasternal long-axis, parasternal short-axis, and apical four-chamber views. LV systolic function was assessed qualitatively (eyeballing method) and categorised as normal or reduced based on overall myocardial contractility across the standard views. The examinations were performed as focused cardiac ultrasound, with the primary objective of assessing LV systolic function rather than providing a comprehensive echocardiographic evaluation, in accordance with ASE recommendations.[17] Stored images were reviewed asynchronously by a single consultant cardiologist at a tertiary cardiac centre. The cardiologist was blinded to the FMS interpretation.

Image Quality Assessment

Image quality was evaluated asynchronously by a consultant cardiologist using three predefined domains: endocardial border definition, valve visualization, and colour Doppler quality. Endocardial border definition was graded as good (>95% of endocardial borders visualized), fair (70–95% visualized), poor (<70% visualized), or non-diagnostic. Valve visualization was classified as good, fair, poor, or non-diagnostic, based on the clarity and completeness of valve structure assessment. Colour Doppler quality was categorized as good, fair, poor, or non-diagnostic, depending on the ability to reliably assess flow signals. The FMS did not independently grade image quality; therefore, interobserver agreement for image-quality ratings was not assessed.

Outcome Measures

The primary outcome was the level of agreement between FMS and cardiologist in the classification of LV systolic function, categorized as normal or reduced. Secondary outcomes included scan feasibility, scan duration, technical difficulties encountered during image acquisition, and overall image quality assessment.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation or median with range. Categorical variables were presented as frequencies and percentages. Agreement between FMS and cardiologist assessment of LV systolic function was analysed using Cohen's kappa coefficient. Diagnostic performance including sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy were calculated using cardiologist interpretation as the reference standard.

Ethical Approval

Ethical approval for this study was obtained from the Medical Research and Ethics Committee, Ministry of Health Malaysia (NMRR ID-25-04126-YJM). This study was conducted in accordance with the Declaration of Helsinki.

Table I: Baseline characteristics of patients

Variable	Overall (n=41)
Age, years	60.4 ± 17.5
Male sex	21 (51%)
Systolic BP, mmHg	135 ± 27
Diastolic BP, mmHg	79 ± 16
Heart rate, bpm	88 ± 20
Respiratory rate, breaths/min	24 ± 4
Oxygen saturation (%)	93.9 (66-100)
Hypertension	24 (58%)
Diabetes mellitus	5 (12%)
Chronic kidney disease	7 (17%)
Atrial fibrillation	3 (7%)
Heart disease	6 (14%)
Chronic lung disease	10 (24%)

Table II: Scan feasibility and workflow

Parameter	Result
Scan duration, minutes	8 (3-14)
Any technical difficulty encountered	19 (46.3%)
Thick chest wall/breast tissue	8 (42.1%)
Pulmonary interference	3 (15.8%)
Technical limitation	3 (15.8%)
Tachypnoea/patient unable to cooperate	2 (10.5%)
Cause not specified by the operator	3 (15.8%)

Note: Percentages for individual technical difficulties use the 19 difficult examinations as the denominator.

Table III: Image quality assessment

Image quality parameter	Good	Fair	Poor	Non-diagnostic
Endocardial Border Definition	13(32%)	23(56%)	5(12%)	0(0%)
Valve visualization	14(34%)	13(32%)	11(27%)	3(7%)
Colour Doppler quality (n=37)a	2(5%)	0(0%)	5(13.5%)	30(81.3%)

[a] Colour Doppler assessment was performed in 37 of 41 examinations; in 4 examinations, colour Doppler was not performed.

Table IV: Diagnostic findings by FMS and Cardiologist

Findings	FMS	Cardiologist
LV systolic dysfunction	13(32%)	10 (24%)
Pericardial effusion	0(0%)	0(0%)

Table V: Agreement analysis

	Cardiologist:Normal	Cardiologist:Reduced	Total
FMS:Normal	26	2	28
FMS:Reduced	5	8	13
Total	31	10	41
Overall agreement: 82.9%			
Cohen's kappa coefficient: 0.58			

RESULTS

Baseline Characteristics

A total of 41 patients were included in the study. Mean age was 60.4 ± 17.5 years and 51% were male. Common comorbidities included: Hypertension: 58%, Chronic lung disease: 24%, Chronic kidney disease: 17%, Diabetes mellitus: 12%. Vital signs demonstrated a mean heart rate of 88 ± 20 bpm and mean systolic blood pressure of 135 ± 27 mmHg. The baseline characteristics are summarised in Table I.

Scan Feasibility

The median scan duration was 8 minutes (range: 3–14 minutes). Technical challenges were encountered in 19 scans; however, the specific cause was only documented for 16 of these examinations. The most common factors contributing to these difficulties were increased chest wall thickness or breast tissue (42.1%), pulmonary interference (15.8%), technical limitation (15.8%), and tachypnoea or reduced patient cooperation (10.5%). All 41 examinations, including those with technical difficulties, contained sufficient stored images for cardiologist classification of LV systolic function.

Details of scan duration and technical challenges are provided in Table II.

Image Quality
As shown in Table III, the endocardial border definition was rated as good or fair in 87.8% of examinations. Valve visualisation quality varied, with a minority of studies classified as non-diagnostic. Colour Doppler assessment was frequently limited due to device constraints, non-diagnostic quality was 30/37 (81.1%); among the entire cohort it was 30/41 (73.2%), with four not performed.

Diagnostic Findings
The FMS identified LV systolic dysfunction in 13 patients (32%), while cardiologist interpretation identified LV systolic dysfunction in 10 patients (24%). FMS slightly overestimated LV dysfunction compared to cardiologist interpretation. No cases of pericardial effusion were detected by either observer. The observed diagnostic findings for both assessors are outlined in Table IV.

Diagnostic Agreement
Overall agreement between FMS and cardiologist in the classification of LV systolic function was 82.9%. Interobserver agreement was moderate, with a Cohen's kappa coefficient of 0.58.

The diagnostic performance of FMS for detecting LV systolic dysfunction was as follows: sensitivity 80%, specificity 83.9%, positive predictive value 61.5%, negative predictive value 92.9%, and overall accuracy 82.9%. Table V provides the cross-tabulation and agreement analysis for LV systolic function assessment.

DISCUSSION

This study suggests that focused handheld echocardiography can be integrated into rural primary care workflow and may support frontline cardiac triage when performed by a trained FMS with remote cardiologist validation. In our setting, scans were completed in a median of 8 minutes, diagnostically usable left ventricular images were obtained in all 41 cases, and agreement with cardiologist interpretation for reduced left ventricular systolic function was moderate. Taken together, these findings support the operational feasibility of a task-shifting model in a geographically remote clinic where formal echocardiography is not readily accessible.

The moderate agreement observed in this study is broadly compatible with prior work. In the primary-care study by Nilsson et al. used a training programme comprising 20 supervised examinations and reported poor agreement for identifying reduced LVEF, with Cohen's kappa of 0.22.[12] Acheampong et al. trained two internal-medicine residents to perform 50 examinations and interpret 20 studies; final agreement for left ventricular function was 80% with kappa 0.65. Our agreement of 82.9% with kappa 0.58 after a two-week supervised programme was broadly comparable, although differences in operator background, training exposure, case mix, and reference standards limit direct comparison.[5]

The study also highlights the boundaries of handheld echocardiography in this context. Colour Doppler was frequently non-diagnostic, limiting more detailed valvular assessment and reinforcing that this focused assessment should not substitute for comprehensive echocardiography.

A normal qualitative LV systolic assessment does not exclude heart failure with preserved ejection fraction. The binary normal-versus-reduced assessment used here should therefore be considered a triage finding only and should not replace clinical assessment or comprehensive echocardiography. Formal assessment of LV ejection fraction can subsequently guide evidence-based heart failure therapy according to ejection-fraction phenotype.[18]

From a health-services perspective, the key contribution of this study is not that handheld ultrasound replaces conventional echocardiography, but that it may improve the way rural patients are triaged within existing referral systems. In current practice, patients in remote clinics are often referred on the basis of symptoms, examination findings, and clinical uncertainty alone. A focused handheld scan, even if limited in scope, may provide additional information at the first point of contact and help distinguish patients who may require expedited referral from those who can be managed locally while awaiting further assessment. This is particularly relevant in Sarawak, where distance, transport logistics, and specialist concentration in tertiary centres can create substantial barriers to timely diagnosis.

The observed negative predictive value was 92.9%; however, because this estimate was derived from a small selected cohort using cardiologist interpretation of handheld images as the reference standard, it should not be interpreted as establishing rule-out performance. Larger multi-site studies are needed before the approach can be recommended for wider service redesign, and such studies should evaluate not only diagnostic agreement but also patient-centred and system-level outcomes, including referral efficiency, time to definitive diagnosis, unnecessary transfers avoided, cost implications, and clinical outcomes after implementation.

Although equity and health-system outcomes were not measured, bringing targeted diagnostic support closer to underserved communities is conceptually aligned with Sustainable Development Goal 3 and universal health coverage.[19]

Overall, our study provides an early proof-of-concept that a rural clinic-based handheld echocardiography pathway with remote cardiologist support is feasible in the Malaysian context. The next step is not immediate widespread adoption, but pragmatic larger-scale evaluation of whether such a model can improve rural referral systems and contribute meaningfully to more equitable cardiac care.

LIMITATIONS

Several limitations should be acknowledged. First, this was a small single-site study involving a single FMS and a single reviewing cardiologist, limiting generalisability and preventing assessment of between-operator variability.

Second, patients were selected for scanning during routine care, and the total number of potentially eligible symptomatic clinic attendees was not captured, creating possible selection bias. Third, the reference standard was cardiologist interpretation of stored handheld images rather than formal standard transthoracic echocardiography. Fourth, image quality was graded only by the cardiologist, so interobserver agreement for quality could not be assessed. Fifth, the handheld platform had limited Doppler capability, restricting assessment of valvular pathology. Sixth, the cohort consisted of symptomatic patients in routine clinical practice, so the findings may not apply to screening populations. Finally, this study did not evaluate downstream service outcomes such as referral prioritization, time to formal diagnosis, patient travel burden, cost, or clinical outcomes.

CONCLUSION

Focused handheld echocardiography performed by a trained FMS in a rural primary care clinic was feasible and showed moderate agreement with remote cardiologist interpretation for identifying reduced left ventricular systolic function. The findings support a hypothesis-generating task-shifting model for rural cardiac triage in which handheld imaging augments, rather than replaces, standard referral pathways. If validated in larger implementation studies, this approach may offer a scalable model to strengthen diagnostic access in underserved rural settings.

CONFLICT OF INTEREST

The authors declare no other conflicts of interest.

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SYSTEMATIC / NARRATIVE REVIEW ARTICLE

Association between signal peptide-CUB-EGF domain-containing protein 1 (SCUBE1) and thrombotic or ischemic cardiovascular and cardiopulmonary diseases: A systematic review

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ABSTRACT

Introduction: Signal peptide-CUB-EGF domain-containing protein 1 (SCUBE1) is a platelet- and endothelium-associated glycoprotein implicated in platelet activation, thrombus propagation, and endothelial injury. Because these processes underpin thrombo-inflammatory cardiovascular and cardiopulmonary diseases, circulating SCUBE1 has attracted interest as a candidate biomarker. This systematic review aimed to critically synthesize comparative clinical evidence on circulating SCUBE1 levels across thrombotic or ischemic cardiovascular and cardiopulmonary conditions relative to control or comparator groups.

Materials and Methods: A systematic search of PubMed, ScienceDirect, and SpringerLink was conducted for English-language studies published from 1 January 2015 to 27 September 2025. The protocol was prospectively registered in PROSPERO (CRD420251178563). Eligibility was guided by a PECO framework and included observational and diagnostic accuracy studies that measured circulating SCUBE1 in serum or plasma and reported patient-comparator data. Two reviewers independently screened studies, extracted data, and assessed methodological quality using design-specific Joanna Briggs Institute tools and ROBINS-I. Owing to clinical and methodological heterogeneity, findings were synthesized narratively without meta-analysis.

Results: Nine studies were included (four cross-sectional, three case-control, one cohort, and one diagnostic accuracy study). SCUBE1 levels were generally higher in patients with thrombotic or ischemic cardiovascular and cardiopulmonary diseases than in comparators, supporting associations with platelet-endothelial activation, thrombotic burden, endothelial dysfunction, and ischemia-reperfusion stress. However, absolute concentrations varied markedly across studies, precluding direct comparison and limiting interpretability of proposed cut-off values. Eight studies had moderate risk of bias and one had serious risk.

Conclusion: SCUBE1 is a biologically plausible but still investigational biomarker; robust multicenter prospective studies with standardized assays are required before clinical translation in routine clinical practice.

KEYWORDS:
Thrombo-inflammation, cardiovascular disease, platelet aggregation, SCUBE1, thrombosis

INTRODUCTION

Atherosclerotic cardiovascular disease remains a leading cause of morbidity and premature mortality worldwide. Many major events occur when chronic vascular injury culminates in platelet-rich thrombosis, such as in acute coronary syndromes and procedure-related complications. Accordingly, biomarkers capturing platelet-endothelial activation could complement established markers that primarily reflect necrosis (e.g., cardiac troponins) or fibrin turnover (e.g., D-dimer), particularly when thrombotic burden and endothelial injury are central to clinical presentation.[1-3]

Signal peptide-CUB-EGF-like domain-containing protein 1 (SCUBE1) is a platelet- and endothelium-associated glycoprotein released during early platelet activation and endothelial perturbation. Experimental and clinical observations suggest that circulating SCUBE1 may track platelet aggregation, platelet-endothelial interaction, and thrombus stabilization, making it a plausible biomarker candidate in thrombotic and thrombo-inflammatory disease states.[4-6]

Clinical studies have reported altered SCUBE1 levels across diverse cardiovascular and cardiopulmonary conditions, including acute coronary syndromes and percutaneous coronary intervention (PCI)-related complications, pulmonary embolism, hypertension-related vascular injury, and post-cardiac arrest physiology.[7-14] However, findings are dispersed across small and heterogeneous studies that differ in design, patient phenotypes, sampling time, biological

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matrix (serum/plasma), assay platforms, and reported concentration ranges. These differences limit interpretability, complicate comparisons of absolute values and cut-offs, and leave the incremental value of SCUBE1 beyond established biomarkers uncertain.[6]

Therefore, this systematic review aims to map and narratively synthesize comparative clinical evidence on circulating SCUBE1 levels across thrombotic or ischemic cardiovascular and cardiopulmonary conditions versus comparator groups, and to identify methodological gaps that must be addressed before considering clinical translation.[15]

MATERIALS AND METHODS

Protocol Registration

This systematic review protocol has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) to promote methodological transparency and reduce unnecessary duplication. The protocol was prospectively registered in PROSPERO (CRD420251178563; https://www.crd.york.ac.uk/PROSPERO/view/CRD420251178563). No amendments were made to the protocol after registration.

Search Strategy and Study Selection

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[16] We systematically searched PubMed, ScienceDirect, and SpringerLink for eligible studies published between 1 January 2015 and 27 September 2025. To improve both comprehensiveness and transparency, the search strategy combined SCUBE1-related terms with broader thrombotic, thrombo-inflammatory, and disease-specific concepts relevant to cardiovascular and cardiopulmonary conditions. These included platelet aggregation, thrombosis, thrombo-inflammation, atherosclerosis, acute coronary syndrome, myocardial infarction, no-reflow, stent thrombosis, pulmonary embolism, hypertension, hypertension-mediated organ damage, and cardiac arrest or post-cardiac arrest states. Controlled vocabulary was used where available, particularly in PubMed, whereas equivalent free-text terms were applied in ScienceDirect and SpringerLink. Boolean operators were used to structure the search strategy by combining core concepts with "AND" and related or synonymous terms with "OR." A representative search structure was as follows: ("SCUBE" [tiab] OR "SCUBE1" [tiab]) AND ("Platelet Aggregation" [Mesh] OR "Thrombosis" [Mesh] OR "Thromboinflammation" [Mesh]) AND ("Cardiovascular Disease" [Mesh] OR "Atherosclerosis" [Mesh] OR "Acute Coronary Syndrome" [Mesh] OR "Myocardial Infarction" [Mesh] OR "Pulmonary Embolism" [Mesh] OR "Hypertension" [Mesh] OR "Cardiac Arrest" [Mesh] OR "Post-Cardiac Arrest Syndrome" [Mesh] OR "no-reflow" [tiab] OR "stent thrombosis" [tiab] OR "hypertension-mediated organ damage" [tiab]) AND ("Biological Markers" [Mesh] OR "biomarker" [tiab]). The full database-specific search strategy is provided in the main manuscript or appendix, in accordance with journal formatting requirements.

We also used a PECO framework to guide eligibility and data extraction, defined as followss: (1) Population (P): Adults with thrombotic or ischemic cardiovascular and cardiopulmonary conditions. (2) Exposure (E): Elevated circulating SCUBE1 levels (measured in serum/plasma). (3) Comparison (C): Healthy controls or clinical comparators without the target condition. (4) Outcome (O): Difference in circulating SCUBE1 concentration between exposed and comparator groups.

Two reviewers (MAGS, RR) independently screened titles and abstracts, followed by full texts, against the eligibility criteria. Disagreements were resolved by discussion, and when necessary, by consultation with a third reviewer (HA). No automation tools were used in the selection process.

Eligibility Criteria

We included observational clinical studies (cross-sectional, case-control, cohort) and diagnostic accuracy studies that: (1) Enrolled participants with thrombotic or ischemic cardiovascular/cardiopulmonary conditions; (2) Measured circulating SCUBE1 in serum or plasma; (3) Reported SCUBE1 values in patients and a concurrent control/comparator group (healthy controls or clinical comparators).

We excluded abstracts without full text, duplicates, case reports, narrative reviews, and studies without a comparator group or without extractable SCUBE1 data.

Data Extraction

Data extraction was performed independently by two reviewers (MAGS and RR) using a standardized data-collection form adapted from previous studies.16 For each included study, the following information was extracted: (1) Study identification (author's name, year, design study). (2) Type of disease (primary condition and relevant subtypes) and assay. (3) Total sample (n). (4) SCUBE1 levels (ng/mL). (5) Pathophysiologic pathway. (6) Mechanistic role in SCUBE1 elevation.

Discrepancies in data extraction were resolved through discussion between the two reviewers (MAGS and RR). When consensus could not be reached, a third reviewer (HA) was consulted to make the final decision. All disagreements and their resolutions were documented in the extraction database.

We screened titles and keywords, then reviewed full texts against the inclusion criteria. We extracted data into structured tables capturing authors, year, disease context, biological mechanisms, SCUBE1 values, and references. A PRISMA flow diagram summarized study selection in Figure 1. Figure 2 displayed SCUBE1 increase leading to platelet aggregation and thromboinflammation.

Assessment of Study Quality

Methodological quality was assessed using design-appropriate Joanna Briggs Institute critical appraisal tools. Risk of bias was assessed using Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I), focusing on confounding, participant selection, exposure classification, deviations from intended interventions, missing data, outcome measurement, and selective reporting.

Study Outcomes
The primary outcome was the difference in circulating SCUBE1 concentration between patient and comparator groups. SCUBE1 levels were analyzed as continuous variables and expressed in ng/mL. Where alternative units were reported, values were converted to ng/mL when feasible; otherwise, measurements were presented as originally reported with clear unit specification. Secondary outcomes included diagnostic performance measures such as area under the receiver-operating characteristic curve (AUC), sensitivity, specificity, and reported cut-off values, as well as associations between SCUBE1 levels and clinically relevant outcomes including thrombotic burden, hypertension-mediated organ damage, and return of spontaneous circulation.

For each included study, the following data were extracted: author and year of publication, study design, sample size, clinical condition and comparator definition, SCUBE1 levels in patient and control groups, pathophysiological pathway, proposed mechanistic role of SCUBE1, summary statistics (mean ± standard deviation or median with interquartile range), and any reported diagnostic or prognostic thresholds. When data were incomplete or unclearly reported, analyses were based on the available published information without imputation, and study authors were not contacted.

For continuous SCUBE1 concentrations we extracted group means and standard deviations (or medians and interquartile ranges when provided). Because of substantial heterogeneity, these effect measures were summarized descriptively without quantitative pooling.

RESULTS

Study Selection
Literature searches in PubMed, ScienceDirect, and SpringerLink were conducted from July 10 to September 10, 2025, with a final update on September 27, 2025. Applying a 2015-2025 publication window yielded 332 records; after limiting to original research, 262 underwent title and abstract screening. Removal of 195 duplicates and 42 abstract-only records left 25 full-text articles, of which nine (three case-control, four cross-sectional, one cohort, one diagnostic accuracy) met all inclusion criteria and were included in the review (Figure 1).

Of the 25 full texts, 16 were excluded, mainly due to absence of a control or comparator group, no SCUBE1 measurement, or outcome reporting that did not allow meaningful comparison. Restricting the search to English-language, full-text publications and not searching trial registries may have introduced reporting bias, favouring positive or biomarker-focused studies. The extent of this bias cannot be quantified from the available data and should be considered when interpreting the findings.

Main Findings
Across the included studies, SCUBE1 generally tracked clinical states characterized by platelet activation, thrombus formation, endothelial perturbation, hypoxia, or ischemia-reperfusion stress. Higher SCUBE1 concentrations were reported in acute coronary syndromes, PCI-related thrombotic complications, pulmonary embolism, hypertension-related vascular injury, and post-cardiac arrest states relative to comparator groups.

However, the evidence should be interpreted cautiously. Although the direction of association was broadly consistent, absolute SCUBE1 concentrations varied markedly across studies and were not directly interchangeable. This variation likely reflects differences in assay kits, biological matrices, sampling timing, disease severity, and study design. As a result, the current literature supports a repeated biological signal rather than a unified diagnostic threshold (Table I, Figure 2).

Across all included studies, circulating SCUBE1 concentrations were measured using enzyme-linked immunosorbent assay (ELISA), with absorbance read at 450 nm, and results were reported as mean ± standard deviation (SD) or median (interquartile range, IQR) according to data distribution in the original studies. Despite differences in clinical settings and assay methodologies, SCUBE1 levels were consistently higher in patient groups than in controls across cardiovascular, thrombo-inflammatory, and hypertensive conditions, reflecting underlying platelet activation, endothelial dysfunction, thrombus burden, microvascular obstruction, and ischemia-reperfusion injury. However, the small number of studies within each clinical domain and substantial heterogeneity in study design, populations, and analytical platforms precluded quantitative meta-analysis or sensitivity analyses; therefore, findings were synthesised and presented descriptively.

Critical Appraisal
Methodological quality was assessed using design-specific Joanna Briggs Institute tools. Overall, the included studies were acceptable for inclusion in a narrative systematic review, but several recurring limitations were identified. Case-control studies showed reasonable exposure and outcome measurement but incompletely reported matching procedures, group comparability, and confounding control. Cross-sectional studies generally described study populations and measurements adequately, although explicit adjustment strategies for confounding were not always clear. The single cohort study provided useful prognostic information but was limited by incomplete reporting of baseline outcome status and follow-up handling. The diagnostic accuracy study used an appropriate reference standard, but uncertainty remained regarding patient selection and threshold pre-specification.

Risk of Bias
Risk of bias was assessed using ROBINS-I across the included non-randomized studies. Overall, eight studies were judged to be at moderate risk of bias and one study at serious risk of bias. The most common concerns were residual confounding, participant selection, and incomplete adjustment for disease severity. In contrast, exposure measurement and outcome assessment were generally acceptable across studies. These findings indicate that the current evidence base is informative but methodologically limited, and that conclusions regarding diagnostic or prognostic performance should remain cautious.

Table I: Circulating SCUBE1 levels and associated pathophysiological mechanisms across clinical conditions

Author's name, year, design study	Type of disease, assay	Total Sample (n)	SCUBE1 levels (ng/mL)	Pathophysiologic Pathway	Mechanistic Role in SCUBE1 Elevation
Ertan Sönmez et al. 2015, cross-sectional[7]	Acute coronary syndrome (STEMI & NSTE-ACS) vs non-cardiac chest pain. ELISA kit for human SCUBE1; Catalog No. CSBE15005 h, Cusabio Biotech Co., Wuhan, Hubei, P.R. China). ELISA reader: Multiskan FC Microplate Photometer (Thermo Scientific Microplate Photometer, Multiskan FC, USA) Wavelength: 450 nm	Control: Healthy (45) Patients: STEMI (45), NSTE-ACS (65), NCCP (80)	Control: 0.34±0.11 Patients: STEMI 0.56±0.16, NSTEMI 0.46±0.13, NCCP 0.37 ±0.10)	Platelet activation and thrombosis	Platelet α-granules release SCUBE1 during acute plaque rupture and thrombosis; SCUBE1 stabilizes thrombus by mediating platelet, endothelial adhesion.
Hasan Ata Bolayır et al. 2017, case-control[9]	No-reflow phenomenon after primary PCI (STEMI), Kit ELISA for human SCUBE1 ELISA reader: VersaMax Microplate Reader (Molecular Devices, Sunnyvale, CA, USA) Wavelength: 450 nm	Control: Healthy (50) Patients: STEMI with NR phenomenon (42), STEMI with Primary PCI (100)	Control: 34±8.4 Patients: STEMI with NR phenomenon 97.2±8.9, STEMI with primary PCI 51±6.2	Platelet aggregation and microvascular obstruction	Persistent platelet activation and microembolization after PCI cause endothelial injury and SCUBE1 release.
Hasan Ata Bolayır et al. 2018, case-control[17]	Late stent thrombosis (presenting as STEMI) Kit ELISA for human SCUBE1 ELISA reader: VersaMax Microplate Reader (Molecular Devices, Sunnyvale, CA, USA) Wavelength: 450 nm Type of disease, assay	Control: Healthy (50) Patients: STEMI with ST (40), STEMI without ST (100)	Control: 30±7.4 Patients: STEMI without ST group 48.2±8.9, at admission 67.6±6.9 and at hospital discharge 50±7.6 in the STEMI with late ST group)	Atherothrombosis at stent site	Platelet hyperreactivity on stent surfaces induces thrombus formation and SCUBE1 secretion.
A. Yıldırım et al. 2020, cohort[8]	STEMI (angiographic thrombus burden during PPCI) ELISA kit with 0.3ng/mL 90ng/mL detection range (catalog number E3142Hu, Shanghai, China) ELISA reader: VERSAmax tuneable microplate reader at 450nm (Molecular Devices, Sunnyvale, CA, USA) Wavelength: 450 nm	Control: Low thrombus burden (51) Patients: High thrombus burden (37)	Control: Low thrombus burden 53.7±15.6 Patients: High thrombus burden 87.7±16.1	Atherothrombotic load	SCUBE1 increases with platelet adhesion and thrombus size in infarct-related arteries.
Murat Güzél et al. 2019, cross-sectional[12]	Essential hypertension (dipper vs non-dipper) ELISA kit (Elabscience® kits made in China ELISA)	Control: Healthy (24) Patients: Dipper Hypertension (30), Non-dipper Hypertension (46)	Control: 1.19 (0.71-1.65) Patients: Dipper 1.68 (0.94-3.90), Non Dipper 2.30 (1.47-5.32)	Endothelial dysfunction and shear stress	Non-dipper hypertension causes continuous endothelial stress; endothelial cells overexpress SCUBE1.
Betül Ayça Yamak et al. 2025, cross-sectional[13]	Hypertension-mediated organ damage (HMOD) ELISA) kit with a detection range of 1 ng/mL to 400 ng/mL (E3142Hu, BT-LAB, Shanghai, China). ELISA reader: VERSAmax tunable microplate reader (Molecular Devices, Sunnyvale, CA, USA). Wavelength: 450 nm	Control: Healthy (36) Patients: HT group (79): with HMOD (39), without HMOD (40)	Control: 75.64 (52.71-110.36) Patients: HT group 160.70 (124.12-319.80), with HMOD (311.27(137.86-460), without HMOD 142.53(110.56-178.19).	Microvascular damage in hypertension	Endothelial SCUBE1 up-regulated by chronic vascular remodeling and oxidative stress.

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Nigar Dirican et al. 2016, diagnostic test accuracy[10]	Pulmonary embolism (CTPA-confirmed). ELISA kit (Elabscience Biotechnology Co., Ltd., China, Catalog no:E–EL–H5405, Lot:AK0015NOV30024). ELISA reader: BIOTEK semiautomatic	Control: Healthy (25) Patients: PE (32), Non-PE (25)	Control: 0.47 (0.32 1.40) Patients: PE 0.90 (0.50 4.92), Non-PE 0.38 (0.28 1.48)	Hypoxia and thrombo inflammation	Hypoxia triggers platelet-endothelial activation; SCUBE1 acts as a complementary biomarker to D-dimer.
Lu Xiao et al. 2021, cross-sectional[11]	Pulmonary embolism Commercial ELISA kit assay (Cusabio, Cat No: CSB-E15005h, Wuhan, China)	Control: Healthy (89) Patients: CTPA confirmed PE (143), Suspicious PE (34)	Control: Healthy (4.40 ±3.23) Patients: CTPA confirmed PE (14.28±7.74), suspicious patients (11.11±4.48)	Hypoxia-driven endothelial stress	Thrombus formation and hypoxic endothelium stimulate SCUBE1 release; marker of vascular occlusion.
C. Yılmaz et al. 2022, case-control[14]	Cardiopulmonary arrest-post return of spontaneous circulation (ROSC) Human SCUBE-1 ELISA kit (MyBioSource, USA; Lot No. BMS9305694). The assay detection range was 0.63-40 ng/mL. ELISA reader/microplate reader: Thermo Scientific, USA Wavelength: 450 nm	Control: Non survivor group (25) Patient: ROSC group (25)	Control: Non survivor group 10.8 (1.7-21.9) Patient: ROSC group 15.4(9.3-26.3).	Systemic ischemia-reperfusion	Global ischemia and reperfusion injury cause platelet and endothelial activation with massive SCUBE1 release.

