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SPECIAL ARTICLE

Wide-Awake Local Anesthesia No Tourniquet for Hand and Wrist Procedures: A Narrative Review of Current Concepts and Evidence

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ABSTRACT

Wide-awake local anesthesia no tourniquet (WALANT) has emerged as an important anesthetic and surgical approach in hand and upper extremity surgery. By combining local anesthetic with epinephrine, WALANT enables procedures to be performed without sedation or tourniquet while allowing intraoperative communication and functional assessment. Beyond its anesthetic role, this technique has implications for surgical precision, patient-centered care, training environments, and health-system efficiency. This narrative review synthesizes current evidence and expert perspectives on WALANT, with emphasis on common procedures, expanding indications (e.g., fracture fixation and tendon repair), patient selection, safety considerations, and economic impact in urban healthcare settings. Available evidence indicates that WALANT achieves clinical outcomes comparable to those of conventional anesthesia techniques, with favorable patient-reported experiences, shorter recovery times, and reduced resource utilization. WALANT may be considered a suitable first-line option for selected upper extremity procedures when applied in appropriately chosen patients.

Keywords: hand surgery, local anesthesia, upper extremity, WALANT, wide-awake surgery

INTRODUCTION

Wide-awake local anesthesia no tourniquet (WALANT) represents a paradigm shift in hand and upper extremity surgery. Traditionally, procedures involving the hand and wrist have been performed under general anesthesia, regional nerve blocks, or intravenous regional anesthesia and almost universally combined with tourniquet use. Although effective, these procedures are associated with anesthesia-related risks, tourniquet discomfort, delayed recovery, and substantial resource utilization. By contrast, WALANT relies on local infiltration of lidocaine combined with epinephrine directly into the surgical field, eliminating the need for sedation and tourniquet application.[1-3]

Early reluctance toward the adoption of WALANT was largely driven by historical concerns regarding epinephrine's safety in digital surgery. However, contemporary clinical and experimental evidence has definitively refuted this dogma, demonstrating that epinephrine at appropriate concentrations does not increase the risk of digital ischemia or necrosis.[4-6] Consequently, WALANT has gained widespread acceptance and is increasingly incorporated into routine hand surgery practice worldwide.

The awake nature of WALANT introduces new dimensions to surgical care. Surgeons can perform real-time functional assessments, patients avoid the physiological and cognitive effects of sedation or general anesthesia, and procedures can be shifted from the main operating room to ambulatory or clinic-based settings. These characteristics are particularly relevant for urban health systems facing increasing procedural volume, workforce constraints, and the need for cost-effective and efficient care delivery.[7-9]

This narrative review was conducted using a targeted literature search of PubMed, Scopus, and Google Scholar databases. Keywords included "WALANT," "wide-awake surgery," "hand surgery," "upper extremity," and "local anesthesia." Relevant articles published in English, including randomized controlled trials, cohort studies, systematic reviews, and key expert opinion papers, were included. Reference lists of selected articles were also screened to identify additional relevant studies. The review aimed to synthesize current concepts and clinically relevant evidence rather than perform a formal systematic review.

CONTENT OF REVIEW

Principles and Techniques

WALANT is based on the principles of tumescent local anesthesia using dilute lidocaine (0.5%-1%) combined with epinephrine (1:100,000-1:200,000). Epinephrine induces localized vasoconstriction, which provides a relatively bloodless surgical field and prolongs the anesthetic duration, thereby obviating the need for a tourniquet. As such, adequate time between injection and incision (typically 20-30 min) is critical to ensure optimal hemostasis and patient comfort.[10]

The injection technique plays an important role in patient tolerance. Slow infiltration, buffering of lidocaine with sodium bicarbonate, and continuous patient communication during injection can significantly reduce discomfort and anxiety.[11,12] These technical considerations are essential for the successful implementation of WALANT, particularly in anxious or first-time patients.

To facilitate practical implementation, a concise checklist for WALANT setup is provided below **(Figure 1)**.

Clinical Efficacy Across Procedures

Strong evidence supports the use of WALANT for common procedures, including carpal tunnel and trigger finger release. According to randomized controlled trials and meta-analyses, WALANT consistently demonstrates equivalent surgical success, functional outcomes, and complication rates when compared with traditional anesthesia methods, with superior patient comfort because of the elimination of tourniquet pain.[13-16] These findings have established WALANT as a first-line anesthesia option for these procedures in many institutions.

The expanding indications for WALANT include fracture fixation of the distal radius, metacarpals, and phalanges. In these settings, awake active motion testing enables the intraoperative assessment of fracture stability, alignment, and hardware positioning. According to cohort studies and comparative analyses, the clinical and radiographic outcomes under WALANT are comparable to those achieved with general or regional anesthesia, with additional benefits including reduced postoperative pain and shorter recovery times.[17-19]

WALANT has also been successfully applied to flexor tendon repair and selected nerve decompression procedures. In tendon repair, the ability to assess active tendon gliding intraoperatively enables the immediate identification and correction of gapping, catching, or excessive tension, reducing postoperative complications and the need for revision surgery.[20,21] Cubital tunnel decompression performed under WALANT has demonstrated comparable efficacy to regional blocks while avoiding prolonged postoperative numbness.[22]

- Lidocaine with epinephrine (1:100,000–1:200,000), dose adjusted to body weight
- Consider buffering with sodium bicarbonate to reduce injection pain
- Slow, staged injection technique to minimize discomfort
- Allow adequate time (approximately 20–30 minutes) before incision for optimal vasoconstriction
- Ensure availability of phentolamine for rare cases of epinephrine-related vasoconstriction
- Maintain continuous patient communication and reassurance throughout the procedure

Figure 1 Checklist for WALANT Procedure Setup

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Patient-Centered Outcomes

From a patient-centered perspective, WALANT is associated with consistently high satisfaction rates. Patients value remaining awake, avoiding preoperative fasting, and maintaining autonomy throughout the surgical process. Moreover, rapid postoperative recovery without prolonged numbness enables earlier return to activities of daily living and work.[7,11,14]

Pain control with WALANT is generally adequate intraoperatively and postoperatively. Compared with traditional local anesthesia techniques, the absence of tourniquet-related discomfort represents a major advantage. Patient anxiety can also be effectively managed through preoperative counseling and intraoperative communication, further enhancing the overall experience of WALANT.[12,15]

Safety Profile

WALANT has a favorable safety profile. Across published studies, the complication rates remain low and comparable to those of traditional anesthesia methods. When established protocols are followed, no increase in infection, nerve injury, or vascular compromise has been reported. The safety of epinephrine in digital surgery is now well supported by high-quality evidence.[4-6,16] In rare cases of prolonged vasoconstriction or suspected digital ischemia, phentolamine can be used as a reversal agent for epinephrine, restoring perfusion effectively. Although such events are uncommon, the availability of phentolamine provides an additional safety measure.

In addition, the elimination of tourniquet use avoids tourniquet-related pain, nerve compression injuries, and time constraints associated with tourniquet tolerance. These factors contribute to patient comfort and surgeon efficiency.[13,15]

Surgeon Experience and Educational Value

Surgeon experience with WALANT has been overwhelmingly positive. The reported advantages of WALANT include improved visualization, unhurried operative conditions, and the ability to communicate with patients during surgery. In addition, WALANT's learning curve is considered manageable, particularly when surgeons begin with simple procedures, including carpal tunnel or trigger finger release.[8,9]

In training hospitals, WALANT offers unique educational value. Trainees can directly observe the relationship between surgical technique and immediate functional outcomes, reinforcing anatomical understanding and surgical decision-making. This real-time feedback may enhance technical learning and confidence among residents and fellows.[23]

Health System and Economic Impact

At the system level, WALANT substantially reduces healthcare resource utilization. According to economic analyses, WALANT reduces procedural costs by approximately 70%-85% by avoiding general anesthesia, operating room time, and postoperative recovery units in selected healthcare systems, particularly in studies conducted in the United States and similar resource settings.[24] These cost savings are derived from reduced staffing requirements, shorter procedural times, and elimination of anesthesia-related resources.

Office-based and ambulatory WALANT programs improve access to care and procedural throughput, which is particularly relevant in urban health systems with high patient volume and limited operating room availability. WALANT consistently demonstrates efficiency gains and improved resource allocation, even in settings where total societal cost differences are less pronounced.[25] Representative clinical and economic evidence from key studies is summarized in **Table 1**.

Clinical Implications

This comprehensive review highlights WALANT as a safe, effective, and increasingly influential anesthetic strategy for upper extremity surgery. Across a range of procedures, WALANT demonstrates comparable anesthetic adequacy, surgical success, and functional outcomes to those of traditional anesthesia techniques while offering distinct advantages in patient experience, intraoperative assessment, and health-system efficiency. Its complication rates remain low, patient satisfaction is consistently high, postoperative recovery is rapid, and pain control is acceptable. Importantly, the long-standing concern regarding epinephrine use in digital surgery has been definitively refuted, with contemporary evidence confirming its safety when used at appropriate concentrations. Appropriate patient selection includes individuals who are cooperative, able to tolerate awake procedures, have no severe anxiety or needle phobia, and have no contraindications to the use of local anesthetics with epinephrine.

From a surgical perspective, WALANT introduces unique technical benefits, including real-time intraoperative functional testing, improved visualization without tourniquet

Table 1 Representative Clinical and Economic Evidence of WALANT in Upper Extremity Surgery

Study	Procedure	Study Design	Sample Size (n)	Comparator	Key Findings
Virtos et al.[14]	Carpal tunnel release	Randomized controlled trial	120	Ultrasound-guided axillary block	Non-inferior outcomes; faster recovery and shorter discharge time
Ki Lee et al.[15]	Minor hand surgery	Randomized controlled trial	60	Local anesthesia with tourniquet	Similar surgical outcomes; reduced pain associated with tourniquet avoidance
Levit et al.[16]	Trigger finger release	Systematic review and meta-analysis	1,233 (pooled)	Local anesthesia with tourniquet	Comparable clinical outcomes; reduced intraoperative discomfort
Lin et al.[18]	Metacarpal fracture fixation	Retrospective cohort study	80	General anesthesia	Lower postoperative pain; reduced resource utilization
Chen et al.[19]	Distal radius fracture fixation	Retrospective cohort study	70	General anesthesia	Comparable radiographic and functional outcomes
Rhee et al.[24]	Clinic-based hand surgery	Cost analysis study	100	Intravenous sedation anesthesia	Approximately 70–85% reduction in procedural cost for the Military Health Care System
Alter et al.[25]	Carpal tunnel release	Cost analysis study	190	Sedation anesthesia	Lower direct and indirect healthcare costs with WALANT

constraints, and direct communication with awake patients. These features may enhance surgical precision and confidence, particularly in tendon repair and selected fracture fixation procedures. Moreover, surgeon experiences with WALANT are largely positive, with a manageable learning curve and high professional satisfaction, especially when implementation begins with common, low-complexity procedures.

At the system level, WALANT offers substantial economic and operational advantages. Compared with operating-room-based procedures under general anesthesia, WALANT reduces costs by approximately 70%-85%, reflecting decreased anesthesia utilization, shorter procedural times, and reduced postoperative recovery requirements. The feasibility of performing WALANT procedures in office-based and ambulatory settings expands access to care, improves throughput, and aligns well with the needs of urban healthcare systems facing increasing demand and resource constraints.

Based on current evidence, WALANT represents a valuable option for selected upper extremity procedures, particularly carpal tunnel release, trigger finger release, and other soft tissue operations. Its use can be extended to fracture fixation, tendon repair, and nerve decompression in carefully selected patients, with consideration of surgeon experience and procedural complexity. Successful implementation requires appropriate training in anesthetic technique, thoughtful patient selection, standardized institutional protocols, and attention to patient communication throughout the perioperative process.

Despite growing evidence supporting the use of WALANT for common hand procedures, several limitations and knowledge gaps remain. Current evidence for more complex reconstructions is largely derived from observational studies, and long-term outcomes beyond 6-12 months are insufficiently reported. In addition, comprehensive cost-effectiveness

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analyses incorporating societal costs, productivity, and quality-adjusted life years are limited.

Future research should therefore focus on high-quality, procedure-specific studies, including large-scale randomized trials for complex reconstructions, long-term outcome evaluations, and robust economic analyses. Further investigation in special populations and low-resource settings is also needed to better define the generalizability and broader applicability of WALANT in contemporary upper extremity surgery.

Limitations and Contraindications

Despite its advantages, WALANT has several limitations that should be considered in routine clinical practice. Patient-related factors remain important, as some individuals may not tolerate awake surgery because of anxiety, needle phobia, or psychological discomfort. Although these concerns can often be mitigated through effective communication and counseling, they may limit the applicability of WALANT in selected cases. From a technical perspective, inadequate anesthesia may occur, particularly in procedures involving extensive dissection or prolonged operative time, requiring supplemental injections or conversion to alternative anesthesia techniques. In addition, although epinephrine-induced vasoconstriction generally provides a bloodless field, minor bleeding may still occur in certain procedures, potentially affecting visualization.

Contraindications to WALANT include known allergy to local anesthetic agents, inability to cooperate during awake procedures, and caution in patients with severe peripheral vascular compromise. Careful patient selection and surgeon experience are therefore essential for optimal outcomes.

CONCLUSION

WALANT has evolved from an alternative anesthetic technique into a comprehensive care model integrating anesthesia, surgery, education, and health-system efficiency. The current evidence supports its safety, efficacy, and high patient acceptance for a broad range of upper extremity procedures. WALANT can be considered an important approach in appropriately selected patients, particularly within urban and resource-conscious healthcare settings.

Conflict of Interest

The author declares no conflicts of interest related to this work.

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Funding acquisition: -

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ORIGINAL ARTICLE

Heart Failure Outcomes with Predischarge Guideline Directed Medical Therapy Prescribing Patterns among Hospitalized Patients with Heart Failure with Reduced Ejection Fraction

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ABSTRACT

Objective: To assess the rates of heart failure (HF) readmission or all-cause mortality at 6 months among hospitalized patients with heart failure with reduced ejection fraction (HFrEF) based on the comprehensiveness of guideline-directed medical therapy (GDMT) prescribed at discharge.

Materials and Methods: This therapeutic study with a retrospective cohort design included patients with a first time hospitalized diagnosis of HFrEF at Vajira Hospital, Faculty of Medicine, Navamindradhiraj University, between January 1, 2018, and May 30, 2022. Patients were categorized into three groups according to the number of GDMT prescribed: GDMT1 (none or one agent), GDMT2 (two agents), and GDMT3 (three agents). The primary outcome is 6-month HF readmission or all-cause mortality were retrospectively collected.

Results: A total of 382 patients (65.2% male, mean age 64.4 ± 14.6 years) were included. Most patients had ischemic cardiomyopathy (43.7%), and the distribution of patients into the three groups was 31.4%, 39.3%, and 29.3% in GDMT1, 2, and 3, respectively. HF readmission or all-cause mortality were significantly lower in patients receiving more comprehensive GDMT: hazard ratio (HR) 0.32 (95% confidenc interval (CI): 0.16-0.65, p = 0.001) for GDMT3 versus GDMT1 and HR 0.42 (95% CI: 0.24-0.72, p = 0.002) for GDMT2 versus GDMT1. However, there was no statistically significant difference in the rate of 6-month all-cause mortality among the three groups.

Conclusion: Achieving three GDMT agents before discharge in patients hospitalized with HFrEF is associated with a significant reduction in 6-month HF readmission or all-cause mortality.

Keywords: guideline-directed medical therapy, heart failure readmission, heart failure with reduced ejection fraction, hospitalization, predischarge medication

INTRODUCTION

Guideline-directed medical therapy (GDMT) for heart failure with reduced ejection fraction (HFrEF) has been strongly supported by randomized controlled trials and is endorsed in international guidelines.[1,2] The four key pharmacologic pillars of GDMT include renin-angiotensin-aldosterone system (RAAS) blockage or angiotensin receptor–neprilysin inhibitors (ARNIs), beta-blockers, mineralocorticoid receptor antagonists (MRAs), and sodium-glucose cotransporter 2 (SGLT2) inhibitors. In addition, these medications have been shown to reduce heart failure (HF)–related hospital readmissions and mortality while significantly improving the quality of life of patients.[3] The benefit of GDMT also extend into the hospitalized and predischarge period, although patients in this phase may not receive the full recommended medication regimen.[4] As a result, in 2021, the European Society of Cardiology HF guidelines[5] recommend that GDMT medications should be initiated as early as possible—preferably during hospitalization—and, when feasible, introduced simultaneously.

However, the recent guideline[5] did not specify the optimal number of medications for predischarge initiation. Furthermore, several trials have highlighted only the benefits of various combinations of contemporary HF therapies, and the real-world evidence remains limited in the predischarge stage of care.[6] In this study, we aim to investigate the HF outcomes in patients discharged with differing degrees of GDMT implementation. Specifically, we compared the outcome between patients received four recommended medications with those received some medications.

MATERIALS AND METHODS

In this retrospective cohort study, we included patients hospitalized at Vajira Hospital, Faculty of Medicine, Navamindradhiraj University, between January 1, 2018, and May 30, 2022. The inclusion criteria were patients aged ≥ 18 years who were either newly diagnosed with HFrEF (left ventricular ejection fraction (LVEF) ≤ 40%) or who had a previous diagnosis and loss to follow up for 6 months. We excluded patients who had septic shock or no medical history, HF caused by severe valvular heart disease, or life-threatening comorbidity with a life expectancy of less than 1 year, including those with dependent for renal replacement therapy. The primary outcome was the composite of HF readmission or all-cause mortality rates at 6 months. The secondary outcomes were the 30-day HF readmission rate, 6-month cardiovascular death rate, 6-month acute myocardial infarction rate, and 6-month acute ischemic stroke rate.

The researchers collected electronic data from patients with acute decompensated HF who were admitted at Vajira Hospital within the previous 5 years. Then, we enrolled patients based on the inclusion and exclusion criteria. We collected basic patient information such as underlying disease, HFrEF etiology, renal function, hematocrit (HCT), LVEF, and medicines prescribed at the time of hospital discharge. We defined GDMT as therapy including angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blockers (ARBs) or ARNIs, beta-blockers (bisoprolol, carvedilol, nebivolol, metoprolol succinate), MRAs, and SGLT2 inhibitors. We stratified the patients into the following three groups: GDMT1, none or one GDMT; GDMT2, two GDMTs; and GDMT3, three or more GDMTs. We collected prognostic information within 6 months after discharge, including 30-day HF readmission, 6-month HF readmission, 6-month all-cause mortality, 6-month cardiovascular mortality, acute myocardial infarction, and acute ischemic stroke. The data were collected and entered into the case record forms. The Ethics Committee of the Faculty of Medicine, Vajira Hospital, Navamindradhiraj University, approved the study (COA 080/2565) and the investigators were certified in Good Clinical Practice.

We determined the sample size used in this research based on the study by Yamaguchi et al.,[7] in which the HF readmission rate was 25.3% when given an error of 20%. We estimated the required sample size in this study to be ≥ 377. The continuous variables are presented as the mean ± standard deviation or median with interquartile range, depending on the distribution. Categorical variables are presented as counts and percentages. The treatment group comparisons were performed using analysis of variance or Kruskal–Wallis test depending on the distribution of the continuous data. We used Chi-square tests to compare the categorical variables between the three groups. The Kaplan–Meier estimates and log-rank tests were used to describe the cumulative incidence of outcomes. We used Cox proportional hazards models, adjusted for key covariates (age, sex, body mass index, anemia, chronic kidney disease (CKD) stage IV–V, type 2 diabetes, hypertension (HT), coronary heart disease, and atrial fibrillation), to calculate the

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hazard ratios with 95% confidence interval (CI). Subgroup analyses (ischemic vs. nonischemic cardiomyopathy) were conducted. A p-value of < 0.05 was considered significant. We performed all analyses using IBM SPSS Statistics version 28.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Of the 1,537 patients admitted to Vajira Hospital with acute decompensated HF over the past 5 years, 382 met the inclusion criteria. The distribution of patients across the groups was 31.4%, 39.3%, and 29.3% in the GDMT1, 2, and 3 groups, respectively. Table 1 summarizes the baseline characteristics. The mean patient age was 64.4 ± 14.6 years, and 62.5% were male. The average LVEF was 30.2% ± 7.3%. The mean systolic blood pressure was 143.6 ± 28.0 mm Hg, the mean heart rate was 99.8 ± 23.7 bpm, and the mean HCT was 37.3% ± 7.2%.

In the investigation for the etiology of HFrEF, 65.2% of patients underwent coronary angiography and 3.7% underwent cardiac magnetic resonance imaging. The findings identified ischemic cardiomyopathy in 43.7% of cases, nonischemic cardiomyopathy in 28.8%, and an undetermined etiology in 27.5%. Toxin exposure—primarily to amphetamines—was reported in 4.2% of nonischemic patients. Common comorbidities included dyslipidemia (88.7%), HT (87.7%), and coronary artery disease (63.1%). However, we found significant differences among the groups in terms of age, creatinine value, CKD stage, HCT value, LVEF, and etiology of cardiomyopathy.

