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Original Article

Effect of Positive Psychological Capital and Self-Management Model Interventions on Pain and Functional Difficulty in Persons With Osteoarthritis

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Abstract

Background: Osteoarthritis is a prevalent global health challenge, particularly among the elderly, and leads to significant physical disability, emotional distress, and socioeconomic burden. Effective interventions addressing these multifaceted effects are limited, especially in patients with severe knee osteoarthritis awaiting a surgical intervention. This study was guided by 2 theoretical frameworks: the positive psychological capital (PsyCap) theory, which focuses on enhancing psychological resilience, motivation, and coping strategies; and the self-management model, which emphasizes goal setting, symptom tracking, and adherence to self-care behaviors.

Objectives: To evaluate the effectiveness of a novel intervention integrating PsyCap theory and self-management model strategies to enhance self-care behavior, alleviate pain, and reduce mobility difficulties among patients with severe knee osteoarthritis (Kellgren-Lawrence grades 3-4).

Methods: A quasi-experimental pretest-posttest design was used between May and July 2023 at the outpatient surgery department of a university hospital. A total of 34 patients with primary knee osteoarthritis were randomly assigned into experimental (n = 17) and control (n = 17) groups. The experimental group received a self-care behavior enhancement program integrating PsyCap and self-management principles. Outcomes were assessed at 3 time points: baseline, postintervention (4 weeks), and follow-up (12 weeks). Statistical analyses included descriptive statistics and 2-way repeated measures analysis of variance (ANOVA) to examine within- and between-group effects over time.

Results: Compared to the control group, the experimental group demonstrated significant improvements in self-care behaviors ($F[1,32] = 24.982$; $P < .001$; $\eta^2 = 0.438$), with significant time-group interaction effects ($F[1.374,43.960] = 38.581$; $P < .001$; $\eta^2 = 0.547$). Additionally, pain and mobility difficulties significantly decreased in the experimental group ($F[1.640,52.473] = 42.261$; $P < .001$; $\eta^2 = 0.569$), whereas no significant changes were observed in the control group.

Conclusions: Integrating PsyCap theory and the self-management model significantly improved self-care behavior and reduced pain and mobility difficulty in patients with severe knee osteoarthritis awaiting surgery. These benefits were sustained over 12 weeks.

Keywords: Positive psychological capital, Self-management model, Osteoarthritis, Joint pain, Mobility limitations, Self-care behavior

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Introduction

Osteoarthritis, particularly knee osteoarthritis, is a major global health concern with growing implications for quality of life and health systems. According to the World Health Organization (WHO), musculoskeletal disorders (MSDs), including osteoarthritis, affect more than 1.71 billion people globally as of 2021, and continue to be a leading cause of disability-adjusted life years (DALYs) worldwide, especially among older adults.[1-2] The burden of osteoarthritis is expected to increase significantly owing to increased life expectancy and population aging. The WHO has reported that noncommunicable diseases (NCDs) account for nearly three-quarters of all deaths globally, and their absolute numbers are projected to increase dramatically, with musculoskeletal conditions playing a key role.[2] This trend underscores the urgent need for integrated interventions that address not only symptom management but also long-term functional health and quality of life for individuals living with osteoarthritis.[1]

The knee is the most frequently involved joint, contributing to substantial disability and making knee osteoarthritis a major public health concern. Its increasing prevalence is associated with aging populations, increasing obesity rates, and a higher incidence of joint injuries.[3-4] In Thailand, knee osteoarthritis predominantly affects the elderly, presenting a substantial burden on their physical, emotional, and social well-being. Patients often experience chronic pain, reduced mobility, and diminished quality of life.[5] Effective osteoarthritis management aims to slow disease progression, prevent complications, and maintain functional independence through a combination of pharmacological and nonpharmacological interventions.[6] Interdisciplinary approaches that integrate both treatment modalities have been emphasized to address the physical and psychological dimensions of the disease.[7] Without timely and appropriate interventions, osteoarthritis can lead to severe mobility impairments, exacerbating psychological challenges, such as anxiety, depression, and dependency.[8-9]

Pain management remains a cornerstone of osteoarthritis treatment, utilizing both pharmacological options, including nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, and emerging innovations such as nanotechnology-based drug delivery and gene therapy. Nonpharmacological interventions, such as structured exercise programs and weight management, are equally crucial, with evidence supporting their effectiveness in reducing pain and improving joint function. Personalized nursing care and therapeutic strategies further enhance patient outcomes by optimizing symptom control and promoting self-management behaviors.[6, 10, 11]

Despite substantial evidence supporting psychological and self-management model, their integration into single-structured programs remains limited. Previous interventions have often addressed psychological strategies or self-management approaches in isolation, failing to account for their combined impact on long-term behavioral adherence and clinical outcomes.[12, 13] Additionally, existing studies frequently suffer from methodological constraints, such as the lack of comprehensive behavioral frameworks, thereby limiting their applicability.