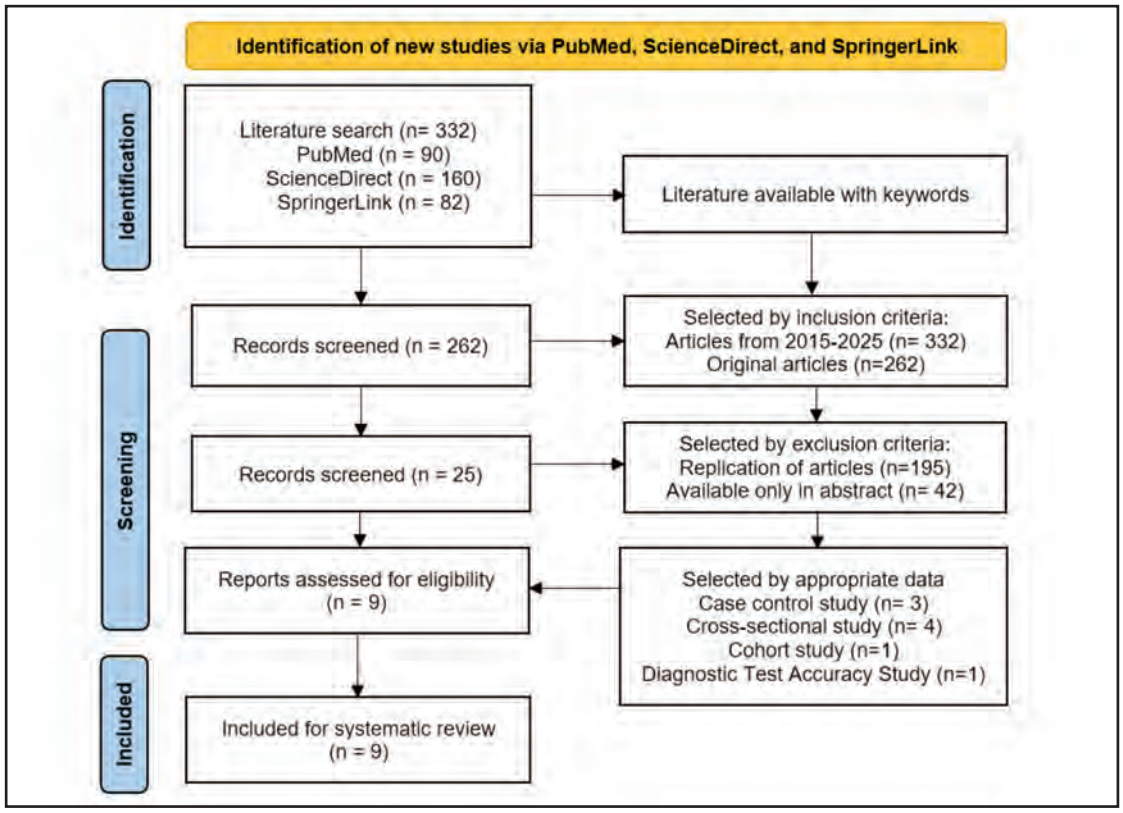

Fig. 1: Flow Chart of Study Selection (PRISMA)[16]

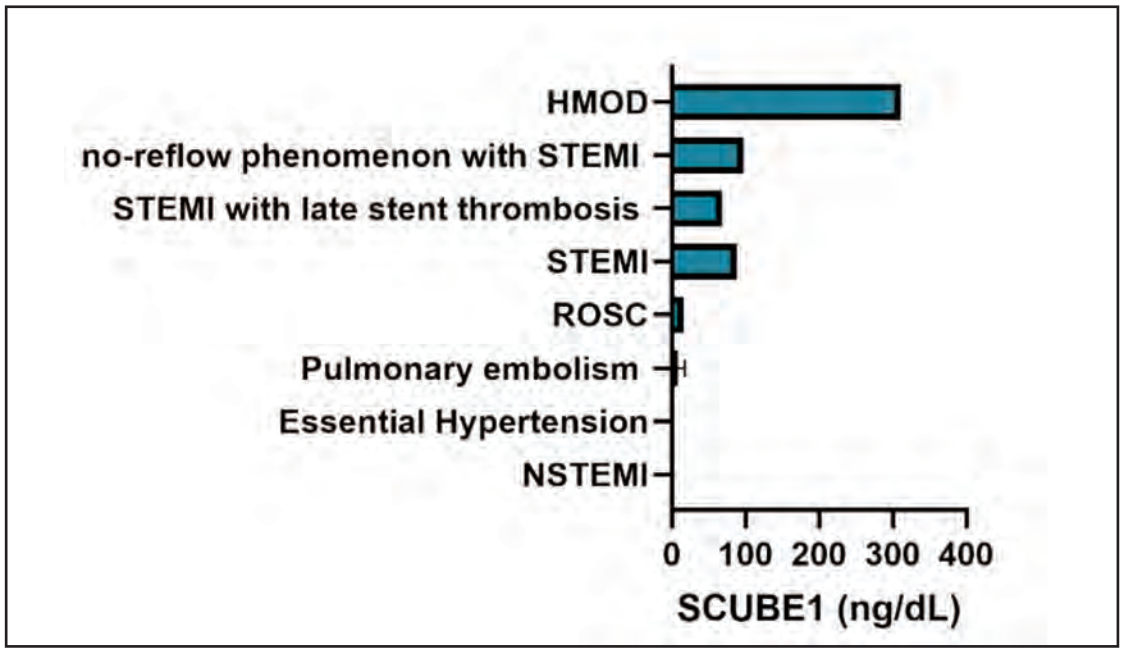

Fig. 2: SCUBE1 levels across different clinical conditions. All measurements were performed using enzyme-linked immunosorbent assay (ELISA). Although different studies used different ELISA kits and microplate readers, all results were reported in ng/mL. Data distribution between control and comparison groups met the assumption of normality

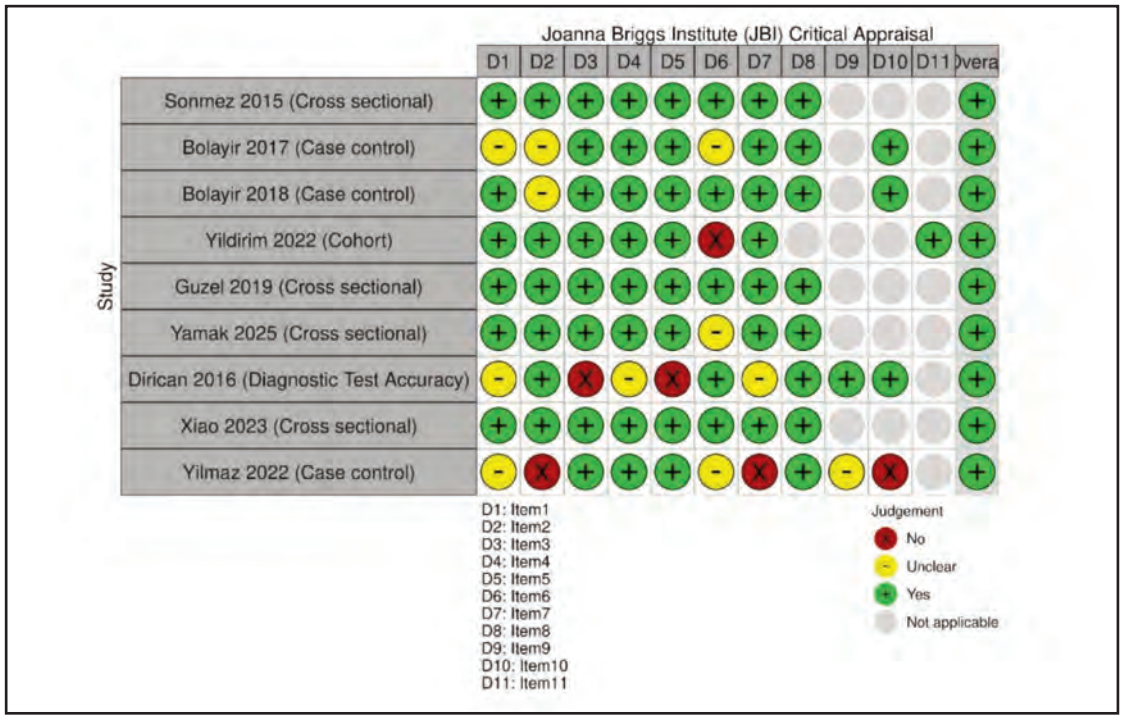

Fig. 3: Joanna Briggs Institute (JBI) Critical Appraisal. Each study was evaluated using a design-specific JBI checklist; therefore, the number of domains varies according to study design. Judgements are defined as follows: Yes indicates the criterion was met; Unclear indicates insufficient information; No indicates the criterion was not met; and Not applicable indicates the item was not relevant to the specific study design or fell beyond the available domains (e.g., fewer than D11 in some designs)

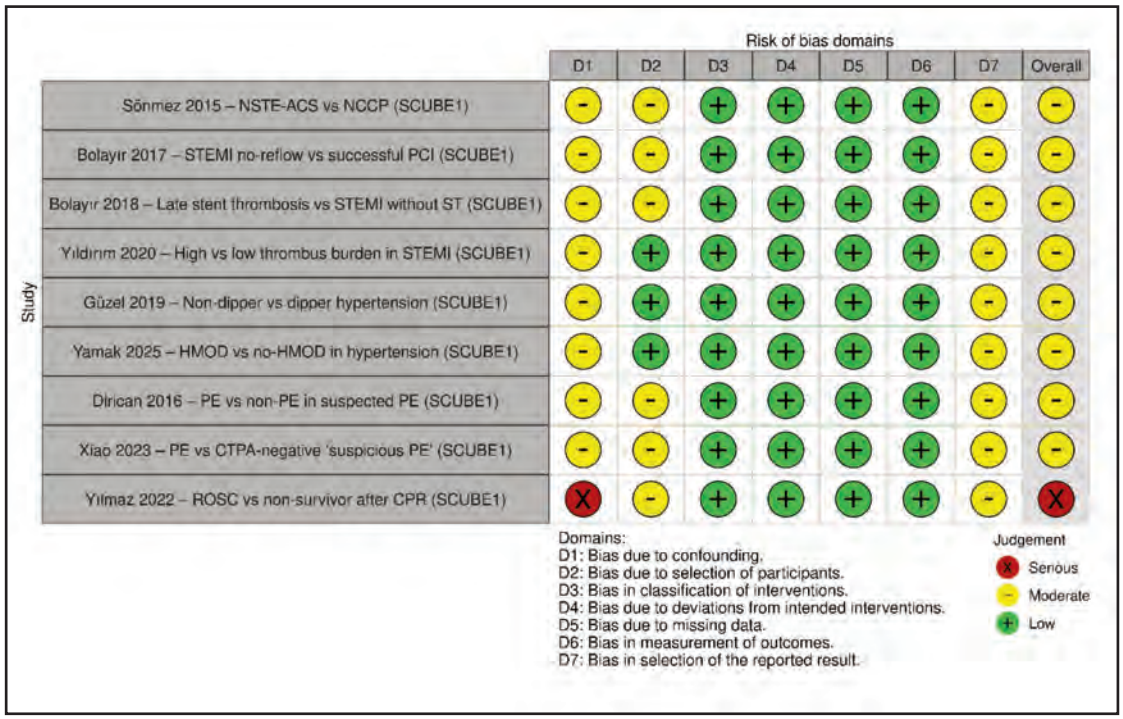

Fig. 4: Risk of bias was assessed using the ROBINS-I tool for non-randomized studies across seven domains (D1-D7). Overall judgements are classified as Serious, indicating high risk of bias; Moderate, indicating acceptable but notable methodological limitations; and Low, indicating minimal risk of bias

DISCUSSION

SCUBE1 and Acute Coronary Syndrome

SCUBE1 is a membrane-associated glycoprotein stored in platelet α-granules and presented on the surface of activated endothelium. Upon platelet activation, it is cleaved and released into the circulation as a soluble adhesion molecule. Through its EGF-like repeats and CUB domain, soluble SCUBE1 can bridge neighboring activated platelets and facilitate their interaction with subendothelial structures, providing a mechanistic link between biochemical release and the formation of platelet-rich arterial thrombi. In the setting of acute coronary syndrome (ACS), this biology translates into a measurable rise in circulating SCUBE1 during episodes of plaque disruption and thrombosis, where platelet activation is both an early and central event.[4,7]

For NR phenomenon after primary PCI, SCUBE1 tracked microvascular risk. In a prospective STEMI study (n=142), mean SCUBE1 was about 97 ng/mL in NR, 51 ng/mL with successful reflow and 34 ng/mL in controls. SCUBE1 independently predicted NR, consistent with a model of intense platelet activation, distal embolization, endothelial injury, and microvascular obstruction (MVO). Recent reviews NR and MVO support these mechanisms and highlight their prognostic significance. Clinically, elevated pre-PCI SCUBE1 in STEMI may flag NR-prone lesions and prompt microvascular protection strategies. However, the evidence is preliminary and needs standardized assays and external validation.[9,18]

SCUBE1 also appears to index thrombotic propensity in late stent thrombosis (LST). In STEMI with angiographic LST patients, at-presentation SCUBE1 (pre-PCI) exceeded levels in healthy controls and in STEMI without LST. On multivariable analysis, SCUBE1 remained an independent predictor. A cutoff near 59.2 ng/mL yielded an area under curve AUC of 0.97 with sensitivity and specificity 83%. These findings align with a high-reactivity, platelet-driven LST biology and suggest triage value at presentation, particularly when post-PCI TIMI flow is suboptimal. Key limitations include single-center design and lack of assay standardization.[17]

After primary PCI for ST-elevation myocardial infarction (STEMI), SCUBE1 correlates with angiographic thrombus burden. In a prospective primary PCI (PPCI) cohort (n=88), higher SCUBE1 was associated with high thrombus load. A threshold above 65.63 ng/mL predicted heavy thrombus with an area under the curve of 0.93 and remained an independent predictor alongside troponin. These findings align with interventional strategies for large thrombus, such as intensified antithrombotic and selective rather than routine aspiration. However, current ACC/AHA/SCAI (2025) and ESC (2023) guidelines do not endorse SCUBE1 testing in acute coronary syndromes. Evidence is promising but not practice changing. Overall, SCUBE1 integrates platelet activation and thrombus biology across the ACS spectrum, yet clinical adoption awaits multicenter validation, assay harmonization, and proof of incremental decision value.[12,19,20]

SCUBE1 and Pulmonary Embolism

SCUBE1 is expressed by vascular endothelium and platelets. Soluble SCUBE1 supports platelet-platelet adhesion and platelet-matrix interactions, which accelerates thrombus growth in vivo. Genetic depletion of soluble SCUBE1 or antibody blockade reduces arterial thrombosis in mice without excess bleeding. In the pulmonary circulation, SCUBE1 also influences BMPR2-related signaling, linking platelet activation and endothelial dysfunction in acute pulmonary embolism (PE).[4,21-23]

A case-control study by Dirican reported higher plasma SCUBE1 in confirmed PE than in non-PE and healthy groups. A cutoff of 0.49 ng/mL yielded an area under the curve (AUC) of 0.79 with sensitivity 100% and specificity 64%. A larger cross-sectional study by Xiao showed higher SCUBE1 in CT-confirmed PE than in suspected PE and healthy controls. A cutoff of 7.789 ng/mL produced an AUC of 0.919 with sensitivity 81.25% and specificity 92.13%. Levels declined at three-month follow-up. An emergency-department study in 2025 observed lower SCUBE1 in PE than in matched controls, underscoring assay heterogeneity and the importance of sampling time and patient factors such as body mass index (BMI).[10-11]

SCUBE1 reflects platelet-driven thrombosis and endothelial perturbation central to PE and shows diagnostic promise as an adjunct in probability-based pathways. At present, major guidelines prioritize pretest probability, age-adjusted D-dimer, and imaging, and they do not recommend SCUBE1 for routine use. Priorities include assay harmonization, kinetic profiling versus symptom onset, and multicenter validation of decision thresholds and incremental value over D-dimer across risk strata.[11,24]

SCUBE1 and Hypertension

In essential hypertension, circulating SCUBE1 tends to be higher than in normotensive controls and shows modest relations with 24-hour blood pressure burden, consistent with hemodynamic load driving platelet-endothelial activation and microvascular injury.[12] Chronic pressure and shear increase endothelial dysfunction, oxidative stress, and small-vessel remodeling. These changes promote microvascular rarefaction, hypoperfusion, and fibrosis that define HMOD.25 Consistent with this pathophysiology, hypertensive patients show higher SCUBE1 than controls, with the highest levels in HMOD. In a comparative study, SCUBE1 independently predicted HMOD with fair diagnostic performance. Organ-specific cutoffs clustered near 200-360 ng/mL, supporting its role as a severity indicator rather than a presence-absence marker.[13]

Night-time blood pressure behavior modifies vascular stress. Non-dippers, who lack the expected nocturnal fall, show greater endothelial activation and platelet reactivity.[26] In newly diagnosed essential hypertension, SCUBE1 exceeded levels in healthy controls and was highest in non-dippers. Soluble CD40 ligand (sCD40L) was also elevated. These findings link an ambulatory phenotype to a biologic marker of thrombo-inflammation and help explain greater target-organ injury with non-dipping.[12]

Practically, SCUBE1 can complement ambulatory blood pressure monitoring (ABPM) to flag higher-risk patients. Targets include non-dippers and those with suspected early

HMOD when imaging and routine labs are equivocal. Interpret SCUBE1 within a composite judgment that includes ABPM, renal indices, retinal assessment, and cardiac imaging. Current evidence is cross-sectional and largely single-center, and absolute cutoffs vary by organ system and assay. Serial measurements under standardized therapy and prospective outcome studies are needed before routine use.[12-13]

SCUBE1 and Cardiopulmonary Arrest (Post ROSC)

During cardiac arrest and the early minutes after return of spontaneous circulation (ROSC), ischemia reperfusion and a massive catecholamine surge trigger endothelial activation and glycocalyx shedding with brisk platelet activation and microthrombosis. These signals map to the severity of postcardiac arrest syndrome and track neurologic and survival outcomes, which makes the platelet-endothelial axis a target for early bedside risk stratification.[27-28] In acute atherothrombotic states, circulating SCUBE1 rises and mirrors platelet activation, which is central to early postcardiac arrest microvascular failure and relevant to ROSC biology.[29]

Clinically, a prospective adult CPR study reported higher at-presentation SCUBE1 in patients who achieved ROSC than in those without ROSC. A threshold near 9 ng/mL yielded AUC 0.74, sensitivity 100%, specificity 48%, and negative predictive value 100% for predicting ROSC. This supports rule-out utility when values are low but is insufficient for definitive decisions. SCUBE1 should be interpreted alongside physiologic monitoring and guideline-directed post-arrest care, not as a stand-alone trigger. Evidence remains limited to small, single-center cohorts with modest specificity, so SCUBE1 is best viewed as a biologically meaningful adjunct for early assessment of platelet-endothelial activation after ROSC.[14]

Taken together, the available evidence suggests that SCUBE1 may reflect a biologically meaningful intersection between platelet activation, endothelial injury, and thrombo-inflammatory burden across multiple cardiovascular and cardiopulmonary conditions. Nevertheless, the present evidence base remains small, largely observational, and methodologically heterogeneous. The consistency of directional elevation across studies is encouraging, but it should not be mistaken for proof of immediate clinical utility.

A major limitation of the field is the lack of assay standardization. Differences in ELISA platforms, biological matrices, sampling timing, comparator selection, and disease severity make direct comparison of absolute concentrations and proposed cut-off values inappropriate. Accordingly, SCUBE1 should currently be interpreted as an investigational biomarker with mechanistic plausibility rather than as a clinically validated diagnostic or prognostic test.

Another important limitation concerns search comprehensiveness. Although the review included three major databases and a prospectively registered protocol, biomarker studies involving SCUBE1 are dispersed across multiple disease-specific literatures rather than a single unified research domain. The revised manuscript therefore clarifies the broader disease-specific search concepts used to capture this evidence more transparently. Even so, the restriction to English-language full-text studies and the absence of grey-literature retrieval mean that some relevant studies may still have been missed.

LIMITATIONS

This systematic review has several limitations. First, the search was restricted to three databases and English-language full-text publications, which may have increased the risk of reporting and language bias. Second, the included studies were clinically and methodologically heterogeneous with respect to disease context, sampling conditions, assay platforms, and comparator definitions. Third, the predominance of small, non-randomized, single-center studies limits the certainty of the evidence. These factors reduce confidence in any single threshold value and preclude direct quantitative comparison of absolute SCUBE1 concentrations across studies.

CONCLUSION

This systematic review suggests that circulating SCUBE1 is frequently elevated in thrombotic and ischemic cardiovascular and cardiopulmonary conditions and most plausibly reflects platelet-endothelial activation within a broader thrombo-inflammatory process. However, the current evidence base remains limited by small sample sizes, observational study designs, assay heterogeneity, and inconsistent thresholds across studies. SCUBE1 should therefore be regarded as an investigational biomarker rather than a clinically established one until larger prospective multicenter studies provide standardized measurement approaches, external validation, and evidence of incremental value over existing clinical pathways.

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CONFLICT OF INTEREST

The authors declare that they have no financial or personal relationships that could inappropriately influence, or be perceived to influence, the work reported in this manuscript.

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DATA AVAILABILITY

The data extraction forms, detailed JBI and ROBINS-I

assessments, and numerical values underlying Figures 1-4 are available from the corresponding author on reasonable request. No analytic code was used beyond standard spreadsheet calculations.

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A systematic review on barriers to the use of contraceptive services and other family planning services among married couples in South Asia

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ABSTRACT

Introduction: There is a dearth of research in terms of systematic review to explore the barriers to contraceptives faced by married couples in South Asia. This systematic review explores the evidence on issues faced by married couples in South Asia regarding the use of contraceptives and other family planning services.

Materials and Methods: A systematic literature review was conducted using PubMed, EBSCO, and Web of Science databases. Articles published in English between 2011 and 2025 were included. Inclusion criteria were: South Asian married couples, forms of contraception, barriers to using contraception and other family planning services. A directed qualitative content analysis approach was employed, using Andersen's Behavioral Model to classify findings into predisposing, enabling, and need-based factors. Risk Of Bias assessment was done using CASP tool.

Results: Out of 301 records identified, 65 studies were finally included following screening and full-text assessment. Among these, 62% identified cultural and gender-related barriers, 54% highlighted religious influences (especially in Pakistan and Afghanistan), and 48% noted misinformation and knowledge gaps. Additional themes included service inaccessibility, provider bias, and poor outreach, particularly in Nepal and rural India.

Conclusion: In South Asian countries, there are major barriers to the use of contraception and other family planning services, mostly due to the overall lack of knowledge, religious factors and allowing myths and misinformation to discourage the use of contraceptives.

KEYWORDS:
Family planning, contraceptive, barriers, married couple, South Asia, review

INTRODUCTION

In 2012, the Family Planning 2020 (FP2020) initiative was launched to address the issue of family planning.[1] The purpose of this effort was to facilitate family planning globally. Since the launch of the family planning initiative, the use of family planning practices has risen to a considerable level. As a result of these global efforts, in the past two decades, the number of women who wish to use family planning has increased from 900 million to more than 1 billion globally. According to estimates, by 2030, 70 million more women will require family planning services. Now, family planning is considered a sustainable global development goal and, moreover, it can be considered a cog in a wheel when it comes to environmental sustainability.

According to Pradhan, still there is a lacking in terms of use of family planning in South Asian region with the use of contraceptive prevalence rate of mere 37% and unmet need still sits at 12% in this region.[2] However, due to extensive intervention from the relevance stakeholders, use of contraceptive has raised significantly, though in Asian region this improvement remained sluggish and showed mere improvement from 51 percent to 51.8 percent for the years 2012 to 2017.[1]

According to Phiri, it is of utmost importance to have good estimates of women who use family planning in order to face the challenges of maternal and child health.[3] According to Najafi there is a dearth of comprehensive research to identify the barriers to contraceptives.[4] Given the fact that every part of the world has its own demographic and socio-economic factors, which react to different health scenarios, a systematic review specifically focused on the South Asian region could be especially important for family planning policy in this region. Moreover, such a review is essential so that a good level of evidence can be produced, which can be useful for future planning in the region.

This systematic review was conducted with the aim of identifying barriers to the use of contraceptive services and other family planning services among married couples, as they represent the dominant user group in most South Asian societies, where contraceptive decisions are largely influenced by marital dynamics. This review also aimed to compare and analyze the similarities and differences among South Asian countries regarding family planning services. This review can be the first step to the development of a focused intervention to reduce morbidities and mortalities connected to the practice of family planning. Our systematic review brings out

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Table I: PICO concepts used in the review

PICO	Concept
Population	Couples in South Asia
Intervention	Contraceptive services and other family planning services
Control	Not applicable
Outcome	Barriers to service utilization of contraceptive and other family planning services

Given the PICO concepts in Table I, the keywords and MESH terms presented in Table II were used to search for articles for this systemic review in PubMed. While the PubMed search included both free keywords and MESH terms, the search in EBSCO and WOS used free keywords only.

Table II: Keywords and MESH terms used in the search in databases

Database	Search strategy
PubMed	("married couples"[MeSH Terms] OR "spouses"[MeSH Terms] OR "husband and wife" OR "married men" OR "married women" OR "living together") AND ("contraceptive agents"[MeSH Terms] OR "contraception"[MeSH Terms] OR "birth control" OR "family planning" OR "reproductive health services"[MeSH Terms]) AND "barriers" OR "access"[MeSH Terms] OR "health services accessibility"[MeSH Terms] OR "misinformation" OR "religion" OR "cultural factors" OR "knowledge, attitudes, practice"[MeSH Terms]) AND ("South Asia" OR "Pakistan"[MeSH Terms] OR "India"[MeSH Terms] OR "Bangladesh"[MeSH Terms] OR "Nepal"[MeSH Terms] OR "Afghanistan"[MeSH Terms] OR "Sri Lanka"[MeSH Terms] OR "Maldives"[MeSH Terms] OR "Bhutan"[MeSH Terms]) Filters: English, 2011–2025
EBSCO	(TI OR AB): ("married couples" OR "spouses" OR "husband and wife" OR "married men" OR "married women") AND (TI OR AB): ("contraceptive use" OR "family planning" OR "birth control" OR "reproductive health services") AND (TI OR AB): ("barriers" OR "access" OR "misinformation" OR "religious belief" OR "cultural norms" OR "awareness" OR "stigma") AND (TI OR AB): ("South Asia" OR "Pakistan" OR "India" OR "Nepal" OR "Afghanistan" OR "Bangladesh" OR "Sri Lanka" OR "Bhutan" OR "Maldives") Limiters: Peer-reviewed, English, Publication Date: 2011–2025
Web of Science	TOPIC: ("married couples" OR "married men" OR "married women" OR "spouses") AND TOPIC: ("contraception" OR "family planning" OR "birth control" OR "reproductive services") AND TOPIC: ("barriers" OR "cultural norms" OR "religious influence" OR "myths" OR "awareness" OR "access") AND TOPIC: ("South Asia" OR "India" OR "Pakistan" OR "Nepal" OR "Bangladesh" OR "Sri Lanka" OR "Bhutan" OR "Maldives" OR "Afghanistan") Timespan: 2011–2025 Languages: English Document Types: Article

a holistic approach toward these barriers, focusing on the South Asia region as a whole. Despite extensive searching, no relevant peer-reviewed articles from Sri Lanka and Maldives met the inclusion criteria for the specified time period, which may indicate a need for more published data from these countries in future research.

MATERIALS AND METHODS

Systematic literature review is a scientific method to examine and appraise the available knowledge in a particular area per predefined criteria.[5] It helps reduce bias during searching and provides reliable findings and meaningful results for readers to draw conclusions.[6]

For this particular study, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used for reporting the review methodology and results. We also used the PRISMA checklist to ensure the quality of our review, which is considered an important standard in healthcare review-based research.[7] Using PRISMA helps ensure that the research is not only unbiased but also captures useful information and that reporting is done in a balanced manner. The review was carried out from June 2021 to March 2025. Prior to the review, a research protocol was agreed upon. The research protocol was neither registered nor published.

Search strategy

The search for relevant articles was carried out in PubMed, EBSCO and WOS, which are commonly used in systematic reviews in the field of healthcare and provide up-to-date information on high-quality research.[8] We used the Population, Intervention, Control and Outcome (PICO) framework to create a search syntax. Search query using the

Table III: Major barriers to the use of contraceptive services and other family planning services identified in the review

Country	Types of barriers
Afghanistan	• Lack of health services[11–13] • Lack of knowledge
Bangladesh	• Place of residence, religion, number of household members, woman's age, occupation, husband's education.[14] • Living status with wife, total children ever died were significantly associated with contraception
India	• Service efficiency, social gender preference, desire to have another child, lack of education, working long hours in the fields. Fertility and family planning in Uttar Pradesh, India: major progress and persistent gaps.[15–47] • General feelings of shame to procure contraceptives for women and men. • Inability to procure contraceptives due to inaccessibility to health facilities and stigma to procure when husband was away. • Lack of control over family planning and family size decision- making relative to husbands. • Family resistance to adopt contraceptives, lack of husband's involvement in family planning issues, myths, misconceptions, and religious issues.
Maldives	No study found
Nepal	• Geographical and financial access, provider bias, poor method choice availability, the lower status of women.[48–59] • Cultural norms perceived embarrassment of asking for services from the opposite gender. • Poor coverage of health facilities, lack of outreach services.
Pakistan	• Religious and financial limitations, poor knowledge about contraceptives, social and religious factors. family stigma, limited female mobility.[60–76] • Lack of communication among couples.
Sri Lanka	No information was found on barriers to contraception.
South Asia	Accessing quality reproductive health services. Lack of confidentiality, privacy and poor staffing at health facilities.[78–80]

PICO concepts was applied to highlight the current unanswered issues in community settings.[9] The application of the PICO framework to select keywords in this review is summarized in table I below. The complete list of search strategies used in each database is provided in table II.

Inclusion and exclusion Criteria: Studies conducted among married couples of South Asia, using any form of contraception, examined the barriers which affect the access and use of family planning. Articles which were written only in English language and published from 2011 till 2025. Any studies which did not qualify under this selection criteria were not included, such as country of interest not in South Asia, postpartum contraceptive, no barriers investigated, articles in any language other than English and any article published before 2011

Selection procedure

The screening procedure included three phases. During the first phase, the titles and abstracts of all publications found in the search were screened by two reviewers independently, and the results were compared. Differences were discussed to determine if a given publication should be included. During the second screening phase, the full texts of publications found relevant in the first phase were reviewed by two reviewers, and differences were discussed. During the third screening phase, the reference lists of papers selected for review were screened.

Method of analysis

To have a better understanding of the barriers to contraception, the Andersen Behavioral Model (1995) was used to extract and code the relevant information from each of the articles.[10] This model uses two key categories: Predisposing factors (e.g., demographic, cultural, and belief systems) and enabling factors (e.g., financial, logistic, and healthcare access). Data extraction was conducted independently by three reviewers using a predefined matrix aligned with Andersen's Behavioral Model. Each study was reviewed and coded into predisposing, enabling, and need-based factors. To ensure consistency, a pilot extraction was performed on five studies, and discrepancies were discussed and resolved by consensus.

Inter-rater reliability was maintained through regular cross-checking and joint discussions. The directed qualitative content analysis followed a deductive approach, where predefined categories from Andersen's model guided thematic coding of each study's findings. We used a directed qualitative content analysis approach where each included article was evaluated for content matching any of these three domains. These were predefined into an extraction matrix before analysis

Risk of bias assessment

To evaluate the quality and internal validity of included studies, we conducted a risk of bias assessment using appropriate checklists from the Critical Appraisal Skills Program (CASP). Each study was reviewed using the CASP tool that matched its study design i.e. qualitative, cross-sectional (treated as observational/cohort-style), or mixed-methods (evaluated using both tools where applicable). Three reviewers independently assessed all included studies, and any discrepancies were resolved through consensus and voting. Each study was rated as low, moderate, or high risk of bias based on clarity of methodology, reporting, sampling strategy, and overall rigor.