Table 2 shows the patterns of predischarge GDMT. In total, 31.4% of patients received one or fewer GDMT agents (GDMT1), 39.3% received two agents (GDMT2), and 29.3% received three or more agents (GDMT3). Beta-blockers were the most frequently prescribed (91.1%), primarily bisoprolol (49%; mean dose 2.9 ± 2.7 mg/day; 21.5% achieved the target dose). This was followed by ACEIs, ARBs, or ARNIs (67.5%), with losartan being the most commonly prescribed (33.5%; mean dose 44.1 ± 27.1 mg/day; 14.8% achieved the target dose), and MRAs, mainly spironolactone (36.1%; mean dose 14.8 ± 6.9 mg/day; 19.6% achieved the target dose). Other commonly used medications included furosemide (78.3%) and SGLT2 inhibitors (4.2%). In the GDMT2 group, RAAS blockage plus beta-blocker was the most common combination (84%). A beta-blocker plus MRAs and RAAS blockage plus MRAs were administered to 10.7% and 4.7% of patients, respectively.

Six months after hospital discharge, 83 patients (21.4%) were readmitted for acute HF, and 21 patients (5.5%) died. The composite event rates across GDMT1, 2, and 3 were 39.2%, 19.3%, and 12.5%, respectively. In addition, the Kaplan–Meier analysis demonstrated a statistically significant difference in cumulative incidence of 6-month heart HF readmission or all-cause mortality among the groups (log-rank test, p = 0.001) (Figure 1). In the multivariate analyses (Table 3), the composite outcome of 6-month HF readmission or all-cause mortality differed significantly among the three groups (p < 0.001). GDMT3 had a 64% decrease in composite outcomes when compared with GDMT1 (hazard ratio (HR) = 0.36, 95% CI: 0.18-0.70, p = 0.003), and GDMT2 had a 31% decrease in composite outcomes compared with GDMT1 (HR = 0.49, 95% CI: 0.29-0.81, p = 0.006).

When analyzed separately (Table 4), the 6-month HF readmission rates were 37.5% in GDMT1, 16.7% in GDMT2, and 11.6% in GDMT3. In the multivariate analyses, the rates of HF readmission at 6 months also showed significant differences among the groups: GDMT3 had a 68% lower rate of HF readmission than GDMT1 did (HR = 0.32,95% CI: 0.16-0.65, p = 0.001), while GDMT2 had a 48% lower rate of HF readmission than GDMT1 did (HR = 0.42, 95% CI: 0.24-0.72, p = 0.002). However, there was no statistically significant difference in the multivariate analyses of 6-month all-cause mortality among the three groups (p = 0.164).

In patients with nonischemic cardiomyopathy, the 6-month HF readmission or all-cause mortality rates were significantly lower (77% of composite outcome) in GDMT3 than in GDMT1 (HR = 0.23 95% CI: 0.07-0.77). Among patients with ischemic cardiomyopathy, there was no statistically significant difference in 6-month all-cause mortality among the three groups (Table 4). Other outcomes including cardiovascular death, stroke, and myocardial infarction, also showed no significant differences.

DISCUSSION

Our results demonstrated that patients with HF who initiated a greater number of appropriate GDMT agents before discharge had a significantly reduced rate of the composite of 6-month HF readmission or all-cause mortality (HR = 0.36 95% CI: 0.18-0.70, p = 0.003).

Table 1 Characteristics of Patients at Baseline

Baseline Characteristics	Total (n = 382)	GDMT1 (n = 120)	GDMT2 (n = 150)	GDMT3 (n = 112)	P-value*
Male	249 (65.2)	77 (64.2)	97 (64.7)	75 (67.0)	0.892
Age (years)	64.4 ± 14.6	68.6 ± 15.3	63.1 ± 14.0	61.7 ± 13.8	0.001
BMI (kg/m²)	24.4 ± 4.9	24.3 ± 5.3	24.2 ± 4.6	24.8 ± 4.9	0.573
SBP (mmHg)	143.6 ± 28.0	142.0 ± 26.9	145.4 ± 29.5	142.8 ± 27.3	0.610
Heart rate (bpm)	99.8 ± 23.7	96.2 ± 22.9	102.2 ± 24.2	100.4 ± 23.5	0.135
HCT (%)	37.3 ± 7.2	35.3 ± 7.6	37.3 ± 7.3	39.4 ± 6.1	< 0.001
Anemia (HCT < 30 %)	64 (16.8)	28 (23.3)	27 (18.0)	9 (8.0)	0.007
Cr (mg/dl)	1.2 (0.9, 1.6)	1.7 (1.2, 2.6)	1.1 (0.9, 1.5)	1.0 (0.8, 1.2)	< 0.001
CKD IV	43 (11.3)	34 (28.3)	7 (4.7)	2 (1.8)	< 0.001
CKD V	33 (8.6)	18 (15.0)	15 (10.1)	-	< 0.001
LVEF (%)	30.2 ± 7.3	30.3 ± 6.5	31.7 ± 7.2	27.9 ± 7.9	< 0.001
T2DM	162 (42.4)	58 (51.7)	90 (60.0)	67 (60.4)	0.297
HT	335 (87.7)	112 (93.3)	131 (87.3)	92 (82.1)	0.034
DLP	339 (88.7)	109 (90.8)	136 (90.7)	94 (83.9)	0.159
Old CVA	52 (13.6)	16 (13.3)	25 (16.7)	11 (9.8)	0.277
CAD	241 (63.1)	83 (69.2)	94 (62.7)	64 (57.1)	0.164
AF	241 (21.7)	29 (24.2)	31 (20.7)	23 (20.5)	0.736
Hyperthyroid	83 (2.4)	1 (0.8)	4 (2.7)	4 (3.6)	0.369
Hypothyroid	9 (4.5)	9 (7.5)	5 (3.3)	3 (2.7)	0.143
Toxin	17 (4.2)	3 (2.5)	8 (5.3)	5 (4.5)	0.506
CAG/MRI					0.002
No	119 (31.2)	49 (40.8)	39 (26.0)	31 (27.7)	
CAG	249 (65.2)	68 (56.7)	109 (72.7)	72 (64.3)	
MRI	14 (3.7)	3 (2.5)	2 (1.3)	9 (8.0)	
Etiology					0.003
Non ischemic cardiomyopathy	110 (28.8)	24 (20.0)	41 (27.3)	45 (40.2)	
Ischemic cardiomyopathy	167 (43.7)	52 (43.3)	74 (49.3)	41 (36.6)	
Undetermined	105 (27.5)	44 (36.7)	35 (23.3)	26 (23.2)	

Abbreviations: AF, atrial fribrillation; BMI, body mass indexed; bpm, beats per minute; CAD, coronary artery disease; CAG, coronary angiogram; CKD, chronic kidney; Cr, creatinine; CVA, cerebrovascular disease; DLP, dyslipidemia; GDMT, guideline directed medical therapy; GDMT1, none or one GDMT; GDMT2, two GDMT; GDMT3, three more than three GDMT; HCT, hematocrit; HT, hypertension; kg/m², kilogram square metre; LVEF, left ventricle ejection fraction; mg/dl, milligrams per deciliter; mmHg, millimeter of mercury; MRI, magnetic resonance imaging; n, number; SBP, systolic blood pressure; T2DM, type2diabetes melitus

Data are presented as frequency (percentage) or mean ± standard deviation or median (interquartile range).

*P-value by Chi-square, Fisher exact test, independent sample t-test, or Mann-Whitney U test. Significant level at P < 0.05.

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Table 2 Medication before Discharge

Medication	Total (n = 382)	GDMT1 (n = 120)	GDMT2 (n = 150)	GDMT3 (n = 112)
ACEI/ ARB / ARNI	258 (67.5)	12 (10.0)	134 (89.3)	112 (100.0)
Enalapril (ACEI)	103 (27.0)	4 (3.3)	52 (34.7)	47 (42.0)
Dose (mg/day)	6.8 ± 5.7	6.3 ± 2.5	7.1 ± 6.7	6.5 ± 4.7
Losartan (ARB)	128 (33.5)	8 (6.7)	67 (44.7)	54 (47.3)
Dose (mg/day)	44.1 ± 27.1	46.9 ± 24.8	44.4 ± 27.3	43.3 ± 27.7
Sacubitril/Valasartan (ARNI)	37 (9.7)	-	9 (6.0)	7 (6.3)
Dose (mg/day)	29.1 ± 44.3	-	29.4 ± 34.5	57.5 ± 62.4
Other ACEI/ ARBs	11 (2.9)	-	6 (4.0)	5 (4.5)
Beta-blocker	348 (91.1)	93 (77.5)	143 (95.3)	112 (100.0)
Bisoprolol	187 (49.0)	50 (41.7)	69 (46.0)	68 (60.7)
Dose (mg/day)	2.9 ± 2.7	2.6 ± 2.1	3.2 ± 3.6	2.9 ± 2.7
Carvedilol	154 (40.3)	42 (35.0)	71 (47.3)	41 (36.6)
Dose (mg/day)	11.2 ± 10.1	13.9 ± 13.1	10.7 ± 9.9	9.1 ± 5.1
Nebivolol	8 (2.1)	2 (1.7)	3 (2.0)	3 (2.7)
Dose (mg/day)	4.2 ± 4.7	6.3 ± 5.3	2.9 ± 1.9	4.2 ± 1.4
Spironolactone/ MRAs	138 (36.1)	4 (3.3)	23 (15.3)	111 (100.0)
Dose (mg/day)	14.8 ± 6.9	12.5 ± 0.0	16.8 ± 9.5	14.4 ± 6.3
Furosemide	299 (78.3)	88 (73.3)	113 (74.3)	98 (87.5)
dose(mg/day)	40 (20, 80)	40 (20, 80)	40 (20, 80)	40 (20, 80)
SGLT2inhibitor	16 (4.2)	3 (2.5)	9 (6.0)	4 (3.6)

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNIs, angiotensin receptor-neprilysin inhibitors; GDMT, guideline directed medical therapy; GDMT1, none or one GDMT; GDMT2, two GDMT; GDMT3, three more than three GDMT; mg, milligrams; MRAs, mineralocorticoid receptor antagonists; SGLT2, sodium-glucose cotransporter

Data are presented as frequency (percentage) or mean ± standard deviation.

Notably, even partial implementation of GDMT was associated with better outcomes compared with no therapy or just one agent. The finding is similar to that of an Asian real-world cohort study,[8] which found that even small doses of GDMT were associated with improved outcomes compared with no dose or nonusage. These results support the current guideline recommendations that encourage the early and comprehensive implementation of GDMT in patients with HFrEF.[1,2]

Furthermore, the findings of this study align with the broader evidence highlighting the benefits of GDMT in the HFrEF predischarge phase.[9,10] For example, a multicenter observational Japanese registry[4] (PRE-UPFRONT-HF) found that the implementation of GDMT in hospitalized patients with HF was significantly associated with a lower incidence of composite outcomes, including death and hospitalization for HF. The only key difference between that study and the current one is that patients in our study had a lower rate of SGLT2 medication use (only 4%), which reflects suboptimal adherence to the recommended GDMT regimen. This may be attributed to our study period (2018-2022), during which the adoption of

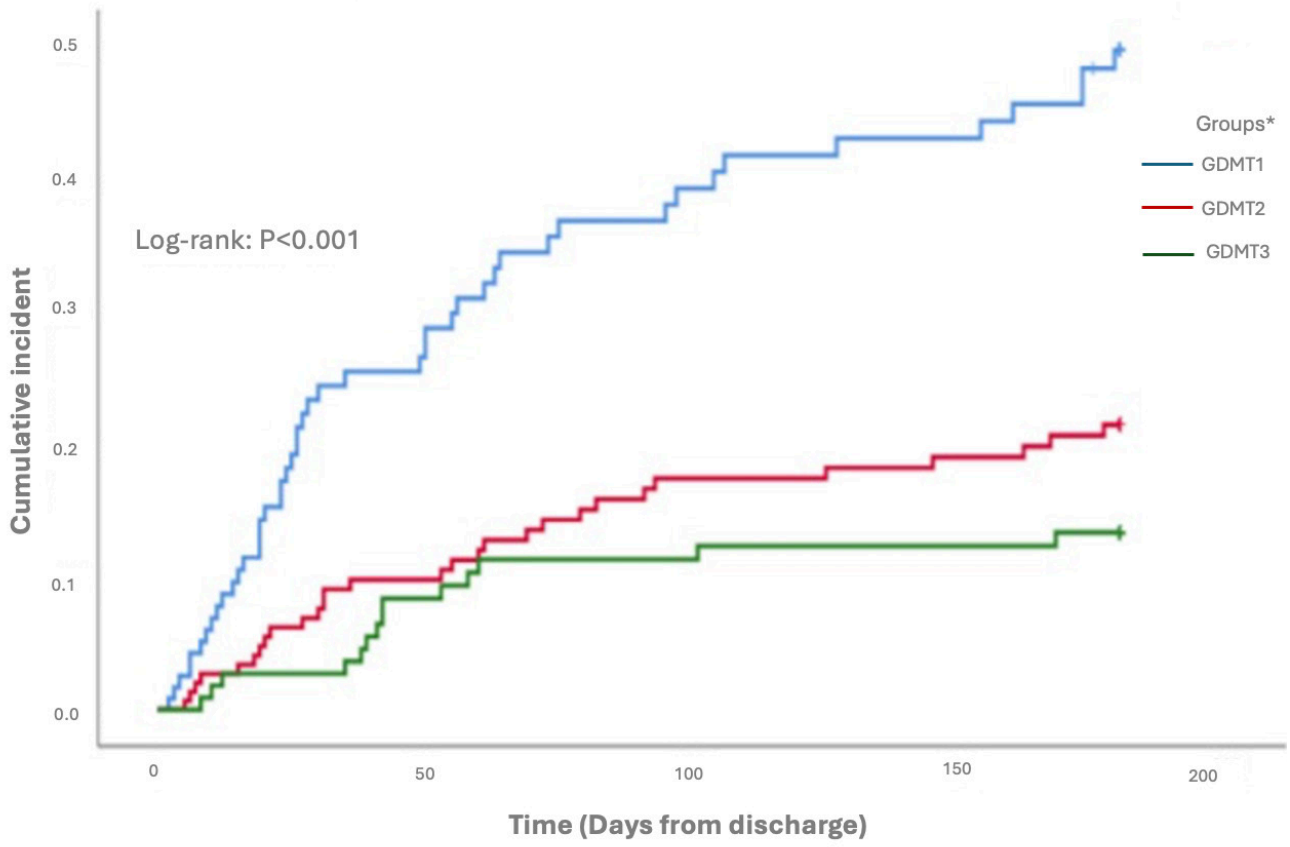

Figure 1 Cumulative Incidence of 6-Month HF Readmission or All-Cause Mortality
Abbreviations: GDMT, guideline-directed medical therapy; GDMT1, none or one GDMT; GDMT2, two GDMT; GDMT3, three more than three GDMT

SGLT2 inhibitors for HFrEF was still evolving or to issues related to drug cost and low socioeconomic status in Thailand. Nevertheless, our findings support the general principle that more comprehensive GDMT initiated before discharge leads to better outcomes, even when the complete four pillar foundation drugs are not used.

Interestingly, although HF readmission rates were signifi antly affected, there was no statistically significant difference in 6-month all-cause mortality among the three groups (p = 0.164). This fin ing contrasts with earlier studies that used intensified GDMT strategies, including earlier initiation of SGLT2 inhibitors and ARNI or more aggressive postdischarge management during the transitional phase.[11] For instance, the STRONG-HF randomized controlled trial[12] achieving at least half target doses within 2 weeks titrated postdischarge, whereas our observational study involved low doses (e.g., enalapril 6.8 mg/day) and optimization of only the three traditional GDMT pillars. This suggests that the advantages of early GDMT may become more obvious over a longer follow-up period. Alternatively, the lack of SGLT2 and the limited statistical power of this outcome could have contributed to the absence of a significant difference in mortality.

The study also explored whether the benefits of predischarge GDMT varied according to the underlying etiology of HFrEF, specifically in patients with ischemic cardiomyopathy (43.7% of the cohort) and nonischemic cardiomyopathy (28.8%). In the nonischemic group, we observed favorable outcomes in GDMT 3, whereas we observed no significant benefit in the ischemic group. These etiology-specific findings are noteworthy. Prior research, such as the study by Silverdal et al.,[13] suggested that patients with nonischemic HFrEF may exhibit a more favorable response to GDMT, whereas those with ischemic HFrEF may be limited by myocardial scar. However, this interpretation should be made

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Table 3 Effectiveness of Groups on 6-Month Readmission or All-Cause Mortality

Groups	6-Month Readmission or All-Cause Mortality		6-Month Readmission		6-Month All-Cause Mortality	
	Multivariable Analysis*		Multivariable Analysis*		Multivariable Analysis*	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
GDMT1	Reference		Reference		Reference	
GDMT2	0.49 (0.29-0.81)	0.006	0.42 (0.24-0.72)	0.002	1.24 (0.40-3.82)	0.708
GDMT3	0.36 (0.18-0.70)	0.003	0.32 (0.16-0.65)	0.001	0.73 (0.15-3.45)	0.688

Abbreviations: CI, confidence interval; GDMT, guideline directed medical therapy; GDMT1, none or one GDMT; GDMT2, two GDMT; GDMT3, three more than three GDMT; HR, hazard ratio

*Multivariable analysis adjusted for sex, age, body mass index, anemia, chronic kidney disease stage IV, chronic kidney disease stage V, Type 2 diabetes mellitus, hypertension, coronary artery disease and atrial fibrillation.

Table 4 Subgroup Analysis of Effectiveness in 6-Month HF Readmission or All-Cause Mortality

Groups	Ischemic		Non-Ischemic	
	Univariable Analysis		Univariable Analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
GDMT1	Reference		Reference	
GDMT2	0.49 (0.22-1.07)	0.074	0.40 (0.14-1.14)	0.086
GDMT3	0.47 (0.18-1.22)	0.122	0.23 (0.07-0.77)	0.017

Abbreviations: CI, confidence interval; GDMT1, none or one GDMT; GDMT2, two GDMT; GDMT3, three more than three GDMT; HR, hazard ratio

cautiously due to limitations in the subgroup analysis, including small sample sizes and the fact that nearly one-third of patients had an undetermined etiology of cardiomyopathy, which might have influenced the results.

Although the data from the network meta-analysis conducted by Tromp et al.[6] offer a benchmark for what is considered "optimal" GDMT and our study provides valuable real-world evidence on predischarge GDMT patterns, we identified a potential gap, with 31.4% of patients discharged on none or monotherapy instead of combined therapy and widespread underdosing. For example, only 15% of those given losartan, 21% of those given bisoprolol, and 20% of those given spironolactone achieved 50% of target recommended doses, and this pattern is consistent with the findings from other observational studies worldwide.[14] Therefore, the current study highlights a significant opportunity for quality improvement in clinical practice. Contributing factors include therapeutic inertia, drug tolerability concerns in the immediate postdecompensation phase, and systemic barriers to GDMT implementation before discharge.[15]

Several crucial limitations must be acknowledged. First, this study is susceptible to inherent limitations, such as selection bias, information bias, and being conducted at a single center. Second, we did not assess dose up-titration: the study categorized patients according to the number of GDMT agents, not by target doses. Postdischarge up-titration data were also unavailable, although this is a critical component of optimal GDMT. Finally, this study is limited by a small sample size, a low number of events, and a relatively short duration, which may not be long enough to observe other important outcomes, such as all-cause mortality and cardiovascular death.

CONCLUSION

Achieving three GDMTs before discharge in patients hospitalized with HFrEF is associated with a significant reduction in 6-month HF readmission or all-cause mortality.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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There is no acknowledgment provided.

Author Contributions

Conceptualization: K.S.
Data curation: W.S.
Formal analysis: K.S.
Funding acquisition: K.S.
Investigation: W.S.
Methodology: W.S.
Project administration: W.S.
Resources: W.S.
Software: W.S.
Supervision: K.S.
Validation: K.S.
Visualization: K.S.
Writing – original draft preparation: K.S.
Writing – review & editing: K.S.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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ORIGINAL ARTICLE

Factors Associated with Nomophobia among First-Year Students at Navamindradhiraj University

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ABSTRACT

Objective: This study aimed to examine the factors associated with nomophobia, the fear or anxiety of being without a mobile phone, including prevalence, sociodemographic, behavioral, psychosocial factors among first-year students at Navamindradhiraj University.

Materials and Methods: A descriptive cross-sectional study was conducted among 605 first-year undergraduate students from 13 academic programs at Navamindradhiraj University between January and May 2025. Data were collected via a structured online questionnaire, which included items on demographics, mobile phone usage behaviors, family relationship quality, and the Nomophobia Questionnaire. Descriptive statistics were used to assess prevalence. Chi-squared tests and binary logistic regression were employed to examine associations and to identify significant factor of moderate to severe nomophobia.