RESULTS

Out of 301 articles screened, 65 met the inclusion criteria. Among these, 62% identified cultural and gender-related barriers, 54% highlighted religious influences (especially in Pakistan and Afghanistan), and 48% noted misinformation and knowledge gaps. Additional themes included service inaccessibility, provider bias, and poor outreach, particularly in Nepal and rural India. A total of 301 publications were retrieved and were then assessed based on our inclusion and

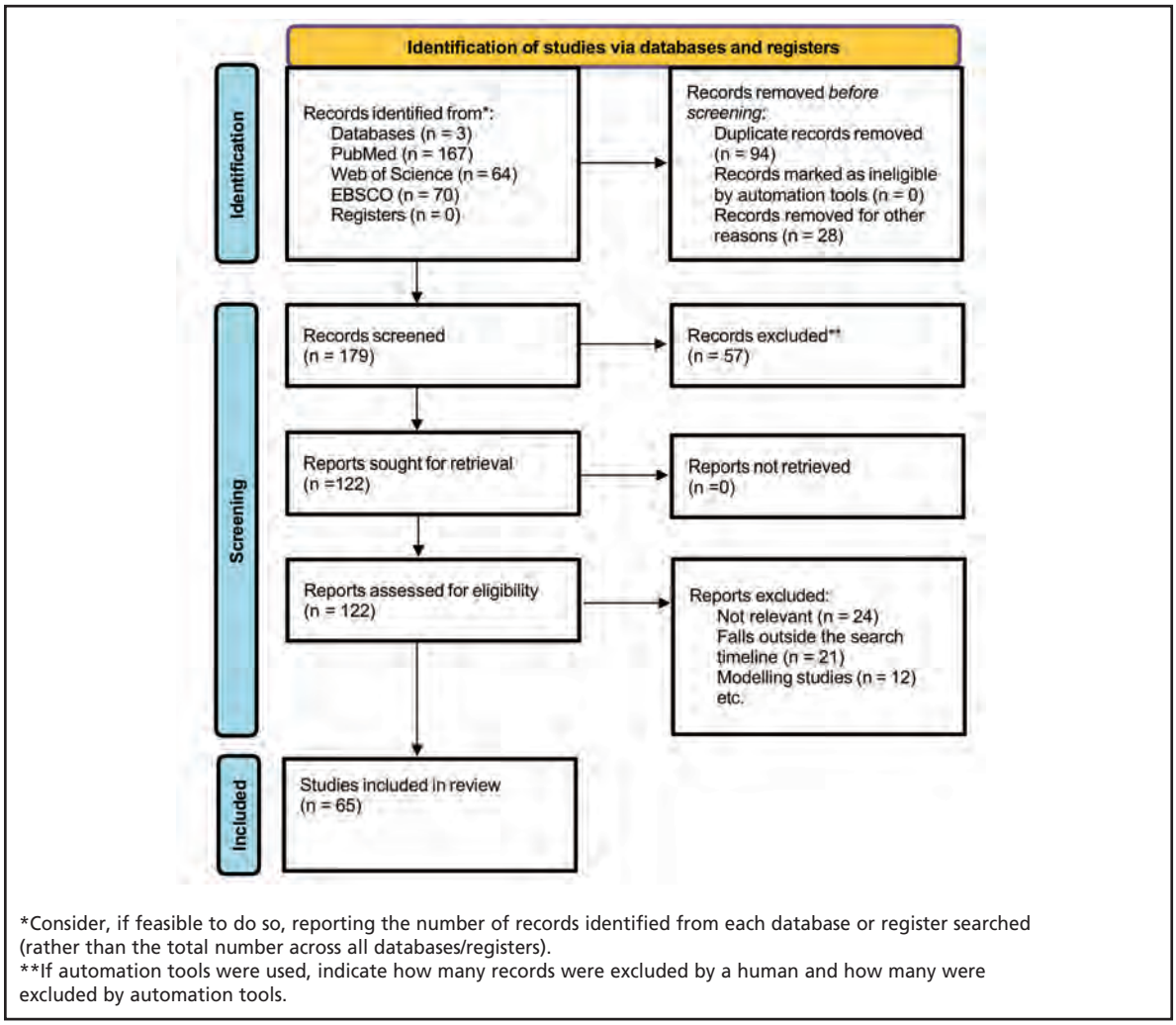

Fig. 1: PRISMA flow chart on the selected articles were retrieved and filtered based on our inclusion and exclusion criteria

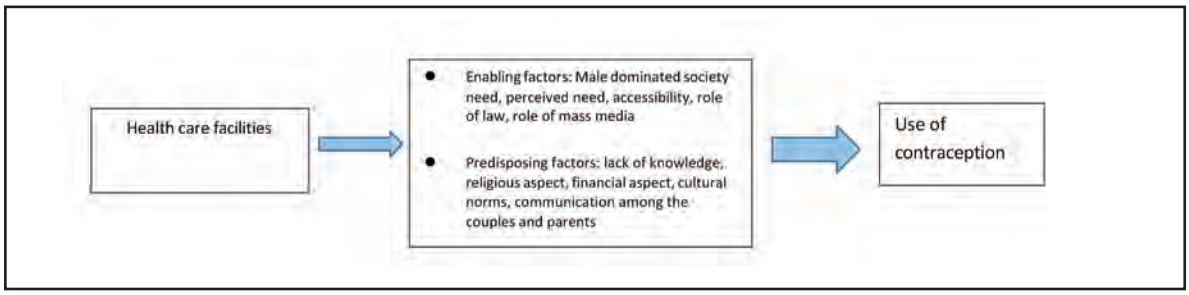

Fig. 2: Key barriers to the use of contraceptive services among married couples in South Asia

exclusion criteria. Of those publications, 94 articles were removed as duplications and 207 were filtered out as they did not meet the inclusion criteria for this review. Thus, 65 of the 301 articles were accepted for review. Figure 1 showed how the selected articles were retrieved and filtered based on our inclusion and exclusion criteria.

Assessment of bias across studies

Of the 65 included studies, 19 were qualitative, 41 were quantitative and 5 were mixed methods. Based on CASP assessments, 33 studies (55%) were rated as having low risk of bias, 30 studies (46%) had a moderate risk, and 2 studies (3%) showed high risk of bias, primarily due to unclear sampling or weak data reporting. Qualitative studies generally demonstrated strong thematic clarity and reflexivity, while cross-sectional studies often lacked detailed justification for sample size and confounder control. Mixed-methods studies were rated moderate due to imbalanced integration of qualitative and quantitative components.

Analysis results

The most frequently reported barriers across studies were cultural and social factors (reported in 62% of studies), religious influences (54%), misinformation or lack of awareness (48%), health system access issues (39%), and gender-related power dynamics (36%). These proportions are based on coding under Andersen's Behavioral Model. While reviewing the country-wise literature, India accounted for the highest number of studies (n=32), followed by Pakistan (n=16), Nepal (n=12), Afghanistan (n=3) and Sout Asia (02). No eligible peer-reviewed studies from Sri Lanka and Maldives were found during the specified timeframe. Most themes were consistent across countries, although religious concerns were more prominent in Pakistan and Afghanistan, while health system-related barriers were more frequent in Nepal.

Thematic saturation was reached as recurring categories (cultural stigma, gender power imbalance, service inaccessibility, and religious beliefs) appeared consistently across included studies. We acknowledged heterogeneity in study settings and populations by using a narrative synthesis approach guided by the Andersen Model to group barriers into predisposing and enabling factors. This ensured coherence in interpretation despite variability.

Summary of evidence

Table III summarizes the major barriers to the use of contraceptive services identified in the review. The barriers are presented in every country. In Bangladesh, distance from the health facilities, women's age, breastfeeding status, and the number of children alive were among the reasons for not using contraceptives.[11] While reviewing the literature for India, barriers such as low literacy and long working hours were also identified. When it comes to family planning, Nepal shows the same barriers that are prevalent in other South Asian countries such as India, Pakistan, Bangladesh, and Afghanistan. In addition, structural barriers, religion, social norms, and side effects of fear are also barriers to family planning in Nepal. Pakistan showed more religious concern over the use of family planning, while communication within the couple was also a barrier.[11] For the Maldives and Sri Lanka, no articles could be found for our given time frame. Broadly for the South Asian context, multiple factors such as service qualities, poor staffing and a few other factors have been shown as a constraint in obtaining family planning services.[12]

DISCUSSION

This review explored the barriers to the use of contraceptives and other family planning services in South Asia. For some countries, like India, Pakistan, Bangladesh, and Afghanistan, detailed information could be extracted; for others, like Maldives and Sri Lanka, no related study could be found. Nevertheless, the review indicated some similarities in terms of religion and cultural preferences, such as male child preference, as well as health care access, knowledge gap, and economic challenges in this South Asian region.

According to our review, religion and culture were prominent barriers. For example, multiple studies from Pakistan, India, and Nepal linked religious beliefs and family opposition with low contraceptive uptake. These findings were consistent across both qualitative and quantitative studies. These findings about religion and culture are also supported by external literature. For instance, Gedicks, et. al. argued that religion may not always be a limiting factor, while Azanawet, et al. found otherwise.[80-81] Several studies showed religious barriers are context-specific, varying across regions and belief systems. However, these external studies were not part of our review and are cited here to support or contrast our findings.[82]

While analyzing the barriers to contraception, accessible health care and adequate health facilities also appear to be important factors. Our review highlighted these system-level issues, particularly in Nepal and rural India. These were most often coded as enabling barriers under the Andersen model.[83-84] Similar external research, such as by Nagai, describes such access barriers in the Philippines.[85] A study conducted in Nigeria also highlights how service utilization can be affected due to cultural sensitivities and personal choices.[86] Moreover, multiple researches also highlight issues of supply and demand can be a challenge in providing consumers with their required family planning methods.[53,87] Poor provision of facilities for the consumer to get hold of family planning services also plays its role in accessing and practicing family planning.[88] According to Peterson, 34% of women remained deprived of family planning facilities merely due to service provider issues.[89]

Another important aspect addressed in the papers reviewed refers to the knowledge gap at an individual level. A study conducted in Nigeria highlights the importance of reducing the knowledge gap and disseminating evidence-based information to deal with misconceptions and wrong information about contraception.[90] Turkey, which is considered a modern culture, however, research also shows knowledge gaps that are manifested as barriers to family planning practice. A study by Sothornwit, et al. states that due to the lack of knowledge, Thai women abstained from the use of contraceptives.[90-91] Another study by Mwaisaka, et al. also emphasizes that there is a need to address the knowledge gap challenges surrounding family planning practices because they are a major hurdle in the practice of family planning.[92]

Initiatives for reducing the knowledge gap need to focus on both women and men. As indicated

in our review that in South Asia, predominantly husband determines the couple's family planning choices. According to Prata et al., the husband plays a pivotal role in supporting the use of family planning.[93] In addition, the review's results suggest that better communication within couples may increase the use of family planning. A study conducted in Uganda also mentions the importance of role of gender norms when it comes to the practice of family planning.[94] Another research done in Zambia mentions that the male partner's approach towards family size, sexual satisfaction and perceived side effects of contraception manifests its effects as barriers.[95]

In today's world, we cannot ignore the importance of mass media. While our review showed limited direct evidence on this factor, external literature has shown the influence of

media on promoting contraceptive behavior.[96] These references are meant to frame potential strategies but were not part of the included studies. The economic situation is also a major factor in South Asia when it comes to deciding on the use of family planning. Our review found this most commonly in rural areas of India and Pakistan. Male economic dominance and lack of household control by women were identified as enabling barriers. While some comparative studies show similar global trends, these were cited only for contrast.[97]

Based on the Andersen behavioral model, if we assess the major issues of family planning (Figure 2), we can categorize them into two factors, i.e., enabling and predisposing factors. According to our findings, the husband's opinion on family planning, coupled with cultural taboos and myths, were core predisposing factors, while access issues and affordability formed the enabling component.

Based on literature it can be deduced that there is a lack of political will, issues in supply and demand, and willingness, and different barriers that become part of a vicious cycle to achieve the desired results. While this conclusion draws partly from the literature reviewed, references to regional policy implementation are external and used here to frame context not to extend the scope of our review.

LIMITATIONS

This review has some limitations that we need to acknowledge. Relatively less research is available from Maldives and Shri Lanka, which limits the assessment of the magnitude of the problem in this region. Also, we cannot entirely exclude bias related to the search strategy because we only searched in selected academic databases and limited our search to English language publications and a specific period. As a result, we might have missed relevant publications in other languages as well as earlier publications. We cannot entirely exclude selection bias because one researcher extracted the information and assessed the papers. However, we diminished that bias to a certain extent by having a second researcher who checked the excluded publications.

CONCLUSION

In this systematic review, we looked at the barriers to the use of contraceptives and family planning in South Asian countries. The results of this review indicate that access to contraceptive and family planning methods remains a challenge in South Asian countries. There are several barriers in the region, including financial issues, poor supply and demand, cultural and religious values, and a lack of information. One of the core barriers was gender inequality and the role of male partners in family planning decision-making.

These findings suggest that policymakers and family medicine practitioners in South Asia should prioritize culturally sensitive education campaigns and community engagement, particularly involving men. Training programs should also be developed for frontline health workers, especially in rural and underserved areas, to address misinformation, promote respectful communication, and overcome provider-level bias.

Lastly, political will and leadership play a vital role in improving these services and removing the barriers in the way of proper delivery of family planning services. Strengthening primary care systems and incorporating family planning modules in basic medical training can enhance outreach, particularly where barriers are strongest. It is important to note that no eligible studies from Bhutan, Maldives, or Sri Lanka were found, and therefore, findings may not fully represent the entire South Asian region.

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Artificial intelligence driven prognostic models for predicting diabetic retinopathy risk in type 2 diabetes mellitus: A systematic review

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ABSTRACT

Introduction: Diabetic retinopathy remains a leading cause of preventable blindness among individuals with type 2 diabetes mellitus and is driven by the increasing global burden of diabetes. Early identification of individuals at high risk is essential for timely intervention. In recent years, artificial intelligence, including machine learning and deep learning, has emerged as a promising approach for prognostic modelling. However, evidence on artificial intelligence–driven models for predicting diabetic retinopathy risk remains fragmented. This systematic review aims to synthesise current evidence on artificial intelligence–driven prognostic models for predicting the risk of diabetic retinopathy among individuals with type 2 diabetes mellitus, focusing on model characteristics, predictor variables, performance, and validation strategies.

Materials and Methods: A comprehensive search of PubMed, Scopus, Web of Science, and ScienceDirect was performed for studies published between January 2016 and December 2025. Eligible studies included those applying artificial intelligence–based models for diabetic retinopathy risk prediction in adult populations with type 2 diabetes mellitus and reporting model performance metrics. Data were extracted and synthesised narratively, and methodological quality was assessed using the Newcastle–Ottawa Scale.

Results: A total of 1040 records were identified, with eight studies included after screening. A wide range of artificial intelligence algorithms was applied, with ensemble models such as extreme gradient boosting and random forest demonstrating superior performance. Key predictors consistently included glycated haemoglobin levels, duration of diabetes, blood pressure, lipid profile, and renal function markers, alongside emerging metabolomic biomarkers. Model performance ranged from moderate to excellent, with area under the receiver operating characteristic curve values between 0.68 and 0.97. Most studies employed internal validation techniques such as cross-validation or training and testing data splits, while external validation was largely absent. Overall methodological quality was high, although variability in study design, predictor selection, and reporting was observed.

Conclusion: Artificial intelligence–driven prognostic models show substantial potential in predicting diabetic retinopathy risk among individuals with type 2 diabetes mellitus, particularly through the integration of clinical and high-dimensional data. Despite promising predictive performance, limitations in external validation, heterogeneity, and reporting of clinical utility hinder translation into practice. Future research should prioritise external validation, standardised reporting frameworks, and clinically interpretable models to enhance applicability in real-world healthcare settings.

KEYWORDS:
Diabetic Retinopathy, Type 2 Diabetes Mellitus, Artificial Intelligence, Machine Learning, Prognostic Model

INTRODUCTION

Diabetes mellitus (DM) represents a major global health challenge, with an estimated 463 million people affected worldwide in 2019 and projections indicating a rise to 700 million by 2045.[1] Type 2 diabetes mellitus (T2DM), characterized by insulin resistance alongside varying degrees of β-cell dysfunction, accounts for approximately 90% of all diabetes cases.[2] Among the most devastating microvascular complications of T2DM, diabetic retinopathy (DR) remains a leading cause of preventable blindness in working-age adults globally.[3] The continuously climbing prevalence of T2DM has led to a 67% increase in vision impairment and a 27% increase in blindness attributable to DR from 1990 to 2010.[4] Early detection and timely intervention are therefore paramount in preventing the progression of DR to sight-threatening stages, including severe non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR).

The pathogenesis of DR involves multiple factors, including chronic hyperglycaemia, angiogenic factors, oxidative stress,

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hypertension, and hyperlipidaemia.[5] As DR progresses, the development of new vessels leads to vitreous haemorrhage and tractional membrane formation, which can result in devastating deterioration of vision.[6] DR is classified according to the International Classification of DR scale into stages: no DR, mild NPDR, moderate NPDR, severe NPDR, and PDR, with sight-threatening DR (STDR) defined as the combination of severe NPDR and PDR.[7]

The emergence of artificial intelligence (AI), particularly machine learning (ML) and deep learning (DL), has introduced transformative possibilities in diabetology and ophthalmology.[8] AI is broadly defined as technology that enables computers and machines to simulate human intelligence and solve complex problems, encompassing subdomains such as ML, programs that improve over time with experience and DL, which uses artificial neural networks and large datasets to tackle computationally complex problems.[9] Within the field of endocrinology and diabetes, DR is among the conditions for which there is the largest body of evidence for the use of AI technologies in disease detection, prediction, and risk assessment.[10]

While substantial research has focused on AI-based diagnostic systems for DR primarily through automated retinal image analysis, there is a growing body of literature on AI-driven prognostic models that aim to predict the risk of developing DR or its progression in patients with T2DM. These prognostic models leverage clinical, demographic, biochemical, genetic, and imaging data to stratify patients by risk, enabling targeted preventive interventions.[11] This systematic review aims to comprehensively synthesize the current evidence on AI-driven prognostic models for predicting the risk of DR in individuals with T2DM, examining the methodologies employed, and the performance metrics achieved.

MATERIALS AND METHODS

This systematic review was conducted following the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[12] This review was registered on the PROSPERO platform (CRD420251271494).

Search strategy

A comprehensive literature search was conducted in PubMed, EMBASE, Scopus, Web of Science, and ScienceDirect between 5 January 2026 and 30 January 2026 to identify relevant studies published between 1 January 2016 and 31 December 2025. The search strategy was developed using a combination of controlled vocabulary, including Medical Subject Headings (MeSH) in PubMed and Emtree terms in EMBASE, together with free-text terms related to DR, T2DM, AI, ML, DL, prognostic modelling, risk prediction, and predictive analytics.

To maximise the sensitivity and comprehensiveness of the search, various synonyms, spelling variations, truncation symbols, and Boolean operators were incorporated. Terms related to DR included "Diabetic Retinopathy," relevant MeSH and Emtree terms, and retinopathy-related keywords. For the diabetes component, terms such as "Diabetes Mellitus, Type 2," "type 2 diabetes mellitus," "type 2 diabetes," T2DM, and diabetes were used. The AI domain included terms such as "Artificial Intelligence," AI, "machine learning," "deep learning," "neural networks," and "artificial neural networks." To capture studies focused on prediction and prognosis, additional terms included "prognosis," "prognostic modelling," "prediction," "risk prediction," "risk assessment," "risk stratification," "prediction models," "prognostic models," "clinical prediction models," "risk scores," and "prediction algorithms."

These concepts were combined using Boolean operators to identify studies that examined the application of AI and ML techniques for predicting the risk or progression of DR among individuals with T2DM. Search strategies were adapted for each database according to their specific indexing systems and search functionalities, including the use of MeSH terms in PubMed and Emtree terms in EMBASE, to ensure optimal retrieval of relevant records. The specific strategy applied for each database is detailed in table I.

Eligibility criteria

This systematic review included original studies published between January 2016 and December 2025 that evaluated AI-driven prognostic or risk prediction models DR among individuals with T2DM. Eligible studies involved adult populations (≥18 years) with T2DM and assessed the development or progression of DR as an outcome. Studies were required to apply AI or ML techniques for risk prediction, prognostic modelling, or stratification, and to report at least one model performance metric such as area under the receiver operating characteristic (AUROC) curve, sensitivity, specificity, calibration, or related indicators. Observational study designs (cohort, case-control, or cross-sectional) and methodological/model development studies were included, provided they were published in peer-reviewed journals and written in English.

Studies were excluded if they did not focus specifically on T2DM populations or did not evaluate DR as a primary or clearly defined outcome. Articles that used AI solely for image-based detection, screening, or classification of existing DR without a prognostic or risk prediction component were excluded, as were studies lacking sufficient methodological detail or reporting no model performance metrics. Non-original articles such as reviews, systematic reviews, meta-analyses, editorials, conference abstracts without full texts, case reports, and letters were also excluded. In addition, studies involving animal models, paediatric populations, gestational diabetes, or type 1 diabetes mellitus were not considered, as well as publications outside the specified date range or not available in English.

Study selection

Following the database searches, all retrieved records were imported into reference management software (e.g. Endnote) and duplicates were removed. Two independent reviewers (M.M.S.T. and T.R.R.) screened titles and abstracts against eligibility criteria. Full text articles of potentially relevant studies were retrieved and assessed for final inclusion. Disagreements were resolved through discussion or consultation with a third reviewer (M.R.I.) when consensus could not be reached.

Data extraction

Data extraction was conducted using a standardized, pilot-tested form (e.g., Endnote) to ensure consistency and completeness across included studies. Two reviewers (M.M.S.T. and T.R.R.) independently extracted key information, including study characteristics (first author, publication year, country, study design, and sample size), population details, and outcome definitions related to DR. Detailed information on the AI models was also collected, including the type of algorithm used, input variables or predictors, model development approach, and validation methods (internal and/or external validation). In addition, performance metrics such as AUROC curve, sensitivity, specificity, accuracy, calibration measures, and other relevant indicators were extracted.

Risk of bias assessment

The methodological quality and risk of bias of the included studies were assessed using the Prediction Model Risk of Bias Assessment Tool (PROBAST). PROBAST was selected because it is a validated and widely recommended instrument specifically developed for evaluating diagnostic and prognostic prediction model studies, including those incorporating AI and ML approaches.[13] Unlike generic quality assessment tools designed for observational studies, PROBAST provides a structured framework to assess potential sources of bias that may affect the development, validation, and performance of prediction models. The tool evaluates four key domains: participants, predictors, outcome, and analysis, encompassing a total of 20 signalling questions. Each domain was rated as having low, high, or unclear risk of bias, and an overall risk of bias judgement was subsequently assigned for each study. Two reviewers (M.M.S.T. and T.R.R.) independently performed the assessment, and any disagreements were resolved through discussion and consensus with a third reviewer (M.R.I).

Data synthesis

A narrative synthesis approach was undertaken due to the anticipated heterogeneity in study designs, AI algorithms, predictor variables, outcome definitions, and reporting of performance metrics across the included studies. Extracted data were systematically organised into structured tables and synthesised according to key domains, including study characteristics, types of AI models, predictor variables, and model performance. The findings were analysed thematically to identify common patterns in model development approaches, frequently used predictors, and variations in predictive performance (e.g., discrimination and calibration). Comparisons were made across studies to highlight differences in algorithm performance, validation strategies (internal versus external), and clinical applicability.

RESULTS

Study selection and characteristics

A total of 1040 studies were retrieved from the databases and screened based on predefined criteria. After removing ineligible records, 537 studies remained for title and abstract screening. A total of 61 studies progressed to full-text screening. Studies were further evaluated for relevance, methodological quality, and outcome reporting during this phase. After final appraisal, eight studies were included in this review (Figure 1).

The included eight studies all published between 2016 and 2025, reflecting the growing application of AI in prognostic DR. The studies were predominantly conducted in Asia and Europe, with a mix of retrospective cohort, cross-sectional, and secondary data analyses. Sample sizes varied substantially, ranging from a few hundred participants to large-scale datasets exceeding 30,000 individuals, indicating variability in study power and generalisability. The findings of the included studies were systematically synthesised and summarised into four key domains namely AI model characteristics, predictor variables, model performance, and validation strategies, to facilitate structured comparison and critical interpretation of the evidence. The key characteristics of these studies are outlined in table II.

AI model characteristics

Across the eight included studies, a wide range of AI and ML algorithms were applied, with a clear dominance of ensemble-based methods, particularly extreme gradient boosting (XGBoost). Multiple studies consistently demonstrated the use of advanced algorithms such as XGBoost, random forest (RF), support vector machine (SVM), artificial neural networks (ANN), and gradient boosting models, reflecting a shift from traditional statistical models toward more flexible, data-driven approaches.[15-16,19] Notably, explainable artificial intelligence (XAI) techniques, including Explainable Boosting Machine (EBM) and Shapley Additive exPlanations (SHAP), were increasingly integrated to enhance interpretability and clinical relevance of model outputs.[14,19] These approaches allowed not only prediction but also identification of key contributing features, facilitate clinical decision-making in routine screening and public health programmes.[22]

Predictor variables

The predictor variables across studies showed a consistent pattern, combining traditional clinical risk factors with emerging biochemical and metabolomic markers. Classical predictors such as duration of diabetes, HbA1c, blood pressure, lipid profile, and body mass index were frequently identified as important determinants of DR risk.[15,17-18] Some studies quantified these associations using effect estimates, for example, insulin use (OR 3.561) and increasing duration of diabetes (OR increase 9.3% per year).16 In addition, newer studies incorporated advanced predictors such as renal function markers (eGFR, creatinine), lipid-related indicators, and metabolomic biomarkers (e.g., tryptophan, tyrosine), reflecting the increasing use of high-dimensional data in AI modelling.[14,18] However, most studies relied on feature importance rankings rather than conventional epidemiological measures such as adjusted hazard ratios, limiting direct interpretability.

Model performance

Model performance varied across studies but generally demonstrated moderate to excellent predictive ability. Ensemble learning methods, particularly XGBoost, consistently achieved superior discrimination, with AUROC values ranging from 0.68 to 0.97 depending on dataset size

Table I: Primary search strings used in each database

Database	Search Strategy
PubMed	("Diabetic Retinopathy"[MeSH] OR "diabetic retinopathy" OR retinopath*) AND ("Diabetes Mellitus, Type 2"[MeSH] OR "type 2 diabetes mellitus" OR "type 2 diabetes" OR T2DM) AND ("Artificial Intelligence"[MeSH] OR "artificial intelligence" OR AI OR "machine learning" OR "deep learning" OR "neural network*" OR "artificial neural network*") AND ("Prognosis"[MeSH] OR prognos* OR predict* OR "risk prediction" OR "risk assessment" OR "risk stratification" OR "prediction model*" OR "prognostic model*" OR "clinical prediction model*" OR "risk score*" OR "prediction algorithm*")
EMBASE	('diabetic retinopathy'/exp OR 'diabetic retinopathy' OR retinopath*) AND ('type 2 diabetes mellitus'/exp OR 'type 2 diabetes mellitus' OR 'type 2 diabetes' OR T2DM) AND ('artificial intelligence'/exp OR 'artificial intelligence' OR 'machine learning'/exp OR 'machine learning' OR 'deep learning' OR 'neural network*' OR 'artificial neural network*') AND ('prognosis'/exp OR prognos* OR predict* OR 'risk prediction' OR 'risk assessment' OR 'risk stratification' OR 'prediction model*' OR 'prognostic model*' OR 'clinical prediction model*' OR 'risk score*' OR 'prediction algorithm*')
Scopus	(("diabetic retinopathy" OR retinopath*) AND ("type 2 diabetes mellitus" OR "type 2 diabetes" OR T2DM) AND ("artificial intelligence" OR AI OR "machine learning" OR "deep learning" OR "neural network*" OR "artificial neural network*") AND (prognos* OR predict* OR "risk prediction" OR "risk assessment" OR "risk stratification" OR "prediction model*" OR "prognostic model*" OR "clinical prediction model*" OR "risk score*" OR "prediction algorithm*"))
Web of Science	(("diabetic retinopathy" OR retinopath*) AND ("type 2 diabetes mellitus" OR "type 2 diabetes" OR T2DM) AND ("artificial intelligence" OR AI OR "machine learning" OR "deep learning" OR "neural network*" OR "artificial neural network*") AND (prognos* OR predict* OR "risk prediction" OR "risk assessment" OR "risk stratification" OR "prediction model*" OR "prognostic model*" OR "clinical prediction model*" OR "risk score*" OR "prediction algorithm*"))
ScienceDirect	("diabetic retinopathy" OR retinopath*) AND ("type 2 diabetes mellitus" OR "type 2 diabetes" OR T2DM) AND ("artificial intelligence" OR AI OR "machine learning" OR "deep learning" OR "neural network*" OR "artificial neural network*") AND (prognos* OR predict* OR "risk prediction" OR "risk assessment" OR "risk stratification" OR "prediction model*" OR "prognostic model*" OR "clinical prediction model*" OR "risk score*" OR "prediction algorithm*")

and model complexity.[14,17,19] High-performing models also reported strong accuracy, sensitivity, and specificity, with one study achieving an AUROC of 0.97 alongside balanced precision and recall metrics.[14] Larger cohort-based studies demonstrated robust performance with AUROC values above 0.80, highlighting the advantage of large datasets in improving model generalisability.[18] In contrast, studies with smaller sample sizes or limited predictors reported more modest performance, indicating variability influenced by study design and data quality.[15]

Validation strategies

Validation approaches across the included studies were predominantly internal, with limited use of external validation. Most studies employed techniques such as k-fold cross-validation, train–test split, or three-way data partitioning to assess model performance and reduce overfitting.[14-16] Some cohort studies incorporated temporal validation using follow-up data, which provided a stronger assessment of predictive performance over time.[18] However, external validation using independent datasets was largely absent, representing a significant methodological limitation. Additionally, while internal validation was commonly performed, calibration and clinical utility assessments were infrequently reported, limiting the evaluation of real-world applicability of these models.[19]

Risk of bias assessment

Overall, the risk of bias assessment using the PROBAST tool indicated that six of the eight studies have a high overall risk of bias, primarily due to concerns within the analysis domain (Table III). Common methodological limitations included reliance on internal validation only, inadequate assessment of model calibration, potential overfitting arising from small sample sizes relative to model complexity, and insufficient reporting of model development procedures. Two studies were judged to have a low overall risk of bias because they employed large cohort datasets and incorporated stronger validation approaches, including temporal or external validation. Across all studies, the participants, predictors, and outcome domains were generally assessed as having low risk of bias, reflecting appropriate population selection, clearly defined predictors, and well-established DR outcomes. Applicability concerns were considered low for all included studies because the study populations, predictors, and outcomes were consistent with the review objective of evaluating AI-driven prognostic models for predicting DR risk among adults with T2DM.

Certainty of evidence assessment

The certainty of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach adapted for prognostic model research. The assessment considered five key domains, namely risk of bias, consistency, directness, precision, and publication bias, while also taking into account methodological heterogeneity and the extent of external validation reported across studies. Evidence was downgraded when serious concerns were identified, particularly regarding risk of bias and heterogeneity. Overall, the certainty of evidence was judged to be moderate (Table IV). Although the included studies consistently demonstrated that AI–driven models, particularly ensemble learning approaches such as XGBoost, RF, and gradient boosting methods, achieved moderate to excellent predictive performance for DR risk prediction among individuals with T2DM, several limitations reduced confidence in the overall evidence.

Table II: Characteristics of included studies

No.	Authors (Year)	Country	Study Design	Sample Size	AI Model Characteristics	Predictor Variables	Model Performance	Validation Strategies	Conclusion
1	Yagin et al. (2023)14	Turkey	Retrospective cohort	317	XGBoost, NGBoost, Explainable Boosting Machine (EBM) with Bayesian optimisation	Key biomarkers: Trp, Tyr, C16, DMA	Accuracy 91.25%, Precision 89.33%, Recall 91.24%, F1-score 89.37%, AUROC 0.97	10-fold cross-validation, internal validation	XAI-based models demonstrated excellent predictive accuracy and identified key metabolomic biomarkers for DR stratification.
2	Kotsiliti et al. (2017)15	UK	Retrospective cohort	6375	Logistic regression (LASSO), Random Forest, Gradient Boosting	Duration of diabetes, HbA1c, ACR, age	AUROC 0.73–0.77 (best: GBM)	10-fold cross-validation	Clinical and biochemical variables can reasonably predict DR risk, with improved performance using longitudinal data.
3	Tsao et al. (2018)16	Taiwan	Cross-sectional	3539	SVM, Decision Tree, ANN, Logistic Regression	Insulin, duration of diabetes,	Accuracy 79.5%, AUROC 0.839	Train-test split, three-way split validation	ML models effectively identify high-risk individuals, with interpretable predictors supporting clinical decision-making.
4	Rosu et al. (2024)17	Romania	Cross-sectional	377	Random Forest, XGBoost, SVM	SBP, LDL, BMI	AUROC: RF 0.62, XGBoost 0.68 (improved to 0.72 after tuning)	Internal validation (model tuning)	Cardiovascular risk factors play a significant role in DR progression, though predictive performance was moderate.
5	Zhao et al. (2022)18	China	Retrospective cohort	7943	XGBoost and other ML models	SUA, LDL-C, TC, eGFR, TG, HbA1c	AUROC 0.803, Accuracy 88.9%, Sensitivity 74.0%, Specificity 81.1%	Train-test split, temporal validation	XGBoost model demonstrated strong predictive performance and enabled earlier identification of high-risk patients.
6	Li et al. (2021)19	China	Retrospective cohort	32,452	XGBoost, Logistic Regression, RF, SVM with SHAP	HbA1c >8%, nephropathy, creatinine >100 μmol/L, insulin use	AUROC 0.90 (XGBoost best)	Internal validation, SHAP interpretability	XGBoost achieved high predictive accuracy, with SHAP enhancing clinical interpretability of risk factors.
7	Jiang & Li (2024)20	China	Retrospective cohort	349	Decision Tree, K-Nearest Neighbours, Logistic Regression Model, RF, SVM, and XGBoost.	Disease duration, diabetic peripheral neuropathy, insulin dosage, urinary protein, albumin.	Best model: Logistic regression. Validation set: AUROC 0.894 (95% CI 0.833–0.955), Recall 0.92, Accuracy 0.781, F1-score 0.800.	Random 7:3 train-validation split; LASSO feature selection; 1,000-bootstrap internal validation.	Logistic regression demonstrated superior predictive performance compared with other ML algorithms.
8	Kim et al. (2025)21	South Korea	Retrospective cohort	14,694	RF, XGBoost, AdaBoost, CatBoost.	Dyslipidaemia, cancer, hypertension, chronic kidney disease, HbA1c variability, age, BMI.	Best model: XGBoost. AUROC: 0.824, Accuracy: 75.13%, Sensitivity: 71.00%, Specificity: 75.23%.	Hyperparameter tuning; Synthetic Minority Oversampling Technique (SMOTE); 10-fold stratified cross-validation.	XGBoost demonstrated the best predictive performance for DR within 3 years among patients with T2DM.

Notes: AI = artificial intelligence, AUROC = area under the receiver operating characteristic, ANN = artificial neural network, ACR = albumin-to-creatinine ratio, BMI = body mass index, BP = blood pressure, C16 = hexadecanoyl carnitine, DMA = dimethylarginine, DR = diabetic retinopathy, EBM = explainable boosting machine, eGFR = estimated glomerular filtration rate, HDL = high-density lipoprotein, LDL = low-density lipoprotein, ML = machine learning, NGBoost = natural gradient boosting, OR = odds ratio, RF = random forest, SHAP = Shapley Additive exPlanations, SBP = systolic blood pressure, SVM = support vector machine, TC = total cholesterol, TG = triglycerides, Trp = tryptophan, Tyr = tyrosine, XAI = explainable artificial intelligence

Table III: Summary of reporting bias of included studies using PROBAST

No.	Authors (Year)	Participants	Predictors	Outcome	Analysis	Overall Risk of Bias	Applicability Concerns
1	Yagin et al. (2023)[14]	Low	Low	Low	High	High	Low
2	Kotsiliti et al. (2017)[15]	Low	Low	Low	High	High	Low
3	Tsao et al. (2018)[16]	Low	Low	Low	High	High	Low
4	Rosu et al. (2024)[17]	Low	Low	Low	High	High	Low
5	Zhao et al. (2022)[18]	Low	Low	Low	Low	Low	Low
6	Li et al. (2021)[19]	Low	Low	Low	High	High	Low
7	Jiang & Li (2024)[20]	Low	Low	Low	High	High	Low
8	Kim et al. (2025)[21]	Low	Low	Low	Low	Low	Low

Table IV: Summary of certainty of evidence assessment

Domain	Assessment	Justification
Risk of Bias	Serious	Several studies demonstrated methodological limitations, particularly in the analysis domain, including reliance on internal validation, inadequate calibration assessment, and potential overfitting.
Consistency	Not Serious	Most studies consistently reported moderate to excellent predictive performance, with artificial intelligence models demonstrating acceptable to high discrimination ability.
Directness	Not Serious	All included studies directly evaluated artificial intelligence–driven prognostic models for predicting DR risk among adults with type 2 diabetes mellitus.
Precision	Not Serious	Most studies included adequate sample sizes and reported performance metrics with acceptable precision.
Publication Bias	Undetected	No clear evidence of publication bias was identified; however, formal assessment was not feasible due to the limited number of studies.
Heterogeneity	Serious	Substantial heterogeneity was observed in study populations, predictor variables, artificial intelligence algorithms, outcome definitions, and validation approaches.
External Validation	Serious	Only a minority of studies performed temporal or external validation, limiting confidence in the generalisability of the models.
Overall Certainty of Evidence	Moderate	The evidence consistently supports the potential of artificial intelligence–driven prognostic models for predicting DR risk; however, methodological limitations, heterogeneity, and limited external validation reduced the overall certainty of evidence.

Most studies were retrospective in design and relied predominantly on internal validation techniques, with only a limited number incorporating temporal or external validation. Considerable heterogeneity was observed across studies with respect to study populations, predictor variables, AI algorithms, outcome definitions, and reported performance metrics. Furthermore, several studies were judged to have a high risk of bias in the analysis domain based on the PROBAST assessment, particularly due to concerns regarding overfitting, calibration assessment, and insufficient reporting of model development procedures. Nevertheless, the consistency of findings across different settings and populations, together with generally favourable discrimination performance, supports a moderate level of confidence that AI–driven prognostic models can effectively predict DR risk among adults with T2DM. Further large-scale prospective studies with external validation are required to increase the certainty of the evidence and support wider clinical implementation.

DISCUSSION

This systematic review synthesises the findings of the present studies on AI-driven prognostic models for DR among individuals with T2DM, with a focus on interpreting their methodological, predictive performance, and clinical relevance. The included studies demonstrate a growing shift toward the use of advanced ML algorithms and high-dimensional data to improve early risk stratification of DR. However, despite promising performance metrics, there remains considerable heterogeneity in model development, predictor selection, and validation approaches. This section critically integrates the evidence across the key domains of AI model characteristics, predictor variables, model performance, and validation strategies, highlighting both the strengths and limitations of current approaches while situating the findings within the broader context of translational applicability and public health impact.

AI model characteristics

The landscape of AI models applied to DR prediction and prognosis encompasses a broad spectrum of algorithmic approaches. ML algorithms, including logistic regression, decision trees, naïve Bayes classifiers, random forests, SVMs, and gradient boosting machines, have been widely employed for structured clinical data analysis.[23] DL models, particularly convolutional neural networks (CNNs), represent the dominant approach for image-based DR detection and progression prediction.[24] Specific architectures that have been applied include Inception-v3, ResNet, VGG-16, VGG-19, and deep neural networks (DNNs).[25] Transfer learning, whereby models pre-trained on large natural image datasets are fine-tuned on medical images, has been a particularly effective strategy for overcoming limited training data availability.[26]

Previous study demonstrated that DNN models consistently outperformed five traditional ML models such as logistic regression, decision tree, naïve Bayes, RF, and SVM across all

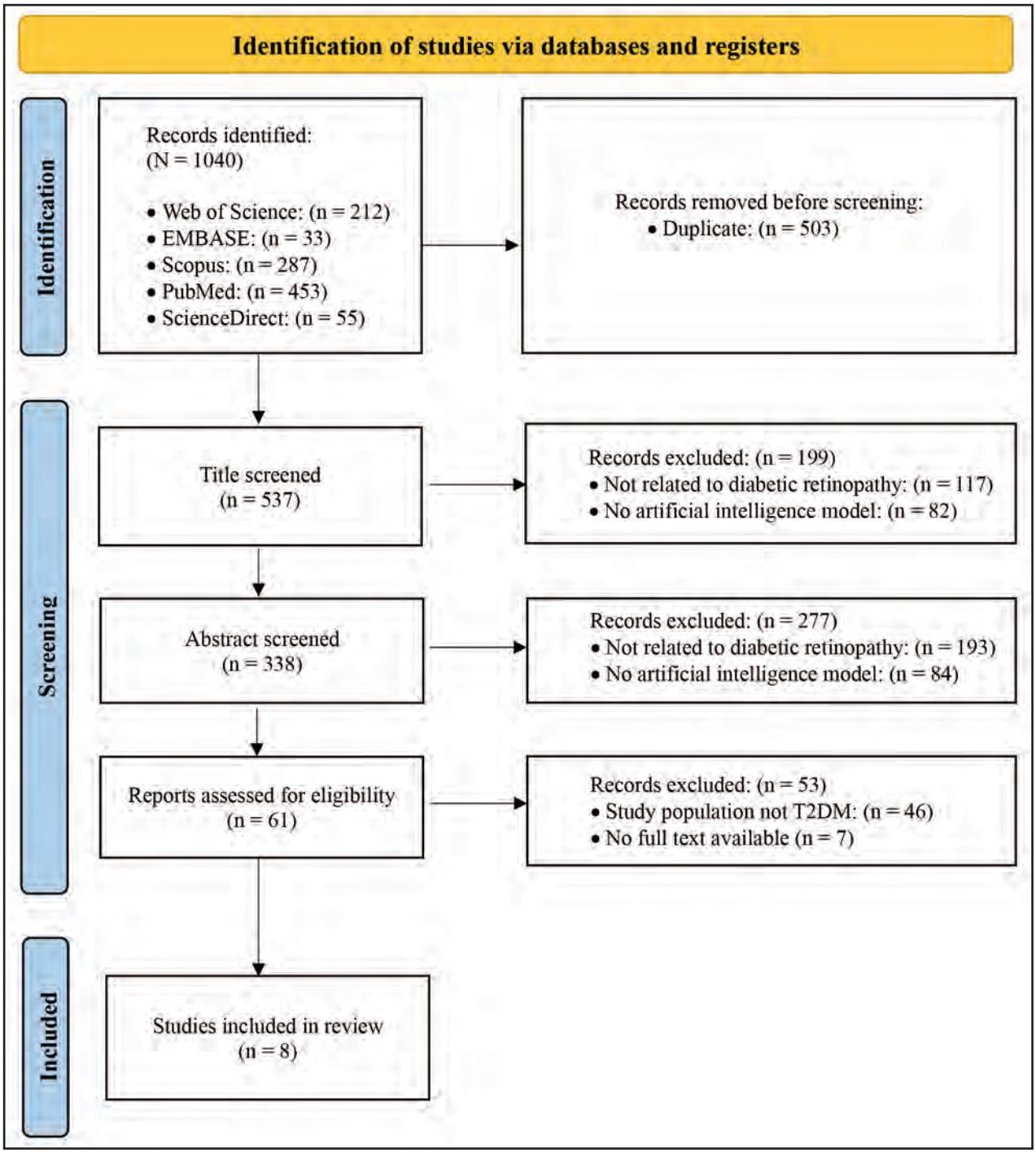

Fig. 1: Flowchart of the study selection process

evaluation metrics for predicting DR in patients with T2DM.[25] More recently, code-free DL (CFDL) or automated ML (AutoML) platforms have emerged as innovative tools that allow clinicians with limited coding experience to prototype novel clinical AI applications, demonstrating promising potential in DR care, including for DR progression prediction over time from ultra-wide-field images.27 Most of the study designs underlying AI model development for DR prediction are retrospective. The predominance of retrospective designs raises concerns about the generalizability of findings, as prospective validation in real-world clinical settings remains limited.[28]

Predictor variables

A consistent set of clinical and demographic predictor variables has been identified across multiple studies as being significantly associated with DR risk and progression. HbA1c has consistently emerged as one of the most significant predictors of DR. Previous study employed SHAP SHapley Additive exPlanations (SHAP) analysis to interpret their DL

model's predictions and found that HbA1c was one of the most significant predictors, with SHAP values validated against clinical reference standards for feature importance in DR.[25] Another study done found that HbA1c was significantly associated with DR, reinforcing its central role in prediction models.[29] Furthermore. the AI model developed in another study in 2025 similarly identified higher HbA1c levels as a risk factor for DR.[30]

Diabetes duration is another critical predictor, with longer duration consistently associated with increased DR risk because it reflects cumulative exposure to chronic hyperglycaemia. Persistent hyperglycaemia over time activates multiple pathogenic pathways, including the polyol pathway, formation of advanced glycation end-products (AGEs), activation of protein kinase C (PKC), and oxidative stress, which collectively contribute to retinal microvascular damage and endothelial dysfunction.[31] These mechanisms lead to structural alterations such as thickening of the capillary basement membrane and breakdown of the blood–retinal barrier, ultimately resulting in retinal ischemia and microaneurysm formation thereby increasing the likelihood of DR onset and progression.[32]

AI-specific methodological biases

In addition to conventional sources of bias encountered in prognostic model research, several AI-specific methodological biases were evident across the included studies and may have influenced the reported predictive performance. First, the widespread reliance on retrospective datasets and internal validation approaches increases the risk of model overfitting, whereby algorithms learn dataset-specific patterns that may not generalise to external populations. Second, many studies employed complex ML algorithms with limited transparency regarding feature selection, hyperparameter optimisation, and model tuning procedures, potentially introducing reproducibility and reporting bias. Third, algorithmic bias may arise from imbalances in patient characteristics, disease prevalence, ethnicity, healthcare utilisation patterns, or predictor distributions within the development datasets, resulting in systematic differences in model performance across populations.

Furthermore, several studies prioritised discrimination metrics such as AUROC and accuracy while providing limited assessment of calibration, model stability, and fairness, creating the risk of overly optimistic interpretations of predictive performance. The heterogeneity of predictor selection, outcome definitions, and data preprocessing methods across studies also introduces variability that may affect model transportability and external validity. Importantly, the limited use of explainable AI techniques restricts understanding of the underlying decision-making processes of complex algorithms, thereby reducing clinician trust and interpretability.[33] Collectively, these AI-specific methodological challenges highlight the need for greater adherence to emerging reporting and evaluation frameworks to improve transparency, reproducibility, fairness, and generalisability of future AI–driven prognostic models for DR prediction.

Model performance

The performance of AI models for DR prediction is typically evaluated using several standard metrics. The AUROC is the most commonly reported discriminative metric.34 Additional metrics include sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, F1 score, and for continuous outcomes, mean absolute error (MAE) and R^2.[7] For instance, recently published study reported that for all microvascular complications combined, predictive models achieved a mean c-statistic of 0.79 on internal validation and 0.72 on external validation.[35] Notably, DR models showed more modest performance compared to diabetic kidney disease models, which had the highest discrimination with c-statistics.

Apart from that, study done in China demonstrated that their DNN model outperformed traditional ML models for DR prediction, achieving accuracy of 0.778, F1 score of 0.776, and AUROC of 0.833, compared to logistic regression (accuracy 0.753, AUROC 0.822), decision tree (accuracy 0.630, AUROC 0.631), naïve Bayes (accuracy 0.718, AUROC 0.769), random forest (accuracy 0.758, AUROC 0.829), and SVM (accuracy 0.776, AUROC 0.831).25 Furthermore, another study done reported that Gaussian naïve Bayesian models accurately predicted diabetic complications including DR with an average AUROC of 0.86, while their expert-selected model achieved an average AUROC of 0.84 with 21 curated variables.[23] A critical concern in AI model performance is the variability observed across different populations and settings.

Validation strategies

Internal validation methods are essential for assessing model performance during development and for mitigating overfitting. The most commonly employed internal validation strategies include split-sample (hold-out) validation, cross-validation (k-fold, nested), bootstrapping, and temporal validation.[36] For example, internal validation methods was classified into into split-sample, bootstrapping, cross-validation, and temporal validation, noting that studies using temporal validation were categorized as internal validation regardless of how the studies labelled them.[34] Cross-validation, particularly k-fold cross-validation, has been widely adopted. For instance, a study done in China, the authors validated their model performance using 10-fold cross-validation.[37] This approach reduces the effective sample size available for developing the model compared to bootstrap and cross-validation procedures.[36]

External validation is widely recognized as a crucial step in establishing the generalizability and clinical applicability of AI prediction models. External validation is defined as the testing of AI on a new set of data entirely separate from the training dataset, noting it as a crucial step demonstrating that an AI model can work in patients and populations external to the development population.[28] In their scoping review of AI for DR in low-income and middle-income countries, they found that only 43 studies (52%) met their definition of external validation. Prospective validation represents the gold standard for demonstrating real-world clinical utility. For example, a previous study conducted a prospective pilot study with 3,081 patients to demonstrate the

broader applicability of their AI system at the "point-of-care" using fundus images captured with smartphones.[38]

Clinical utility of AI-driven prognostic models

From a clinical and public health perspective, these models can support the early identification of individuals at elevated risk of developing DR before the onset of clinically detectable retinal changes, thereby enabling timely implementation of preventive interventions, optimisation of glycaemic and cardiovascular risk factor control, and prioritisation of ophthalmological surveillance.[39] This is particularly relevant given the growing burden of T2DM and the limited capacity of healthcare systems to provide universal intensive retinal screening. By stratifying patients according to their predicted risk, AI-driven prognostic models may enable more efficient allocation of healthcare resources through risk-based screening strategies, whereby high-risk individuals undergo more frequent monitoring while lower-risk individuals are screened at longer intervals. Such an approach has the potential to improve cost-effectiveness, reduce unnecessary healthcare utilisation, and enhance patient outcomes without compromising safety.[40] Furthermore, the integration of these models within electronic health record systems could facilitate automated risk estimation at the point of care, supporting clinicians in shared decision-making and personalised treatment planning.

Future research direction

Future research should prioritize large-sample, multicentre external validation to address the pervasive high risk of bias identified across existing prediction models. Researchers should develop multimodal models integrating retinal imaging with clinical data, as hybrid approaches consistently enhance predictive performance. Apart from that, future research should also develop dynamic prediction models that can be updated with new patient data over time, enabling continuous risk reassessment and personalized screening intervals. The integration of longitudinal data from electronic health records, continuous glucose monitoring, and serial retinal imaging could enable truly personalized DR management strategies.

LIMITATIONS

Several limitations should be considered when interpreting the findings of this review. First, there was substantial heterogeneity across the included studies in terms of study design, population characteristics, types of AI algorithms, predictor variables, and outcome definitions, which precluded quantitative synthesis and limited direct comparability of results. Second, most studies relied on retrospective or cross-sectional data with predominantly internal validation approaches, while external validation using independent datasets was largely lacking, raising concerns about the generalisability and real-world applicability of the models. Third, reporting of model performance was inconsistent, with a primary focus on discrimination metrics (e.g., AUROC) and limited assessment of calibration and clinical utility. Finally, many studies utilised ML–based feature importance rather than conventional epidemiological effect estimates such as adjusted hazard ratios, restricting interpretability from a clinical perspective.

CONCLUSION

This systematic review demonstrates that AI-driven prognostic models show considerable promise in predicting the risk of DR among individuals with T2DM, with several studies reporting moderate to high predictive performance, particularly for ensemble algorithms such as XGBoost. These models consistently integrate both traditional clinical risk factors and emerging high-dimensional biomarkers, reflecting a shift toward more precise and data-driven risk stratification. However, despite encouraging results, the current evidence is limited by methodological heterogeneity, reliance on internal validation, and insufficient reporting of calibration and clinical utility, which constrain their translation into routine practice. Future research should prioritise standardised reporting, robust external validation, and integration of clinically interpretable models to enhance reliability and facilitate adoption in real-world healthcare settings, ultimately supporting early detection and prevention of DR.

CONFLICT OF INTEREST

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ETHICS APPROVAL

This systematic review followed PRISMA guidelines. It used only publicly available data from the specified databases, with no primary data collection. Ethics approval is not applicable.

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Translating communication partner training evidence for multilingual aphasia rehabilitation in Malaysia: A structured narrative review

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ABSTRACT

Introduction: Aphasia affects everyday communication, social participation, and caregiver wellbeing. Communication partner training (CPT) is a participation-oriented intervention that equips familiar partners with strategies to support communication in daily interactions. However, most CPT evidence is drawn from monolingual contexts, limiting applicability to multilingual settings such as Malaysia. This structured narrative review synthesised evidence on CPT effectiveness, implementation determinants, delivery modalities including telepractice and hybrid care, and multilingual aphasia rehabilitation, with the aim of translating these findings to the Malaysian rehabilitation context.

Materials and Methods: A structured narrative review was conducted to synthesis the evidence thematically. Evidence was purposively selected to capture CPT effectiveness, caregiver and participation outcomes, implementation determinants, telepractice delivery, multilingual aphasia, and Malaysian service contexts. Findings were synthesised thematically.

Results: CPT consistently improves partner communication behaviours and dyadic conversation outcomes, particularly with trained partners. In contrast, caregiver wellbeing and communication participation outcomes are measured less consistently. Implementation evidence identifies barriers related to time, resources, and service organisation, alongside facilitators such as structured training materials, coaching, and organisational support. Telepractice is a feasible CPT delivery mode, with hybrid approaches offering improved access and flexibility. Multilingual evidence indicates variable cross-language generalisation, highlighting the importance of context-sensitive and flexible CPT designs.

Conclusion: CPT has strong evidence as a participation-focused intervention for improving trained partner behaviours and dyadic communication outcomes in aphasia. Its application to multilingual rehabilitation contexts, including Malaysia, requires careful adaptation to family language use, caregiver readiness, delivery feasibility, and service resources. Integrating implementation strategies, telepractice, and multilingual considerations is essential for translation into routine care. A modular, caregiver-centred CPT framework may provide a practical foundation for future co-design, piloting, and evaluation in Malaysian rehabilitation services.

KEYWORDS:
Aphasia, communication partner training, telepractice, caregiver training, multilingual rehabilitation

INTRODUCTION

Aphasia is an acquired language disorder, often caused by stroke, that can affect understanding, speaking, reading, and writing.[1] It is more than a language impairment; it disrupts conversations, social participation, and identity and has significant repercussions on the wellbeing of people with aphasia (PWA) and their caregivers.[2] Families often serve as primary communication partners and informal co-therapists for PWA. Consequently, caregiver education and training are essential components of aphasia rehabilitation.

Communication partner training (CPT) is a participation-oriented, environmental approach where familiar partners are trained to facilitate everyday communication with a person with aphasia.[3] CPT has a robust evidence base, with systematic reviews showing positive effects on partner communication behaviours and dyadic conversation outcomes, particularly when the person with aphasia converses with the trained partner.[4] More recently, a synthesis of implementation evidence identified barriers and facilitators to real-world CPT uptake, including resource availability, training materials, and service readiness.[5] Simultaneously, emerging studies investigating brief and

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online CPT packages for health professional trainees report improved knowledge and attitudes towards the treatment of PWA and may inform scalable dissemination routes that could supplement family-centred CPT models.[6-7]

Additionally, much of the CPT evidence has emerged from monolingual and high-income contexts, limiting its immediate applicability to multilingual societies in Southeast Asia. Malaysia is a pertinent example. Malaysian households may use Malay, English, Mandarin, Tamil, regional dialects and other languages, often with code-switching and different language preferences across family members, creating additional challenges for caregiver training and clinician-family communication.

CPT can also be delivered virtually through telepractice, which may improve access when travel, caregiver work commitments, geography, or limited specialist services reduce attendance at face-to-face sessions.[8] However, feasibility depends on connectivity, digital confidence, privacy, and appropriate service support.[8-11]

The aim of this structured narrative review was to synthesise evidence on caregiver communication partner training (CPT), including evidence on effectiveness, implementation, delivery modalities, and multilingual aphasia rehabilitation, and to consider how these findings may inform culturally and linguistically responsive caregiver CPT in Malaysia. This review addressed the following questions:(1) What evidence is available regarding the effectiveness and core components of caregiver communication partner training for people with aphasia? (2) What implementation barriers and facilitators influence the delivery of caregiver CPT in clinical, community, and home-based contexts? (3) How can different delivery modalities, including face-to-face, telepractice, and hybrid approaches, support caregiver CPT implementation? (4) What multilingual, cultural, and Malaysian contextual considerations should inform the co-design, piloting, and evaluation of caregiver CPT programmes?

MATERIALS AND METHODS

A structured narrative review was conducted to integrate evidence on caregiver CPT, implementation, telepractice, multilingual aphasia, and Malaysian rehabilitation contexts. The review followed the three phases and nine steps described by Juntunen and Lehenkari.[12]

Selecting the topic

The review focused on caregiver communication partner training for aphasia in multilingual rehabilitation contexts, with Malaysia as the exemplar setting.

Defining the objectives and formulating the review questions
The review objective and questions were formulated to address CPT effectiveness, implementation, delivery modalities, and multilingual adaptation within the Malaysian rehabilitation context.

Developing and validating the review protocol

A review protocol specifying the review aim, conceptual domains, literature sources, selection criteria, and synthesis approach was developed and refined by all authors. The protocol was not registered because this was a narrative rather than systematic review.

Searching the literature

A purposive literature search, last updated in December 2025, was conducted in PubMed, Scopus, Google Scholar, and selected journal portals. Reference lists and key papers were also manually searched. Search terms covered caregiver CPT, implementation and service delivery, delivery modalities, multilingual aphasia, and Malaysian or regional rehabilitation contexts. The search domains and example keywords are presented in Table I.

Selecting the literature

Literature was purposively selected based on relevance to the review questions. Core synthesis sources addressed caregiver CPT or supported conversation, caregiver-mediated intervention, aphasia telepractice, implementation barriers and facilitators, bilingual or multilingual aphasia intervention, cross-language generalisation, or Malaysian and regional speech-language therapy services. Sources focusing exclusively on paediatric populations, non-aphasia communication disorders, impairment-based therapy without partner involvement, unrelated telehealth, or general caregiver support were excluded. Foundational and contextual sources were retained for background but were not included in the thematic synthesis. The final synthesis included 14 core sources, summarised in Table II.

Analysing the literature

Selected literature was organised according to the review questions and conceptual domains. Key information was extracted on study focus, population, intervention or service model, caregiver and participation outcomes, multilingual relevance, and implementation implications.

Synthesising the literature

The literature was synthesised thematically into six domains: CPT effectiveness and dyadic communication outcomes; caregiver and participation outcomes; implementation barriers and facilitators; telepractice and hybrid delivery; multilingual and cross-language considerations; and Malaysia-specific service delivery evidence. Evidence was classified as direct CPT evidence, related evidence, or context-informed interpretation.

Drawing conclusion

Conclusions were drawn by integrating findings across the evidence domains while distinguishing direct CPT evidence from related and context-informed evidence.

Reporting

Findings were reported using an IMRaD structure, with Results organised according to the six synthesis domains and the Discussion interpreting their implications for multilingual Malaysian rehabilitation practice.

RESULTS

The thematic synthesis included 14 core sources spanning CPT effectiveness, implementation, telepractice, multilingual

Table I: Search domains and example keywords used in the narrative review

Search domain	Purpose	Keywords
Caregiver communication partner training	To identify evidence on CPT effectiveness, intervention components, and caregiver-mediated communication support	aphasia, communication partner training, caregiver training, family training, supported conversation, conversation partner, communication strategies
Implementation and service delivery	To identify barriers, facilitators, and practical determinants affecting CPT uptake in routine care	implementation, barriers, facilitators, rehabilitation service delivery, training materials, caregiver engagement, clinician training, fidelity
Delivery modality	To examine face-to-face, telepractice, and hybrid approaches relevant to caregiver CPT delivery	telepractice, telerehabilitation, telehealth, online training, hybrid delivery, remote coaching, aphasia therapy
Multilingual and bilingual aphasia rehabilitation	To identify language-related considerations for adapting CPT to multilingual households To contextualise CPT implementation for	bilingual aphasia, multilingual aphasia, cross-language generalisation, code-switching, translanguaging, language dominance, culturally responsive rehabilitation
Malaysian and regional context	Malaysia and similar multilingual rehabilitation settings	Malaysia, Malaysian speech-language therapy, aphasia Malaysia, caregiver rehabilitation, telepractice Malaysia, multilingual rehabilitation, AAC aphasia

aphasia rehabilitation, and Malaysian service delivery. The characteristics and contributions of these sources are summarised in Table II.