Results: The majority of participants experienced moderate (56.20%) or severe (21.70%) levels of nomophobia. The severity of nomophobia was significantly associated with daily phone usage ($p = 0.021$) and frequency of phone checking ($p = 0.006$). Logistic regression analysis further indicated that students who spent more time using their phones ($p < 0.001$), frequent phone checking ($p < 0.001$), and lower family relationship scores ($p = 0.005$) were significant factors associated with of moderate-to-severe nomophobia. Demographic variables such as gender, income, and gaming were not significant.

Conclusion: Nomophobia is alarmingly prevalent among first-year university students, with behavioral and psychosocial factors, especially patterns of phone use and perceived family support, playing a more critical role than demographic characteristics. Targeted interventions that promote digital well-being, strengthen emotional resilience, and enhance family support are essential to reduce its psychological impact and encourage healthier digital habits.

Keywords: digital age, first-year students, Navamindradhiraj University, nomophobia

INTRODUCTION

In the 21st century, technology has evolved beyond its original role as a tool for communication to become an indispensable part of daily life. Technology has become more than just a way to communicate; it is now a part of everyday life. Smartphones, in particular, help people stay connected through messages, social media, online learning, and searching for information. While these tools offer many benefits, using them too much, especially among young people, can lead to mental and emotional problems. One growing issue is nomophobia, short for "no mobile phone phobia." This is the fear or anxiety people feel when they don't have access to their phones or can't connect to the internet.[1-2] Although nomophobia is not officially listed in medical books, it is now seen as a modern type of phobia. People with this condition may feel nervous, irritated, or even panicked when they are away from their phones. Some may also have physical reactions like a fast heartbeat, eye strain, neck and shoulder pain, trouble focusing, mood swings, and feeling easily frustrated.[3-6]

Nomophobia, or the fear of being without a mobile phone, has become a growing concern, especially among university students, the most frequent smartphone users. They often depend on their devices for studying, communication, and entertainment, using them continuously to stay connected. Globally, nomophobia is common among university students. Around 20% experience mild, 50% moderate, and 20% severe symptoms.[7] In Saudi Arabia, over 27.20% stated that they spent more than 8 hours per day using their smartphones,[8] while in Thailand, approximately 99.50% of undergraduates' students had nomophobia.[9] First-year university students may be especially at risk, as this transitional stage involves adjusting to new academic demands, forming new social connections, and often living away from their families conditions that may increase reliance on smartphones to maintain communication and social connectedness.[10-11] These changes can lead to a heavier dependence on smartphones, which may increase the risk of nomophobia. Research from different countries has shown that nomophobia can be linked to several personal and behavioral factors.[12] These factors include age, gender, self-esteem, anxiety levels, frequency of phone use, time spent on social media, feelings of loneliness, and perceived social support.[13-14]

Navamindradhiraj University, located in central Bangkok, attracts students from diverse backgrounds. First-year students often rely on smartphones for connection and support during their transition to university life. While helpful, excessive use can harm mental health, academics, and relationships. Nomophobia is linked to increate anxiety, stress, poor concentration, low academic performance and sleep issues.

However, research on this issue among Thai students remains limited, highlighting the need for further study within this cultural context. Therefore, this study aimed to examine the factors associated with nomophobia, including prevalence, sociodemographic, behavioral, psychosocial factors among first-year students at Navamindradhiraj University. The goal of the study is expanding the body of knowledge on digital health and student well-being in the digital age.

MATERIALS AND METHODS

This descriptive cross-sectional study was conducted to examine the prevalence of nomophobia among first-year undergraduate students in 13 programs, including Medicine, Radiologic Technology, Emergency Medical Technology, Nursing Science, Occupational Health and Safety in Hospital, Medical Instrumentation and Operating Room Technology, Disaster Management, Aviation Business Services, Urban Administration and Management, Early Childhood Education, Facility Management, Bachelor of Technology, and Early Childhood Development at Navamindradhiraj University during the second semester of the 2024 academic year (January-May 2025). The sample size was calculated using a standard formula ($n = Z\alpha^2$ (P) (1-P)/d^2) and adjusted for a finite population of 743 students,[15] resulting in a required sample of 568 (corrected sample size = N*n / N+n-1). All first-year students were invited, and 605 complete responses were received, exceeding the required number and ensuring sufficient statistical power.

Data collection commenced after obtaining approval from the Institutional Ethics Committee (COA No. 229/2567). A structured questionnaire comprising 4 sections was used. The questionnaire was administered electronically via Google Forms, and informed consent was obtained online prior to participation.

The questionnaire consisted of four sections. The first section assessed demographic characteristics, including gender, age, program of study, average monthly allowance, and residence. The second section examined mobile phone usage behavior over the past month, covering daily duration of smartphone use, frequency of phone checking, commonly used applications, primary purposes of use, and the most frequent locations

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and times of smartphone use. The third section evaluated family-related factors, focusing on perceived interactions, communication, and support between students and their parents or guardians; this section comprised 15 items rated on a 5-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree). The fourth section measured nomophobia using the Nomophobia Questionnaire (NMP-Q) developed by Yildirim and Correia (2015). For this study, the NMP-Q was translated into Thai and reviewed by bilingual experts to ensure linguistic clarity and conceptual equivalence; however, the Thai version has not yet been formally validated. The instrument includes 20 items rated on a 7-point Likert scale (1 = strongly disagree to 7 = strongly agree) and demonstrated excellent internal consistency (Cronbach's α = 0.945). Total scores range from 20 to 140 and were classified as mild (21-60), moderate (61-100), and severe (101-140) nomophobia.

Statistical data analysis was conducted using Statistical Package for the Social Sciences version 28. We calculated the descriptive statistics, such as frequency, percentage, mean, and standard deviation, which were used to describe the general characteristics of the respondents and to determine the prevalence of nomophobia across varying severity levels. Inferential statistics including the Chi-squared test, analysis of variance (ANOVA), and binary logistic regression were employed to examine the associations and differences between variables hypothesized to be risk factors for high-severity nomophobia. A p-value of less than 0.05 was considered statistically significant.

RESULTS

The demographic characteristics of the 605 students, 23.63% were male and 76.36% were female. The largest proportion of respondents were from Nursing 28.76%, followed by Medicine 15.87%. Regarding residence, a notable proportion of students, 242 (40%), reported living alone, whereas 221 (36.53%) lived with their parents. Smaller groups lived with friends, 103 (17.02%), relatives, 28 (4.60%), or a partner, 11 (1.82%). Patterns of mobile phone use also varied across the sample. In terms of daily phone usage, 79 (13.05%) students used their phones for about 6 hours/day, while 99 (16.36%) used them for 8 hours/day, and 81 (13.39%) reported using their phones for 10 hours or more per day.

The frequency of checking the phone was another important indicator: 126 (20.83%) students checked their phones every 5 minutes, 110 every 10 minutes (18.18%), and 102 every 30 minutes (16.86%). Regarding playing games: 224 (37.02%) participants did not play games at all, while 150 (24.79%) played for an hour per day, and 99 (16.36%) played for 2 or more hours daily. Students also identified their favorite mobile applications, with Instagram at 271 (44.79%) being the most preferred, followed by TikTok at 155 (25.62%), and YouTube at 70 (11.57%). In terms of contextual use, most students, 375 (61.98%), reported using their phones freely, without linking use to specific activities. Some used phones alone, 108 (17.85%), and others during meals, 75 (12.40%). Finally, when looking at the location and time, most students used their phones in their rooms, 497 (82.14%), and the most common time of use was between 16:01 and 19:00, 366 (60.50%). Chi-squared analysis revealed that daily phone usage time (p = 0.021) and frequency of phone checking (p = 0.006) were significantly associated with nomophobia severity. Students who used their phones for extended hours or checked them frequently were more likely to experience moderate to severe levels of nomophobia. Other variables, including gender, residence, favorite applications, and phone use location, showed no statistically significant relationship with nomophobia levels **(Table 1)**.

The highest nomophobia was reported among students living with relatives (M = 85.46), while the lowest was among those living with romantic partners (M = 73.64). Similarly, the nomophobia mean score was highest in the relative group (M = 4.27) and lowest in the partner group (M = 3.68). However, the differences in nomophobia scores among the groups were not statistically significant (one-way ANOVA, p = 0.377). **(Table 2)**

The results of the binary logistic regression analysis for factors associated with moderate-to-severe nomophobia. Gender and monthly allowance were not significantly associated with nomophobia severity. In contrast, daily phone usage was found to be a significant factor; each additional hour of daily phone use increased the odds of experiencing moderate-to-severe nomophobia by approximately 9% (odds ratio (OR) = 1.09, 95% confidence interval (CI): 1.02-1.17, p = 0.015). Similarly, frequency of phone checking was significantly associated with higher nomophobia severity, as shorter checking intervals increased the likelihood of moderate-to-severe symptoms (OR = 0.98, 95% CI: 0.96-0.99, p = 0.007). Playing games on mobile phones was not significantly related to nomophobia severity. Importantly, family relationship score emerged as a significant factor; students

Table 1 Distribution of Nomophobia Severity Across Demographic and Behavioral Characteristics

		Nomophobia n (%)			
	n (%)	Mild n = 134 (22.14)	Moderate n = 340 (56.19)	Severe n = 131(21.65)	P-value**
Gender					
Male	143(23.63)	36 (25.17)	83 (58.04)	24 (16.78)	0.230
Female	462 (76.36)	98 (21.21)	257 (55.63)	107 (23.16)	
Program					
MD	96 (15.87)	17 (17.71)	56 (58.33)	23 (23.96)	0.386
RT	33 (5.45)	11 (33.33)	16 (48.48)	6 (18.18)	
VIP	34 (5.62)	8 (23.53)	18 (52.94)	8 (23.53)	
NR	174 (28.76)	38 (21.84)	97 (55.75)	39 (22.41)	
OHHS	48 (7.93)	6 (12.50)	30 (62.50)	12 (25.0)	
MIORT	38 (6.28)	6 (15.79)	21 (55.26)	11 (28.95)	
DNT	16 (2.64)	7 (43.75)	8 (50.00)	1 (6.25)	
SI	43 (7.11)	11 (25.58)	22 (51.16)	10 (23.26)	
PAUAM	32 (5.29)	6 (18.75)	18 (56.25)	8 (25.00)	
ECE	20 (3.31)	8 (40.00)	11 (55.00)	1 (5.00)	
FM	9 (1.49)	1 (11.11)	4 (44.44)	4 (44.44)	
B. TECH	23 (3.80)	7 (30.43)	14 (60.87)	2 (8.70)	
ECD	39 (6.45)	8 (20.51)	24 (61.54)	7 (17.95)	
Residence					
Parents	221(36.53)	44 (19.91)	130 (58.82)	47 (21.27)	0.338
Relative	28 (4.63)	5 (17.86)	15 (53.57)	8 (28.57)	
Alone	242 (40.00)	64 (26.45)	127 (52.48)	51 (21.07)	
Friends	103 (17.02)	19 (18.45)	59 (57.28)	25 (24.27)	
Partner	11 (1.82)	2 (18.18)	9 (81.82)	0	
Daily Phone Usage*					
6 hrs/day	79 (13.05)	20 (25.32)	45 (56.96)	14 (17.72)	0.021**
8 hrs/day	99 (16.36)	23 (23.23)	55 (55.56)	21 (21.21)	
10 hrs/day	81 (13.39)	24 (29.63)	40 (49.38)	17 (20.99)	
Frequency of Checking the Phone*					
5 min	126 (20.83)	14 (11.11)	73 (57.94)	39 (30.95)	0.006**
10 min	110 (18.18)	24 (21.82)	60 (54.55)	26 (23.64)	
30 min	102 (16.86)	28 (27.45)	61 (59.80)	13 (12.75)	
Play Games (hrs/day)*					
None	224 (37.02)	58 (25.89)	113 (50.45)	53 (23.66)	0.257
1	150 (24.79)	33 (22.00)	90 (60.00)	27 (18.00)	
2	99 (16.36)	14 (14.14)	63 (63.64)	22 (22.22)	

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Table 1 Distribution of Nomophobia Severity Across Demographic and Behavioral Characteristics (cont.)

		Nomophobia n (%)			
	n (%)	Mild n = 134 (22.14)	Moderate n = 340 (56.19)	Severe n = 131(21.65)	P-value**
Favorite Applications*					
Instagram	271 (44.79)	47 (17.34)	158 (58.30)	66 (24.35)	0.100
TikTok	155 (25.62)	38 (24.52)	87 (56.13)	30 (19.35)	
YouTube	70 (11.57)	18 (25.71)	43 (61.43)	9 (12.86)	
Most Phone Activity*					
Free	375 (61.98)	87 (23.20)	203 (54.13)	85 (22.67)	0.636
Alone	108 (17.85)	27 (25.00)	57 (52.78)	24 (22.22)	
Meal	75 (12.40)	12 (16.00)	50 (66.67)	13 (17.33)	
Place of Phone Use					
Room	497 (82.14)	112 (22.54)	278 (55.94)	107 (21.53)	0.688
Public	55 (9.09)	11 (20.00)	32 (58.18)	12 (21.82)	
Time*					
16.01-19.00	366 (60.50)	12 (18.46)	39 (60.00)	14 (21.54)	0.877
19.01-22.00	82 (13.55)	84 (22.95)	205 (56.01)	77 (21.04)	
22.00 up	65 (10.74)	16 (19.51)	45 (54.88)	21 (25.61)	

Abbreviations: B. TECH, bachelor of technology; cont, continue; DNT, disaster management; ECD, early childhood development; ECE, early childhood education; FM, facility management; hrs, hours; MD, medicine; MIORT, medical instrumentation and operating room technology; n, number; NR, nursing science; OHHS, occupational health and safety in hospital; PAUAM, urban administration and management; RT, radiologic technology; SI, aviation business service; VIP, emergency medical technology

The data were analyzed using the Chi-squared test.

*Top 3 of this topic

**Significance level at p-value = $p < 0.05$

Note: "Daily Phone Usage" refers to hours spent on phone per day. "Frequency of Checking the Phone" refers to how often the phone is picked up. "Play Games" refers to hours spent gaming per day. "Favorite Applications" refers to most frequently used applications. "Most Phone Activity" refers to situations when phone is used most. "Place of Phone Use" refers to location where phone is mostly used. "Time" refer to typical time of phone usage.

reporting lower family support had nearly twice the odds of experiencing moderate-to-severe nomophobia compared to those with stronger family relationships (OR = 1.83, 95% CI: 1.09-3.08, p = 0.022). **(Table 3)**

DISCUSSION

The findings of this study confirm that nomophobia is a prevalent condition among first-year university students at Navamindradhiraj University, with 56.20% of participants experiencing moderate levels and 21.70% experiencing severe levels of nomophobia. These study comparable to those reported by Al-Mamun, who found prevalence rates of 56.10% for moderate nomophobia and 34.50% for severe nomophobia, highlighting the first-year students had higher levels of nomophobia than other years.[16] This aligns with evidence from a systematic review and meta-analysis showing that approximately 70.76% of individuals experience moderate to severe nomophobia, with about 20.81% suffering severe nomophobia, indicating a consistently high prevalence across diverse populations.[17] The association between excessive smartphone use and higher nomophobia levels may be explained by behavioral reinforcement mechanisms. Frequent phone checking activates reward pathways through dopamine

Table 2 Descriptive Statistics of Nomophobia by Living Arrangement

Living Arrangement	n	Nomophobia Total Score (mean ± SD)	95% CI For Mean	Min	Max	Nomophobia Item Mean (mean ± SD)
Parents	221	78.70 ± 25.25	75.35-82.04	22.00	140.00	3.93 ± 1.26
Relative	28	85.00 ± 27.49	74.81-96.12	23.00	136.00	4.27 ± 1.37
Alone	242	78.09 ± 25.79	74.82-81.35	20.00	140.00	3.90 ± 1.29
With Friends	103	82.23 ± 25.25	77.30-87.17	22.00	133.00	4.11 ± 1.26
Partner	11	73.64 ± 16.24	62.72-84.55	54.00	98.00	3.68 ± 0.81
Total	605	79.28 ± 25.46	77.24-81.31	20.00	140.00	3.96 ± 1.27
P-value 0.377*						

Abbreviations: CI, confidence interval; n, number; SD, standard deviation

The data were analyzed using the one-way ANOVA.

*Significance level at p-value = $p < 0.05$

Table 3 Factors Associated with Moderate-to-Severe Nomophobia

Independent Variable	OR (Exp(B))	95% CI for OR	P-value
Gender (male vs. female)	1.35	0.70-2.59	0.366
Monthly Allowance (salary)	1.00	1.00-1.00	0.260
Daily Phone Use (hrs/day)	1.09	1.02-1.17	0.015*
Checking Frequency (min)	0.98	0.96-0.99	0.007*
Playing Games (hrs/day)	0.96	0.88-1.06	0.404
Family Relationship Score	1.83	1.09-3.08	0.022*

Abbreviations: CI, confidence interval; Exp(B), exponentiated beta coefficient; hrs, hours; OR, odd ratios

The data were analyzed using the binary logistic regression.

*Significance level at p-value = $p < 0.05$

release, reinforcing habitual smartphone use and leading to dependency-like behavior.[18-20]

Among the key behavioral factors identified, both daily phone usage time and frequency of checking phones were significantly associated with higher levels of nomophobia. Students who reported using their phones for more than 8-10 hours per day or checking their phones every 5-10 minutes were significantly more likely to experience moderate to severe nomophobia. These findings align with Shkodra, Albania, 48.10% of students reported using their smartphones for 4-6 hours daily, while students who used their phones for more than 8-10 hours per day were at an even higher risk of experiencing moderate to severe nomophobia.[21]

Importantly, the family relationship scores also emerged as a significant factor associated with nomophobia, suggesting that the perceived quality of communication and emotional support within the family plays a role in mobile phone dependency. Students who experience weaker familial bonds may rely more on their smartphones to fulfill unmet emotional or social needs, consistent with the compensatory internet use theory.[22] This supports the theory that students lacking strong in-person social or familial support may turn to their smartphones for connection, validation, and stress relief.[23] In this context, smartphones may function as a substitute for real-life connection, validation, and stress relief, explaining the link between lower family support and higher nomophobia

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scores. In contrast, demographic variables, such as gender, monthly income, and playing mobile games, were not significantly associated with nomophobia levels.[24] This suggests that nomophobia is less related to socioeconomic factors or specific content use, and more associated with usage habits and psychological needs. Contextual factors like residence or application preference showed no significant impact.

This study adds new insights to the understanding of nomophobia within the Thai cultural context. While international research shows similar behavioral patterns, factors such as Thailand's collectivist values, close family bonds, and rapid digitalization in education may influence how students experience and cope with smartphone dependency.[25-26]

The study adopted a comprehensive approach by assessing both behavioral factors (e.g., daily phone usage, frequency of checking) and psychosocial factors (family relationships), providing a holistic view of nomophobia determinants. However, the NMP-Q has not been formally validated in Thai, which may affect item interpretation, and the cut-off scores applied were derived from other cultural contexts, potentially limiting their appropriateness for Thai students.

CONCLUSION

Overall, these results show that it is important to have specific strategies to help students develop healthier digital habits, especially when it comes to managing their time and being more mindful about phone use. For example, universities could offer workshops and resources that support digital well-being and help students build stronger offline relationships. In addition, getting families more involved in student support may also help reduce emotional reliance on mobile phones. Looking ahead, future research should explore long-term trends to better understand how nomophobia changes over time and how factors like school pressure or emotional challenges affect phone use. Moreover, since Thai student culture is unique, more studies in different schools and age groups would help confirm and expand on these findings.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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Author Contributions

Conceptualization: K.C.
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Formal analysis: K.C.
Funding acquisition: K.C.
Investigation: -
Methodology: K.C.
Project administration: K.C.
Resources: -
Software: K.C.
Supervision: K.C.
Validation: -
Visualization: -
Writing – original draft preparation: K.C.
Writing – review & editing: K.C.

Data Availability Statement

The data sets generated and analyzed during the current study are not publicly available. However, they will be made available by the corresponding author upon any reasonable request.

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ORIGINAL ARTICLE

The Study of Causative Organisms Affecting Fungal Nail Perforation Test

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ABSTRACT

Objective: To evaluate the capacity of dermatophytes, non-dermatophyte, and yeast to invade nails.

Materials and Methods: Nine normal nails were clipped from healthy volunteers and sterilized in an autoclave. Each nail was inoculated with one of nine fungal species, including dermatophytes, non-dermatophyte (*Neoscytalidium dimidiatum, N. dimidiatum*), and yeast (*Candida albicans, C. albicans*) for two, four, and eight weeks at 26 °C. A positive result was determined by the presence of fungal hyphae or pseudohyphae penetrating the nail plate.