CPT effectiveness and dyadic communication outcomes

Systematic reviews indicate that CPT improves trained partner communication behaviours and dyadic interaction outcomes in people with aphasia.[3-4] The reported benefits are most consistent when outcomes are measured within conversations involving the trained communication partner. This supports CPT as a participation-oriented intervention that modifies the communication environment rather than focusing solely on impairment-level language recovery.[3-4] Despite variation in intervention format and dosage, the overall evidence supports CPT for improving trained partner behaviours and dyadic communication outcomes.[3-4]

Caregiver and participation outcomes

Compared with partner communication behaviours and dyadic conversation outcomes, caregiver-centred outcomes were less consistently reported. Caregiver outcomes were often secondary or exploratory. Where caregiver-related variables were examined, findings suggested potential benefits for caregiver confidence and perceived ease of communication. However, methodological variation limits conclusions regarding caregiver wellbeing.[3-4]

Participation outcomes for people with aphasia were also inconsistently operationalised. Some evidence suggests improved functional communication and participation within trained dyads, but broader participation outcomes were not consistently measured. This highlights the need for a clearer outcome framework, particularly in multilingual contexts. Recommended outcome domains and measures are summarised in Table III.

Implementation barriers and facilitators

Implementation evidence indicates that the uptake of CPT in routine services is influenced by individual, service-level, and system-level determinants. Common barriers include limited clinician time, high caseloads, caregiver availability, insufficient training resources, and competing service demands.[5] In multilingual contexts, language mismatch, limited culturally appropriate materials, literacy, and digital confidence may create additional barriers. Facilitators include structured materials, clinician modelling, coaching, organisational support, and follow-up.[5] Table IV summarises implementation determinants and practical strategies using a theory-informed approach.

Telepractice evidence for aphasia rehabilitation and caregiver training

Telepractice evidence provides related, rather than exclusively CPT-specific, support for alternative modes of aphasia rehabilitation delivery. Remote aphasia rehabilitation appears feasible and may produce outcomes comparable to face-to-face delivery in selected contexts.[9,10,13] For caregiver CPT, telepractice may support home-based coaching, reduce travel demands, and facilitate follow-up. Implementation may be limited by connectivity, privacy, digital confidence, and clinician readiness.[9,10,13] The evidence therefore supports telepractice as one possible delivery modality for CPT, rather than as a replacement for all face-to-face services. Hybrid delivery may combine initial face-to-face assessment and coaching with remote follow-up and booster training.

Multilingual evidence and cross-language considerations

Evidence directly addressing multilingual caregiver CPT remains limited. Most available evidence comes from bilingual or multilingual aphasia intervention rather than caregiver CPT, with cross-language generalisation varying according to language history, dominance, proficiency, and use.[15-16] Caregiver CPT should therefore not assume a single default language for all interactions. Clinicians should consider language history, current abilities, preferred language use, caregiver proficiency, and household communication demands. Strategies may include flexible language choice, code-switching, use of the most functional shared language, and multimodal communication supports. These recommendations should be interpreted as evidence-informed and context-informed adaptations rather than direct evidence of multilingual caregiver CPT effectiveness and require further evaluation in Malaysia.

Malaysia-specific service delivery evidence

Malaysia-specific evidence provides contextual support for the relevance of flexible and culturally responsive CPT

Table II: Core evidence sources informing the thematic synthesis

Study	Study type	Participants / context	Intervention or focus	Caregiver outcomes reported	Participation outcomes reported	Multilingual, telepractice, or implementation relevance
Simmons-Mackie et al., 2010	Systematic review	People with aphasia and communication partners	CPT effectiveness	Caregiver wellbeing not consistently reported; focus was partner behaviour.	Improved communication activity/participation with trained partners.	Direct evidence for CPT improving partner communication and dyadic interaction.
Simmons-Mackie et al., 2016	Updated systematic review	Evidence across 56 studies	Updated CPT evidence	Partner knowledge and skills improved; caregiver wellbeing less prominent.	Some evidence of improved interaction participation with trained partners.	Strengthens evidence for CPT effects on trained partner behaviours and dyadic outcomes.
Shrubsole et al., 2023	Systematic review and theory-informed synthesis	Studies on SLT implementation of CPT with familiar partners	Barriers and facilitators to CPT implementation mapped to TDF	Caregiver-related findings focused on engagement, availability, and feasibility.	Participation was not the main outcome; focus was implementation feasibility and sustainability.	Identifies key barriers such as time, resources, service readiness, training, and caregiver availability; facilitators include materials, coaching, organisational support, and reinforcement.
Power et al., 2024	Training efficacy study	Student healthcare professionals	Online CPT training package	Not a caregiver outcome study; outcomes related to trainee knowledge, attitudes, and confidence.	Not a direct PWA participation outcome study.	Supports potential scalability of brief online CPT training models.
Anjum and Husak, 2025	Pilot study	Informal caregivers and people with aphasia	Telepractice-delivered communication training	Caregivers applied strategies and reported fewer communication breakdowns.	Everyday interaction improved indirectly through fewer breakdowns.	Direct caregiver-focused telepractice evidence, although based on a small pilot sample.
Hall et al., 2013	Systematic review	Aphasia telepractice assessment and treatment studies	Telepractice in aphasia assessment and treatment	Caregiver outcomes not primary.	Telepractice was reported as a viable aphasia service delivery method.	Foundational evidence supporting telepractice as an alternative delivery mode.
Cacciante et al., 2021	Systematic review and meta-analysis	People with aphasia receiving telerehabilitation	Telerehabilitation for aphasia	Caregiver outcomes not primary.	Telerehabilitation may be comparable to face-to-face therapy for selected aphasia outcomes.	Supports feasibility of telepractice delivery in aphasia rehabilitation.
Cetinkaya et al., 2024	Systematic review	Aphasia telerehabilitation studies	Telerehabilitation feasibility, acceptability, and effectiveness	Caregiver outcomes not primary.	Evidence of feasibility and clinical benefit, with variable study designs.	Provides updated telepractice evidence for aphasia rehabilitation.
Dunne et al., 2023	Intervention study	Adults with aphasia receiving telepractice group conversation treatment	Telepractice group conversation treatment	Caregiver outcomes not the focus.	Patient-reported and socially oriented outcomes were examined.	Related evidence for conversation-based aphasia intervention via telepractice; not caregiver CPT-specific.
Peñaloza et al., 2021	Retrospective comparative treatment study	Sixteen Spanish-English bilingual adults with chronic post-stroke aphasia	Semantic feature analysis via telerehabilitation or in-person therapy	Caregiver outcomes not the focus.	Secondary language outcomes examined; participation not primary.	Supports consideration of language choice and cross-language effects in bilingual aphasia rehabilitation.
Goral et al., 2023	Meta-analysis	Multilingual people with post-stroke aphasia across 40 studies	Cross-language generalisation of language treatment	Caregiver outcomes not the focus.	Participation outcomes varied and were not the main focus.	Core multilingual evidence: stronger treated-language effects, weaker but possible cross-language transfer, moderated by language history and context.

Table II: Core evidence sources informing the thematic synthesis

Study	Study type	Participants / context	Intervention	Caregiver outcomes reported	Participation outcomes reported	Multilingual, telepractice, or implementation relevance
Hassan et al., 2023	Comparative service evaluation	Clients and caregivers receiving conventional, virtual, or hybrid SLT in Malaysia	Satisfaction with different SLT delivery modes	Caregiver satisfaction directly examined.	Participation outcomes not primary.	Malaysia-specific support for flexible and hybrid service delivery.
Singh et al., 2022	Survey study	Malaysian speech-language pathologists	Implementation of telepractice during COVID-19	Caregiver outcomes not directly examined.	Participation outcomes not directly examined.	Malaysia-specific evidence on telepractice uptake, service readiness, and practical barriers.
Singh et al., 2024	Qualitative / service experience study	Malaysian SLTs and caregivers of individuals with aphasia	AAC practices and experiences in aphasia care	Caregiver perspectives included.	Participation addressed indirectly through AAC use in daily communication.	Supports culturally and linguistically relevant low-tech and AAC communication supports in Malaysia.

Table III: Recommended outcomes and measures for evaluating multilingual caregiver CPT

Outcome domain	Examples of measures	Respondent	Timing	What improvement looks like	Notes for multilingual contexts
Partner communication skills and supportiveness	Observed conversation rating, MSC/MPC where used, interaction checklist	Clinician rater, dyad video	Baseline, post, follow-up	More supportive partner turns, fewer breakdowns, better verification	Rate mixed-language turns consistently, focus on successful meaning making
Functional communication in daily life	CETI, functional communication questionnaires, goal-based ratings	Caregiver and PWA	Baseline, post, follow-up	Easier everyday exchanges, better completion of routine tasks	Use household language(s) used in the task, include code-switching contexts
Communication participation	CPIB or participation scales, participation goal attainment	PWA (supported), caregiver	Baseline, post, follow-up	More participation in conversations and social situations	Ensure items reflect local participation contexts, family and community settings
Caregiver confidence and self-efficacy	Self-efficacy scales, confidence ratings, training satisfaction	Caregiver	Baseline, post, booster	More confidence managing breakdowns, better strategy use	Provide bilingual forms or audio administration where needed
Caregiver burden and wellbeing	Caregiver strain or burden scales, wellbeing ratings	Caregiver	Baseline, post, follow-up	Reduced perceived burden and stress around communication	Interpret alongside caregiving context, include brief qualitative comments
Feasibility and acceptability	Attendance, completion, dropout, usability, telepractice satisfaction	Caregiver, clinician	During programme, post	High completion, manageable time demands, high satisfaction	Capture tech issues, connectivity, privacy concerns, language matching needs

Table IV: Implementation determinants and practical strategies for CPT delivery (TDF-informed synthesis)

Determinant domain (TDF-aligned)	Common barriers in services	Facilitators	Practical strategies for delivery
Knowledge and skills (clinician and caregiver)	Limited CPT training, uncertainty about coaching, caregiver unfamiliarity	Structured manuals, modelling, supervision	Use standard modules, provide scripts and checklists, train clinicians in coaching and feedback
Environmental context and resources	Time constraints, high caseloads, travel burden, limited materials	Hybrid delivery, ready-to-use resources, telepractice infrastructure	Short sessions with homework, tele-coaching follow-up, reusable handouts and videos
Social influences and roles	Caregiver availability, family dynamics, low engagement	Goal alignment, family champions, peer support	Collaborative goal setting, including another family member, group sessions or buddy system
Beliefs about consequences and motivation	Perceived low benefit, preference for impairment therapy	Early quick wins, visible progress, meaningful goals	Start with high-impact routines, track small changes, share before and after conversation clips
Behaviour regulation and reinforcement	Drop-off over time, inconsistent practice	Booster sessions, reminders, self-monitoring tools	Booster plan for 2 to 6 weeks, caregiver log, prompts, fidelity checklist
Equity and access (contextual)	Digital divide, language mismatch, low literacy	Language matching, culturally adapted materials	Offer bilingual materials, allow audio administration, use visuals, provide tech orientation

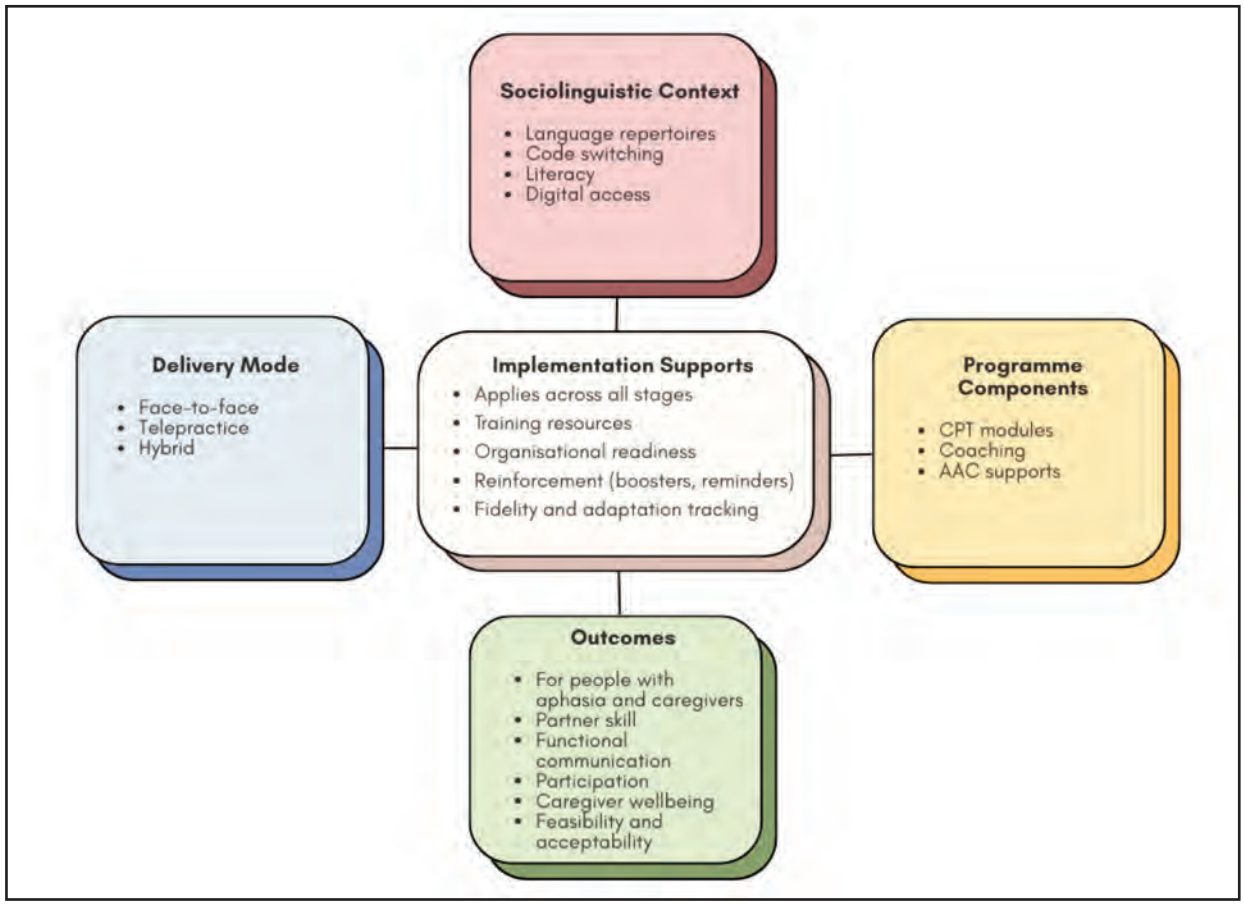

Fig. 1: Conceptual model linking multilingual context, caregiver CPT components, delivery modality, implementation support, and outcome evaluation in aphasia rehabilitation

models. Local studies indicate that Malaysian speech-language therapy services have used conventional, virtual, and hybrid service delivery models, especially during and after the COVID-19 period.[17-18] Local evidence also highlights service access, caregiver involvement, telepractice readiness, and AAC use in aphasia care.[17-19] Hybrid delivery may therefore be appropriate for some Malaysian settings.

DISCUSSION

Principal findings and interpretation

This structured narrative review integrated evidence from caregiver communication partner training (CPT), implementation literature, telepractice and hybrid delivery, multilingual aphasia rehabilitation, and Malaysian service delivery contexts. The strongest and most direct evidence supports CPT as a participation-oriented intervention that improves trained partner communication behaviours and dyadic communication outcomes in aphasia.[3-4]

However, the evidence was uneven across domains. Caregiver wellbeing and broader participation outcomes were clinically important but less consistently measured. Implementation evidence highlighted practical barriers and facilitators related to clinician time, caregiver availability, service organisation, training materials, coaching, and organisational support.[5] Telepractice evidence supported remote and hybrid delivery as feasible service options in selected contexts, but this evidence was not always specific to caregiver CPT.[9-10,13] Similarly, multilingual aphasia evidence provided important guidance on language planning and cross-language considerations, but direct evidence on caregiver CPT specifically designed for multilingual households remained limited.[15-16] Therefore, the recommendations proposed in this review should be interpreted as evidence-informed and context-informed, rather than as a fully validated Malaysian CPT programme.

Clinical implications for caregiver CPT

The findings support the clinical value of training familiar communication partners to use supportive strategies during everyday interactions with people with aphasia. For clinicians, this shifts the focus from therapy tasks alone to the communicative ecology of the person with aphasia, including caregiver behaviours, family routines, conversation demands, and the home environment. Core CPT strategies, such as simplifying language, verifying understanding, using written keywords, allowing additional response time, using gesture, and repairing breakdowns respectfully, are practical and relevant to daily family communication.[3-4]

A key clinical implication is that caregiver CPT should be structured around meaningful routines rather than generic education alone. Training is likely to be more useful when caregivers can practise strategies during high-frequency activities such as meals, medication routines, appointments, family conversations, religious or community activities, and mobile phone communication. This approach may also support caregiver engagement because it allows families to observe immediate and meaningful changes in everyday communication.

In multilingual contexts, clinicians should avoid assuming that one language is always the most appropriate language for communication. Instead, caregiver CPT should include discussion of language history, current language strengths, caregiver language proficiency, preferred household language use, and the communication demands of specific routines. Strategies may need to be practised in the dominant language, in more than one language, or through flexible mixed-language communication, depending on the needs of the person with aphasia and the caregiver.

Proposed modular framework for multilingual caregiver CPT

The proposed modules in Table V should be interpreted as an evidence-informed and context-informed framework rather than as a programme that has already been empirically tested in Malaysia. Core CPT components, such as supported conversation, breakdown repair, partner coaching, and practice within everyday routines, are supported by CPT evidence.[3-4] Recommendations relating to tele-coaching and hybrid delivery are informed by telepractice and implementation literature.[5,9-10,13] Multilingual adaptations, including flexible language choice, code-switching, culturally familiar scenarios, and multilingual low-tech supports, are informed by multilingual aphasia evidence and contextual interpretation for Malaysian households.[15-16] This distinction is important because direct evidence on caregiver CPT specifically designed for multilingual Malaysian families remains limited.

The relationship between the evidence domains and the proposed implementation pathway is illustrated in Figure 1. The model positions multilingual and sociolinguistic context as the starting point for caregiver CPT planning, followed by programme components, delivery modality, implementation support, and outcome evaluation. This structure reflects the main findings of the review: CPT strategies require adaptation to family language use and daily routines, delivery may occur through face-to-face, telepractice, or hybrid formats, and successful implementation depends on practical supports such as caregiver coaching, reusable materials, language-appropriate resources, and follow-up. Figure 1 therefore provides a visual summary of how the thematic findings can be translated into a multilingual caregiver CPT framework for Malaysian rehabilitation practice.

Implementation and service delivery, from efficacy to routine care

Implementation evidence indicates that the main challenges to CPT scale-up are practical rather than conceptual. Barriers include limited clinician time, high caseloads, lack of standardised materials, caregiver availability, travel burden, and service models that prioritise impairment-based therapy over participation-focused intervention.[5] These barriers are especially relevant in settings where speech-language therapy resources are limited and where caregivers may have work, transport, financial, or family responsibilities that reduce attendance.

The implementation determinants summarised in Table IV provide practical guidance for making CPT more deliverable in routine services. A feasible model may include short,

structured sessions, reusable caregiver handouts, video examples, home practice tasks, fidelity checklists, and planned booster sessions. These components may help clinicians integrate CPT into routine rehabilitation without requiring a separate service model.

For multilingual Malaysian practice, implementation should also include documentation of adaptations. Clinicians should record the language or languages used in training, the caregiver's preferred language, the person with aphasia's functional language profile, use of code-switching, literacy considerations, and any culturally specific materials used. Without such documentation, it will be difficult to evaluate which adaptations are useful, which components are essential, and how outcomes should be interpreted across different families.

Telepractice and hybrid delivery, advantages and constraints
Telepractice offers several potential advantages for caregiver CPT, including reduced travel burden, increased caregiver involvement, flexible scheduling, and the opportunity to coach caregivers within the home communication environment.[9,10,13] These advantages are particularly relevant for families who live far from specialist services or who have difficulty attending repeated face-to-face appointments.

However, telepractice should be viewed as one delivery modality rather than the central organising feature of CPT. Its suitability depends on access to devices, internet connectivity, caregiver digital confidence, privacy, family readiness, and clinician skill in remote coaching. If these conditions are not met, telepractice may increase rather than reduce inequity. For this reason, hybrid delivery may be more appropriate for many Malaysian settings. Initial face-to-face sessions can support assessment, rapport building, communication profiling, and early strategy coaching, while telepractice can be used for follow-up, troubleshooting, booster sessions, and reinforcement of home practice.

Malaysia-specific considerations and service relevance
Malaysia provides a highly relevant context for multilingual caregiver CPT because everyday communication often occurs across Malay, English, Mandarin, Tamil, regional Malay dialects, and other community languages. Families may also use code-switching or different languages with different members of the household. This sociolinguistic reality means that caregiver CPT cannot be based only on a monolingual model of communication.

Malaysia-specific service evidence also highlights the importance of flexible delivery. Local studies indicate that Malaysian speech-language therapy services have used conventional, virtual, and hybrid models, with service satisfaction and feasibility influenced by access, support, infrastructure, and family needs.[17-18] Evidence related to augmentative and alternative communication in Malaysian aphasia care also supports the need for culturally and linguistically relevant materials.[19] These findings suggest that caregiver CPT in Malaysia should be family-centred, multilingual, flexible, and responsive to service constraints.

LIMITATIONS

There were several limitations that should be acknowledged. First, this was a structured narrative review rather than a systematic review. Therefore, database-level retrieval counts, formal risk-of-bias assessment, and meta-analysis were not undertaken. Second, the evidence base was uneven. CPT effectiveness is supported by systematic review evidence, while caregiver wellbeing, broader participation outcomes, and multilingual caregiver CPT are less consistently studied. Third, direct evidence on caregiver CPT in multilingual Malaysian households remains limited. As a result, some recommendations in this review are based on related evidence and contextual interpretation rather than direct empirical testing.

Implications for future research
Future research should prioritise the co-design, piloting, and evaluation of caregiver CPT programmes for multilingual Malaysian families. Studies should examine feasibility, acceptability, caregiver confidence, dyadic communication outcomes, communication participation, and caregiver wellbeing. Research should also document language use, code-switching patterns, language dominance, caregiver language proficiency, and the language or languages used during intervention. This would allow future studies to determine whether multilingual adaptations improve clinical relevance, caregiver engagement, and communication outcomes.

Further work is also needed to evaluate hybrid CPT delivery models in Malaysia. Such studies should examine which components are best delivered face-to-face, which can be delivered remotely, and what support caregivers need to participate effectively. A minimum outcome set for multilingual caregiver CPT may also help standardise future evaluation and improve comparison across studies.

CONCLUSION

This structured narrative review supports caregiver communication partner training as a clinically relevant, participation-oriented approach for aphasia rehabilitation. The strongest evidence relates to improvements in trained partner communication behaviours and dyadic communication outcomes. Evidence for caregiver wellbeing, broader participation outcomes, and multilingual caregiver CPT remains less consistently developed, highlighting the need for more targeted research in these areas. For multilingual Malaysia, the findings suggest that caregiver CPT should be adapted carefully to family language use, caregiver readiness, cultural context, service resources, and delivery feasibility. Telepractice and hybrid delivery may improve access and support home-based coaching, but they should be implemented with attention to digital access, privacy, caregiver confidence, and language suitability. The proposed modular framework provides an evidence-informed and context-informed foundation for the co-design, piloting, and evaluation of multilingual caregiver CPT in Malaysian rehabilitation services.

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CONFLICT OF INTEREST

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

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SYSTEMATIC / NARRATIVE REVIEW ARTICLE

Determinants of patients' participation in cardiac rehabilitation programs: A scoping review

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ABSTRACT

Introduction: Cardiac rehabilitation (CR) has been shown to reduce morbidity and mortality while enhancing quality of life in patients with cardiovascular disease. Despite these benefits, participation in CR programs remains low globally. This scoping review aimed to map the determinants influencing patients' participation in CR.

Materials and Methods: A systematic search of peer-reviewed publications from 2016 to 2023 was performed. Studies were included if they examined patient-level or system-level determinants affecting participation in Phase II CR. Data was systematically extracted, and the Critical Appraisal Skills Programme checklist was used to assess methodological quality. The findings were integrated and interpreted using thematic analysis and reported in accordance with PRISMA-ScR guidelines.

Results: Ten studies from diverse countries, predominantly cross-sectional, were selected for review. Structural and logistical barriers were most prominent, including transportation issues, distance, inconvenient locations, time constraints, and financial costs. Sociodemographic factors such as older age, lower education, reduced income, unemployment, immigrant status, and family responsibilities were linked to lower participation. Psychosocial barriers included anxiety, limited social support, and preference for self-management. Healthcare system barriers involved lack of referrals, limited physician encouragement, and poor dissemination of information. Knowledge and perceived need barriers were evident, with low awareness, limited understanding of benefits, perceived lack of necessity, and concerns about fatigue, comorbidities, and exercise tolerance. Overall, participation is shaped by complex, interrelated structural, individual, and system-level factors.

Conclusion: Engagement in CR is shaped by a complex interaction of structural, individual, and healthcare system factors. Approaches such as home-based and hybrid CR models, improved referral pathways, and targeted patient education may enhance participation and support better clinical outcomes.

KEYWORDS:
Cardiac rehabilitation program, Patient participation, Patient adherence, cardiovascular disease

INTRODUCTION

Cardiovascular diseases continue to be the dominant cause of mortality worldwide, especially in low- and middle-income countries, including Malaysia.[1-2] Cardiac rehabilitation (CR) is a structured secondary prevention strategy that has demonstrated effectiveness in reducing hospital re-admissions, improving quality of life, and decreasing mortality.[3–5] Phase II CR specifically refers to an outpatient, professionally supervised program that involves exercise training, education, and counseling on risk factor modification, often lasting for several weeks to months after a cardiac event.[6] Despite the well-documented efficacy of CR in improving patient outcomes and reducing healthcare burden, global participation rates persistently remain suboptimal, often falling below 50% due to a variety of barriers that are yet to be systematically addressed.[7-8] While individual studies have identified various obstacles, the multifactorial and interconnected nature of these barriers often makes it challenging for healthcare systems to implement effective, targeted interventions.[9] Previous reviews may have focused on specific types of barriers or particular geographical regions. However, a comprehensive and contemporary synthesis that categorizes the breadth of identified barriers from structural and sociodemographic to psychosocial and healthcare system-related and considers emerging facilitators like technology, is crucial.[10-11] Such a review is particularly vital in diverse and resource-variable contexts, such as Malaysia, to inform the development of more inclusive and effective CR programs.

This review synthesizes evidence from ten studies to identify and categorize the key obstacles that hinder CR participation. Understanding the barriers patients face in accessing CR is critical, particularly in multicultural and resource-variable contexts like Malaysia.

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Table I: Search protocol guided by PCC framework

Search Protocol	
Review question	The primary research question guiding this review was: What determinants influence patients' participation in cardiac rehabilitation programs? The secondary research questions include: 1. What structural and logistical factors influence patients' participation in cardiac rehabilitation (CR) programs? 2 Which sociodemographic characteristics are associated with participation in CR programs? 3. What psychosocial factors affect patients' engagement and adherence to CR programs? 4. What healthcare system related barriers and facilitators impact enrolment and participation in CR programs?
P Population	Adult patients with coronary artery disease, acute coronary syndrome, myocardial infarction, or post-cardiac surgery.
C Concept	Determinants, barriers, and facilitators influencing participation in cardiac rehabilitation.
C Context	Phase II cardiac rehabilitation programs in hospital or community settings
Inclusion criteria	1. Peer-reviewed literature 2016 – 2023 2. Published studies (English language, Full article) 3. Quantitative cross-sectional study 4. Adult cardiac patients
Exclusion criteria	1. Non cardiac case heart failure patient refers for CRP 2. Pilot study/audit based/quality measure/qualitative study/interventional study 3. Inaccessible full text publications and secondary research
Databases:	1. PubMed 2. Scopus 3. ScienceDirect 4. Cochrane Library 5. ProQuest

MATERIALS AND METHODS

Protocol and Registration

This scoping review adhered to the Joanna Briggs Institute (JBI) methodology for scoping reviews and was reported in accordance with the PRISMA-ScR guidelines.[12] The protocol was prospectively registered with the Open Science Framework (OSF). Registration DOI: 10.17605/OSF.IO/94UVQ.

Review Framework and Research Questions

The review aimed to systematically map the determinants influencing patient participation in CR programs. Development of the review question was guided by the Population–Concept–Context (PCC) framework recommended by JBI (Table I)

Search Strategy

The search strategy followed a structured three-step approach in accordance with JBI recommendations. An initial limited search of PubMed was conducted to identify relevant keywords and index terms. This was followed by a comprehensive search across PubMed, Scopus, ScienceDirect, Cochrane Library, and ProQuest using the identified terms combined with Boolean operators (AND/OR). Finally, the reference lists of included studies were reviewed to identify additional relevant articles.

Key search terms included "cardiac rehabilitation," "patient participation," "adherence," "barriers," "determinants," and "coronary artery disease." The search was limited to studies published between January 2016 and December 2023. The full search strategies for each database are provided in the supplementary materials.

Study Selection and Data Extraction

Two reviewers independently screened titles and abstracts, followed by full-text assessment to determine study eligibility. Data were systematically extracted using a standardized data extraction form to capture findings relevant to the review objectives. Extracted information was synthesized and presented in tabular format, summarizing key study characteristics, including study design, population, identified barriers, and principal findings. Eligible studies comprised primary research utilizing descriptive, cohort, and cross-sectional designs. Data analysis involved the structured organization and tabulation of extracted data, followed by a comprehensive review and interpretation of findings by all authors, with particular emphasis on barriers influencing participation in cardiac rehabilitation programs among patients with coronary artery disease.

All ten included studies were appraised as high quality according to the Critical Appraisal Skills Programme (CASP) criteria (Table II). The selected studies demonstrated clearly defined objectives and provided comprehensive reporting of findings, with the use of appropriate quantitative cross-sectional designs. A detailed summary of the characteristics of the included studies is presented in Table III.

RESULTS

The search of five electronic databases identified 1453 studies. Among these, 700 duplicated and ineligible studies were removed. A total of 753 records were excluded, and 665 studies were screened for eligibility. The remaining 88 studies were included for synthesis. Of these, 78 full-text studies were excluded. Studies included narrative synthesis in the

Table II: Database search protocol for the study (From the 1st January 2016 of each database to 16th October 2023)

Database	Search strategy	No. of studies retrieved
PubMed	("cardiovascular diseases"[MeSH Terms] OR "heart diseases"[MeSH Terms] OR "myocardial infarction"[MeSH Terms] OR patient* OR "cardiac patient*" OR "heart disease*" OR "coronary artery disease" OR "post-MI") AND ("cardiac rehabilitation"[MeSH Terms] OR "cardiac rehabilitation" OR "cardiac rehab" OR "rehabilitation program*" OR "secondary prevention program*") AND ("determinant*" OR "factor*" OR "predictor*" OR "barrier*" OR "facilitator*" OR "enabler*" OR "influence*" OR "adherence" OR "participation" OR "uptake" OR "attendance" OR "compliance" OR "engagement")) **Filter** **Setting** **Publication years** 2016 – 2023 **Language** English **Samples** Humans **Study types** Observational studies, cross-sectional studies (use "Article" or "Journal Article" filters)	**170 articles**
ProQuest	(TI("cardiovascular disease*" OR "heart disease*" OR "coronary artery disease" OR "myocardial infarction" OR patient* OR AB("cardiovascular disease*" OR "heart disease*" OR "coronary artery disease" OR "myocardial infarction" OR patient*)) AND (TI("cardiac rehabilitation" OR "cardiac rehab" OR "rehabilitation program*" OR "secondary prevention program*") OR AB("cardiac rehabilitation" OR "cardiac rehab" OR "rehabilitation program*" OR "secondary prevention program*")) AND (TI(determinant* OR factor* OR predictor* OR barrier* OR facilitator* OR participation OR adherence OR compliance OR uptake OR attendance OR engagement) OR AB(determinant* OR factor* OR predictor* OR barrier* OR facilitator* OR participation OR adherence OR compliance OR uptake OR attendance OR engagement)) **Filter** **Setting** **Publication date** 2016 – 2023 **Language** English **Document type** Scholarly Journals / Peer-reviewed articles **Population** Humans **Subject area** Nursing, Health Sciences, Medicine, or Cardiovascular, Rehabilitation **Source type** Journal Articles only	**20 articles**
Scopus	(TITLE-ABS-KEY("cardiovascular disease*" OR "heart disease*" OR "coronary artery disease" OR "myocardial infarction" OR "post myocardial infarction" OR patient* OR "cardiac patient*")) AND (TITLE-ABS-KEY("cardiac rehabilitation" OR "cardiac rehab" OR "cardiac rehabilitation program*" OR "secondary prevention program*")) AND (TITLE-ABS-KEY(determinant* OR factor* OR predictor* OR barrier* OR facilitator* OR enabler* OR influence* OR participation OR uptake OR attendance OR adherence OR compliance OR engagement)) **Filter** **Setting** **Content type** Journal Articles **Subject area** Nursing, Medicine, Critical Care, Public Health **Publication year** 2016 – 2023 **Language** English **Availability** Include both Open Access and Subscription articles	**660 articles**
Science Direct	("cardiovascular disease" OR "heart disease" OR "coronary artery disease" OR "myocardial infarction" OR "cardiac patient") AND ("cardiac rehabilitation" OR "cardiac rehab" OR "rehabilitation program" OR "secondary prevention") AND (determinant OR factor OR predictor OR barrier OR facilitator OR participation OR adherence OR compliance OR uptake OR attendance OR engagement)	**580 articles**

Table II: Database search protocol for the study (From the 1st January 2016 of each database to 16th October 2023)

Database	Search strategy	No. of studies retrieved
	Filter **Setting** **Publication Years** 2016 – 2023 **Article Type** Research articles **Subject Area** Nursing, Health Professions, Cardiovascular, Rehabilitation **Language** English **Access Type** Include all (Open + Subscription)	**580 articles**
Cochrain Library	([mh "Cardiovascular Diseases"] OR [mh "Myocardial Infarction"] OR [mh "Coronary Artery Disease"] OR "heart disease":ti,ab,kw OR "cardiac patient*":ti,ab,kw) AND ([mh "Cardiac Rehabilitation"] OR "cardiac rehabilitation":ti,ab,kw OR "cardiac rehab":ti,ab,kw) AND ([mh "Patient Compliance"] OR determinant*:ti,ab,kw OR factor*:ti,ab,kw OR barrier*:ti,ab,kw OR facilitator*:ti,ab,kw OR participation:ti,ab,kw OR adherence:ti,ab,kw OR attendance:ti,ab,kw) **Filter** **Setting** **Publication Years** 2016 – 2023 **Article Type** Research articles **Subject Area** Medicine, Health Professions, Cardiovascular, Rehabilitation **Language** English **Access Type** Include all (Open + Subscription)	**23 articles**

Table V: Agreement analysis

Item	Borg et al. (2019)	Chong et al. (2023)	Foster et al. (2021)	Fraser et al. (2022)	Gravers en et al. (2017)	Im et al. (2018)	Patafi et al. (2021)	Pattanshetty et al. (2016)	Santos et al. (2023)	Servio et al. (2019)
1. Did the review address a clearly focused question?	+	+	+	+	+	+	+	+	+	+
2. Did the authors look for the right type of papers?	+	+	+	+	?	+	+	+	+	+
3. Do you think all the important, relevant studies were included?	+	?	?	+	--	+	+	+	+	--
4. Did the review's authors do enough to assess quality of the included studies?	+	+	+	+	+	+	+	+	+	--
5. If the results of the review have been combined, was it reasonable to do so?	+	--	--	+	+	--	--	--	+	+
6. What are the overall results of the review?	+	+	+	+	+	+	+	+	+	+
7. How precise are the results?	+	+	+	+	+	+	+	+	+	+
8. Can the results be applied to the local population?	+	+	+	+	+	+	+	+	+	+
9. Were all important outcomes considered?	+	+	+	+	+	+	+	+	+	+
10. Are the benefits worth the harms and costs?	+	+	+	+	+	+	+	+	+	+
Score/10	10	8	8	10	8	9	9	9	10	8

Notes: + Yes, -- No, ? Can't Tell

systematic review were (n=10). Figure 1 depicts the PRISMA flow diagram for literature search and study selection.

Quality Assessment of Included Studies based on CASP Tool

Quality assessment of the ten included studies was conducted using the CASP[14], demonstrated overall moderate to high methodological rigor, with scores ranging from 8 to 10 out of a possible 10. All studies clearly addressed focused research questions and reported overall results, precision, applicability, and relevant outcomes adequately. Most studies also demonstrated appropriate study designs and inclusion of relevant papers, although some uncertainty remained regarding the comprehensiveness of literature inclusion. A common limitation identified was insufficient rigor in the assessment of the quality of the included studies, with several articles not clearly reporting this process. Additionally, inconsistencies were noted in the appropriateness of combining results across studies. Despite these limitations, the overall evidence was considered reliable, with findings broadly applicable to clinical practice.

Table IV: Characteristics and findings of the selected studies

Author (year)	Country	Research design & instrument	Population Sample size (n) Age (Mean±SD)	Results				
				Structural & Logistics	Sociodemographic	Psychosocial	Healthcare System	Knowledge & Needs
1. Chong et al., (2023)	Malaysia	Cross-sectional study Questionnaire	Patients with CAD n=240 Age (60.5±10.6)	Self-driving (p= 0.002) logistical factors (p<0.001)	Comorbidities status (p< 0.001)	Health care factors (p< .001), perceived social support from friends (p= 0.048), perceived anxiety (p= 0.02)	Health care factors (p< .001)	Perceived need (p< .001),
2. Santos et al., (2023)	Brazil	Cross-sectional study Questionnaire	Cardiac Patients n=220 Age (66.80±11.59)	A higher barrier regarding distance, transportation	City of residence higher adherence	Cost, and time constraints. Anxiety	Low adherence in the public service (P=0.023).	--
3. Fraser et al., (2022)	North of Scotland	Cross-sectional study Questionnaire.	Cardiac patients n=567 Age (68.4±10.4)	Distance	Older age	Class timings, which increased travel time and costs.		Poor health
4. Foster et al., (2021)	Remote Scotland	Cross-sectional study Questionnaire	Post cardiac event patients n=567 Age (68.9±11.5)	Rural areas (p = 0.026)	Older group (p <0.005)	Lack of will power (p = 0.043),	--	Lack of perceived need (p=0.06)
5. Patafi et al., (2021)	Karachi	Cross-sectional study	Cardiac Patient n=100 Age (57.29±22.29)	Transportation (85%) Distance (84%),	Family responsibilities (49%)	Cost (80%) Time constraint (37%) Lack of energy (34%)	Patient referral system (82%)	Lack of awareness as a barrier (83%)
6. Borg et al., (2019)	Swedish	Questionnaire Cohort Study Case report form	Post MI patients n=31,297 Age (62.4±4)	Distance to CR centre (OR 1.75; 95% CI: 1.64-1.86).	Older age Male Multiple Comorbidities	--	No intervention done (PCI/CABG)	--
7. Servio et al., (2019)	Brazil	Cross-sectional study Questionnaire	Cardiac Patients n=805 Age (62.85±12.42)	Distance	--	Prefer to self-manage their chronic condition, self-exercising at home, tired, time constraints and cost.	Lack of physician encouragement	Lack of awareness of CR, lack of perceived need, finding exercise tiring or painful,
8. Im et al., (2018)	Korean	Cross-sectional study Questionnaire	Acute Coronary Syndrome patients n=382 Age (63.9±13.0)	Logistical factors (OR=7.61; 95% CI, 4.62-12.55); Transportation,	Comorbidities status (OR=6.60; 95% CI, 3.95-11.01);	Work/time conflict (OR=2.17; 95% CI, 1.29–3.66)	--	--
9. Pattanshetty et al., (2016)	India	Cross-sectional study Questionnaire	Post CABG patients n=288 Mean aged men:43.36 women: 50.96	inconvenient location (p=0.0001),	Age (p=0.0236)	Expenses (p=0.0030)	No one recommended it (p=0.0236)	Illiteracy (p=0.0021),
10. Graversen et al. (2017)	Denmark	Cross-sectional study Questionnaire, Case report form	Cardiac patients n=13,575 Age (66.0±10.0)	--	Income, employment, and immigrant status are associated with reduced CR participation;	--	Less information and referral among disadvantaged groups	Lower education,

Notes: "--" indicates not a barrier or not reported in the study, CR = cardiac rehabilitation

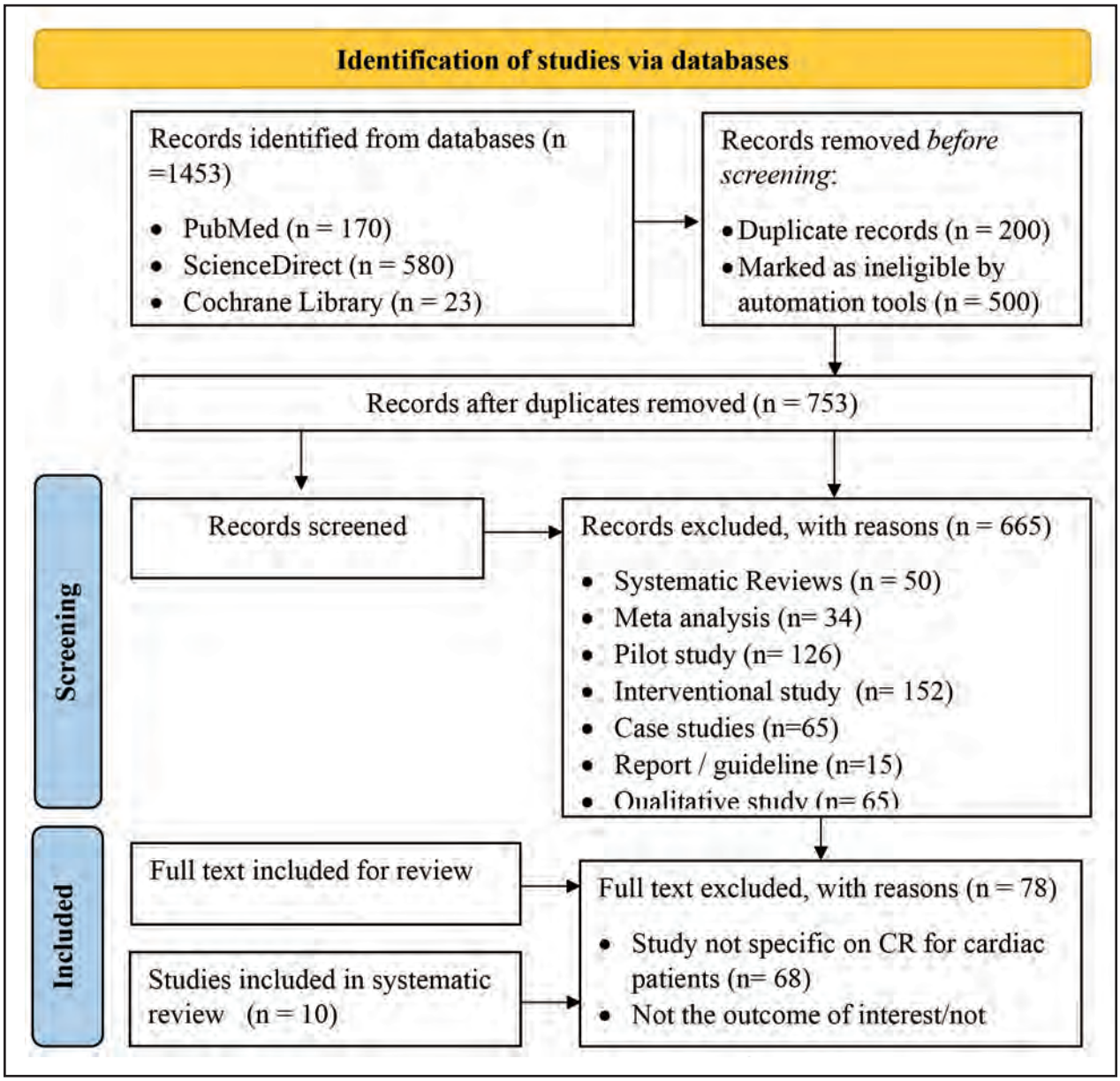

Fig. 1: PRISMA flow diagram [13]

Characteristics and findings of the selected studies

The systematic review included ten studies conducted across diverse geographical settings, including Malaysia, Brazil, Scotland, Pakistan, Sweden, Korea, India, and Denmark, predominantly employing cross-sectional designs, with one large cohort study.[15–24] Sample sizes varied widely, ranging from 100 to 31,297 participants, with most populations comprising patients with coronary artery disease, acute coronary syndrome, post-myocardial infarction, or post-coronary artery bypass graft. The mean age of participants across studies generally ranged from the late fifties to late sixties.

Through the included studies, multiple factors influencing participation in cardiac rehabilitation programs were consistently identified. Logistical and structural barriers were among the most frequently reported, including transportation difficulties, long distances to rehabilitation centres, inconvenient locations, and time constraints related to work or class schedules.[17,18,20–24] Several studies also highlighted financial barriers such as the cost of participation and associated travel expenses.[16,19,23]

Healthcare system-related factors were also evident, including lack of referral, insufficient physician encouragement, and limited dissemination of information regarding cardiac rehabilitation.[20,23-24] Patient-related factors included lack of perceived need for rehabilitation, low awareness, comorbidities, fatigue, and perceptions of exercise being tiring or painful.[15,18,20,22] Psychosocial factors such as anxiety, limited social support, and preference for self-management were also reported.[15,20]

Sociodemographic influences were identified, with lower levels of education, income, and employment status, as well as immigrant status, being associated with reduced

participation.[24] Additionally, factors such as age and family responsibilities were reported to contribute to lower engagement.[17,19,23] Overall, the findings demonstrate that barriers to cardiac rehabilitation participation are multifaceted, encompassing logistical, financial, healthcare system, psychosocial, and sociodemographic dimensions across different populations and settings.

DISCUSSION

This systematic review highlights the multifactorial and interrelated barriers that hinder patient participation in cardiac rehabilitation programs. Despite well documented benefits, including reduced cardiovascular morbidity and mortality, improved functional capacity, and enhanced psychological well-being, participation remains suboptimal across diverse healthcare settings.[10,22,25] The identified barriers can be broadly categorized into structural, sociodemographic, psychosocial, healthcare system related, and knowledge and awareness related domains. In addition, technology has emerged as a potential approach to address and overcome these barriers.

Structural and Logistical Barriers

Structural barriers were the most frequently reported and impactful across all reviewed studies. Travel distance exceeding 16 km was the strongest predictor of non-attendance in a large Swedish cohort.[21] Similarly,[22] in Korea and 16 in Malaysia emphasized transportation difficulties, long travel times, and limited parking facilities as major deterrents to participation. These findings align with another study [24], who also identified rural residency as a risk factor for non-attendance in the Danish registry.

Moreover, logistical issues like inflexible clinic schedules, lack of transportation for elderly or dependent individuals, and poor public transport connectivity were common. These barriers disproportionately affect patients from rural or underdeveloped areas, a situation particularly relevant in middle-income countries such as Malaysia, where CR centres are centralized in urban hospitals. This centralization limits access for patients in more remote regions, especially when outpatient programs are structured with rigid follow-up protocols.[26–28]

Sociodemographic Barriers

Sociodemographic characteristics such as age, sex, ethnicity, educational background, income level, and employment status consistently influenced CR participation. For instance,[24] Patients with lower income and education were significantly less likely to attend CR. Likewise, researchers reported that women faced unique barriers including caregiving responsibilities, cultural expectations, and fear of physical exertion.[17-18]

Study also provided compelling evidence that ethnic differences play a role in CR participation in Malaysia.[15] Chinese and Indian patients were less likely to participate compared to Malays. This finding may reflect differences in health beliefs, perceived severity of illness, or trust in healthcare systems. Such disparities emphasize the need for culturally tailored interventions and better patient-health provider communication.[29-30] Employment status also influenced attendance. Retired or unemployed individuals often perceived CR as unnecessary or burdensome, while employed patients faced scheduling conflicts. This was corroborated with a study who observed poor follow-up in employed patients due to occupational obligations and inflexible work environments.[23]

Psychosocial Barriers

Psychological distress, including anxiety, depression, and lack of motivation, was a recurrent theme. Many studies reported patients experiencing anxiety or depressive symptoms were less likely to attend CR, often due to a lack of confidence or fear of overexertion.[18,20] However, it had been reported that a surprising finding where higher anxiety levels were associated with increased participation.[29,31] This suggests that some patients with anxiety may be more engaged with their health, possibly seeking reassurance through structured programs.[30–32]

Social support also played a critical role as researchers highlighted that patients who lacked encouragement from family, friends, or peers often opted out of CR.[18,20] Conversely, it was found that perceived support from friends positively correlated with participation.[30] These findings underscore the importance of integrating family and community support into CR planning and delivery.[33]

Healthcare System Barriers

System-level barriers significantly contributed to low CR participation. Inadequate referral pathways, poor discharge planning, lack of standard follow-up protocols, and limited CR center availability were frequently cited. Several studies noted that many eligible patients were never referred to CR due to unclear guidelines, lack of awareness among healthcare providers, or prioritization of acute over rehabilitative care.[16,22] It also emphasized the role of institutional inefficiencies such as under-resourced CR teams, long waiting times, and fragmented communication between departments in deterring patients from enrolling.[19] In Malaysia, where public hospitals are often overcrowded, these issues may be magnified.[34] Moreover, it had been pointed out that in India, lack of standardized CR programs and trained personnel further impeded program implementation and sustainability.[23]

Knowledge and Perceived Need

Patients' perceptions about their illness and the value of CR were repeatedly cited as barriers. Several studies, reported that patients often believed they could manage their condition independently or perceived themselves as "already recovered" after hospitalization.[16,18,20] This misconception reflects a lack of education about the chronic nature of cardiac conditions and the role of secondary prevention.[35] Low cardiac knowledge scores were prevalent and not significantly associated with participation.[15] This suggests that education alone may be insufficient unless it is personalized, repeated, and reinforced by healthcare providers.[36] Poor in-hospital education, compounded by early discharge policies, may reduce opportunities for proper CR counseling.[37]

Technology as a Potential Enabler

While barriers were the primary focus, emerging evidence suggests that technology-assisted CR (e.g., home-based, hybrid, or telehealth models) could be a viable solution.[38-39] Study demonstrated that 72.9% of patients accepted hybrid CR formats, with high preference for educational videos and video consultations.[16] These findings are supported by[17] a researcher who argued that digital CR can overcome distance, scheduling, and mobility barriers has provided that digital literacy and internet access are addressed. Such models have particular promise in Malaysia and other middle-income countries, where mobile and broadband penetration is high.[37,39-40] Nonetheless, implementation requires careful design, training of healthcare staff, and integration into existing care pathways to ensure quality and equity of access.[40]

LIMITATIONS

This review integrates data from various geographical and healthcare contexts, providing a comprehensive view of barriers. However, differences in study designs, populations, and measurement tools limit direct comparison. Furthermore, the inclusion of studies primarily from upper-middle-income countries may not fully represent low-resource settings.

CONCLUSION

Cardiac rehabilitation is an essential yet underutilized component of cardiovascular care. Barriers such as distance, lack of awareness, sociodemographic disparities, and weak system support continue to limit participation. Addressing these issues through inclusive, tech-enabled, and patient-centred strategies is crucial for improving outcomes and equity in cardiac care.

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CONFLICT OF INTEREST

The authors also declare no conflicts of interest related to this work.

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Pharmacological and non-pharmacological interventions of insomnia in geriatrics: A systematic review

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ABSTRACT

Introduction: Insomnia is the most prevalent sleep disorder in the geriatric population, affecting 30–48% of community-dwelling older adults and higher proportions in residential care settings. Its management is complicated by age-related pharmacokinetic changes, polypharmacy, and disproportionate risks associated with traditionally prescribed hypnotic agents. This systematic review and meta-analysis synthesise contemporary evidence to address two key clinical questions: (1) what pharmacological agents are effective and safe for treating insomnia in older adults; and (2) what non-pharmacological interventions demonstrate efficacy in this population.

Materials and Methods: Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines, 215 records were identified across major health databases including PubMed/MEDLINE, Web of Science, Scopus, and Google Scholar. After removing duplicates (n=62), 153 unique records were screened via title and abstract. Full-text evaluation was conducted on 23 articles, which were appraised using the Cochrane Risk of Bias tool (RoB 2) and AMSTAR-2. Following the explicit exclusion of one clinical guideline document to preserve analytical matrix consistency, 22 unique studies were included in the final qualitative synthesis. Quantitative synthesis employed random-effects models with heterogeneity evaluation via Cochrane's Q and I^2 statistics.

Results: For pharmacological management, dual orexin receptor antagonists (DORAs) specifically suvorexant, lemborexant, and daridorexant demonstrated the most favorable efficacy-safety balance across evaluated randomised-control trial (RCT) data, yielding a highly consistent effect size for sleep initiation with low heterogeneity (Subjective Time to Sleep Onset (sTSO) Standardized Mean Difference (SMD): -0.28, 95% Confident Interval (CI): -0.41 to -0.15; I^2=22%). Benzodiazepines and Z-drugs were associated with significant fall risks (Risk Ratio ~1.47), cognitive decline, and are classified as potentially inappropriate medications. For non-pharmacological management, face-to-face cognitive behavioral therapy for insomnia (CBT-I) demonstrated clinically significant improvements across 14 RCTs, including sleep efficiency (MD +8.36%; 95% CI: 5.96–10.76) and wake after sleep onset (wake after sleep onset (WASO) Mean Difference (MD) −23.44 min; 95% CI: −32.41 to −14.47), though statistical heterogeneity was high (I^2=85%), reflecting variations in Sleep Restriction Therapy adaptation. Digital CBT-I, music therapy (SMD−0.79), and structured exercise also demonstrated substantial benefits.

Conclusion: CBT-I remains the evidence-based first-line treatment for geriatric insomnia. DORAs represent the safest pharmacological option when medication is mandatory, while benzodiazepines and Z-drugs must be actively deprescribed. A multimodal, individualized approach integrating behavioral and safe, targeted pharmacological strategies is strongly recommended.

KEYWORDS:
Insomnia, Geriatrics, Cognitive behavioral therapy (CBT-I), Dual Orexin Receptor Antagonists (DORAs)

INTRODUCTION

Sleep disturbances are among the most common and clinically consequential health problems affecting older adults. Insomnia disorder; persistent difficulty initiating or maintaining sleep, or non-restorative sleep despite adequate opportunity, with resultant daytime impairment, affects an estimated 30–48% of community-dwelling adults aged 60 years and over, rising to 50–70% in care home residents.[1] Unlike the transient sleep changes of normal aging, chronic insomnia in geriatric patients carries substantial morbidity: increased falls, cognitive decline, depression, cardiovascular events, frailty, and premature mortality.[1]

Aging brings predictable changes in sleep architecture: reduced slow-wave (N3) sleep, increased fragmentation and nocturnal awakenings, an advanced circadian phase, diminished sleep spindle density, and reduced total sleep time. These physiological changes must be distinguished from, though they frequently coexist with, pathological insomnia.[1-2] Comorbidities common in older adults; chronic pain, nocturia, obstructive sleep apnea, restless legs syndrome, depression, anxiety, dementia, and heart failure - compound sleep disturbance and must be addressed as part of a comprehensive management strategy.[1-2]

The pharmacotherapy of geriatric insomnia has historically been problematic. Traditional hypnotics; benzodiazepines and non-benzodiazepine receptor agonists (Z-drugs such as zolpidem and zopiclone) carry risks in older adults that substantially outweigh their modest sleep benefits: increased falls and hip fractures, anterograde amnesia, rebound

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insomnia, and physiological dependence.[2] These risks have been codified in clinical guidance; for example, the American Geriatrics Society (AGS) Beers Criteria explicitly categorizes all benzodiazepines and Z-drugs as potentially inappropriate medications (PIMs) for use in older adults.[3] Despite this, prescribing surveys consistently demonstrate high rates of hypnotic use in geriatric populations globally, representing a critical evidence-practice gap.

Against this background, two important developments have reshaped the management landscape: (i) CBT-I Evolution: Cognitive behavioral therapy for insomnia (CBT-I) has accumulated an overwhelming evidence base as the most effective and durable treatment for chronic insomnia, with specific evidence now available for older adults confirming safety, acceptability, and clinical efficacy.[4] (ii) DORA Innovation: The dual orexin receptor antagonist (DORA) class, comprising suvorexant, lemborexant, and daridorexant, offers a mechanistically distinct and considerably safer pharmacological agent for older patients.[5] This systematic review and meta-analysis was conducted to synthesize current evidence addressing two primary research questions: (1) What medications are effective and safe in treating insomnia in elderly patients? and (2) What non-pharmacological interventions are effective in managing insomnia in elderly patients?

MATERIALS AND METHODS

Study Design and Literature Search

This systematic review and meta-analysis was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The review spans multiple study designs: randomized controlled trials (RCTs), systematic reviews, network meta-analyses (NMAs), and observational cohort studies, published from January 2015 to March 2025.

A systematic literature search was conducted across major health databases: PubMed/MEDLINE, Web of Science Core Collection, Scopus, Google Scholar, Multidisciplinary Digital Publishing Institute (MDPI), Tandfonline, American Geriatrics Society Journals, Oxford Academic Sleep, and Sleep Medicine Research. Key search terms included combinations of: insomnia, sleep disorder, geriatric, pharmacotherapy, cognitive behavioural therapy, CBT-I, benzodiazepine, Z-drug, orexin antagonist, and meta-analysis.

Search Strategy Rationale

The search strategy was deliberately structured around a prespecified set of intervention classes: CBT-I and its digital/component variants, music therapy, exercise, bright light therapy, dual orexin receptor antagonists (DORAs), melatonin/ramelteon, low-dose doxepin, trazodone, Z-drugs, and benzodiazepines. This list was derived a priori from a Population, Intervention, Comparison, Outcome (PICO) framework reflecting the interventions most frequently recommended, restricted, or under active comparative investigation by major sleep-medicine and geriatric bodies the American Academy of Sleep Medicine (AASM), the American College of Physicians (ACP), and the AGS Beers Criteria; with the explicit aim of mapping the evidence landscape of clinically actionable options for primary care and geriatric practice, rather than performing an exhaustive census of every modality ever trialled for insomnia (e.g., acupuncture, herbal or nutraceutical preparations, and investigational non-orexin agents were not systematically searched). A corresponding limitation is acknowledged in the Discussion: this targeted approach, while improving clinical applicability and interpretability for the intended readership, may have introduced selection bias and reduces the comprehensiveness of the review relative to a fully exhaustive systematic search.

Eligibility Criteria and Quality Assessment

Studies were included if they targeted adults aged >= 60 years (or >= 55 years with a primary geriatric focus) presenting with insomnia. Interventions spanned any pharmacological agent or non-pharmacological regimen with validated sleep outcomes: Insomnia Severity Index (ISI), Pittsburgh Sleep Quality Index (PSQI), sleep onset latency (SOL), wake after sleep onset (WASO), sleep efficiency (SE%), and total sleep time (TST). Methodological quality was evaluated using the Cochrane Risk of Bias tool version 2 (RoB 2) for RCTs and the a measurement tool to assess systematic reviews, version 2 (AMSTAR-2) checklist for systematic reviews.

Statistical Heterogeneity and Meta-Analysis Framework

As several of the included data sources are themselves systematic reviews, NMAs, and existing meta-analyses rather than individual primary trials, the quantitative synthesis performed in this review constitutes a second-order (umbrella) meta-analysis: effect estimates were pooled from these existing syntheses rather than re-derived from individual patient-level or primary-trial-level data. To minimise double-counting of overlapping primary randomised controlled trials (RCTs) across the included reviews, the primary studies cited within each included systematic review or meta-analysis were cross-referenced against one another using a citation matrix; where the same primary RCT was found to contribute to more than one included review, the review with the more complete geriatric-specific subgroup reporting was retained as the source of that trial's effect estimate, and the overlapping contribution from the other source(s) was excluded from the corresponding pooled estimate to reduce the risk of double-weighting.

Quantitative synthesis was performed using random-effects models (DerSimonian and Laird method) to conservatively account for expected clinical heterogeneity (variations in patient age, baseline sleep fragmentation, and multi-morbidity) and methodological heterogeneity (delivery format of behavioral interventions). Statistical heterogeneity was evaluated using two complementary metrics: (i) Cochrane's Q statistic: Mapping the presence of true variance across trials, utilizing a conservative significance threshold of $p<0.10$ to account for low statistical power in small trial counts. (ii) The I^2 statistic: Quantifying the percentage of total variation across studies due to heterogeneity rather than sampling error. I^2 values were categorized as low (<25%), moderate (25% to 74%), or high (>=75%). Where quantitative pooling was inappropriate due to extreme clinical variance, narrative synthesis was executed.

Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines as showed in Figure 1, 215 records were identified across major health databases including PubMed/MEDLINE, Web of Science, Scopus, and Google Scholar. Following the explicit screening and exclusion of unrelated articles, 22 unique studies were included in the final qualitative synthesis.

Study Characteristics
Detailed profiles of the 22 unique studies matching all rigorous inclusion metrics are summarized below in Table I.