Results: Fungal penetration increased with longer durations. At two weeks, *Trichophyton mentagrophytes (T. mentagrophytes)* variety *mentagrophytes, Nannizzia gypsea, Microsporum canis*, and *N. dimidiatum* showed positive nail perforation. At four weeks, *T. mentagrophytes* variety *interdigitale* also tested positive. The remaining fungi (*Trichophyton rubrum, Trichophyton tonsurans, Epidermophyton floccosum*, and *C. albicans*) demonstrated negative test results at eight weeks.

Conclusion: This *in vitro* study confirmed the highly virulent dermatophytes can penetrate the nail plate in a short time. Furthermore, this study highlighted the significant virulence of *N. dimidiatum* in nail invasion.

Keywords: dermatophytes, fungal infection, nail perforation test, non-dermatophytes, onychomycosis

INTRODUCTION

Onychomycosis is a common disorder among the elderly population.[1] However, most patients do not seek diagnosis or treatment due to its asymptomatic nature and minimal impact on quality of life. The prevalence of onychomycosis is estimated to be 4-10% among general population,[2,3] while the prevalence of onychomycosis in Thailand was reported about 1.7% among all the patients visiting the Institute of Dermatology.[4] Several factors increase the risk of onychomycosis, including diabetes mellitus, peripheral vascular disease, frequent use of slippers, corticosteroid use, and repetitive foot injury.[4-6] Additionally, the causative organism plays a key role in determining prognosis and achieving a cure.

Onychomycosis can be caused by dermatophytes, non-dermatophyte molds and yeast.[6-8] While dermatophyte infections occur worldwide, non-dermatophyte infections are more common in tropical countries like Thailand and Brazil.[5,9] Pathogenic non-dermatophytes play an

important role in nail infection and vary by region.[7,10-12] In Thailand, *Neoscytalidium dimidiatum* (*N. dimidiatum*) and *Fusarium* spp. are common non-dermatophyte molds.[5,6,13] The explanation for non-dermatophytes like *N. dimidiatum* to be reported more prevalent in tropical countries is that they are frequently found in the soil of tropical and subtropical zones.[14] *Candida* spp. is the leading yeast pathogen in fingernail onychomycosis in women, particularly women engaged in wet work.[8]

N. dimidiatum commonly causes both nail and superfici l skin infections, with its prevalence rising over time.[5,7,10,12] In France, *N. dimidiatum* accounts for up to 34% of fungal infections, with skin infections accounting for 65.3% of cases and onychomycosis 34.7%.[10] In Thailand, its prevalence in onychomycosis has been reported at 20%-36.4%.[4,6] However, the pathogenesis of *N. dimidiatum* infection remains unclear.

In order to diagnose onychomycosis, each patient should have a history taking and physical examination. To further confirm th diagnosis, diagnostic laboratory tests such as potassium hydroxide preparation for microscopic examination, and fungal culture, should be performed. In several instances, nevertheless, the diagnosis is challenging. The histopathology from nail clipping is required to confi m the diagnosis[3] by presence of hyphae or pseudohyphae in the nail plate.[15] Currently, some studies have proposed the pathogenesis of onychomycosis that the nail keratin was destroyed by extracellular enzymes produced from fungi.[16] Furthermore, the site and pattern of nail invasion influence he type of onychomycosis which varies depending on the virulence of the fungal species. However, the exact mechanisms including the time of penetration after inoculation and the depth of penetration by which different fungal species cause onychomycosis remain poorly understood due to limited research. Thus, the *in vitro* study can help to determine these mechanisms without confounding factors. This study aims to investigate the nail-perforation ability of dermatophytes, non-dermatophyte molds, and yeasts using an *in vitro* model.

MATERIALS AND METHODS

The protocol for this pilot study (Siriraj Protocol Number: 067/2558) was submitted to the Ethics Committee and was officially approved as exempt. Nine normal fingernails were clipped from a healthy volunteer whose age 29 years and screened using potassium hydroxide preparation and fungal cultures, both of which revealed negative results for infection. Nine fungal species including dermatophytes (*Trichophyton mentagrophytes (T. mentagrophytes)* variety *mentagrophytes*, *T. mentagrophytes* variety *interdigitale, Trichophyton rubrum (T. rubrum), Trichophyton tonsurans (T. tonsurans), Epidermophyton floccosum (E. floccosum), Nannizzia gypsea (N. gypsea), Microsporum canis (M. canis)*), non-dermatophyte (*N. dimidiatum*), yeast (*Candida albicans, C. albicans)* were chosen from the reported pathogens of onychomycosis. The nails were then sterilized in an autoclave and inoculated with one of nine fungal species in sterile water for two, four, and eight weeks at 26 °C. After incubation, the nails were fixed in 10% formalin, stained with periodic acid-Schiff, and microscopically examined by two independent dermatologists. Disagreements were resolved through consensus-based discussion. A positive result was defined by the presence of fungal penetration.

RESULTS

The nail perforation results are shown in **Figure 1** and **Table 1**. At two weeks, positive penetration was observed for *T. mentagrophytes* variety *mentagrophytes*, *N. gypsea, M. canis*, and *N. dimidiatum*. *T. mentagrophytes* variety *interdigitale* exhibited penetration at four weeks. The remaining fungi (*T. rubrum, T. tonsurans, E. floccosum*, and *C. albicans*) showed no signs of nail penetration.

DISCUSSION

This study demonstrated the nail-perforation ability of dermatophytes, non-dermatophytes and yeasts. The results of this *in vitro* study may reflect the onset and severity of onychomycosis depending on the fungal virulence. The higher virulence fungi such as *T. mentagrophytes* variety *mentagrophytes*, *N. gypsea, M. canis*, and *N. dimidiatum* could produce more severity of onychomycosis and earlier onset than lower virulence fungi. Additionally, it is challenging to get therapeutic improvement when treating onychomycosis from certain fungi, particularly *N. dimidiatum*.[17] This could account for its pathogenicity.

The results support *N. dimidiatum* as a virulent agent in onychomycosis, given its ability to penetrate the nail *in vitro*. *N. dimidiatum* is a common non-dermatophyte with distinct characteristics.[5] It was able to penetrate the nail within two weeks, similar to *T. mentagrophytes*. Following *N. dimidiatum*

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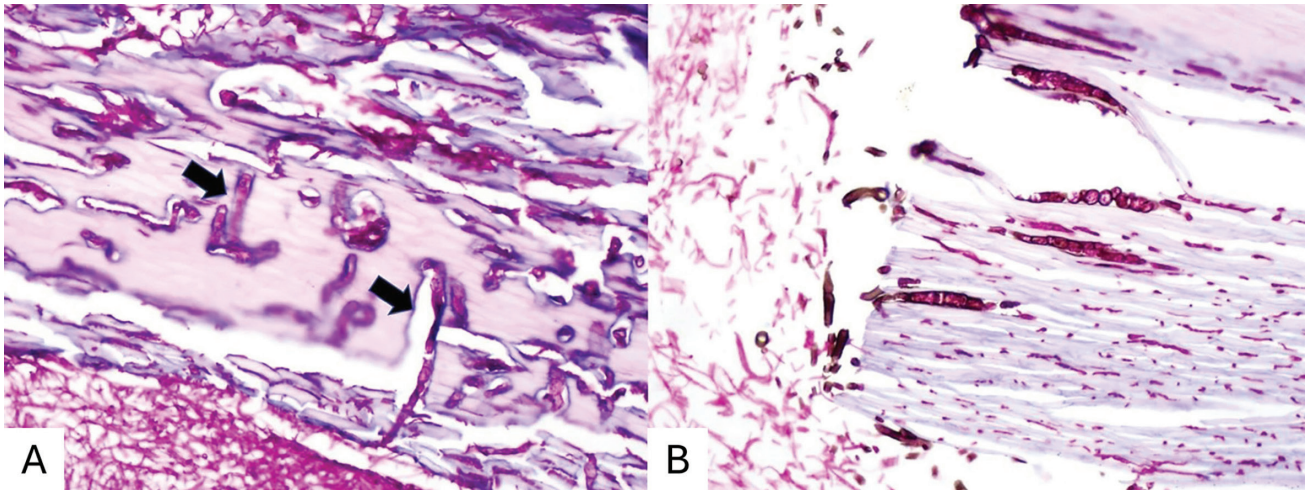

Figure 1 Fungal Penetration of the Nail Plate
(A) *Trichophyton mentagrophytes* variety *mentagrophytes* showed elongated hyphae invading the nail plate perpendicularly (arrow). (periodic acid-Schiff stain, original magnification X400
(B) *Neoscytalidium dimidiatum* demonstrated brownish septate hyphae with arthroconidia penetrating the nail plate longitudinally. (periodic acid-Schiff stain, original magnific tion X400)

Table 1 Results of Nail Invasion for Each Fungus

Fungi	Result	Duration of Nail Invasion (weeks)
Trichophyton mentagrophytes variety *mentagrophytes*	+	2
Trichophyton mentagrophytes variety *interdigitale*	+	4
Trichophyton rubrum	-	–
Trichophyton tonsurans	-	–
Nannizzia gypsea	+	2
Microsporum canis	+	2
Epidermophyton floccosum	-	–
Neoscytalidium dimidiatum	+	2
Candida albicans	-	–

penetration, nail damage was seen both clinically and histologically, indicating that its virulence contributes to the quick and severe onset of onychomycosis. Previous reports have linked this mechanism to its ability to produce extracellular enzymes such as amylase, proteases, and lipase, which degrade keratin. Its proteolytic activity facilitates keratin breakdown, enabling penetration and contributing to nail and cutaneous fungal infections.[12]

Although previous research has demonstrated the ability of *T. mentagrophytes* and *M. canis* to perforate nails,[18-21] findings on *T. rubrum* and *T. tonsurans* have been inconsistent.[18,21] This disparity may be due to environmental factors, such as continuous shaking during inoculation[21] and variations in culture media.[18] Interestingly, different fungal subspecies exhibit varying onsets of nail perforation, as observed with *T. mentagrophytes*.

Conversely, *E. floccosum and C. albicans*, showed no evidence of nail perforation. This suggests that mammalian keratin penetration by fungi depends on multiple factors, including environmental conditions and host immune response.

This study had some limitations. As a pilot study, it involved a small nail sample size. Additionally, longer culture periods may be necessary to confirm the negative results. Lastly, the results from *in vitro* study may alter from *in vivo* study because there are host factors such as immune status, underlying diseases and environmental factors such as humidity which can affect the ability of fungal penetration into nails. Thus, these factors should be studied in future research.

CONCLUSION

This study confirmed hat the highly virulent dermatophytes can penetrate the nail plate in a short time causing onychomycosis. Furthermore, *N. dimidiatum* can invade the nail plate under *in vitro* conditions, which may explain its virulence in the development of onychomycosis. Additionally, certain dermatophyte species were shown to penetrate the hard keratin of nail plates.

Conflict of Interest

All authors declare that there are no conflicts of interest related to this study.

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Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data is not publicly available due to privacy or ethical restrictions.

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J M U H
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ORIGINAL ARTICLE

Prevalence and Associated Factors of Mild Cognitive Impairment in Parkinson's Disease: A Single-Center Study in Thailand

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ABSTRACT

Objectives: Mild cognitive impairment (MCI) is a frequent non-motor complication and a strong predictor of dementia in patients with Parkinson's disease (PD). Reported prevalence rates vary considerably due to differences in diagnostic criteria and study populations, with limited data available from Thai cohorts. This study aimed to determine the prevalence of PD-MCI and identify associated factors among Thai patients with PD.

Materials and Methods: A cross-sectional study was conducted involving 100 patients with mild to moderate PD who attended the Movement Disorders Clinic at Vajira Hospital, Bangkok, between February and October 2023. Patients with disabilities, dementia, or major neurological comorbidities were excluded. Cognitive function was assessed using the Thai version of the Montreal Cognitive Assessment in patients with PD who reported cognitive concerns, as reported by patients, caregivers, or both, applying a cutoff score of < 25 points and adding one point for participants with ≤ 6 years of education. Demographic, clinical, and comorbidity data were collected. Independent predictors of PD-MCI were analyzed using univariate and multivariate logistic regression models.

Results: Among 100 patients with PD, 54% were female. Nearly one-third of participants (31%) had completed education beyond grade 12, and the median disease duration was 3 years. The prevalence of PD-MCI was 81%. Patients with PD-MCI were significantly older (74.3 ± 8.3 vs. 66.5 ± 8.7 years, $p < 0.001$), had lower educational attainment (45.7% vs. 10.5% below grade 6, $p = 0.005$), and lower body mass index (BMI) (23.2 ± 4.1 vs. 25.5 ± 4.2 kg/m², $p = 0.035$). Hypertension, hyperlipidemia, later age at onset, and mixed phenotype were also associated in univariate analyses. In multivariate regression, age ≥ 70 years (adjusted odds ratio (OR), 6.77; 95% confidence interval (CI), 1.35-34.08), education below grade 6 (adjusted OR, 10.35; 95% CI, 1.68-63.88), and obesity (BMI ≥ 25 kg/m²; adjusted OR, 0.07; 95% CI, 0.01-0.55) remained independent predictors.

Conclusion: PD-MCI is highly prevalent among Thai patients with PD. Older age, low education level, and lower BMI independently increased risk, whereas obesity appeared protective. Routine cognitive screening and targeted interventions are essential for this population. Further longitudinal studies are warranted to explore causal mechanisms.

Keywords: cognitive screening, mild cognitive impairment, Parkinson's disease

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder globally. It is characterized not only by classic motor symptoms such as bradykinesia, rigidity and tremor, but also by various non-motor complications such as neuropsychiatric disturbances, autonomic dysfunction, constipation, sleep problems, and cognitive decline, all of which significantly impair quality of life.[1] Mild cognitive impairment (MCI) in patients with PD (PD-MCI) has gained increasing recognition as a key non-motor manifestation and a major risk factor for subsequent PD dementia (PDD).[2,3] Longitudinal studies indicate that several individuals with PD-MCI eventually progress to PDD, whereas other remain cognitively stable or revert to normal cognition, highlighting its heterogeneous clinical course.[4] Early identification of PD-MCI is therefore essential to facilitate preventive strategies, timely counseling, and cognitive rehabilitation, which may collectively help delay functional decline.[5]

Previous research has shown wide variability in the prevalence of PD-MCI, ranging from 20% to 70%. This variation is largely explained by differences in study design, diagnostic criteria, cognitive assessment tools, and population characteristics.[6-12] Several clinical and demographic factors have been associated with PD-MCI, including advanced age, male sex, lower educational attainment, longer disease duration, greater disease severity, and vascular comorbidities such as hypertension and diabetes mellitus.[8,9,13]

Thailand, now an aging society, faces a rising prevalence of PD, particularly in urban areas with a tertiary hospital where differences in education level, healthcare accessibility, and vascular risk profiles may affect the risk of cognitive decline.[14] Despite this trend, limited data exist regarding PD-MCI among Thai populations. This study therefore aimed to determine the prevalence of PD-MCI and to identify its associated factors among patients with PD attending a tertiary hospital in Thailand.

MATERIALS AND METHODS

This cross-sectional study was conducted at the Movement Disorders Clinic, Vajira Hospital, Navamindradhiraj University, between February and October 2023. Ethical approval was obtained from the Institutional Review Board of Vajira Hospital (COA number 092/2566). The sample size was calculated using the single population proportion formula, with a significance level of 0.05, a margin of error of 0.10, and an expected prevalence of PD-MCI of 23.3% based on a previous study.[15] The minimum required sample size was 69 participants. After adjusting for an anticipated 30% rate of incomplete data, the final target sample size was set at 100 participants. Consecutive patients with a clinical diagnosis of PD according to the United Kingdom Parkinson's Disease Society Brain Bank diagnostic criteria by movement disorders specialists were invited to participate.

Eligible patients were aged ≥ 40 years, had mild to moderate disease defined by Hoehn and Yahr (H&Y) stages 1-4, and had no prior diagnosis of dementia. Exclusion criteria included severe disability (H&Y stage 5), impairment in activities of daily living due to cognitive decline, or comorbid neurological disorders such as stroke, dementia and intellectual disability.

The primary outcome was the prevalence of PD-MCI among patients with PD in a Thai cohort. The secondary outcome was the identification of clinical and demographic factors associated with PD-MCI. Data collected included demographic characteristics (sex, age, educational level, and body mass index (BMI)), PD-related features (disease duration, motor phenotype, lateralization, H&Y stage, and levodopa equivalent daily dose), and comorbidities (hypertension, diabetes mellitus, and hyperlipidemia).

PD-MCI was identified using a screening-based definition consistent with the Movement Disorder Society Task Force Level I criteria, which require the presence of subjective cognitive complaints together with objective cognitive impairment detected by a validated cognitive screening tool.[7] All patients underwent cognitive screening reported cognitive concerns, as noted by the patients themselves, caregivers, or both, during routine clinic visits. Cognitive function was evaluated using the Thai version of the Montreal Cognitive Assessment (Thai-MoCA), applying a cutoff score of < 25 points for MCI diagnosis. An additional point was added for participants with ≤ 6 years of education, following the Thai Clinical Practice Guideline for Dementia.[16] The assessment was administered by trained neurology residents during the same outpatient visit and required approximately 15 minutes to complete. Patients were instructed to take their PD medications as prescribed before cognitive testing to ensure assessment during their "on" state.

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Data analyses were performed using IBM SPSS Statistics version 29.0. Between-group comparisons (PD-MCI vs non-MCI) were conducted using the Chi-square or Fisher's exact test for categorical variables and the independent t-test or Mann-Whitney U test for continuous variables, as appropriate. Univariate analyses were followed by multivariate logistic regression to identify independent predictors of PD-MCI. Odds ratio (OR) with 95% confidence interval (CI) were reported, and a p-value < 0.05 was considered statistically significant.

RESULTS

A total of 100 patients with PD were enrolled. The mean age was 72.82 ± 8.90 years, most participants (43%) aged between 65 and 74 years. Females comprised 54% of the cohort. Regarding education, 31% had completed studies beyond grade 12.

The mean BMI was 23.65 ± 4.19 kg/m², with 47% falling within the normal BMI range (18.5-22.9 kg/m²). Comorbidities were highly prevalent, as 88% of patients had at least one chronic condition. Hypertension was the most common (61%), followed by hyperlipidemia (52%) and diabetes mellitus (29%). Smoking and alcohol consumption were reported by 14% and 9% of patients, respectively. The mean hemoglobin A1c (HbA1c) was 6.13 ± 0.81, and 27.1% had HbA1c levels > 6.5%. Other biochemical parameters were generally within normal limits.

The mean age at PD onset was 68.06 ± 9.63 years, and the median disease duration was 3 years (interquartile range (IQR) 1.5-6.5). Most patients (71%) had a disease duration of ≤ 5 years. The majority were classified as H&Y stage 1 (62%). Regarding motor phenotype, the tremor-dominant subtype was most common (36%), followed by the mixed phenotype (30%), and the remainder were akinetic-rigid. Family history of PD was reported in 7% of participants. The median levodopa equivalent daily dose was 372.5 mg (IQR 200-757), with 51% receiving < 400 mg daily **(Table 1)**.

The prevalence of PD-MCI was 81% **(Table 2)**. The mean Thai-MoCA total score was 19.0 ± 5.1, with an education-adjusted mean of 19.4 ± 4.9. Domain analysis revealed mean scores as follows: visuospatial 2.36 ± 1.64, naming 2.80 ± 0.57, attention 4.42 ± 1.40, language 1.43 ± 0.98, abstraction 1.10 ± 0.75, and delayed recall 1.37 ± 1.46. Orientation was relatively preserved (5.54 ± 1.06).

Table 1 Demographic and Clinical Characteristics of Patients with Parkinson's Disease

Characteristics	Total (n = 100)
Age (years), mean ± SD	72.82 ± 8.9
Min-Max	(48-91)
< 65	14 (14.0)
65-74	43 (43.0)
75-84	36 (36.0)
> 85	7 (7.0)
Gender	
Female	54 (54.0)
Education level	
Below grade 4	22 (22.0)
Grade 4-6	17 (17.0)
Grade 7-9	10 (10.0)
Grade 10-12	20 (20.0)
Above grade 12	31 (31.0)

Table 1 Demographic and Clinical Characteristics of Patients with Parkinson's Disease (cont.)