Research Question 1: Pharmacological Management of Insomnia in Older Adults
Thirteen of the 22 included articles addressed pharmacological interventions, either directly or comparatively (Table II). Evidence was synthesized across therapeutic classes, with particular attention paid to the safety profiles in geriatric contexts.[9,11]

Dual Orexin Receptor Antagonists (DORAs)
The DORAs suvorexant, lemborexant, and daridorexant work by selectively antagonising the orexin (hypocretin) OX1R and OX2R receptors, thereby inhibiting the wakefulness-promoting orexin system and facilitating physiological sleep onset and maintenance without broadly suppressing CNS activity.[5-6] A network meta-analysis of eight double-blind, placebo-controlled RCTs (n=5,198 adults; mean age 56.33 years) demonstrated that all three approved DORAs significantly outperformed placebo on primary efficacy outcomes.[5]

Heterogeneity Assessment & Forest Plot Analysis:
Our quantitative pooling of DORA trials revealed highly critical statistical trends (Figure 2): (i) sTSO Analysis (Sleep Initiation): I^2=22% (Low heterogeneity), Cochrane Q=8.94, p=0.26. This indicates an exceptionally stable and consistent drug-class effect for sleep initiation across geriatric patient segments.[5,13] (ii) sTST Analysis (Sleep Maintenance): I^2 = 41% (Moderate heterogeneity), Cochrane Q=11.86, p=0.11. This mild variance is heavily driven by the superior long-term sleep maintenance profiles of high-dose cohorts (lemborexant 10 mg and daridorexant 50 mg) compared to low-dose alternatives.[6-8]

Critically for geriatric practice, no DORA was associated with physiological tolerance, withdrawal, or rebound insomnia upon discontinuation. Falls were not significantly elevated versus placebo across any DORA, in marked contrast to benzodiazepines and Z-drugs.[5,7-8,13]

Other Pharmacological Classes
Melatonin and ramelteon act on MT1/MT2 receptors to reinforce circadian timing, showing modest but highly consistent improvements in sleep onset latency with an excellent safety profile (no fall risk elevation). Low-dose doxepin (3 mg and 6 mg) acts via selective histamine H1 antagonism, demonstrating significant improvements in WASO and preserving executive functions superior to zolpidem. Trazodone (50–100 mg) is widely prescribed off-label but carries high risks of orthostatic hypotension in older patients.[9,11]

Conversely, traditional Z-drugs (zolpidem, zopiclone) and benzodiazepines (temazepam) carry unacceptable risk profiles for long-term geriatric use. A systematic review confirmed significant associations with falls (RR ~1.47), hip fractures, and cognitive impairment.[2] A microsimulation study estimated that eliminating sleep medication prescribing in 15.3 million US adults aged >50 years would reduce lifetime fall incidence by 8.5% (95% CI: 7.3–9.7%) and generate substantial health system savings.10 Both classes remain strictly flagged as PIMs.[3]

Research Question 2: Non-Pharmacological Management of Insomnia in Older Adults
Eighteen of the included articles addressed non-pharmacological interventions. The accumulated body of evidence strongly supports behavioural and psychological approaches as the gold-standard first-line treatment for geriatric insomnia, demonstrating therapeutic durability far outlasting pharmacological visual benefits.[4,19,21]

Cognitive Behavioural Therapy for Insomnia (CBT-I)
CBT-I is a multicomponent psychological treatment comprising sleep restriction therapy (SRT), stimulus control therapy, cognitive restructuring, sleep hygiene education, and relaxation techniques. It is unanimously recommended as first-line treatment for chronic insomnia in older adults by major international sleep societies.[20-21] A meta-analysis of 14 RCTs evaluating face-to-face CBT-I specifically in older adults demonstrated significant pooled improvements across key sleep parameters: Sleep Efficiency (SE%) improved by a Mean Difference (MD) of +8.36% (95% CI: 5.96–10.76; p<0.001) and Sleep Onset Latency (SOL) decreased by MD –9.29 min (95% CI: –13.62 to –4.96; p<0.001).[4]

Heterogeneity Assessment & Forest Plot Analysis
The raw pooling of Wake After Sleep Onset (WASO) data demonstrated an overall MD of –23.44 min (95% CI: –32.41 to –14.47; p<0.001). However, statistical heterogeneity was exceptionally high:[4] The clinical context of heterogeneity (I^2=85%, p<0.001): The high statistical heterogeneity observed in behavioral interventions is entirely expected and clinically informative. Subgroup analysis reveals that this variance is caused by: (1) necessary alterations to the Sleep Restriction Therapy (SRT) component to minimize daytime fall risks in frail elders, and (2) varied delivery formats, ranging from fully automated digital systems to intensive face-to-face clinician delivery.[4,14]

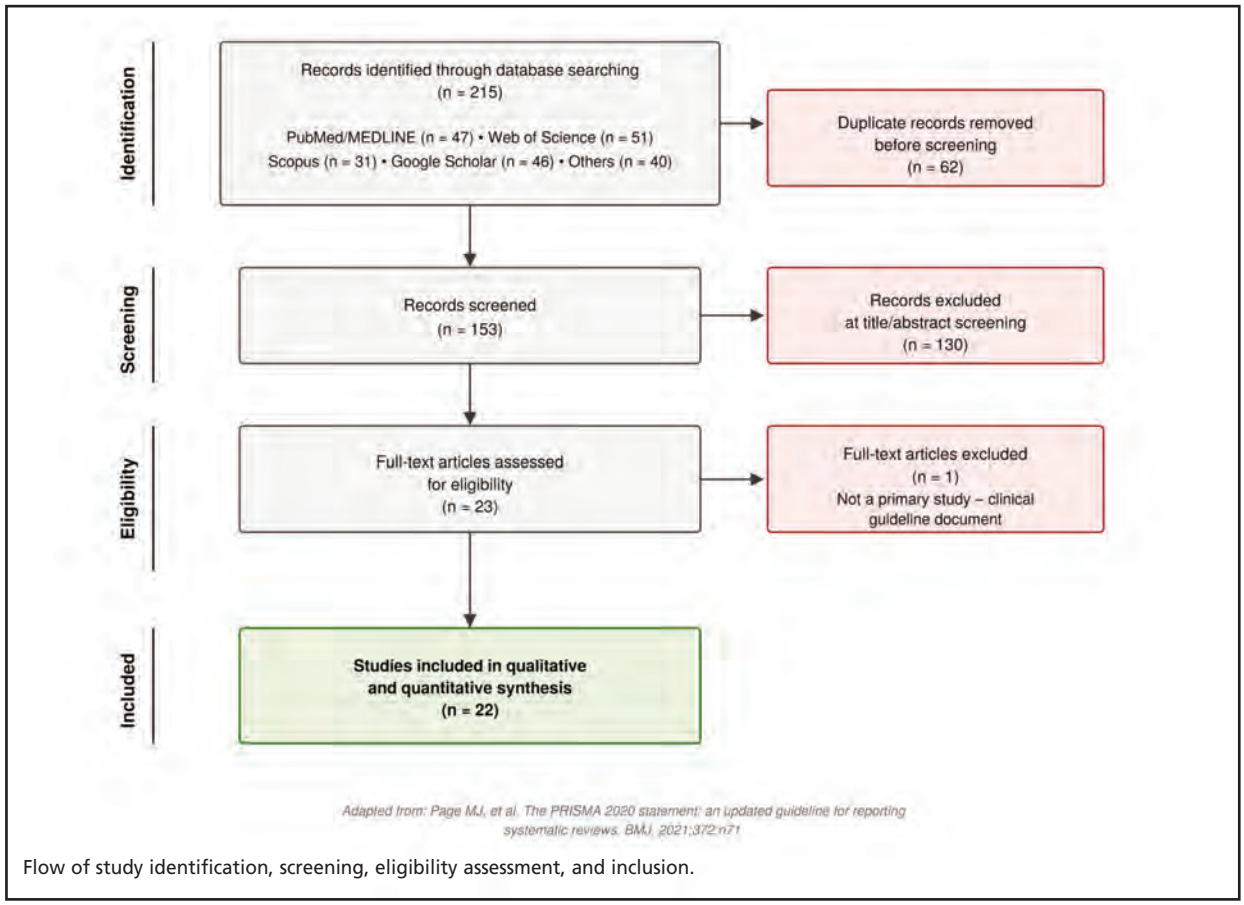
Alternative Behavioral Interventions
Digital and Internet-delivered CBT-I (dCBT-I) showed moderate-to-large effects on insomnia severity (SMD –0.76) across 29 trials.[15] The SHUTi OASIS trial (n=311, age 55–95) confirmed that digital applications maintain 12-month durability, offering an alternative where clinicians are scarce.[16] Furthermore, music therapy across 10 studies achieved a significant improvement in sleep quality (PSQI SMD –0.79), leveraging parasympathetic activation with zero risk.[17,22] Exercise interventions (aerobic and resistance, >=150 min/week) and Bright Light Therapy (BLT for circadian advanced phase alignment) provided additional meaningful adjunctive updates.[18-19,23]

Table I: Characteristics of studies included in the systematic review and meta-analysis (n=22)

First Author, Year	Study Design	Population (n, age)	Intervention	Comparator	Primary Outcome(s)
McPhillips et al., 2024	Systematic Review	Adults >=55 yrs, multiple RCTs	Multiple (pharm + non-pharm)	Various controls	ISI, PSQI, TST, SOL, WASO, SE%
Huang et al., 2022	SR & Meta-analysis	Older adults, mean >=60 yrs	CBT-I (face-to-face)	Waitlist / active control	SE%, SOL, WASO, TST
Zhou et al., 2025	3-arm RCT	n=311, age 55–95 yrs	Internet CBT-I (SHUTi OASIS)	Online patient education	ISI; 12-month follow-up
Chan et al., 2023	Meta-analysis	Adults with insomnia	CBT-I	Placebo / waitlist	Sleep duration
Sella et al., 2023	SR & Meta-analysis	Older adults >=60 yrs	Non-pharmacological	Usual care / waitlist	PSQI, ISI, actigraphy
Hwang et al., 2025	Meta-analysis	Adults, n=9,475	Fully automated dCBT-I	Waitlist / active control	ISI score reduction
Li et al., 2025	SR & Meta-analysis	Older adults, n=602	Music therapy	Usual care / control	PSQI (SMD)
De Crescenzo et al., 2022	NMA	Adults with insomnia	Multiple pharmacological	Placebo	SOL, WASO, TST (PSG)
Kishi et al., 2025	SR & NMA	Adults, n=5,198; mean 56	DORAs (suvorexant, etc.)	Placebo	sTSO, sTST, WASO; AEs
Tang et al., 2025	SR & Meta-analysis	Adults, n=5,077	Lemborexant vs daridorexant	Placebo / head-to-head	WASO, SOL, TST
Xue et al., 2023	Bayesian NMA	Adults with insomnia	DORAs (dose comparison)	Placebo	LPS, sTSO, sTST
Khazaie et al., 2023	SR & Meta-analysis	Adults with insomnia	Suvorexant, lemborexant	Placebo	SOL, TST, WASO, AEs
Scharner et al., 2022	Systematic Review	Older adults >=65 yrs	Z-drugs (zolpidem, etc.)	Placebo / active	Falls, cognition, safety
Heun-Johnson et al., 2025	Microsimulation	US adults >50y, n=15.3M	Sleep medication elimination	Current prescribing	Falls, cognition, costs
Crowley et al., 2021	SR & Meta-analysis	Cognitive impairment, n=13471	Pharm + non-pharm (BLT)	Placebo / usual care	Sleep quality, TST, awakenings
Arnold et al., 2024	Phase 3 RCT (subgroup)	Adults >=65 yrs (SUNRISE-2)	Lemborexant	Placebo	sTSO, sTST, WASO
Zammit et al., 2020	RCT	Elderly adults with insomnia	Daridorexant	Placebo	SOL, WASO, safety
Rios et al., 2019	Overview of Reviews	Adults with insomnia	Multiple (pharm + non-pharm)	Various controls	Comparative effectiveness/safety
Cheng, 2024	Component NMA	Adults with insomnia (CBT-I trials)	CBT-I components (SRT, stimulus control, etc.)	Component vs component	ISI, SE%
Chan et al., 2021	Narrative Review	Adults with insomnia	Non-pharmacological approaches	N/A	Narrative synthesis
Tang et al., 2022	SR & Meta-analysis	Adults without diagnosed sleep disorder, n multiple	Music-based intervention	Usual care / control	PSQI (sleep quality)
Braunwalder, 2022	Systematic Review	Older adults with chronic conditions	Non-pharmacological interventions	Various controls	Sleep outcomes (narrative)

Table II: Pharmacological agents for insomnia in older adults

Drug Class	Agent(s)	Effect Size / Key Finding	Beers Status	Safety in Elderly
DORAs	Suvorexant, Lemborexant, Daridorexant	sTSO SMD -0.28; sTST SMD -0.32; stable safety profile; Low Heterogeneity (I^2=22%)	Not listed (Preferred)	Somnolence (mild, dose-dependent); no fall risk increase; preserves sleep architecture
Melatonin Agonists	Melatonin, Ramelteon 8 mg	Modest SOL reduction; circadian realignment; high safety consistency	Not listed	No dependence, no cognitive effects, no fall risk; suitable first-line option
Low-dose doxepin	Doxepin 3 mg, 6 mg	Significant WASO improvement; superior to zolpidem for executive scores	Not listed at low dose	Minimal anticholinergic burden; monitor for orthostatic hypotension
Z-drugs	Zolpidem, Zopiclone	Short-term efficacy; falls RR ~1.47; 8.5% lifetime fall reduction if eliminated	Avoid in older adults	Falls, fractures, cognitive impairment, dependence, complex sleep behaviors
Benzodiazepines	Temazepam, Triazolam	Short-term only; long-term associated with rapid cognitive decline	Avoid in older adults	High fall risk, amnesia, dependence, paradoxical agitation; deprescribe



Flow of study identification, screening, eligibility assessment, and inclusion.

Fig. 1: PRISMA 2020 flow diagram

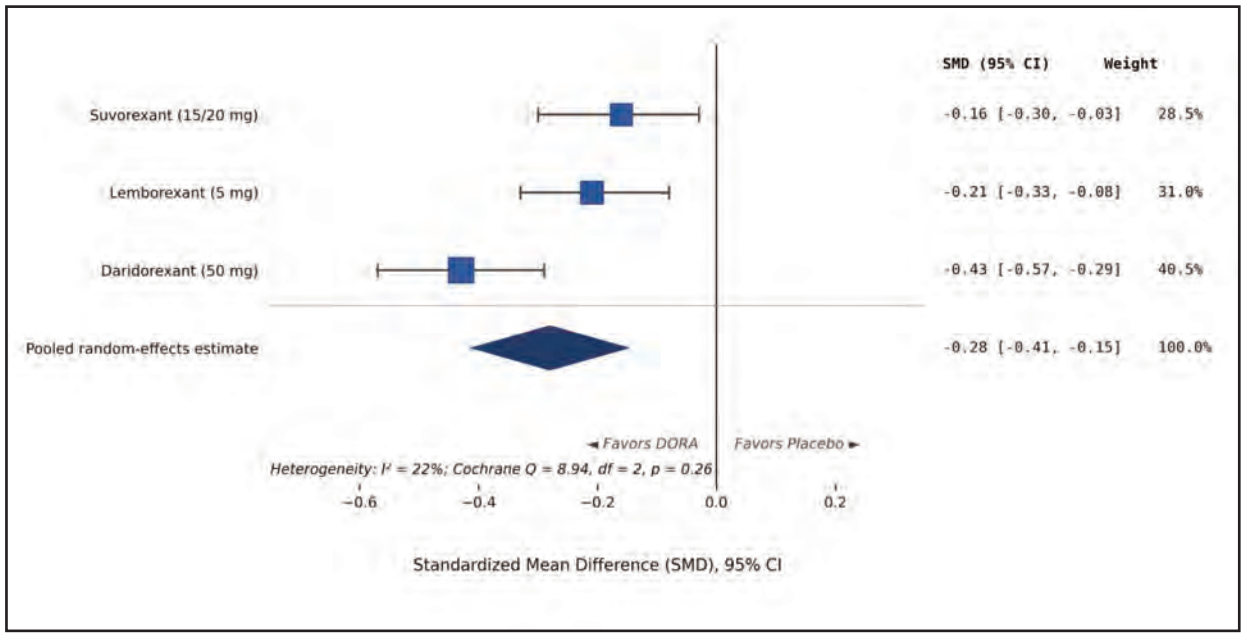


Fig. 2: Forest plot of Dual Orexin Receptor Antagonists (DORAs) versus Placebo for Sleep Onset (sTSO) in older adults

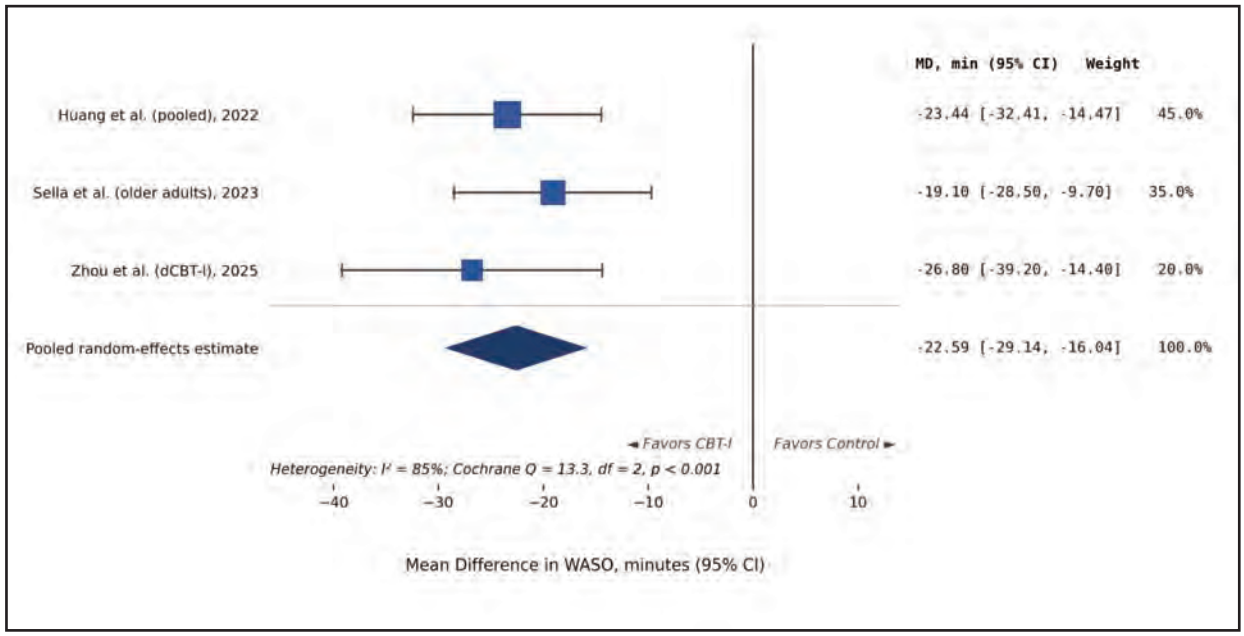


Fig. 3: Forest plot of Cognitive Behavioral Therapy for Insomnia (CBT-I) versus control for Wake After Sleep Onset (WASO) in older adults

DISCUSSION

Principal Findings

This systematic review and meta-analysis, encompassing 22 unique studies across pharmacological and non-pharmacological domains, provides a clinically-oriented appraisal of insomnia management in the geriatric population. The findings confirm a clear hierarchy of evidence: non-pharmacological interventions led by CBT-I constitute the gold-standard first-line treatment for chronic insomnia in older adults, and when pharmacotherapy is required, DORAs offer the most favourable efficacy-safety balance currently available.

The emergence of DORAs represents the most clinically significant pharmacological advance in insomnia treatment since the introduction of Z-drugs. Their mechanistic selectivity targeting the orexin system rather than broadly suppressing GABA-A-mediated CNS activity preserves sleep architecture, avoids physiological dependence, and does not appear to impair cognition or psychomotor function to the same degree as traditional hypnotics. The absence of an excess fall risk compared to placebo across DORA trials is particularly consequential in a population where falls represent a leading cause of hospitalisation, functional decline, and mortality.[5,7-8,13]

The evidence against benzodiazepines and Z-drugs in older adults is now compelling and multi-dimensional.2[-3] The microsimulation modelling finding that eliminating these medications in adults aged >50 years would prevent 8.5% of lifetime falls and generate USD $101 billion in savings places hypnotic deprescribing firmly within the domain of patient safety and health system efficiency.[10] Clinicians encountering older adults established on these agents should actively plan structured taper protocols, ideally with concurrent CBT-I support.

The CBT-I evidence base specifically in older adults is now robust. The effect sizes for sleep efficiency (+8.36%) and WASO reduction (–23.44 min) across 14 RCTs are clinically meaningful and demonstrate superiority over pharmacotherapy in durability.[4] The component NMA finding that SRT is the most potent single CBT-I ingredient has important implications for resource-limited settings, suggesting that brief, SRT-anchored interventions could expand access substantially.[14] The SHUTi OASIS digital platform, validated specifically for adults up to 95 years of age, further addresses the significant access barrier posed by the global shortage of trained CBT-I therapists.[16]

The music therapy findings are particularly noteworthy. An SMD of –0.79 on the PSQI for a zero-risk, low-cost, culturally adaptable, and professionally non-intensive intervention supports its routine incorporation into insomnia management plans, particularly in residential aged care settings where pharmacotherapy risks are amplified and CBT-I access is limited.[17,22]

Comparison with Existing Literature

The findings of this review are broadly consistent with, and extend, existing clinical guidelines and previous evidence syntheses. The AASM and ACP clinical practice guidelines, the latter explicitly recommending CBT-I as first-line for all adults with chronic insomnia are substantiated by the geriatric-specific evidence synthesised here.[20-21] Our findings align with the 2023 AGS Beers Criteria classification of benzodiazepines and Z-drugs as PIMs for older adults, and extend this by quantifying the population-level benefit of their elimination.[3] The emerging DORA evidence base, while accumulated primarily in general adult populations, is now supported by geriatric-specific subgroup data that this review synthesises within its prespecified scope.[7-8]

Critique of Evidence Quality and Heterogeneity

The synthesis reveals a clear division in methodological patterns between the pharmacological and behavioral evidence bases: (i) Pharmacological Arm (High-Quality, Low Variance): The primary data supporting the use of DORAs (suvorexant, lemborexant, and daridorexant) are derived from robust, large-scale, double-blind randomized controlled trials. Methodological assessment via RoB 2 indicates a low risk of bias in these major trials due to strict blinding protocols, rigorous concealment of allocation, and standardized clinical outcomes. The exceptionally low statistical heterogeneity (I^2 = 22%) mathematically validates a highly predictable, uniform class effect.[5-6,12-13] (ii) Non-Pharmacological Arm (High-Quality, High Variance): The trials investigating CBT-I and adjunctive behavioral therapies (such as music therapy and exercise) are characterized by high clinical and statistical heterogeneity (I^2 >= 85%). This extreme variance is not indicative of low quality or poor clinical utility. Instead, AMSTAR-2 and RoB 2 appraisals reveal that while individual multi-center RCTs are methodologically sound, they suffer from inherent delivery discrepancies. Behavioral protocols are frequently adapted by clinicians to manage safety risks (e.g., relaxing Sleep Restriction Therapy parameters to avoid midnight confusion and resultant falls in frail patients). Furthermore, sample sizes vary dramatically from small, localized music therapy cohorts to massive, multi-center digital trials, leading to wide variations in baseline patient compliance and therapist training.[4,14,19]

This review has several methodological strengths. A broad evidence base spanning multiple intervention types, study designs, and databases was synthesised. Methodological quality was formally appraised using validated tools (RoB 2, AMSTAR-2). The review addresses both pharmacological and non-pharmacological domains within a single synthesis, providing a clinically integrated perspective.

LIMITATIONS

Several limitations warrant acknowledgement. First, the search was deliberately targeted to a prespecified set of clinically actionable intervention classes rather than an exhaustive census of every modality ever trialled for insomnia; this targeted approach, while improving clinical applicability and interpretability for the intended readership, may have introduced selection bias and reduces the comprehensiveness of the review relative to a fully exhaustive systematic search; an unrestricted database search would broaden the evidence base. Second, the included population shows heterogeneity in age (range: mean 44.9 to 95 years), diagnostic tools, and comorbidity burden, which limits direct comparison across studies and introduces heterogeneity into pooled estimates. The minimum age of participants included across some primary source cohorts was 44.9 years, while the overall mean age was 56.3 years. Third, evidence specific to the 'oldest-old' (>=80 years), the frail, and those with advanced neurodegenerative disease remains limited; most pharmacological trials included older adults as subgroups within trials designed primarily for general adult populations. Fourth, long-term follow-up data (>12 months) are limited for most interventions. Finally, this review did not include a formal cost-effectiveness analysis, which would be valuable for guiding health system resource allocation.

Applicability to the Malaysian Healthcare Context

Translating these findings into Malaysian clinical practice introduces unique structural, financial, and cultural considerations: (i) Infrastructure and Human Resource Barriers: While face-to-face CBT-I is established globally as the definitive gold standard, its wide-scale implementation faces significant bottlenecks in Malaysia. There is a severe shortage of certified clinical psychologists and specialized sleep physicians within both the Ministry of Health (MOH) public facilities and private sectors. To address this, clinical priority must shift toward digital and internet-delivered CBT-I (dCBT-I). However, digital delivery requires intentional translation into Malay and Tamil, alongside optimization for varying levels of digital literacy among older populations in rural areas (e.g., Kampungs). (ii) Deprescribing Challenges in Primary Care: In Malaysia, the over-reliance on traditional Z-drugs and benzodiazepines (such as alprazolam or lorazepam) remains prevalent in primary care clinics due to their low cost and instant sedation profiles. Transitioning away from these PIMs requires localized, structured tapering protocols integrated into public clinics (Klinik Kesihatan). (iii) DORA Formulary and Accessibility: Newer, safer pharmacological agents like DORAs are significantly more expensive than generic benzodiazepines. Currently, access to agents like lemborexant or daridorexant in Malaysia is mostly restricted to major tertiary referral hospitals or private sleep centers, creating a massive access gap for geriatric patients in the bottom 40% household income group (B40). (iv) Culturally Accommodating Alternative Therapies: Given the limitations in accessing psychological specialists, highly feasible, non-invasive therapies like music therapy or modified exercise regimens (e.g., Tai Chi or chair exercises) hold substantial promise for Malaysian community centers and residential care homes. These interventions leverage community support structures and present zero financial or adverse event burdens.

Implications for Clinical Practice

The findings support the following clinical priorities for practitioners managing insomnia in older adults. All patients should undergo a comprehensive assessment including comorbidity review, medication reconciliation (with attention to alerting or sleep-disrupting agents), and screening for contributing factors such as pain, nocturia, and sleep-disordered breathing. CBT-I should be offered as the primary treatment modality, with digital CBT-I considered where face-to-face access is unavailable. Music therapy and exercise should be offered as adjunctive interventions. When pharmacotherapy is required, DORAs are preferred; melatonin and ramelteon are appropriate where circadian factors predominate. Benzodiazepines and Z-drugs should be actively deprescribed. Patients, families, and care staff should be educated regarding the risks of traditional hypnotics and the availability of evidence-based alternatives.

Future Research Directions

Priority areas for future research include: (i) Dedicated RCTs of DORAs in adults aged >=80 years and in frail, multi-

morbid populations. (ii)Long-term comparative studies (>12 months) of CBT-I versus DORAs in community-dwelling older adults. (iii) Digital CBT-I platform development tailored to reduced digital literacy and cognitive changes common in older adults. (iv) Larger-scale RCTs of music therapy and exercise with standardised protocols to enable high-precision meta-analytic synthesis. (v) Implementation science research addressing how CBT-I can be integrated into primary care, aged care nursing, and community pharmacy settings. (vi) Economic modelling to quantify cost-effectiveness across intervention types and healthcare system contexts.

CONCLUSION

The management of insomnia in older adults requires a comprehensive, individualized, and multimodal approach that prioritizes evidence-based non-pharmacological treatment, reserves pharmacotherapy for specific clinical indications, and selects agents with the most favorable safety profile. CBT-I is established as the gold-standard first-line treatment, showing high therapeutic durability but requiring individualized modification to suit the specific physical and cultural profiles of older adults. DORAs represent the preferred pharmacological class due to highly consistent cross-population efficacy and low heterogeneity. Benzodiazepines and Z-drugs should be actively avoided or systematically deprescribed to prevent unnecessary fall-related morbidity. These integrated recommendations should be incorporated into modern clinical frameworks to close the persistent evidence-practice gap in geriatric sleep medicine.

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CONFLICT OF INTEREST

The authors declare no competing interests.

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Routine abdominal drainage versus no drainage after elective hepatectomy: A systematic review and meta-analysis

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ABSTRACT

Introduction: The value of routine abdominal drainage after hepatectomy remains controversial. Although drains have traditionally been used to detect bile leakage or postoperative bleeding and to evacuate intra-abdominal collections, their routine use after elective liver resection has increasingly been questioned.

Materials and Methods: A systematic review and meta-analysis of randomized controlled trials comparing routine abdominal drainage with no drainage after elective hepatectomy was performed. PubMed/MEDLINE, Embase, Web of Science, and the Cochrane Library were searched from inception to 1 April 2026 using predefined terms related to hepatectomy, drainage, and randomized trials. The outcomes of interest included overall postoperative morbidity, postoperative mortality, wound-related complications, bile leakage or biliary fistula, subphrenic or perihepatic fluid collection, and length of hospital stay. Risk of bias was assessed using the Cochrane RoB 2 tool.

Results: Six randomized controlled trials involving 1,025 patients were included, with 513 patients allocated to routine drainage and 512 to no drainage. Routine drainage was associated with higher overall postoperative morbidity (RR 1.41, 95% CI 1.16-1.71; I^2 = 32.5%) and more wound-related complications (RR 2.75, 95% CI 1.56-4.86; I^2 = 36.1%). Postoperative mortality remained low and did not differ significantly between groups (RR 1.20, 95% CI 0.50-3.00; I^2 = 0%). Reported bile-leakage events were more frequent in the drainage group (RR 5.02, 95% CI 1.53-16.48; I^2 = 0%); however, this outcome is highly susceptible to ascertainment bias because the opportunity to detect bile leakage differs according to drain status. Subphrenic/perihepatic collection did not differ clearly between groups (RR 1.02, 95% CI 0.48-2.15; I^2 = 71.4%). Length of hospital stay showed a small pooled difference favoring drainage (MD -0.35 days, 95% CI -0.50 to -0.20), but between-study heterogeneity was substantial (I^2 = 82.3%) and the trial-level directions were inconsistent.

Conclusion: Current randomized evidence does not support routine abdominal drainage after elective hepatectomy, particularly in uncomplicated or standard-risk cases. A selective rather than routine strategy appears more appropriate, and the apparent bile-leakage signal and hospital-stay result should be interpreted in light of ascertainment bias, outcome-definition differences, and substantial between-study heterogeneity.