Characteristics	Total (n = 100)
Body mass index (kg/m^2), mean ± SD	23.65 ± 4.19
Min-Max	(14.95-42.68)
Normal (18.5-22.9)	47 (47.0)
Overweight (23.0-24.9)	23 (23.0)
Obesity (≥ 25)	30 (30.0)
Comorbidity	88 (88.0)
Hypertension	61 (61.0)
Diabetes mellitus	29 (29.0)
Dyslipidemia	52 (52.0)
Coronary artery disease	9 (9.0)
Atrial fibrillation	5 (5.0)
Chronic kidney disease	13 (13.0)
Chronic obstructive pulmonary disease	4 (4.0)
Thyroid disease	4 (4.0)
Fatty liver	2 (2.0)
Others[a]	22 (22.0)
Smoking[b]	14 (14.0)
Alcohol[b]	9 (9.0)
HbA1c, (n = 59) mean ± SD	6.13 ± 0.81
≥ 6.5	16 (27.1)
Total cholesterol (mg/dL), (n = 91) mean ± SD	170.38 ± 43.56
> 200	17 (18.7)
Triglyceride (mg/dL), (n = 93) mean ± SD	110.90 ± 52.00
> 150	19 (20.4)
HDL-cholesterol (mg/dL), (n = 91) mean ± SD	55.13 ± 16.37
LDL-cholesterol (mg/dL), (n = 93) mean ± SD	106.12 ± 38.75
> 100	2 (2.2)
Creatinine (mg/dL), (n = 97) mean ± SD	0.97 ± 0.26
eGFR (mL/min/1.73m^2), (n = 97) mean ± SD	70.43 ± 17.56
> 90	12 (12.4)
60-89	56 (57.7)
30-59	29 (29.9)
Onset age (years), mean ± SD	68.06 ± 9.63

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Table 1 Demographic and Clinical Characteristics of Patients with Parkinson's Disease (cont.)

Characteristics	Total (n = 100)
Duration (years), median (IQR)	3 (1.5-6.5)
≤ 5	71 (71.0)
> 5	29 (29.0)
H&Y stage	
1	62 (62.0)
2	20 (20.0)
3	10 (10.0)
4	8 (8.0)
Phenotype	
Tremor	36 (36.0)
Akinetic rigid	33 (33.0)
Mixed	31 (31.0)
Lateralization	
Right	55 (55.0)
Left	45 (45.0)
Family history	7 (7.0)
Levodopaequivalent dose (mg)	372.5 (200 - 757)
< 400	51 (51.0)
400-599	13 (13.0)
≥ 600	36 (36.0)

Abbreviations: dL, deciliter; eGFR, estimated glomerular filtration rate; H&Y, Hoehn and Yahr; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; IQR, interquartile range; kg, kilogram; LDL, low-density lipoprotein; m^2, square meter; Max, maximum; mg, milligram; Min, minimum; min, minute; mL, milliliter; n, number; SD, standard deviation

Data are presented as number (%), mean ± standard deviation or median (interquartile range).

[a] Others include gastroesophageal reflux disease, benign prostatic hyperplasia, rheumatoid arthritis, asthma, nonalcoholic steatohepatitis, gout and knee osteoarthritis.

[b] Smoking and alcohol consumption refer to current use at the time of assessment.

Comparative analyses revealed several factors associated with PD-MCI **(Table 3)**. Patients with PD-MCI were significantly older than those without MCI (74.31 ± 8.31 vs. 66.47 ± 8.74 years; p < 0.001). A higher proportion of patients with PD-MCI were aged ≥ 70 years (75.3% vs. 31.6%; p < 0.001).

Education attainment was a strong determinant, as nearly half of patients with PD-MCI (45.7%) had not completed grade 6, compared with only 10.5% among those with normal cognition (p = 0.005). BMI demonstrated an inverse relationship with cognitive impairment. The mean BMI was lower in the MCI group than in the normal cognition group (23.22 ± 4.10 vs. 25.47 ± 4.21 kg/m²; p = 0.035). Normal BMI (18.5-22.9 kg/m²) was more common in the PD-MCI group (53.1%), whereas overweight status (BMI ≥ 25 kg/m²) was more common among those without MCI (52.6%, p = 0.024).

Comorbidities also showed significant differences. Hypertension was more prevalent in the PD-MCI group (69.1% vs. 26.3%; p = 0.001), as was hyperlipidemia (56.8% vs. 31.6%; p = 0.048).

Table 2 Thai-MoCA Scores and Cognitive Impairments among Patients with Parkinson's Disease

Variables	Total (n = 100)		
	Mean ± SD	Min	Max
Visuospatial (0-5)	2.36 ± 1.64	0	5
Naming (0-3)	2.80 ± 0.57	0	3
Attention (0-6)	4.42 ± 1.40	1	6
Language (0-3)	1.43 ± 0.98	0	3
Abstraction (0-2)	1.10 ± 0.75	0	2
Delayed recall (0-5)	1.37 ± 1.46	0	5
Orientation (0-6)	5.54 ± 1.06	0	6
Total score (0-30)	19.02 ± 5.12	3	28
Total score (education-adjusted)	19.41 ± 4.91	4	28
Memory index score (0-15)	7.55 ± 4.44	0	15
< 7 - n (%)	38 (38.0)		
≥ 7 - n (%)	62 (62.0)		
Cognitive impairments			
Mild cognitive impairment - n (%)	81 (81.0)		
Normal - n (%)	19 (19.0)		

Abbreviation: n, number

Patients with PD-MCI had a later mean age at PD onset (69.79 ± 8.64 vs. 60.68 ± 10.37 years, p < 0.001). Regarding motor subtype, mixed phenotype was more common among PD-MCI patients (37.0%), while the tremor-dominant subtype predominated in those with normal cognition (52.6%, p = 0.025).

Univariate logistic regression confirmed these associations **(Table 4)**. Age ≥ 70 years was significantly associated with PD-MCI (OR, 6.61; 95% CI, 2.22-19.68; p = 0.001), as was education below grade 6 (OR, 7.15; 95% CI, 1.55-32.98; p = 0.012). Obesity (BMI ≥ 25 kg/m²) was inversely associated with PD-MCI (OR, 0.19; 95% CI, 0.05-0.67; p = 0.010). Hypertension was a significant factor (OR, 6.27; 95% CI, 2.04–19.31; p = 0.001). Furthermore, later age at PD onset (OR, 1.11; 95% CI, 1.04-1.18; p = 0.001) and mixed phenotype (OR, 11.54; 95% CI, 1.38-96.29; p = 0.024) increased PD-MCI risk.

In the multivariate logistic regression model, after adjustment for confounding variables, three independent predictors remained: age ≥ 70 years (adjusted OR, 6.77; 95% CI, 1.35-34.08; p = 0.020), education below grade 6 (adjusted OR, 10.35; 95% CI, 1.68-63.88; p = 0.012), and obesity BMI ≥ 25 kg/m², which was protective (adjusted OR, 0.07; 95% CI, 0.01-0.55; p = 0.012). Although hypertension and later PD onset were significant in univariate analysis, they did not remain independent predictors in the multivariate model, likely due to collinearity with age and education.

DISCUSSION

In this Thai cohort of patients with PD, we found a strikingly high prevalence of PD-MCI, affecting 81% of participants. This rate exceeds the range reported in most international studies (20%-70%), which may be attributed to differences in diagnostic approaches, study populations, and sociocultural factors. In Thailand, many older adults live in extended families where relatives often compensate for their functional deficits,

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Table 3 Factors Associated with PD-MCI

Variables	MCI (n = 81)	Normal (n = 19)	P-value
Age (years), mean ± SD	74.31 ± 8.31	66.47 ± 8.74	< 0.001[t]
Min-Max	(49-91)	(48-81)	
< 70	20 (24.7)	13 (68.4)	< 0.001[c]
≥ 70	61 (75.3)	6 (31.6)	
Gender			
Female	43 (53.1)	11 (57.9)	0.705[c]
Education level			
> Grade 6	44 (54.3)	17 (89.5)	0.005[c]
< Grade 6	37 (45.7)	2 (10.5)	
Body mass index (kg/m^2), mean ± SD	23.22 ± 4.10	25.47 ± 4.21	0.035[t]
Min-Max	(14.95-42.68)	(19.72-36.79)	
Normal (18.5-22.9)	43 (53.1)	4 (21.1)	0.024[c]
Overweight (23.0-24.9)	18 (22.2)	5 (26.3)	
Obesity (≥ 25)	20 (24.7)	10 (52.6)	
Comorbidity	73 (90.1)	15 (78.9)	0.234[f]
Hypertension	56 (69.1)	5 (26.3)	0.001[c]
Diabetes mellitus	22 (27.2)	7 (36.8)	0.403[c]
Dyslipidemia	46 (56.8)	6 (31.6)	0.048[c]
Coronary artery disease	8 (9.9)	1 (5.3)	1.000[f]
Atrial fibrillation	5 (6.2)	0 (0.0)	0.580[f]
Chronic kidney disease	12 (14.8)	1 (5.3)	0.452[f]
Chronic obstructive pulmonary disease	4 (4.9)	0 (0.0)	1.000[f]
Thyroid disease	4 (4.9)	0 (0.0)	1.000[f]
Fatty liver	2 (2.5)	0 (0.0)	1.000[f]
Others[a]	18 (22.2)	4 (21.1)	1.000[f]
Smoking[b]	13 (16.0)	1 (5.3)	0.296[f]
Alcohol[b]	9 (11.1)	0 (0.0)	0.201[f]
HbA1c, (n = 59) mean ± SD	6.06 ± 0.79	6.37 ± 0.88	0.225[t]
≥ 6.5	11 (23.9)	5 (38.5)	
Total cholesterol (mg/dL), (n = 91) mean ± SD	168.86 ± 42.74	176.56 ± 47.53	0.505[t]
> 200	11 (15.1)	6 (33.3)	0.094[f]
Triglyceride (mg/dL), (n = 93) mean ± SD	108.37 ± 49.70	121.44 ± 61.13	0.341[t]
> 150	16 (21.3)	3 (16.7)	1.000[f]
HDL-cholesterol (mg/dL), (n = 91) mean ± SD	54.51 ± 16.41	57.67 ± 16.40	0.466[t]

Table 3 Factors Associated with PD-MCI (cont.)

Variables	MCI (n = 81)	Normal (n = 19)	P-value
LDL-cholesterol (mg/dL), (n = 93) mean ± SD	106.67 ± 39.77	103.83 ± 35.10	0.782[t]
> 100	2 (2.7)	0 (0.0)	1.000[f]
Creatinine (mg/dL), (n = 97) mean ± SD	0.98 ± 0.28	0.94 ± 0.20	0.625[t]
eGFR (mL/min/1.73m^2), (n = 97) mean ± SD	69.12 ± 17.78	76.19 ± 15.78	0.124[t]
> 90	9 (11.4)	3 (16.7)	0.667[c]
60-89	45 (57.0)	11 (61.1)	
30-59	25 (31.6)	4 (22.2)	
Onset age (years), mean ± SD	69.79 ± 8.64	60.68 ± 10.37	< 0.001[t]
Duration (years), median (IQR)	3 (1-6.5)	4 (2-8)	0.307[m]
≤ 5	57 (70.4)	14 (73.7)	0.774[c]
> 5	24 (29.6)	5 (26.3)	
H&Y stage			
1-2	64 (79.0)	18 (94.7)	0.183[f]
3-4	17 (21.0)	1 (5.3)	
Phenotype			
Tremor	26 (32.1)	10 (52.6)	0.025[c]
Akinetic rigid	25 (30.9)	8 (42.1)	
Mixed	30 (37.0)	1 (5.3)	
Lateralization			
Right	47 (58.0)	8 (42.1)	0.209[c]
Left	34 (42.0)	11 (57.9)	
Family history	6 (7.4)	1 (5.3)	1.000[f]
Levodopa equivalent dose (mg)	440 (200 - 790)	250 (150 - 575)	0.302[m]
< 400	39 (48.1)	12 (63.2)	0.320[c]
400-599	10 (12.3)	3 (15.8)	
≥ 600	32 (39.5)	4 (21.1)	

Abbreviations: dL, deciliter; eGFR, estimated glomerular filtration rate; H&Y, Hoehn and Yahr; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; IQR, interquartile range; kg, kilogram; LDL, low-density lipoprotein; m^2, square meter; Max, maximum; MCI, mild cognitive impairment; mg, milligram; Min, minimum; min, minute; mL, milliliter; n, number; PD, Parkinson's disease; SD, standard deviation

Data are presented as number (%), mean ± standard deviation or median (interquartile range).

P-value corresponds to [t]Independent samples t-test, [m]Mann-Whitney U test, [c]Chi-square test or [f]Fisher's exact test.

[a] Others include gastroesophageal reflux disease, benign prostatic hyperplasia, rheumatoid arthritis, asthma, nonalcoholic steatohepatitis, gout and knee osteoarthritis.

[b] Smoking and alcohol consumption refer to current use at the time of assessment.

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potentially masking early signs of cognitive impairment. Furthermore, since this study was conducted in a specialized Movement Disorders Clinic, it likely included patients with more complex disease profiles or treatment-refractory disease and a higher burden of non-motor symptoms, including cognitive complaints. Since all patients included in this study presented with subjective cognitive concerns that prompted screening. The advanced age of the sample may have further contributed to the high prevalence observed.

Consistent with prior research, older age and lower educational attainment emerged as strong independent predictors of PD-MCI. Age is a well-established risk factor reflecting both disease-related and age-associated neurodegeneration. Meanwhile, lower educational attainment—an indicator of reduced cognitive reserve—has been repeatedly linked to increased vulnerability to cognitive impairment in PD and the general population.[17] These findings highlight the need for targeted screening among older and

Table 4 Univariable and Multivariable Analysis using Multiple Logistic Regression Analysis of Associated Factors of PD-MCI in Parkinson's Disease

Factors	Univariable Analysis			Multivariable Analysis		
	OR[a]	95% CI	P-value	OR_{adj}[b]	95% CI	P-value
Age (years)						
< 70	1.00	Reference		1.00	Reference	
≥ 70	6.61	(2.22-19.68)	0.001	6.77	(1.35-34.08)	0.020
Gender						
Female	1.00	Reference				
Male	1.22	(0.44-3.34)	0.705			
Education level						
> Grade 6	1.00	Reference		1.00	Reference	
< Grade 6	7.15	(1.55-32.98)	0.012	10.35	(1.68-63.88)	0.012
BMI (kg/m^2)						
Normal (18.5-22.9)	1.00	Reference		1.00	Reference	
Overweight (23.0-24.9)	0.34	(0.08-1.39)	0.132	0.12	(0.01-1.24)	0.075
Obesity (≥ 25)	0.19	(0.05-0.67)	0.010	0.07	(0.01-0.55)	0.012
Comorbidity	2.43	(0.65-9.13)	0.188			
Hypertension	6.27	(2.04-19.31)	0.001	4.49	(0.80-25.15)	0.088
Diabetes mellitus	0.64	(0.22-1.83)	0.405			
Dyslipidemia	2.85	(0.98-8.24)	0.054	1.63	(0.32-8.24)	0.556
Coronary artery disease	1.97	(0.23-16.8)	0.534			
Atrial fibrillation	-	-	NA			
Chronic kidney disease	3.13	(0.38-25.69)	0.288			
Chronic obstructive pulmonary disease	-	-	NA			
Thyroid disease	-	-	NA			
Fatty liver	-	-	NA			
Others	1.07	(0.32-3.63)	0.912			

Table 4 Univariable and Multivariable Analysis using Multiple Logistic Regression Analysis of Associated Factors of PD-MCI in Parkinson's Disease (cont.)

Factors	Univariable Analysis			Multivariable Analysis		
	OR[a]	95% CI	P-value	OR_{adj} [b]	95% CI	P-value
Smoking	3.44	(0.42-28.08)	0.249			
Alcohol	-	-	NA			
HbA1c, (n = 59)						
< 6.5	1.00	Reference				
> 6.5	0.50	(0.14-1.86)	0.302			
Total cholesterol > 200 mg/dL	0.36	(0.11-1.15)	0.083			
Triglyceride > 150 mg/dL	1.36	(0.35-5.27)	0.660			
LDL-cholesterol > 100 mg/dL	-	-	NA			
Onset age (years)	1.11	(1.04-1.18)	0.001			
Duration (years)						
≤ 5	1.00	Reference				
> 5	1.18	(0.38-3.64)	0.775			
H&Y stage						
1-2	1.00	Reference				
3-4	4.78	(0.6-38.41)	0.141	0.64	(0.05-8.63)	0.735
Phenotype						
Tremor	1.00	Reference		1.00	Reference	
Akinetic rigid	1.20	(0.41-3.54)	0.738	0.93	(0.16-5.48)	0.932
Mixed	11.54	(1.38-96.29)	0.024	14.92	(0.91-245.13)	0.058
Lateralization						
Right	1.90	(0.69-5.23)	0.214			
Left	1.00	Reference				
Family history	1.44	(0.16-12.72)	0.743			
Levodopa equivalent dose (mg)						
< 400	1.00	Reference		1.00	Reference	
400-599	1.03	(0.24-4.34)	0.973	4.12	(0.37-45.78)	0.249
≥ 600	2.46	(0.72-8.37)	0.149	2.64	(0.44-15.90)	0.290

Abbreviations: BMI, body mass index; CI, confidence interval; dL, deciliter; H&Y, Hoehn and Yahr; HbA1c, hemoglobin A1c; kg, kilogram; LDL, low-density lipoprotein; m^2, square meter; MCI, mild cognitive impairment; mg, milligram; n, number; NA, not applicable; OR, odds ratio; ORadj, adjusted odds ratio; PD, Parkinson's disease

Variable was included in multivariable model due to have p-value < 0.200 in univariable analysis.

[a] Crude odds ratio estimated by binary logistic regression.

[b] Adjusted odds ratio estimated by multiple logistic regression.

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less-educated patients with PD, particularly in developing countries such as Thailand, where educational attainment varies widely across generations and regions.[18]

Interestingly, obesity (BMI ≥ 25 kg/m²) was inversely associated with PD-MCI. This finding supports previous observations in PD and other neurodegenerative conditions, where higher BMI has sometimes been linked to a lower risk of cognitive decline.[19] This phenomenon, known as the "obesity paradox," refers to the counterintuitive observation that overweight or mildly obese older adults may experience better functional outcomes than those with normal or low BMI.[20] Possible mechanisms include greater nutritional status and metabolic reserve, which may protect against neurodegenerative processes, whereas low BMI may indicate frailty—a condition strongly associated with poor cognitive outcomes and increased dementia risk.[21]

Weight loss is common as PD progresses, and lower BMI may reflect disease advancement and greater neurodegenerative burden.[22] However, BMI alone does not differentiate fat from lean mass. Evidence suggests that muscle mass and strength (sarcopenia) are more closely related to cognition than fat mass.[23] These findings suggest that body composition, rather than BMI alone, may play a critical role in PD-related cognitive outcomes. Future research should incorporate measures of muscle mass, fat distribution, and frailty indices to clarify the underlying biological mechanisms.

Although hypertension, hyperlipidemia, and later age at disease onset were significantly associated with MCI in univariate analyses, they did not remain significant in the multivariate model, likely due to collinearity with age and education. Nevertheless, vascular comorbidities remain biologically plausible contributors to cognitive decline in PD, as cerebral small-vessel disease and white matter changes have been linked to impaired cognition.[24] In this cohort, brain imaging was not routinely performed; therefore, subclinical cerebrovascular pathology may have contributed to cognitive impairment in some patients, particularly those with vascular risk factors. However, vascular comorbidities were not independent predictors of PD-MCI after multivariable adjustment, suggesting that age and education were the primary contributors in this cohort. Future studies using neuroimaging to assess vascular burden in Thai patients with PD could further elucidate these associations.

The findings of this study have several clinical implications. First, the high prevalence of PD-MCI in Thai populations underscores the importance of incorporating cognitive screening into routine PD management, particularly for patients aged ≥ 70 years or with limited education. The MoCA, which is sensitive to executive and visuospatial deficits, is practical for outpatient use and allows early detection of cognitive decline. Preventive measures such as cognitive training, patient education, and aggressive management of vascular risk factors should be prioritized in this high-risk group.

This study has several limitations. First, the relatively small sample size (n = 100), recruitment from a single tertiary center in Bangkok and all participants were presented with cognitive concerns which may limit generalizability, particularly to rural populations where educational and health access profiles differ. Second, the use of a single cognitive screening tool (MoCA) without comprehensive neuropsychological testing based on the Movement Disorder Society Level II criteria limits diagnostic precision. Third, brain imaging was not systematically obtained, which limits the ability to exclude subclinical cerebrovascular disease or other structural brain abnormalities as contributors to cognitive impairment. Finally, the absence of a non-PD control group restricts comparison and external validation of the identified risk factors.

CONCLUSION

This study revealed a notably high prevalence of MCI among patients with PD in a Thai population, affecting more than 80% of participants. Older age, lower educational attainment, and lower BMI were identified as independent predictors of PD-MCI. Although vascular comorbidities such as hypertension and hyperlipidemia were associated with PD-MCI in univariate analyses, they did not remain independent predictors after adjustment. These findings emphasize the need for routine cognitive screening in PD care, particularly for elderly and less-educated patients, to facilitate early detection and timely management of cognitive decline. Considering Thailand's rapidly aging population and increasing prevalence of PD, integrating cognitive assessment into standard clinical care is crucial. Future longitudinal, multicenter studies and incorporating direct measures of body composition are recommended to elucidate causal mechanisms and inform prevention

and management strategies for cognitive impairment in PD.

Conflict of Interest

The authors have no financial interest related to the topic of this manuscript.

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Author Contributions

Conceptualization: S.S., T.B.

Data curation: T.B.

Formal analysis: S.S., T.B.

Funding acquisition: -

Investigation: S.S.

Methodology: S.S., T.B.

Project administration: S.S.

Resources: T.B.

Software: T.B.

Supervision: T.B.

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Visualization: S.S.

Writing – original draft preparation: S.S., T.B.

Writing – review & editing: T.B.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to restrictions.

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ORIGINAL ARTICLE

Long COVID's Gender-Specific Determinants: 3- and 6-Month Evidence from Thai Females During the Delta and Omicron Waves

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ABSTRACT

Objectives: To prospectively identify determinants of Long COVID in Thai females and compare outcomes across the Delta and Omicron periods through structured follow-up assessments at 3 and 6 months post-infection.

Materials and Methods: From May 2021 through June 2022, this prospective cohort study was conducted in Thailand at Thammasat University Hospital and its field hospital. We enrolled 1,484 females aged 18 and older with laboratory-confirmed SARS-CoV-2 infection. Using a standardized questionnaire and trained interviewers to assess Long COVID symptoms, we followed up with participants via telephone interviews at 3- and 6-months post-diagnosis. Multivariable logistic regression was used to identify independent risk factors for Long COVID.

Results: At the 3-month follow-up, 806 participants (54.3%) reported Long COVID symptoms, which persisted in 418 (38.6%) at 6 months. At 3 months, infection during the Omicron-dominant wave (adjusted odds ratio (OR) 1.75, 95% confidenc interval (CI): 1.26–2.43) and acute myalgia (adjusted OR 1.52, 95% CI: 1.04–2.22) were significant predictors. At the 6-month follow-up, moderate-to-critical initial illness severity (adjusted OR 2.17, 95% CI: 1.01–4.69) and loss of smell during the acute phase (adjusted OR 1.61, 95% CI: 1.04–2.49) were significant predictors of persistent Long COVID.

Conclusion: In Thai females, determinants for Long COVID shift between 3 and 6 months post-infection. While acute myalgia and the Omicron variant are early predictors, initial illness severity and loss of smell better indicate symptom persistence at 6 months. These findings highlight Long COVID's dynamic nature and can help identify female patients at higher risk for prolonged symptoms.

Keywords: associated factor, female, long COVID, point prevalence, Thai

INTRODUCTION

Since its emergence in late 2019, COVID-19 has profoundly impacted global health over the past 5 years. Clinical presentation of acute SARS-CoV-2 infection demonstrates remarkable heterogeneity, ranging from asymptomatic to severe, life-threatening cases. Beyond the acute phase, a substantial proportion of infected individuals—estimated at 65 million globally—develop persistent symptoms lasting more than 3 months, a condition the World Health Organization and the Centers for Disease Control and Prevention formally recognize as Long COVID.[1-3]

In the post-pandemic era, Long COVID has evolved into a major public health challenge because this complex, multi-system disorder presents with debilitating symptoms that compromise individual quality of life, reduce workforce productivity, and strain healthcare infrastructure.[4] Recognizing Long COVID's substantial burden, health authorities and governments increasingly acknowledge the disease as requiring—rather than individualized management alone—coordinated, sustained public health interventions.

Current therapeutic approaches remain largely empirical. As new evidence emerges, approaches rely on trial-and-error methodologies and personalized-management strategies. Critically, standardized care protocols for high-risk populations remain underdeveloped, representing a significant limitation, particularly given consistent evidence that Long COVID disproportionately affects females.[4] Multiple large-scale studies and meta-analyses have identified being female as a primary risk factor for developing Long COVID, creating a clinical paradox. Although compared to males, females typically exhibit more robust immune responses during acute COVID-19 infection, paradoxically they experience higher rates of persistent symptoms.[5]

Leading hypotheses propose that female immunological advantages during acute infection may predispose them to Long COVID through immunological hyperactivation. The enhanced immune response that provides initial protection may subsequently trigger sustained infl mmatory cascades and autoimmune-like processes, wherein immune mechanisms inappropriately target host tissues, perpetuating Long COVID's multi-systemic symptomatology.[6]

Females' risk of Long COVID extends beyond biological sex to combine with multiple interacting determinants. Key predisposing factors include: perimenopausal status, particularly from age 40 to 55, when hormonal fluctuations alter immune regulation and elevated body mass index is associated with chronic inflammatory states, specifi SARS-CoV-2 variants with differential risk profil s between Delta and Omicron waves, vaccination status, and acute infection symptom severity.

Complex interactions among these predisposing factors across viral variant periods remain inadequately characterized, particularly within Thai populations. Therefore, this prospective study aimed to identify Long COVID's gender-specific determinants among Thai females by employing systematic follow-up assessments at 3 and 6 months post-infection during both the Delta and Omicron variant periods.

Furthermore, variations in genetic phenotypes affecting host immune responses, differences in vaccine types and completeness of vaccination regimens among Thai populations, together with other contextual and sociocultural factors, preclude the direct generalization of evidence from previous studies to this setting. Consequently, population-specific investigation is essential to accurately characterize Long COVID determinants among Thai females.

This study prospectively aimed to identify gender-specific determinants of Long COVID in Thai females using structured follow-up assessments at 3 and 6 months post-infection, comparing outcomes across Delta and Omicron variant periods.

MATERIALS AND METHODS

This study was approved by the Human Research Ethics Committee of Thammasat University (Medicine, MTU-EC-PE-1-280/65).To investigate Long COVID's risk factors among Thai females, this prospective cohort study was conducted at Thammasat University Hospital (TUH) and its affiliated Thammasat Field Hospital (TFH). Recruitment occurred from May 2021 to June 2022, spanning Thailand's Delta- and Omicron-variant dominant waves. TUH is a 700-bed tertiary-care academic medical center, providing comprehensive healthcare services to populations across northern Bangkok and central Thailand. The facility maintains established infectious disease protocols and electronic health records system essential for longitudinal patient tracking. TFH operates as a 490-bed specialized facility for patients with asymptomatic-to-mild COVID-19, allowing capture of the full spectrum of disease severity in the study population.

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The investigation employed a gender-focused approach, targeting female participants to address knowledge gaps on gender-specifi Long COVID patterns. Participants were monitored via telephone interviews at 3 and 6 months post SARS-CoV-2 diagnosis, enabling comprehensive assessment of symptom evolution and persistence. Participants were monitored via telephone interviews at 3 and 6 months after recovery from acute SARS-CoV-2 infection to assess symptom evolution and persistence. Nonetheless, the study did not employ a longitudinal design; data at each time point were collected independently, and individual-level follow-up across assessments was not performed.

Eligibility included female patients aged 18 and older with laboratory confirm d SARS-CoV-2 infection via nasopharyngeal reverse transcription polymerase chain reaction performed at either facility. This molecular approach ensured accurate case identification and standardized detection criteria across hospitals.

Participants were identified systematically through hospital databases and contacted by telephone for follow-up interviews. The recruitment strategy captured diverse clinical presentations, ranging from asymptomatic infections at the field hospital to severe cases at the tertiary center. All participants provided written informed consent at initial presentation and additional verbal consent was obtained for telephone interviews.

The study protocol received approval from both hospitals' institutional review boards, and participant confidentiality was maintained through coded identification systems in compliance with privacy standards.

Sample size determination followed a feasibility-based cohort design, with cohort size defined by real-world case accrual rather than an a prior power calculation, corresponding to the number of eligible female patients with laboratory-confirme SARS-CoV-2 infection presenting to the participating hospitals during the study period. A post-hoc assessment of statistical precision indicated that the achieved sample size was sufficien for descriptive and exploratory analyses, sufficient to achieve acceptable precision of parameter estimates, as reflect d by the width of corresponding confidenc intervals, permitting estimation of key epidemiological parameters and hypothesis generation within an observational epidemiological framework.

Long COVID was assessed using a standardized, symptom-based questionnaire developed by the Thai Ministry of Public Health and validated for telephonic administration. This instrument was generated through rigorous developmental processes, incorporating international Long COVID diagnostic criteria and also adapting to local linguistic and cultural considerations. Trained interviewers conducted structured telephone interviews at 3 and 6 months post-diagnosis evaluating symptom presence, functional status evaluation, and healthcare utilization. Interviewers followed standardized questioning techniques, symptom severity grading, and quality assurance procedures.

To ensure complete characterization of potential Long COVID determinants, comprehensive data collection integrated information from multiple sources. Primary data extraction was from the TUH electronic health record system, supplemented by structured interviews to capture variables not routinely documented in clinical records.

Demographic variables included chronological age, educational attainment categorized according to Thai educational system standards, and smoking history with detailed quantification of exposure duration and intensity. During the study period, vaccination status was recorded based on manufacturer specifications dose timing relative to infection, and completion status according to recommended schedules.

Comorbidities were assessed through systematic review of documented medical conditions, including coronary artery disease, heart failure, arrhythmias, chronic pulmonary conditions including asthma and chronic obstructive pulmonary disease, diabetes mellitus with glycemic control status, chronic kidney disease staged according to estimated glomerular filtration rate, cerebrovascular disease history, and active or prior malignancy.

Initial COVID-19 illness severity classificatio followed the National Institute for Health and Care Excellence guidelines, providing standardized frameworks for symptom categorization and severity grading. Symptom documentation employed systematic organ system classification, including respiratory manifestations such as cough, dyspnea, and chest discomfort; neurological symptoms such as headache and altered consciousness; musculoskeletal complaints including myalgia and arthralgia; gastrointestinal symptoms such as diarrhea, nausea, and abdominal pain; and constitutional symptoms including fever, fatigue, and anorexia.

Overall illness severity was classified according to World Health Organization criteria, ranging from

asymptomatic infection to mild illness not requiring hospitalization, moderate illness requiring medical intervention, severe illness necessitating intensive monitoring, and critical illness requiring life support measures. This classificatio enabled systematic comparison across severity categories and their associated Long COVID risks.

Comprehensive symptom evaluation included 21 distinct manifestations identified through literature review and clinical expertise as commonly associated with Long COVID. Respiratory symptoms included persistent dyspnea, chronic cough, and chest tightness or discomfort; cardiovascular manifestations included palpitations and exercise intolerance; neurological symptoms included headache, attention defici s, memory impairment, and sleep disturbances. Gastrointestinal assessment focused on persistent diarrhea and appetite changes. Musculoskeletal evaluation included ongoing myalgia and arthralgia. Sensory symptoms encompassed anosmia and ageusia, representing persistent chemosensory dysfunction. Dermatological manifestations included skin rash and alopecia. Psychological symptoms comprised depression and stress responses, while constitutional symptoms included persistent exhaustion, generalized weakness, and dizziness.

Each symptom was systematically assessed for onset, duration, severity impact on daily functioning, and relationship to initial acute infection. Participants reported both new onset symptoms not present before COVID-19 and persistent symptoms continuing from the acute phase beyond the 3-month diagnostic threshold.

Patient characteristics were summarized through comprehensive descriptive statistics appropriate for variable types and distributions. Categorical variables were presented as absolute frequencies with corresponding percentages, enabling clarity of demographics and clinical profiles. Continuous variables were assessed for distribution normality, with appropriate measures of central tendency and variability selected accordingly. Categorical variable associations were analyzed using Chi-square testing for variables meeting expected frequency assumptions, with Fisher's exact testing applied for sparse data scenarios. These analytical approaches identifie statistically significan relationships among potential determinants and Long COVID development.

For prognostic modeling, acute-phase symptom inclusion required prevalence exceeding 5% in the study population, ensuring adequate statistical power for meaningful effect estimation. This threshold prevented analytical instability associated with rare exposures while also maintaining clinical relevance for commonly occurring symptoms.

Univariate logistic regression analysis assessed individual relationships between each potential determinant and Long COVID development. Results were presented as crude odds ratios (ORs) with corresponding 95% confidence intervals, providing effect magnitude estimates and statistical significance assessment for each variable. Independent prognostic factor identification employed multivariable logistic regression modeling with systematic variable selection procedures. The initial model included all variables demonstrating univariate associations with $p < 0.20$, thus providing a sufficiently liberal threshold to capture potential confounding relationships while also maintaining analytical feasibility. Final model development utilized backward elimination procedures, systematically removing variables that failed to demonstrate independent associations while maintaining overall model performance and clinical interpretability. This approach balanced statistical significance with practical clinical relevance, ensuring that final models provided meaningful prognostic information for Long COVID risk assessment. In the presence of missing data, analyses were conducted using a complete case approach, whereby only observations with complete data for all variables included in each specific analysis were retained. No data imputation procedures were performed.

All statistical analyses employed STATA version 14.2 software, which provides robust analytical capabilities for complex epidemiological data analysis. Statistical significance was established at $p < 0.05$, with confidence interval calculated at 95%.

RESULTS

A total of 1,484 female participants were enrolled and prospectively followed after hospital discharge to assess Long COVID outcomes during the Delta- and Omicron-dominant waves. At the 3-month follow-up, 806 participants (54.3%) reported persistent symptoms consistent with Long COVID, while 678 (45.7%) reported no persistent symptoms. At 6 months, 418 (38.6%) continued to experience Long COVID, while 664 (61.4%) had recovered. Fluctuating immune responses among participants aged 40-55 did not differ significantly between groups at either time point.

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Baseline characteristics further indicated that obesity (body mass index (BMI) ≥ 30.0) was more prevalent among those with Long COVID at 3 months, while vaccination status and acute disease severity showed differential distributions across groups, particularly during the Delta-dominant wave. These findings provide the foundation for examining Long COVID's female-specifi determinants across distinct viral variants and follow-up intervals. (Table 1)

Significant differences in baseline characteristics were observed between females with and without Long COVID. At 3 months, Long COVID occurred more frequently following Omicron infections (60.0% vs. 47.0%, p < 0.001). Vaccination status showed a marked association at 3 months: individuals with incomplete or no vaccination and those without booster doses, were overrepresented in the Long COVID group (p < 0.001). At 6 months, although obesity and overall comorbidity prevalence did not differ significantl between groups, disease severity demonstrated an association, with moderate-to-severe acute illness more frequently reported among those with Long COVID (19.6% vs. 16.3%, p = 0.044). Collectively, these findings highlight the roles of obesity, vaccination coverage, variant type, and acute illness severity as determinants of Long COVID persistence in Thai females. (Table 1)

Regarding acute symptomatology, several clinical manifestations during initial infection were significa tly associated with subsequent Long COVID among females. At 3 months, compared with those without persistent symptoms, myalgia was more

Table 1 Patient Characteristics of Females for Long COVID at 3- and 6-Month Follow-Up after the Delta and Omicron Variant COVID Infections

	3 Months (n = 1484)			6 Months (n = 1082)		
	Long COVID (n = 806)	Without Long COVID (n = 678)	P-value[a]	Long COVID (n = 418)	Without Long COVID (n = 664)	P-value[b]
Age between 40 and 55 years – no (%)	207 (25.7)	148 (21.8)	0.083	111 (26.6)	153 (23.0)	0.190
Obesity – no (%)						
Normal Weight (BMI ≤ 24.9 kg/m^2)	379 (47.0)	348 (51.3)	0.228	201 (48.1)	320 (48.2)	0.883
Overweight (BMI ≥ 25.0-29.9 kg/m^2)	111 (13.8)	91 (13.4)		49 (11.7)	84 (12.7)	
Obesity (BMI 30.0 kg/m^2)	316 (39.2)	239 (35.3)		168 (40.2)	260 (39.2)	
Comorbidities – no (%)						
CVD	127 (15.8)	111 (16.4)	0.748	59 (14.1)	91 (13.7)	0.849
COPD	31 (3.9)	25 (3.7)	0.873	17 (4.1)	23 (3.5)	0.609
DM	79 (9.8)	69 (10.2)	0.810	29 (6.9)	57 (8.6)	0.330
CKD	17 (2.1)	8 (1.2)	0.224	4 (0.96)	5 (0.75)	0.740
Stroke	11 (1.4)	8 (1.2)	0.752	2 (0.48)	4 (0.60)	1.000
Cancer	16 (2.0)	12 (1.8)	0.761	6 (1.4)	14 (2.1)	0.424
Variant of Concern – no (%)[c]						
Delta	303 (47.0)	342 (53.0)	< 0.001*	229 (41.1)	328 (58.9)	0.084
Omicron	503 (60.0)	336 (40.0)		189 (36.0)	336 (64.0)	

Table 1 Patient Characteristics of Females for Long COVID at 3- and 6-Month Follow-Up after the Delta and Omicron Variant COVID Infections (cont.)

	3 Months (n = 1484)			6 Months (n = 1082)		
	Long COVID (n = 806)	Without Long COVID (n = 678)	P-value[a]	Long COVID (n = 418)	Without Long COVID (n = 664)	P-value[b]
Vaccine History – no (%)						
Not Complete	265 (32.9)	262 (38.6)	< 0.001*	252 (38.0)	182 (43.5)	0.170
Complete	217 (26.9)	229 (33.8)		228 (34.3)	135 (32.3)	
Booster	324 (40.2)	187 (27.6)		184 (27.7)	101 (24.2)	
Severity at Acute Illness – no (%)						
Asymptomatic	25 (3.1)	35 (5.2)	0.102	11 (2.6)	36 (5.4)	0.044*
Mild	632 (78.4)	530 (78.2)		325 (77.8)	520 (78.3)	
Moderate-to-Critical	149 (18.5)	113 (16.7)		82 (19.6)	108 (16.3)	
Symptoms during Acute Illness – no (%)						
At Least 1 Symptom	677 (84.0)	547 (80.7)	0.094	352 (84.2)	534 (80.4)	0.115
Cough	465 (57.7)	358 (52.8)	0.059	231 (55.3)	344 (51.8)	0.267
Sore Throat	404 (50.1)	312 (46.0)	0.115	180 (43.1)	318 (47.9)	0.121
Myalgia	84 (10.4)	50 (7.4)	0.041*	41 (9.8)	58 (8.7)	0.551
Rhinorrhea	178 (22.1)	152 (22.4)	0.877	85 (20.3)	144 (21.7)	0.596
Sputum Production	96 (11.9)	63 (9.3)	0.104	41 (9.8)	71 (10.7)	0.642
Dyspnea	63 (7.8)	49 (7.2)	0.669	38 (9.1)	48 (7.2)	0.270
Headache	163 (20.2)	123 (18.1)	0.311	87 (20.8)	117 (17.6)	0.191
Diarrhea	19 (2.4)	13 (1.9)	0.561	15 (3.59)	10 (1.51)	0.026*
Loss of Smell	59 (7.3)	50 (7.4)	0.968	52 (12.4)	48 (7.2)	0.004*
Loss of Taste	21 (2.6)	19 (2.8)	0.816	21 (5.0)	17 (2.6)	0.032*

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COVID, coronavirus disease; CVD, cardiovascular diseases; DM, diabetes mellitus; kg, kilogram m^2, square metre; n, number

[a] Comparison between long COVID and without long COVID at 3 months

[b] Comparison between long COVID and without long COVID at 6 months

[c] Row percentage

* Statistical significan e

Note: Data are numbers (%).

frequently reported in the Long COVID group (10.4% vs. 7.4%, p = 0.041). By 6 months, gastrointestinal and sensory symptoms emerged as notable determinants: diarrhea (3.6% vs. 1.5%, p = 0.026), loss of smell (12.4% vs. 7.2%, p = 0.004), and loss of taste (5.0% vs. 2.6%, p = 0.032) were significantly more common among individuals with ongoing Long COVID. These finding suggest that the presence of systemic and sensory disturbances during the acute phase may predispose female patients to prolonged symptoms, highlighting the need for early clinical indicators to identify those at elevated risk.

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As shown in **Table 2**, the point prevalence of Long COVID symptoms was evaluated at 3 months (n = 1484) and 6 months (n = 1082) post-infection. At 3 months, 54.3% (n = 806) reported at least one symptom. This proportion decreased by 6 months, with 38.6% (n = 418) reporting at least one symptom.

At 3 months, the most frequently reported symptom category was fatigue and weakness, affecting 31.9% (n = 474). Within this category, weakness was the most common individual symptom (30.3%, n = 449). Neurological symptoms were also prevalent (30.1%, n = 447), with memory loss the most frequent (20.3%, n = 299), followed by insomnia (14.1%, n = 209) and attention deficit (11.5%, n = 171). Dermatological symptoms were reported by 24.7% (n = 366), driven primarily by alopecia (21.5%, n = 319). Respiratory symptoms were present in 23.9% (n = 354), with dyspnea (15.7%, n = 233) more common than cough (13.2%, n = 196).

By 6 months, the prevalence of all symptom categories had declined. Fatigue and weakness remained the most common category but decreased to 21.0% (n = 224). The prevalence of weakness specifically fell to 18.5% (n = 200). Neurological symptoms decreased to 17.3% (n = 187), with memory loss reducing to 9.0% (n = 97). Dermatological symptoms reduced to 15.9% (n = 172), with alopecia dropping to 13.9% (n = 150). Respiratory symptoms also declined to 12.4% (n = 134).