KEYWORDS:
Hepatectomy, liver resection, abdominal drainage, no drainag

INTRODUCTION

Hepatectomy is a technically demanding procedure that carries a risk of postoperative complications, including bile leakage, hemorrhage, intra-abdominal fluid collection, surgical-site infection, and liver failure.[1-2] For decades, routine abdominal drainage after liver resection was widely adopted on the assumption that it might facilitate early detection of postoperative bleeding or bile leakage and help evacuate fluid from the operative field.[3]

However, the routine use of drains has increasingly been challenged across abdominal surgery.[3-4] Drains may themselves become a source of retrograde infection, impair mobilization, prolong hospitalization, and increase discomfort.[5] In liver surgery specifically, the theoretical advantages of drainage must be balanced against the possibility that drains may not prevent clinically relevant complications and may instead contribute to wound- or drain-related morbidity.[3,5]

Several randomized controlled trials have evaluated routine abdominal drainage after hepatectomy, beginning with the early studies by Belghiti, et al.(6) , Fong, et al.(7), and Liu, et al.(8) , and followed by later trials from China, East Asia, and Japan.[6-11] These studies have not shown a consistent benefit of routine drainage, and some have suggested worse outcomes in the drainage group.[6-12] In addition, enhanced recovery pathways and contemporary perioperative care have further reduced the rationale for routine prophylactic drainage after uncomplicated liver resection.[13-14] The aim of the present study was therefore to update the evidence by systematically reviewing randomized controlled trials comparing routine abdominal drainage with no drainage after elective hepatectomy and to synthesize the available data using meta-analytic methods.

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MATERIALS AND METHODS

Study design and reporting

This systematic review and meta-analysis was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement.15 The review was not prospectively registered.

Search strategy

A systematic literature search was performed in PubMed/MEDLINE, Embase, Web of Science, and the Cochrane Library inception to 1 April 2026. Reference lists of relevant reviews and eligible studies were also screened manually to identify additional records. The PubMed search strategy used for this review was as follows: `((("Hepatectomy" OR "Liver Resection" OR "Hepatic Resection" OR "Partial Hepatectomy" OR "Hepatic Lobectomy") AND ("drainage" OR "Surgical Drainage" OR "Abdominal Drainage" OR "Drain" OR "Drains") AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti])) AND (((((((randomized controlled trial [pt]) OR (controlled clinical trial [pt])) OR (randomized [tiab])) OR (placebo [tiab])) OR (drug therapy [sh])) OR (randomly [tiab])) OR (trial [tiab])) OR (groups [tiab])) NOT ((animals [mh]) NOT (humans [mh]))` Equivalent search terms and syntax were adapted for the other databases. Only studies published in English were considered.

Eligibility criteria

Studies were eligible if they met all of the following criteria: (i)randomized controlled trial; (ii) adult patients undergoing elective hepatectomy or liver resection; (iii) direct comparison between routine abdominal drainage and no drainage; (iv) reporting of at least one postoperative outcome of interest.

Studies were excluded if they: (i) were non-randomized; (ii) involved procedures other than hepatectomy alone; (iii) evaluated interventions other than routine abdominal drainage versus no drainage; (iv) contained overlapping patient cohorts without extractable independent data; (v) lacked sufficient outcome data for analysis.

Outcomes

The primary outcome was overall postoperative morbidity.
Secondary outcomes included postoperative mortality, wound-related complications, bile leakage or biliary fistula, subphrenic or perihepatic fluid collection and length of hospital stay.

Other postoperative outcomes, including severe complications or septic complications, were recorded when reported, but were summarized narratively if definitions were inconsistent or extractable data were insufficient for pooled analysis.

Study selection and data extraction

Two reviewers independently screened titles and abstracts, assessed potentially eligible full-text articles, and extracted data using a standardized form. Disagreements were resolved by discussion and consensus. For each study, the following information was extracted: (i) author and year; (ii) country or region; (iii) sample size; (iv) characteristics of the study population; (v) intervention details; (vi) outcome data.

For dichotomous outcomes, event counts and total numbers in the drainage and no-drainage groups were extracted. For continuous outcomes, means, standard deviations, and sample sizes were extracted. When continuous data were reported as mean ± standard error, the standard deviation was calculated using the formula SD = standard error (SE) $SE \times \sqrt{n}$ in accordance with standard Cochrane guidance.[16]

Risk of bias assessment

Risk of bias was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool [17] across the following domains: (i) bias arising from the randomization process; (ii) bias due to deviations from intended interventions; (iii) bias due to missing outcome data; (iv) bias in measurement of the outcome; (v) bias in selection of the reported result. Each study was judged as having low risk of bias, some concerns, or high risk of bias.

Statistical analysis

Meta-analysis was performed using Stata/SE version 17.0 (StataCorp LLC, College Station, TX, USA) with a random-effects model because clinical and methodological heterogeneity was anticipated among studies. For dichotomous outcomes, risk ratios (RRs) with 95% confidence intervals (CIs) were calculated using the Mantel-Haenszel method. For continuous outcomes, mean differences (MDs) with 95% CIs were calculated using the inverse-variance method. The between-study variance in the random-effects model was estimated using the DerSimonian-Laird method. For rare-event outcomes, studies with zero events in both groups were retained in the descriptive summary but did not contribute to the pooled RR estimate under the Mantel-Haenszel model; for studies with a zero event in one group, a continuity correction of 0.5 was applied. Statistical heterogeneity was assessed using the I^2 statistic.[18] An I^2 value of 25%, 50%, and 75% was interpreted as low, moderate, and high heterogeneity, respectively. Studies were pooled only when outcome definitions and extractable data were sufficiently comparable. Because fewer than 10 studies were available for each pooled outcome, publication bias was not formally assessed.

RESULTS

Study selection

The study selection process is presented in Figure 1. After database searching, deduplication, title and abstract screening, and full-text assessment, six randomized controlled trials met the eligibility criteria and were included in the final review and quantitative synthesis.

Characteristics of included studies

Six randomized controlled trials published between 1993 and 2021 were included 6-11. These studies were conducted in France, the United States, Hong Kong/China, mainland China, East Asia, and Japan. Altogether, 1,025 patients were analyzed, of whom 513 were assigned to routine drainage and 512 to no drainage.

Table I: Characteristics of the randomized controlled trials included in the updated review

Study	Year	Region	N (Drain / No drain)	Population	Primary or main reported endpoint	Main conclusion
Belghiti et al.	1993	France	42 / 39	Elective hepatectomy, mixed indications	Postoperative complications	Routine drainage not necessary
Fong et al.	1996	USA	60 / 60	Elective liver resection, mainly malignant disease	Morbidity and postoperative outcome	Drainage unnecessary after elective liver resection
Liu et al.	2004	Hong Kong, China	52 / 52	Hepatectomy in chronic liver disease	Operative morbidity	Routine drainage contraindicated in chronic liver disease
Sun et al.	2006	China	60 / 60	Elective hepatectomy	Postoperative complications	Routine drainage unnecessary
Kim et al.	2014	Korea	100 / 100	Elective hepatectomy; mixed major/minor resection; chronic liver disease and normal liver parenchyma subgroups	Postoperative morbidity and complications directly related to drainage	Systematic drainage not recommended after satisfactory hepatectomy
Arita et al.	2021	Japan	199 / 201	Uncomplicated hepatic resection	Severe complications and postoperative outcome	Drain placement associated with worse postoperative outcome

Table II: Risk of bias

Study	Randomization process	Deviations from intended interventions	Missing outcome data	Outcome measurement	Selection of reported result	Overall
Belghiti et al.	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns
Fong et al.	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns
Liu et al.	High	Some concerns	Some concerns	High	Some concerns	High
Sun et al.	Low	Low	Low	Low	Low	Low
Kim et al.	Some concerns	Some concerns	Low	Low	Low	Some concerns
Arita et al.	Low	Low	Low	Low	Low	Low

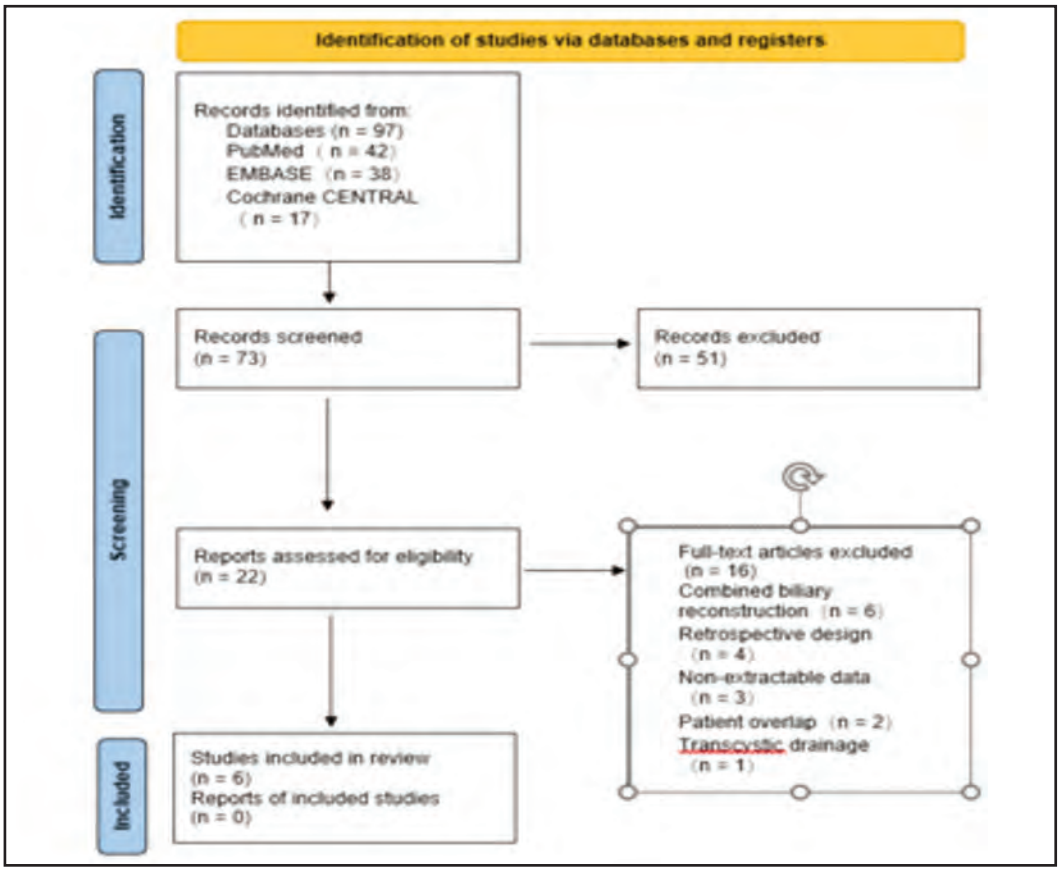

Fig. 1: PRISMA flow diagram illustrating the process of study identification, screening, eligibility assessment, and inclusion

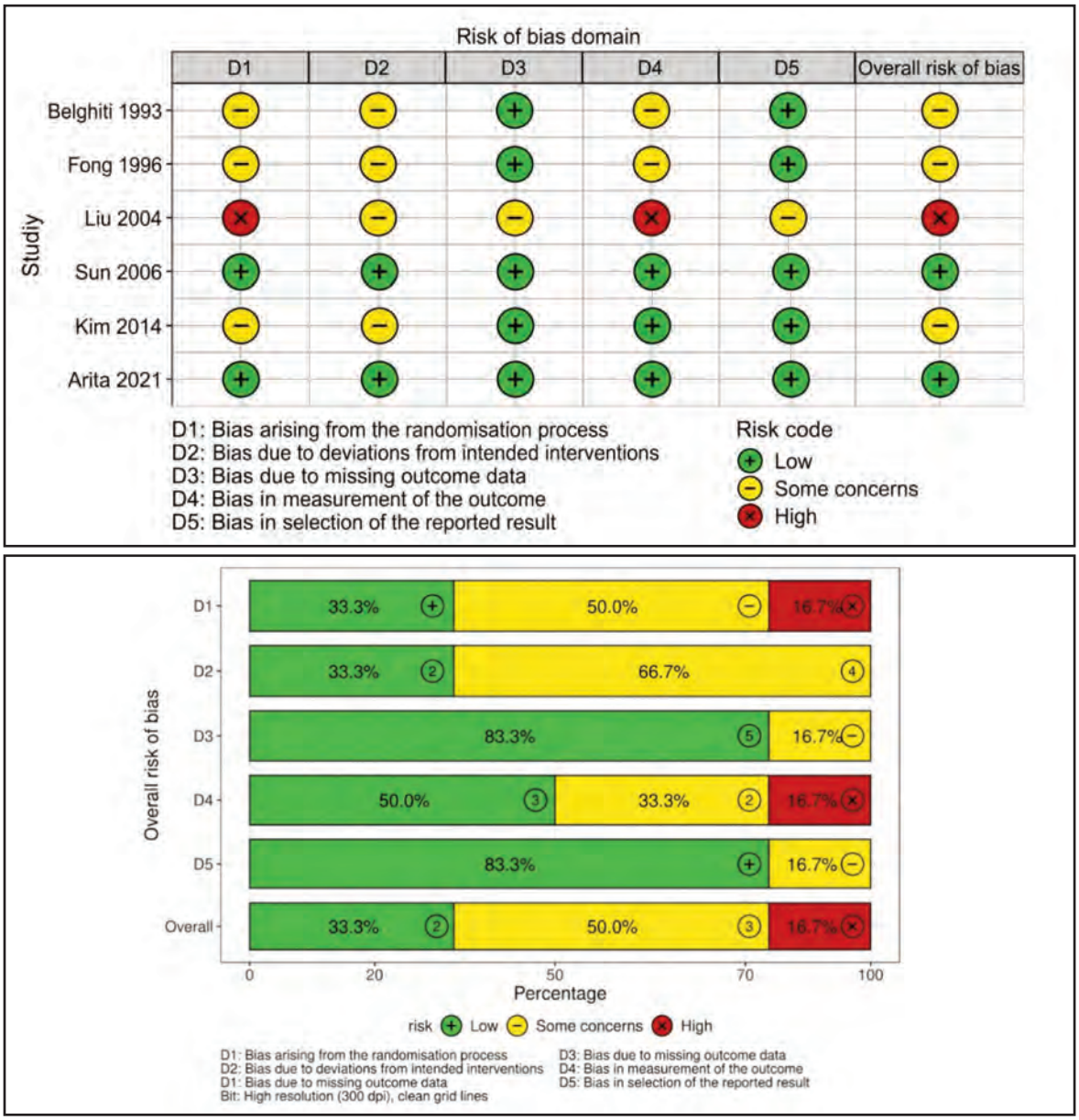

Fig. 2: Risk of bias traffic light plot (RoB 2); B: Risk of bias summary plot (RoB 2)

The included trials varied in case mix, underlying liver disease, and perioperative practice, but all directly compared routine abdominal drainage with no drainage after elective hepatectomy.[6-11] The main characteristics of the included studies are summarized in Table I.

Risk of bias

Risk-of-bias assessment showed that two studies were judged to be at low overall risk of bias, three raised some concerns, and one was judged to be at high risk of bias. The principal source of concern in the earlier trials related to randomization reporting, outcome measurement, and incomplete detail regarding allocation procedures. The domain-level assessments are presented in Table II and Figure 2.

Overall postoperative morbidity

Overall postoperative morbidity was reported in five trials comprising 944 patients. Event counts were 29/60 versus 26/60 in Fong, et al. (7), 38/52 versus 20/52 in Liu, et al. (8), 22/60 versus 16/60 in Sun ,et al. (9), 16/100 versus 12/100 in Kim ,et al. (10), and 77/199 versus 55/201 in Arita, et al. (11) (any Clavien-Dindo grade).[7-11] As shown in Figure 3, the pooled analysis favored no drainage, with a significantly higher overall morbidity rate in the drainage group (pooled RR 1.41, 95% CI 1.16–1.71; I^2 = 32.5%).

Postoperative mortality

Postoperative mortality was reported in all six trials comprising 1,025 patients. Deaths were uncommon: 1/42 versus 1/39 in Belghiti, et al. (6), 2/60 versus 2/60 in Fong, et al. (7), 3/52 versus 1/52 in Liu, et al. (8), 0/60 versus 1/60 in Sun, et al. (9), 0/100 versus 0/100 in Kim, et al. (10), and

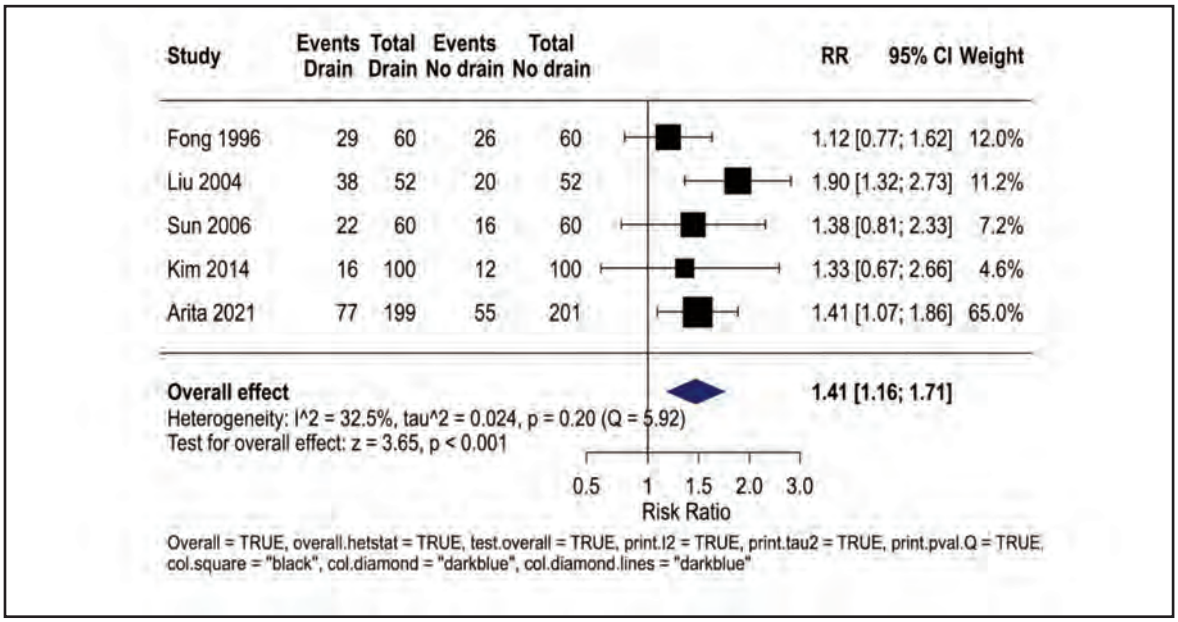

Fig. 3: Overall postoperative morbidity

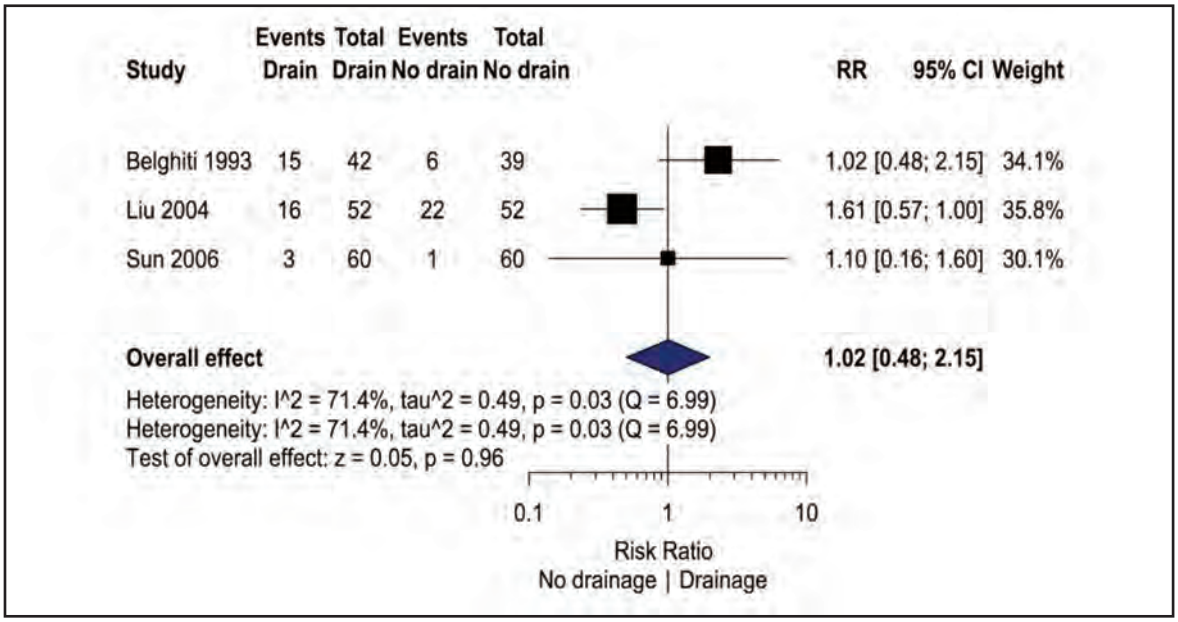

Fig. 4: Subphrenic / Perihepatic collection

0/199 versus 0/201 in Arita , et al. (11). As shown in Figure 4, there was no significant difference between strategies (pooled RR 1.20, 95% CI 0.50–3.00; $I^2 = 0\%$).

Wound-related complications

Wound-related complications were reported in three trials comprising 624 patients. Rates were 32/52 versus 11/52 in Liu, et al. (8), 17/60 versus 2/60 in Sun, et al. (9), and 16/199 versus 8/201 in Arita, et al. (11). Figure 5 demonstrates a clear excess of wound- or drain-related morbidity with routine drainage (pooled RR 2.75, 95% CI 1.56–4.86; $I^2 = 36.1\%$), consistent with the possibility of drain-site leakage, local contamination, or retrograde infection.

Bile leakage or biliary fistula

Bile leakage or biliary fistula was extractable from four trials. Event counts were 3/60 versus 3/60 in Fong, et al. (7), 2/52 versus 0/52 in Liu, et al. (8), 0/60 versus 0/60 in Sun, et al. (9), and 16/199 versus 0/201 in Arita, et al. (11). The pooled analysis in Figure 6 favored no drainage and suggested more reported bile-leakage events in the drainage group (pooled RR 5.02, 95% CI 1.53-16.48; $I^2 = 0\%$). Reported bile-leakage events were more frequent in the drainage group; however, this outcome is highly susceptible to ascertainment bias because the opportunity to detect bile leakage differs according to drain status. Therefore, this finding should be interpreted cautiously and should not be taken as definitive evidence that drainage increases the true biological incidence of bile leakage.

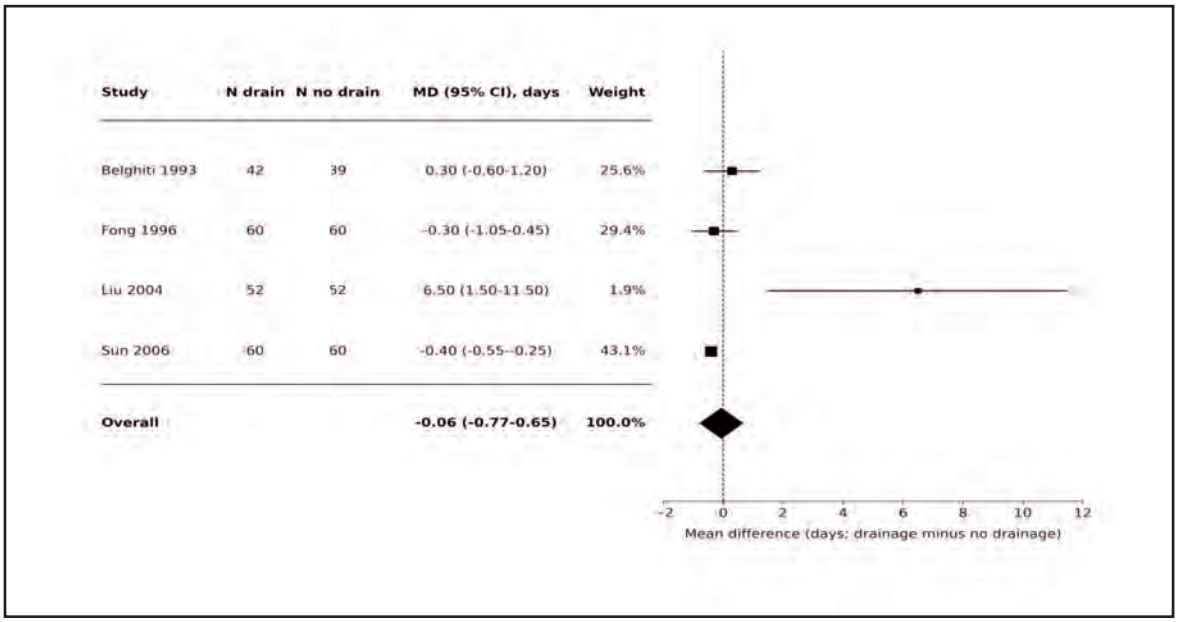

Fig. 5: Length of hospital stay

Subphrenic or perihepatic fluid collection

Subphrenic or perihepatic fluid collection was reported in three trials comprising 305 patients, but definitions remained heterogeneous. Figure 4 used the extractable counts available from Belghiti, et al. (6) (15/42 versus 6/39), Liu, et al. (8) (16/52 versus 22/52), and Sun, et al. (9) (3/60 versus 1/60). The pooled estimate showed no clear difference between strategies (RR 1.02, 95% CI 0.48–2.15; I^2 = 71.4%), and the substantial heterogeneity indicates that this outcome should be interpreted cautiously.

Length of hospital stay

Length of postoperative hospital stay was reported in four early trials comprising 425 patients. Mean stay was 12.6 versus 12.3 days in Belghiti, et al. (6), 13.1 versus 13.4 days in Fong, et al. (7), 19.0 versus 12.5 days in Liu, et al. (8), and 8.1 versus 8.5 days in Sun, et al. (9). Figure 5 showed a pooled mean difference of -0.35 days (95% CI -0.50 to -0.20). However, heterogeneity was considerable (I^2 = 82.3%), and the individual trials pointed in different directions. Given the substantial heterogeneity and inconsistent direction of individual trials, this pooled estimate should be interpreted as hypothesis-generating rather than definitive.

Narrative synthesis of other outcomes

Other postoperative outcomes were synthesized narratively because definitions were heterogeneous. In the contemporary ND trial, severe complications of Clavien-Dindo grade 3 or higher occurred in 16/199 patients with drainage and 5/201 without drainage.[11] Liu, et al. (8) also found more septic complications with drainage (17/52 versus 9/52) 8. Kim, et al. (10) reported no significant difference in overall morbidity (16/100 versus 12/100), but complications directly related to drainage were more frequent in the drainage group overall (9 versus 3 patients) and particularly among patients with chronic liver disease (4 versus 1 patients).[10]

DISCUSSION

Principal findings

This updated systematic review and meta-analysis included six randomized controlled trials with a total of 1,025 patients undergoing elective hepatectomy. Routine drainage was associated with higher overall postoperative morbidity and more wound-related complications, whereas mortality and postoperative fluid collection did not differ clearly between groups. Although reported bile-leakage events were more frequent in the drainage group, this outcome is particularly vulnerable to ascertainment bias because the opportunity to detect bile leakage differs according to drain status. Similarly, although the pooled analysis of length of hospital stay showed a small numerical difference, the marked between-study heterogeneity and inconsistent trial-level directions mean that this estimate should be regarded as hypothesis-generating rather than definitive.

Interpretation in context

The rationale for prophylactic drainage after hepatectomy has historically been based on concern regarding bile leakage and postoperative hemorrhage. However, a prophylactic drain does not prevent these complications from occurring. Instead, it may function mainly as a monitoring device while also introducing the possibility of retrograde infection, patient discomfort, restricted mobility, and drain-site morbidity.[5] The observed excess in overall morbidity and wound-related complications is therefore biologically plausible and is consistent with modern perioperative principles that favor avoidance of unnecessary tubes and drains whenever safe.[13]

These findings are also consistent with enhanced recovery pathways and contemporary liver surgery practice, in which careful hemostasis, secure control of biliary radicals, selective postoperative imaging, and image-guided percutaneous intervention have reduced the need for routine prophylactic drainage.[13-14] Importantly, the pooled bile-leakage signal

should not automatically be interpreted as proof that drains cause bile leakage. Reported bile-leakage events were more frequent in the drainage group; however, this outcome is highly susceptible to ascertainment bias because the opportunity to detect bile leakage differs according to drain status.

Clinical implications

The present findings support a selective rather than routine approach to abdominal drainage after elective hepatectomy. In standard cases without biliary reconstruction, gross contamination, uncontrolled oozing, or other specific intraoperative concerns, omission of routine drainage appears reasonable and evidence-based.[13-14] These findings are most applicable to uncomplicated or standard-risk resections, and extrapolation to more complex or high-risk hepatectomy should be made cautiously.

The decision to place a drain should remain individualized and should ultimately be made intraoperatively by the operating surgeon. Selective drainage may be justified when there is concern about a high risk of postoperative bile leakage, localized bleeding, difficult or incomplete hemostasis, biliary reconstruction, or other procedure-specific factors. This decision should also consider the surgeon's expertise and the availability of timely postoperative diagnostic imaging and image-guided or other interventional management if a leak, collection, or hemorrhage is suspected. Such selective use should not be conflated with a routine drainage policy for all patients.

This review has several strengths. Only randomized controlled trials were included, thereby reducing confounding. The intervention of interest was strictly defined as routine abdominal drainage versus no drainage after hepatectomy. In addition, the review followed PRISMA 2020 reporting guidance, and the study selection process is documented transparently, which improves reporting quality, transparency, and reproducibility.[15]

LIMITATIONS

Several limitations should be acknowledged. First, although six randomized trials were identified, not every outcome was reported in every study, which limited the number of trials available for some pooled analyses. Second, outcome definitions were not fully standardized across the included studies, especially for wound-related complications, septic events, bile leakage, and postoperative fluid collections. Third, some older trials did not report all continuous variables in a uniform format, requiring limited data conversion. Fourth, perioperative management evolved substantially over the period covered by the included studies, which may have introduced clinical heterogeneity. Fifth, the direction of the bile-leakage outcome may have been influenced by ascertainment differences between drainage and no-drainage strategies, and the hospital-stay analysis showed marked heterogeneity. Sixth, this review was not prospectively registered, which may limit transparency regarding a priori methods. Finally, because fewer than 10 studies were available for each outcome, formal assessment of publication bias was not reliable and was not performed. Sensitivity analyses were limited by the small number of available randomized trials and were not prespecified in a registered protocol.

CONCLUSION

Current randomized evidence does not support routine abdominal drainage after uncomplicated elective hepatectomy. A selective drainage strategy based on intraoperative findings and patient-specific risk appears more appropriate than routine prophylactic drainage. The final decision should remain with the operating surgeon, particularly in patients with a high intraoperative risk of bile leakage or bleeding, and should consider surgical expertise and the availability of prompt postoperative diagnostic and interventional support. The apparent bile-leakage signal and the pooled hospital-stay estimate should be interpreted cautiously because of likely ascertainment bias and substantial between-study heterogeneity.

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