As shown in **Table 3 and 4**, this study investigated associations between various factors and individual Long COVID symptoms in females at 3 and 6 months—including both Delta and Omicron variants—by selecting only determinants with a prevalence greater than 5% for each variable. Analysis at each time point was conducted in two stages. First, unadjusted ORs were calculated, followed by multivariable adjusted ORs including factors with a $p < 0.2$ in the unadjusted analysis.

At 3 months, several factors demonstrated significant association with Long COVID symptoms after adjustment. Infection during the Omicron-dominant wave strongly predicted Long COVID, with an adjusted OR of 1.68 (95% CI: 1.22–2.30, $p < 0.001$). Myalgia's presence as an initial symptom was also a significan factor, with an adjusted OR of 1.52 (95% CI: 1.04–2.21, $p = 0.030$). Other factors, for instance, BMI and moderate-to-critical disease severity, showed some association in the unadjusted analysis but did not

Table 2 Point Prevalence of Individual Symptoms of Females for Long COVID Follow-up at 3 and 6 Months after the Delta and Omicron Variant COVID Infection

	At 3 Months (n = 1484)	At 6 Months (n = 1082)
At Least 1 Symptom – No (%)	806 (54.3)	418 (38.6)
Respiratory Symptoms	354 (23.9)	134 (12.4)
Dyspnea	233 (15.7)	76 (7.0)
Cough	196 (13.2)	53 (4.9)
Cardiovascular Symptoms	204 (13.8)	52 (4.8)
Chest Tightness	94 (6.3)	24 (2.2)
Palpitation	108 (7.3)	31 (2.9)
Neurological Symptoms	447 (30.1)	187 (17.3)
Headache	151 (10.2)	44 (4.1)
Attention Defici	171 (11.5)	32 (3.0)
Memory Loss	299 (20.2)	97 (9.0)
Insomnia	209 (14.1)	72 (6.7)
Gastrointestinal Symptoms		
Diarrhea	44 (3.0)	6 (0.6)
Musculoskeletal Symptoms	225 (15.2)	77 (7.1)
Myalgia	164 (11.1)	45 (4.2)
Arthralgia	143 (9.6)	44 (4.1)
Ear, Nose, and Throat Symptoms	228 (15.4)	77 (7.1)
Dizziness	172 (11.6)	42 (3.9)
Loss of Appetite	116 (7.8)	16 (1.5)
Anosmia	58 (3.9)	23 (2.1)
Ageusia	47 (3.2)	8 (0.7)
Dermatological Symptoms	366 (24.7)	172 (15.9)
Rash	79 (5.3)	16 (1.5)
Alopecia	319 (21.5)	150 (13.9)
Psychological/ Psychiatric Symptoms	131 (8.8)	28 (2.6)
Depression	43 (2.9)	7 (0.7)
Stress	116 (7.8)	22 (2.0)
Fatigue & Weakness Symptoms	474 (31.9)	224 (21.0)
Fatigue	183 (12.3)	47 (4.3)
Weakness	449 (30.3)	200 (18.5)

Abbreviation: n, number

Table 3 Univariable Analysis of Associations between Individual Symptoms and Long COVID in Females at 3 and 6 Months after Delta and Omicron Variant SARS-CoV-2 Infection

Factor	3 Month		6 Month	
	Unadjusted OR [95%CI]	P-value[a]	Unadjusted OR [95%CI]	P-value[b]
Age between 40 and 55	1.24 [0.97-1.58]	0.083	1.21 [0.91-1.60]	0.191
Obesity				
Normal	Ref		Ref	
Overweight	1.04 [0.81-1.32]	0.772	0.95 [0.71-1.27]	0.742
≥ BMI 30 kg/m^2	1.51 [1.10-2.07]	0.010*	1.23 [0.86-1.76]	0.265
Comorbidities				
Cardiovascular	0.96 [0.72-1.26]	0.748	1.03 [0.73-1.47]	0.849
Diabetes Mellitus	0.96 [0.68-1.35]	0.810	0.79 [0.50-1.26]	0.330
COVID Waves				
Delta Waves	Ref		Ref	
Omicron Waves	1.69 [1.38-2.08]	< 0.001*	0.81 [0.63-1.03]	0.084
Vaccine History				
0-1 Dose	Ref		Ref	
Completed Vaccine	0.94 [0.73-1.21]	0.612	0.82 [0.62-1.09]	0.173
Booster Vaccine	1.71 [1.34-2.20]	< 0.001*	0.76 [0.56-1.03]	0.081
Severity Level				
Asymptomatic	Ref		Ref	
Mild	1.67 [0.99-2.83]	0.056	2.05 [1.03-4.07]	0.042*
Moderate-to-Critical	1.85 [1.05-3.26]	0.035*	2.49 [1.19-5.18]	0.015*
Symptoms during Acute Illness – No (%)				
Cough	1.21 [0.99-1.50]	0.059	1.15 [0.90-1.47]	0.267
Sore Throat	1.18 [0.96-1.45]	0.115	0.82 [0.64-1.05]	0.121
Myalgia	1.46 [1.01-2.11]	0.042*	1.14 [0.75-1.73]	0.551
Rhinorrhea	0.98[0.77-1.25]	0.877	0.92 [0.68-1.25]	0.596
Sputum Production	1.32 [0.94-1.85]	0.105	0.90 [0.61-1.36]	0.642
Dyspnea	1.09 [0.74-1.60]	0.669	1.28 [0.82-2.00]	0.271
Headache	1.14 [0.88-1.48]	0.311	1.26 [0.90-1.67]	0.192
Loss of Smell	0.99 [0.67-1.47]	0.968	1.82 [1.21-2.76]	0.004*

Abbreviations: BMI, body mass index; CI, confidence nterval; kg, kilogram; m^2, square metre; OR, odds ratio

[a] Comparison between Long COVID and no Long COVID at 3 months

[b] Comparison between Long COVID and no Long COVID at 6 months

* Statistical significanc

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Table 4 Multivariable Analysis of Associations between Individual Symptoms and Long COVID in Females at 3 and 6 Months after Delta and Omicron Variant SARS-CoV-2 Infection

Factor	3 Month		6 Month	
	Adjusted OR[c] [95%CI]	P-value[a]	Adjusted OR[d] [95%CI]	P-value[b]
Age between 40 and 55	1.26 [0.98-1.62]	0.075	1.15 [0.87-1.55]	0.315
Obesity				
Normal	Ref		NA	NA
Overweight	1.04 [0.76-1.44]	0.792	NA	NA
≥ BMI 30 kg/m^2	1.24 [0.98-1.56]	0.077	NA	NA
COVID Waves				
Delta	Ref		Ref	
Omicron	1.68 [1.22-2.30]	0.001*	0.98 [0.67-1.43]	0.909
Vaccine History				
0-1 Dose	Ref		Ref	
Completed Vaccine	0.75 [0.55-1.03]	0.073	0.91 [0.64-1.30]	0.597
Booster Vaccine	1.19 [0.81-1.73]	0.378	0.91 [0.57-1.44]	0.678
Severity Level				
Asymptomatic	Ref		Ref	
Mild	1.29 [0.74-2.23]	0.372	2.07 [1.02-4.19]	0.043*
Moderate-to-Critical	1.55 [0.85-2.80]	0.152	2.34 [1.11-4.94]	0.026*
Symptoms during Acute Illness – No (%)				
Cough	1.15 [0.93-1.43]	0.205	NA	NA
Sore Throat	1.00 [0.80-1.25]	0.980	0.82 [0.63-1.07]	0.137
Myalgia	1.52 [1.04-2.21]	0.030*	NA	NA
Sputum Production	1.20 [0.85-1.69]	0.304	NA	NA
Headache	NA	NA	1.24 [0.91-1.70]	0.179
Loss of Smell	NA	NA	1.62 [1.05-2.50]	0.029*

Abbreviations: BMI, body mass index; CI, confidence interval; kg, kilogram; m^2, square metre; NA, not applicable; OR, odds ratio

[a] Comparison between Long COVID and no Long COVID at 3 months

[b] Comparison between Long COVID and no Long COVID at 6 months

[c] Adjusted odds ratio at 3 months by age, obesity, Dominant waves, vaccine doses, severity and symptoms during acute illness

[d] Adjusted odds ratio at 6 months by female sex, Dominant waves, vaccine doses, severity and symptoms during acute illness

* Statistical significanc

reach statistical significance in the adjusted model.

Analysis at the 6-month follow-up revealed shifts in factors associated with persistent Long COVID symptoms. The initial illness's severity became a more prominent predictor: compared with asymptomatic cases, mild disease had an adjusted OR of 2.07 (95% CI: 1.02–4.19; p = 0.043), and moderate-to-critical disease had an adjusted OR of 2.34 (95% CI: 1.11–4.94; p = 0.026). Loss of smell during the initial illness was also a significan predictor, with an adjusted OR of 1.62 (95% CI: 1.05–2.50; p = 0.029). Notably, at the 6-month follow-up, factors significant at 3 months, such as the Omicron-dominant wave and myalgia as an initial symptom, were no longer statistically significant At this later time point, other variables, including the Omicron-dominant wave and myalgia, did not demonstrate significant associations in either unadjusted or adjusted models.

DISCUSSION

This prospective cohort investigation provides a comprehensive analysis of female-specifi determinants and Long COVID's phenotypic evolution among Thai females during recovery from Delta- and Omicron-dominant waves. The documented decline in Long COVID prevalence from 54.3% at 3 months to 38.6% at 6 months demonstrates substantial, although incomplete, natural recovery trajectories. This evidence aligns with several studies reporting a higher burden of Long COVID among females across settings.[7-11] Moreover, these findings indicate a fundamental temporal shift in principal risk factors, suggesting that Long COVID pathophysiology may evolve from an initial systemic inflammatory phase to subsequent organ-specific sequelae

The observed recovery pattern indicates that although symptoms resolve substantially during the initial 6-month period, more than one-third of affected individuals continue experiencing persistent manifestations. This incomplete recovery trajectory has profound implications for global healthcare resource allocation, occupational health policies, and long-term disability planning. The temporal evolution of risk factor profil s suggests distinct pathophysiological phases requiring various therapeutic approaches and clinical management strategies.

At 3 months, infection during the Omicron-dominant wave emerged as an independent predictor of Long COVID (adjusted OR 1.68) despite its generally milder acute clinical presentation than the Delta-dominant wave. This observation contrasts with several international reports but aligns with finding from studies conducted in Thailand. Other investigations have similarly noted Long COVID's higher prevalence following Omicron compared with Delta. These differences may be infl enced by circulating viral sublineages, host immunity profiles, and variations in primary vaccination series and booster-type combinations across populations.[12] This paradox likely reflects Omicron's enhanced immune evasion, distinct tissue tropism, and altered inflammatory responses. Immune escape mutations in spike protein epitopes might influenc viral persistence, immune memory formation, and inflammatory resolution, thereby generating variant-specifi , post-acute morbidity profiles

Myalgia's prominence as a predictor (adjusted OR 1.52) supports systemic inflammator etiologies, representing a cardinal manifestation of virally induced systemic inflammation that reflects widespread inflammatory mediator release that, in turn, affects skeletal muscle tissues and pain perception pathways. The mechanistic basis involves cytokine-mediated muscle fiber inflammation mitochondrial dysfunction, and altered pain processing mechanisms that might persist beyond viral clearance. Persistent myalgia suggests ongoing inflammatory activation or residual tissue damage affecting neuromuscular function and pain modulation systems, providing clinical evidence for sustained inflammatory processes underlying early Long COVID. In studying COVID-19 acute-phase clinical characteristics that predict Long COVID, Guzman-Esquivel et al. and Fernández-de-Las-Peñas et al. found myalgia to be a risk factor with an odds ratio of 1.5 compared to without Long COVID.[13,14] Their results relate to ours for myalgia and severity levels in univariable analysis at 3 months.

At 6 months, the risk factor profile shifted, with infection during the Omicron-dominant wave and myalgia at initial infection losing significance, while initial disease severity and loss of smell emerged as predominant predictors. This transition suggests Long COVID evolves from early inflammation-drive mechanisms to later phases characterized by residual organ damage.[15] This temporal specificity highlights distinct pathophysiological stages and implies that early interventions targeting inflammation may mitigate progression to long-term structural impairment.[15] At 6 months, moderate-to-critical initial disease severity

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was strongly associated with persistent symptoms (adjusted OR 2.34).[16] Severity levels reflect higher viral loads, extensive multi-organ involvement, and cumulative tissue damage, leading to long-term impairments. Evidence consistently indicates that hospitalized patients are at greater risk of developing persistent symptoms, reinforcing acute viral burden and inflammatory injury's contributions as Long COVID's key determinants. These findings emphasize the importance of early, intensive clinical interventions. At 6 months, loss of smell emerged as an independent Long COVID predictor (adjusted OR 1.62).[17-19] Persistent olfactory dysfunction likely reflect unresolved olfactory bulb inflammation and broader neuronal dysregulation, consistent with neuroimaging evidence of structural brain changes in regions linked to olfactory processing.[20]

Persistent loss of smell might be explained via a neurological pathway in Long COVID, suggesting central nervous system involvement through viral persistence, chronic neuroinflammation, or structural brain alterations.[21] Symptom cluster trajectories revealed heterogeneous decline rates by 6 months, indicating distinct biological mechanisms contributing to varied recovery patterns.[22] Fatigue and weakness remained the most persistent symptoms, consistent with mechanisms involving mitochondrial dysfunction, viral reservoirs, and autonomic dysregulation.[23] Emerging evidence implicates microclot formation and endothelial dysfunction in impaired oxygen delivery and energy metabolism, offering plausible explanations for sustained fatigue and highlighting the need for targeted vascular and metabolic interventions.[24,25] Dermatological symptoms —predominantly alopecia—resolved more rapidly, likely reflecting alopecia's emergence due to acute physiological stress, which typically normalizes with hair cycle restoration.[26] Neurological symptoms declined by half, yet they persisted in nearly one-fifth of patients, emphasizing the central nervous system's particular involvement in Long COVID and the need for specialized management.[27] Heterogeneous recovery patterns across symptom domains suggest multiple underlying pathophysiological processes, supporting the need for crucial individualized diagnostic and therapeutic approaches.[28]

This investigation possesses notable methodological strengths that enhance its validity and clinical relevance. The prospective cohort design allows real-time monitoring of symptoms and risk factors, reducing concerns about retrospective reporting. The substantial cohort of 1,476 female participants provides considerable statistical power for examining gender-specific determinants and addressing an important knowledge gap, given recognized gender disparities in Long COVID's prevalence. Conducting the study during both the Delta and Omicron variant dominant waves enabled comparative analysis of variant-specific risk profiles and symptom evolution. Additionally, comprehensive data collection encompassing demographic, clinical, and symptomatic variables across multiple assessment points further strengthens the study's methodological rigor. Systematic follow-up protocols—with trained interviewers—adapted from the Ministry of Public Health ensure consistent data quality and comparability. Furthermore, integrating hospital database information into structured interview data provides comprehensive characterization of clinical profile and Long COVID manifestations.

Despite these strengths, several limitations warrant consideration. The absence of pre-COVID baseline assessments presents challenges to definitivel attributing symptoms to post-viral pathology rather than to pre-existing conditions. Reliance on self-reported symptoms introduces potential interpretation variations and possible over- or underestimation, which are partially mitigated by structured questionnaires and trained interviewer protocols. Additionally, symptoms were not routinely confirmed by objective clinical, laboratory, or functional assessments, which may have led to symptom misclassification, particularly for subjective or fluctuating manifestations such as fatigue, dyspnea, or anosmia. The study population derives from specifi Thai healthcare settings, potentially limiting generalizability to other ethnic populations, healthcare systems, or regions with different baseline health profil s, variant circulation, or vaccination strategies. Thus, future investigations should replicate findings across diverse populations and contexts. These findings offer important insights for evidence-based clinical care and Long COVID management. The temporal evolution of risk factors suggests that early interventions should focus on preventing systemic inflammatory complications, while later phase management should address organ-specific sequelae and functional rehabilitation needs.

Early interventions should target systemic inflammat on, whereas later management should focus on rehabilitating end-organ damage. Evolving risk profile indicate that short-term morbidity at 3 months

is driven by inflammation influenced by obesity, vaccination status, and viral variant, while 6-month sequelae refle t acute organ injury and neurological involvement, including persistent anosmia. These findings suggest the need for time-sensitive, gender-specific anagement strategies, multidisciplinary rehabilitation, and long-term support, along with implications for clinical practice, public health planning, and resource allocation. Future research should validate these mechanisms through longitudinal biomarker studies.

CONCLUSION

This study shows that determinants of Long COVID in Thai females change over time. Acute myalgia and infection during the Omicron wave are early predictors at 3 months, whereas initial disease severity and loss of smell more strongly predict symptom persistence at 6 months. These findings eflec the evolving course of Long COVID and indicate the importance of time-specific isk stratification. ecognizing these shifting predictors may enhance early identification and enable more targeted follow-up of females at higher risk for prolonged symptoms.

Conflict of Interest

All authors declare no conflicts of interest

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REVIEW ARTICLE

Mpox in Neonates and Children: A Review Article

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ABSTRACT

Mpox, caused by the monkeypox virus, has expanded beyond its historical African boundaries, with significant global outbreaks, including a 2022 surge. While traditionally affecting adults, recent cases in neonates and children show more severe complications, including respiratory failure, encephalitis, and sepsis. Children are more vulnerable due to an immature immune system and at higher risk for multi-organ involvement. Prevention focuses on vaccination, personal hygiene, and safe sexual practices, with JYNNEOS® and ACAM2000® vaccines recommended for high-risk groups. Early diagnosis, supportive care, and antiviral treatment are crucial in managing severe cases. This review highlights differences in disease severity between adults and children and outlines key prevention and treatment strategies.

Keywords: children, monkeypox, Mpox, neonate, transmission

INTRODUCTION

Mpox, formerly known as monkeypox, is caused by the monkeypox virus (MPXV), an enveloped double-stranded deoxyribonucleic acid (DNA) virus belonging to the Orthopoxvirus genus in the Poxviridae family. First identified in 1958, Mpox's initial human case was reported in a 9-month-old boy in the Democratic Republic of the Congo.[1] Historically, Mpox outbreaks were sporadic and largely confined to Central and West Africa until the 21st century. In these settings, infections were reported predominantly among children, accounting for up to 90% of cases, with case fatality rates of approximately 11%, particularly among unvaccinated group.[2] However, the virus has demonstrated its ability to cause significant outbreaks outside Africa, such as the 2003 U.S. outbreak and the global outbreak in 2022.[3] The virus comprises two distinct clades: Clade I (with subclades Ia and Ib) and Clade II (with subclades IIa and IIb), which differ in various aspects, as summarized in Table 1.[4-7]

In 2022, a global outbreak of Clade IIb began and persists, including in several African countries. Concurrently, there have been increasing outbreaks of Clades Ia and Ib, particularly impacting the Democratic Republic of the Congo and other African nations.[8] By August 2024, Clade Ib had also been detected outside Africa. World Health Organization (WHO) Director-General Dr. Tedros Adhanom Ghebreyesus has declared Mpox a Public Health Emergency of International Concern (PHEIC) on two occasions: first in May 2022 and again in August 2024.[3] Among the 2022-2024 cases, the majority (61.8%, 691) were reported in the WHO Region of the Americas, followed by the African Region (30.3%, 339), the European Region (7.5%, 84), the Eastern Mediterranean Region (< 1%, 3), and the Western Pacific Region (< 1%, 1).[9]

Table 1 Comparison of Clade I and Clade II of Mpox[4-7]

	Clade I	Clade II
Distribution	Central Africa, especially in the Congo Basin region	West Africa, with notable outbreaks in Nigeria, Sierra Leone, and Liberia and Global spread in 2022
Virulence	More severe disease, estimated 10% mortality	Milder disease, estimated 3% mortality
Transmission	More efficient human-to-human transmission and larger outbreak potential	Less efficient transmission, especially in close contact group

Between January 2022 and August 2024, more than 120 countries reported cases of Clade II Mpox, with over 100,000 laboratory-confirmed infections and more than 220 associated deaths. Clade II Mpox continues to primarily spread through sexual and intimate contact, with men who have sex with men at the highest risk. Cases in children remain rare, accounting for just 0.3% of cases in the United States.

In 2024, the WHO declared a PHEIC due to the spread of Clade Ib in Africa. In some African regions, Mpox transmission among children has been notably high, with 30% of cases in the Democratic Republic of Congo—rising to over 50% in children under 5 years in certain areas—and 47% of cases in Burundi. More than 50% of Mpox-related deaths have occurred in children under 15 years old, underscoring the need for focused pediatric epidemiological attention.[10] The increased transmission in children may be due to household contact, a weaker immune response, and a lack of prior smallpox vaccination. Additionally, Clade I may be more severe, contributing to the higher fatality rate in the pediatric population.

Nowadays, the number of Mpox cases in neonates and children is increasing. The differences in symptoms, severity, and transmission methods compared to adults are interesting topics, which we review to improve knowledge and develop the best prevention strategies.

CONTENT OF REVIEW

WHO Case Definition for Mpox Outbreak[11]

1. Suspected case: an individual with clinical features compatible with Mpox, including

1.1 Fever or systemic symptoms (e.g., fever > 38.5°C, headache, myalgia, back pain, or marked fatigue) occurring within 21 days of contact with a probable or confirmed case, or

1.2 An unexplained acute rash, mucosal lesions, or lymphadenopathy since January 2022. Lesions may be single or multiple and involve the ano-genital region, oral cavity, conjunctiva, or other body sites, and may present with proctitis, pain, or bleeding.

2. Probable case: an individual with an unexplained acute rash, mucosal lesions, or lymphadenopathy and at least one of the following:

2.1 An epidemiologic link to a probable or confirmed Mpox case within 21 days before symptom onset.

2.2 High-risk exposure, including multiple or casual sexual partners within 21 days prior to symptom onset.

2.3 Gay, bisexual or other cis or trans man who has sex with men.

2.4 Serologic evidence of orthopoxvirus infection (antibody against orthopoxvirus immunoglobulin M during 4-56 days after rash onset or a fourfold rising in immunoglobulin G) in the absence of recent orthopoxvirus vaccination.

2.5 A positive orthopoxvirus test without MPXV-specific confirmation.

3. Confirmed case: an individual with laboratory-confirmed Mpox, demonstrated by detection of MPXV-specific DNA using real-time polymerase chain reaction (PCR) and/or genomic sequencing.

Transmission[12-14]

Incubation period is between 3-21 days, sometimes noted as 6-13 days. Mpox can be transmitted from 4 days before symptoms appear until all lesions are fully healed (infectious period). There are four main methods of transmission:

1. Close contact: Mpox is transmitted primarily

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through direct contact with an infected person's skin lesions, scabs, or bodily fluids. Infection can also occur via contact with contaminated objects, such as clothing, bedding, or towels used by an infected individual. Sexual contact and intimate activities, including kissing, are recognized routes of transmission. In addition, close contact with lesions may result in transmission during specific situations, such as vaginal delivery. Regarding breastfeeding, data on transmission through breast milk remain limited. Nevertheless, breastfeeding should be temporarily deferred if the mother has active Mpox infection or lesions involving the breast, to reduce the risk of transmission to the infant.

2. Droplet transmission: The virus can spread through respiratory droplets from coughing or sneezing.

3. Maternal-to-child transmission (in utero): Mpox can be transmitted from a mother to the fetus, with reported outcomes including miscarriage of fetal death, congenital anomalies, and chorioamnionitis.

4. Animal-to-human transmission of Mpox is rare in children and neonates. When it does occur, infection may result from scratches or bites from infected animals, consumption of undercooked meat from infected animals, or direct exposure during activities such as hunting or trapping infected animals.

Diagnosis

Diagnosis is based on compatible clinical manifestations with laboratory confirmation.

Clinical Manifestations in Children[15-17]

In children, Mpox commonly presents with skin rash, which is reported in nearly all cases (100%). The rash typically follows a chronological progression, beginning as maculopapular lesions and evolving into vesicles, pustules, lesions with umbilication, and eventually scab formation. In children younger than 12 years, the rash is most frequently distributed on the face and trunk, whereas in adolescents it is more commonly localized to the anogenital region. In some cases, lesions on the tongue or within the oral cavity may be the earliest clinical manifestation. Systemic symptoms are also common. Fever occurs in approximately 73% of pediatric patients, and lymphadenopathy or adenitis is observed in about 47%. Other clinical features include pharyngotonsillitis (17%) and conjunctivitis (10%). Less frequent manifestations, reported in fewer than 10% of cases, include myalgia, headache, hepatosplenomegaly, nausea and vomiting, facial edema, cough, and abdominal pain.

Clinical Manifestations in Neonates[16-19]

There are similar to older children, including fever and axillary lymphadenitis; however, the rash pattern differs. Neonatal disease typically presents with vesicular eruption beginning on the palms and soles, followed by spread to the face and trunk, with subsequent progression to pustular lesions. Additional reported features include irritability and respiratory failure, and affected neonates frequently have a history of maternal or parental rash occurring within 3 weeks prior to delivery.

Furthermore, 3 cases of congenital Mpox have been reported, all confirmed by MPXV PCR from placental, oropharyngeal, and/or skin swabs. In all cases, maternal Mpox infection was documented one to four weeks before delivery. Two cases resulted in fetal death: one at 8 weeks' gestation due to spontaneous abortion, and another at 18 weeks' gestation with intrauterine fetal death, accompanied by macular lesions with small vesicles on the face, chest, abdomen, and upper limbs. The third case survived after birth and presented with 17 ulcerative lesions distributed over the face, upper and lower limbs, abdomen, and dorsum, while other findings were unremarkable; the skin lesions resolved within 7 days.[19]

Laboratory Investigation for Diagnosis[1,14,20]

Mpox is confirmed by detecting the virus using PCR from a vigorous swab of a rash, crust, or fluid. If no lesions are present, swab the throat or anus. It is recommended to swab more than one lesion for accurate results. Blood tests for Mpox antigen and antibody are not recommended.

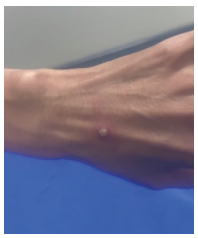
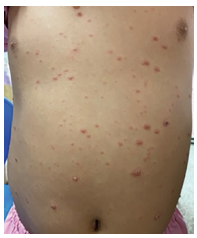
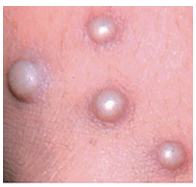
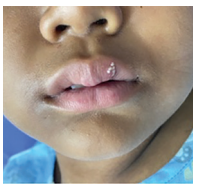
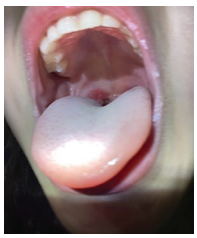
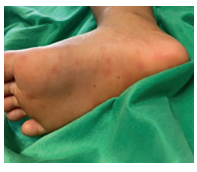
Differential Diagnosis[21-22]

Mpox in children should be differentiated with other infectious diseases such as chicken pox, smallpox, herpes simplex virus (HSV) infection, hand-foot-mouth disease (HFMD) as shown in the **Table 2**.

Complication in Children and Neonates[15,21,23-26]

In neonates and children, the complications tend to be more severe, encompassing extensive skin infections, respiratory distress, neurological problems such as encephalitis, dehydration, malnutrition, septicemia,

Table 2 Differential Diagnosis of Mpox

	Mpox	Chicken Pox	Smallpox*	HSV	HFMD
Common age	Adolescents and adults	2-10 years old	Children and young adults	HSV-1: toddlers and school-aged HSV-2: adolescents and young adults	1-5 years old
Clinical manifestations	Fever Malaise precede rash	Fever Fatigue	High fever Toxemia precede rash	Fever Stomatitis	Fever Sore throat Malaise
Lymphadenopathy	Common	Rare	None	Possible	None
Incubation	5-21 days	10-21 days	7-19 days	2-12 days	3-6 days
Rash	Deep, umbilicated pustules Synchronous in area	Superficial, pruritic vesicles Multiple stages	Deep, firm pustules Synchronous in area	Painful vesicles	Vesicles, flat spots Same stage
Distribution	Palms, soles, face, body	Trunk → face, limbs	Face → extremities → trunk	Localized	Palms, soles, mouth
Example					  

Abbreviations: HFMD, hand-foot-mouth disease; HSV, herpes simplex virus

* Smallpox was declared eradicated in 1980

ophthalmologic issues, multi-organ involvement, and deaths as summarized in **Figure 1**.

Treatment[21-24,27-32]

The treatment for Mpox includes both supportive and specific care **(Table 3)**.

1. Supportive care include hydration, nutrition, avoidance of eye contact with lesions, and wound care, with gentle cleaning and protective dressings. Patients with ocular involvement should be consulted ophthalmologist. Pain management is addressed with acetaminophen (paracetamol), non-steroidal anti-inflammatory drugs, and for severe pain, opioids or gabapentin. Indications for hospital admission in

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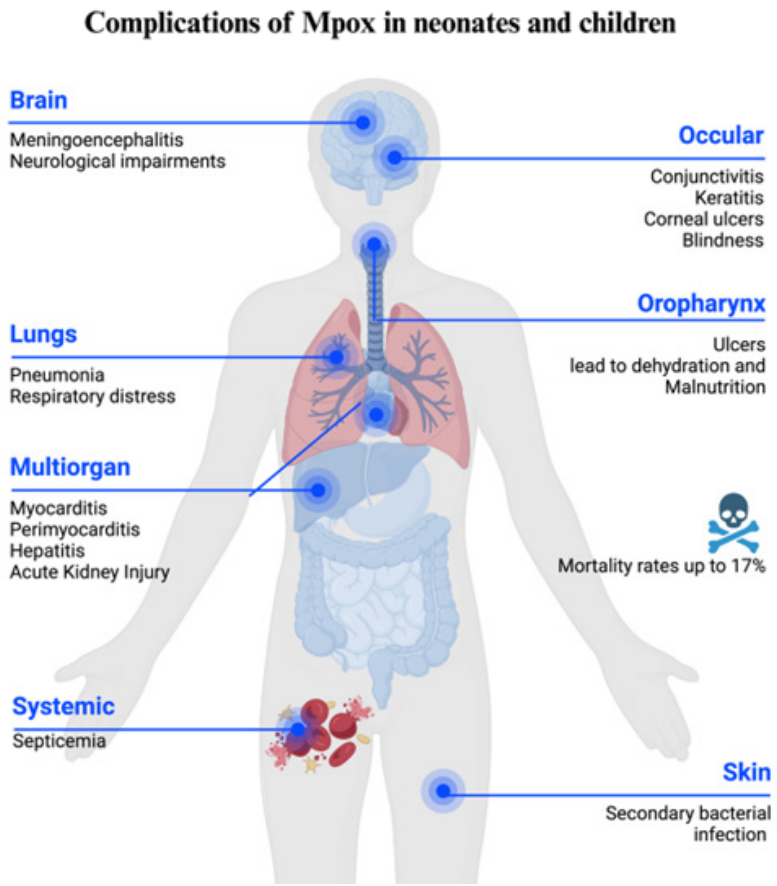

Figure 1 Complication of Mpox in Neonate and Children

Table 3 Treatment of Mpox in Adults, Children, and Neonates

Treatment	Details
Supportive care	1. Ensure proper hydration and nutrition 2. Cleansing wounds with gentle soap and water or an antimicrobial soak 3. Creating a moist wound healing environment 4. Applying a protective coating, such as white petrolatum, zinc oxide paste, or a silicone film
Pain control	1. NSAIDs for mild to moderate pain 2. Opioids and gabapentin for severe pain 3. Topical steroids and anesthetics
Antiviral for 1. Severe disease: ocular, neurological, myocarditis, multi organ involvement, sepsis, and disseminated rash 2. High risk group: infants, immunocompromised hosts, pregnant, breastfeeding, skin integrity	1. Tecovirimat: The drug of choice for severe Mpox or in high-risk groups (body weight 13-25 kg: 200 mg every 12 hours, 25-40 kg: 400 mg every 12 hours, 40-120 kg: 600 mg every 12 hours) for 14 days 2. Brincidofovir / Cidofovir: consider in cases of significant disease progression while on tecovirimat. Use if there are contraindications to tecovirimat. 3. Maybe used in combination with tecovirimat for severely immunocompromised hosts.
Vaccinia immune globulin intravenous	1. Considered in severe cases

Abbreviations: kg, kilogram; mg, milligram; NSAIDs, non-steroidal anti-inflammatory drugs

children and neonates with Mpox are not clearly defined and largely depend on the clinical judgment of the pediatrician. Admission is generally recommended for patients with severe clinical manifestations.

2. Specific antiviral treatment is recommended for severe cases including hemorrhagic disease, confluent lesions, secondary bacterial infections, sepsis, encephalitis, lesions on the penile or strictures involving the urethral meatus, severe involvement of other anatomic sites, such as anorectal disease impairing bowel movements or significant dysphagia, conditions requiring hospitalization and antiviral drugs indicated for high-risk groups, including infants, immunocompromised hosts, and pregnant or breast-feeding women.

2.1 Tecovirimat is the preferred antiviral agent, it acts by inhibiting the viral p37 protein, thereby interfering with viral maturation and preventing release of virions from infected cells. Clinical data suggest that tecovirimat is associated with reduced mortality and fewer severe outcomes, particularly when initiated early in the course of illness, although the time to lesion resolution has not been shown to differ significantly from placebo. Oral tecovirimat is approved for patients weighing ≥ 13 kg and should be administered with moderate- to high-fat meals, while the intravenous formulation is approved for patients weighing ≥ 3 kg. Tecovirimat is not recommended during pregnancy or breastfeeding. Common adverse effects include headache, dizziness, and gastrointestinal symptoms.[32]

2.2 Brincidofovir and cidofovir may be considered as alternative options when tecovirimat is contraindicated or ineffective; however, evidence supporting their effectiveness remains limited.

2.3 Vaccinia Immune Globulin Intravenous (VIGIV) may be used for severe cases, although data on its effectiveness is limited.

Infection Control[23-24, 32-33]

Infection control measures for Mpox include standard, droplet, and contact precautions, with airborne precautions required during aerosol-generating procedures, which the patient should be placed in a negative-pressure ventilation room. Isolation duration for Mpox patients depends on their case status. For suspected cases, isolation is required until Mpox is excluded as a differential diagnosis. For confirmed cases, isolation should continue until all lesions have crusted and no new lesions appear. Confirmed or suspected cases should be reported to the local Public Health Department. Patients diagnosed with Mpox who do not require hospital admission should follow home isolation measures. These include staying in a separate room, using a separate bathroom if available, avoiding the sharing of dishes or towels, and minimizing close physical contact with others. Shared surfaces and common areas should be cleaned and disinfected after use by the patient. When close contact is unavoidable, the patient should wear a surgical mask. These measures reflect the core principles of contact and droplet precautions.

For individuals who have had contact with Mpox patients, asymptomatic contacts do not need isolation. Healthcare personnel may continue working but should monitor for symptoms of Mpox daily for 21 days after the last exposure. Symptomatic contacts should undergo empirical isolation precautions until test results confirm or exclude Mpox. If no rash is present, isolation should continue for at least 5 days, and isolation can be discontinued if no new symptoms or lesions develop.[32-33]

Post-exposure prophylaxis (PEP) with the Mpox vaccine should be administered as soon as possible, ideally within 4 days of exposure. Vaccination within 4–14 days after exposure may still offer protection, and after 14 days, vaccination may be considered on a case-by-case basis. Monitoring and PEP recommendations depend on the risk level of exposure.[33] **(Table 4)**

For neonates born to individuals with suspected, probable, or confirmed Mpox, they should be bathed promptly with soap and water after birth. PEP is recommended for newborns exposed to Mpox, and they should be closely monitored for symptoms for 21 days after birth or their last exposure. Routine care can be provided by caregivers or family members who are not infected with Mpox.[23]

Prevention[1,34-36]

1. Vaccination

Vaccination is prioritised for individuals with occupational exposure (such as laboratory personnel and healthcare workers), travellers spending time in areas of sustained high Mpox transmission and those with sexual practices that predispose to higher rates of transmission:

1. People with multiple sexual partners in areas of ongoing Mpox transmission.

2. Gay, bisexual, and other men who have sex

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Table 4 Monitoring and PEP Recommendations Based on Risk Level[33]

	Definition	Monitoring	PEP
High risk	Unprotected contact with lesions or fluids of a Mpox patient involving broken skin or mucous membranes.	Yes	Yes
Intermediate risk	Unprotected contact with lesions or fluids of a Mpox patient involving intact skin or clothing. Or Not wear PPE while inside a Mpox patient's room. Or Examining the oral or laryngeal cavity of a Mpox patient without appropriate PPE.	Yes	+/-
Low risk	Unprotected contact with a fully covered Mpox patient with no contact with skin, fluids, or contaminated equipment.	+/-	No
No risk	No contact with a Mpox patient, and only transient time spent in their vicinity.	No	No

Abbreviations: PEP, post-exposure prophylaxis; PPE, personal protective equipment

with men.

3. Transgender or nonbinary individuals who, in the past 6 months, have had:

3.1 A new diagnosis of ≥ 1 sexually transmitted infection.

3.2 More than one sexual partner.

3.3 Sex at a commercial sex venue.

3.4 Sex associated with a large public event in a geographic area where Mpox transmission is occurring.

There are two licensed vaccines for the prevention of Mpox infection:

a) JYNNEOS® is a live, attenuated orthopoxvirus vaccine that is non-replicating in humans.

JYNNEOS® is licensed for the prevention of both smallpox and Mpox and is recommended by the Advisory Committee on Immunization Practices (ACIP). Because of its favorable safety profile, it is considered the preferred vaccine for Mpox prevention. The vaccine is administered as a two-dose series, with doses given 28 days (4 weeks) apart. Subcutaneous administration is preferred, while intradermal injection is approved only for individuals 18 years of age and older.

JYNNEOS® is authorized for PEP in children following potential exposure. However, in infants younger than 6 months, VIGIV should be considered as an alternative to vaccination. The vaccine may also be considered for pregnant or breastfeeding individuals, with decisions guided by shared clinical decision-making that carefully balances potential risks and benefits.

In terms of effectiveness, vaccine efficacy is estimated to be approximately 75% after a single dose and 86% after completion of the two-dose series. The most commonly reported adverse events are local injection-site reactions, including pain, erythema, swelling, and induration. Serious adverse events are rare, occurring in about 1% of vaccine recipients.

b) ACAM2000® vaccine is a live, attenuated vaccine capable of replication in the human host.

ACAM2000® is licensed for the prevention of smallpox and is recommended by the ACIP for individuals at risk of exposure to orthopoxvirus infections. It is considered an alternative to JYNNEOS®; however, its use is limited by a higher risk of adverse events and it is not recommended for infants.

Vaccine effectiveness has been reported to be approximately 95%. Common adverse events include local reactions at the inoculation site, lymphadenitis, and systemic (constitutional) symptoms. More serious adverse events have also been reported, including myocarditis and pericarditis (approximately 5.7 per 1,000 persons), encephalitis, encephalopathy, and ocular vaccinia. Because of these safety concerns, ACAM2000® is not recommended for use in pregnant or lactating individuals, or in children, particularly those younger than 12 months of age.

2. Personal Hygiene

Prevention of Mpox relies on avoiding direct contact with the skin, lesions, or bodily fluids of infected individuals. It is also important to refrain from sharing personal items, such as towels, bedding, or clothing, that may be contaminated. In addition, good hand hygiene should be practiced consistently, including frequent handwashing with soap and water or the use of alcohol-based hand sanitizers.

3. Safe Sexual Practices

Sexual transmission of Mpox can be reduced by using barrier protection methods, such as condoms, and by avoiding sexual contact with individuals who have symptoms suggestive of Mpox, particularly those with active rashes or lesions.

4. Community Awareness and Education

Public health measures should focus on educating the public about Mpox transmission, clinical manifestations, and prevention strategies. In addition, early medical consultation should be encouraged for individuals who develop symptoms, particularly when there is a history of potential exposure, to facilitate timely diagnosis and management.

Prevention of Mpox in children and neonates extends beyond infection control measures, and awareness of preventive strategies is essential. The general principles of prevention do not differ substantially between children and adult populations. However, particular emphasis should be placed on vaccination for high-risk groups. In children, Mpox vaccination is generally recommended only as PEP. Hand hygiene and general hygiene should be strongly encouraged. Age-appropriate education regarding safe behaviors, including sexual health in adolescents, is also important as part of broader preventive strategies. In newborns born to mothers with Mpox infection, additional precautions are recommended. These include early bathing after birth to reduce potential viral exposure and temporary avoidance of breastfeeding, particularly if the mother has active disease or lesions involving the breast.

CONCLUSION

Mpox poses a significant risk to neonates and children, with more severe outcomes compared to adults. Early diagnosis, appropriate isolation and treatment and ongoing community education are crucial. Preventive measures like vaccination and safe sexual practices are essential to controlling transmission, especially in high-risk groups. Future directions should focus on improving surveillance, understanding the long-term effects of the disease, enhancing treatment options, and refining vaccination strategies to ensure effective prevention. Ongoing research and targeted interventions will be key to reducing the global impact of Mpox.

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Conflict of Interest

All authors declare no conflict of interest.

Author Contributions

Conceptualization: T.K., M.G.
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Formal analysis: -
Funding acquisition: -
Investigation: -
Methodology: -
Project administration: T.K.
Resources: -
Software: -
Supervision: M.G.
Validation: -
Visualization: T.K.
Writing – original draft preparation: T.K.
Writing – review & editing: T.K., M.G.

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