This study was guided by 2 theoretical frameworks: PsyCap theory and the self-management model. PsyCap comprises psychological assets hope, resilience, optimism, and self-efficacy that enhance patients' ability to manage chronic conditions through motivation and persistence.[14] In contrast, the self-management model emphasizes patient-driven behaviors such as goal setting, symptom tracking, and treatment adherence, empowering individuals to take an active role in their care and sustain long-term health behaviors.[15] Integrating these frameworks provides a holistic approach by addressing both psychological resilience and behavioral engagement, which is particularly relevant for patients with knee osteoarthritis awaiting surgery who experience prolonged pain and functional decline.[16]

Building on prior research demonstrating that interventions grounded in the self-management model alleviate osteoarthritis symptoms and PsyCap strengthens adherence to self-care behaviors, this study sought to bridge these strategies into a unified intervention. Systematic reviews have emphasized the necessity of such an integrated approach; however, few studies have implemented this within a structured program for patients with knee osteoarthritis. A rigorous validation process was conducted by orthopedic specialists, behavioral psychologists, and rehabilitation experts reviewing the program's content to ensure scientific rigor and clinical applicability.[17]

This study aimed to evaluate the effectiveness of integrating PsyCap theory and a self-management model to improve self-care behaviors in patients with knee osteoarthritis. Specifically, it examines whether the intervention enhances self-care behaviors, reduces pain and mobility difficulties, and sustains its effects over time. It is hypothesized that the intervention group will demonstrate significantly improved self-care behaviors and reductions in pain and mobility difficulties compared to the control group, with sustained benefits observed at follow-up. By addressing these considerations, this study contributes to the advancement of knee osteoarthritis management through an integrative approach that bridges the psychological and self-management models, ultimately improving patients' quality of life, particularly for those awaiting surgical treatment.

Methods

Study Design

This quasi-experimental study employed a 2-group design, comprising an experimental group and a control group. Data were collected at 3 time points: baseline (prior to the intervention), postintervention (4 weeks), and follow-up (12 weeks). To minimize contamination, data collection for the control group was completed before enrolling the experimental group.

Data Collection

Data collection occurred between May and July 2023 in 3 phases: baseline assessment, intervention implementation, and evaluation. In the baseline phase, demographic and physical data, including body mass index (BMI), weight, height, and osteoarthritis severity, were recorded. The intervention phase involved delivering a structured PsyCap and self-management program to the experimental group, while the control group received standard care. This phase included three structured sessions conducted in weeks 1, 2, and 4, delivered both in-person and online. During the self-management model period, participants documented their daily activities, weight, and self-reported pain, stiffness, and joint function based on their set goals. In the evaluation phase, osteoarthritis severity was reassessed at the end of the intervention (week 4) and at follow-up (week 12). To minimize contamination, the control group completed all assessments before the experimental group began the intervention. Research assistants blinded to group allocation conducted all assessments using standardized procedures to ensure consistency and reliability.

Sample Selection and Randomization

Participants were selected based on inclusion and exclusion criteria. Eligible particpants were at least 50 years, provided informed consent, had no history of total knee replacement surgery, and had not received corticosteroid knee injections or experienced severe knee pain in the last 3 months. They were required to have an activities of daily living (ADLs) score of 12 or higher. For participants aged 60 years and older, cognitive function was assessed using the mini-cognitive assessment instrument (Mini-Cog), with a score of at least 3 required for inclusion. All participants were also required to obtain medical clearance from a physician prior to enrollment.

Exclusion criteria included severe, uncontrolled medical conditions such as acute heart failure or stroke, an inability to participate throughout the study, severe comorbidities like knee infections or neurological disorders impairing daily function, use of medications affecting balance, or corticosteroid knee injections during data collection.

Participants were randomly assigned to either the experimental group (n = 17) or the control group (n = 17) using simple random sampling. A power analysis using G*Power software version 3.0.1 determined the required sample size based on an estimated effect size (Cohen $f = 0.25$) from Bunsanong et al.[18] The statistical test applied was analysis of variance (ANOVA): repeated measures, within-between interaction, with a power of 0.80, an α level of 0.05, and a confidence level of 95%. The analysis recommended a total of 28 participants. Allowing for a 16% attrition rate,[19] the final sample size was 34 participants, with 17 per group.

Measures

The instruments used in this study consist of 3 components. The first component included screening tools: the Kellgren-Lawrence (KL) grading system for classifying knee osteoarthritis severity, the Barthel ADL Index for assessing daily activity performance, and the Mini-Cog for cognitive function evaluation (administered to participants aged 60 years and older).

The second component comprised instruments for data collection, including a general information questionnaire covering demographic and health-related data, such as age, weight, height, marital status, occupation, education level, comorbidities, frequency of exercise, medication and supplement use, and engagement in alternative treatments. A self-care behavior questionnaire was developed based on relevant literature to assess self-care behaviors in 3 domains: exercise (5 items), weight management (6 items), and joint care practices (8 items), with responses recorded on a Likert scale. Higher scores indicate better adherence to self-care practices. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was used to assess symptom severity. The instrument consists of 24 items divided into 3 subscales: pain (5 items), joint stiffness (2 items), and physical function (17 items). In this study, pain was assessed using the WOMAC pain subscale and mobility difficulty was assessed using the WOMAC physical function subscale. Each item was scored on a 5-point Likert scale (0 = none to 4 = extreme), with higher scores indicating greater severity. The subscale scores were summed to represent each outcome. The Thai version of the WOMAC used in this study has been validated previously, with a Cronbach α exceeding 0.80, indicating high internal consistency.

The third component included the PsyCap and self-management program, which underwent expert validation to ensure alignment with the theoretical constructs and practical relevance. Five experts an orthopedic specialist, a physical activity expert, a nurse specializing in osteoarthritis management, a health behavior modification expert, and a musculoskeletal nursing educator assessed its content. The item-level content validity index (I-CVI) and scale-level validity index (S-CVI) were both 1.00.[20-21] Pilot testing confirmed clarity and feasibility, and reliability was supported with a Cohen coefficient of 1.00.[22]

Intervention

The intervention was based on a self-management model and PsyCap theory. Self-management model-guided strategies such as goal setting, osteoarthritis education, decision-making exercises, and behavioral adjustment, and PsyCap theory were embedded to promote a positive mindset toward self-care and symptom control.

The program consisted of 3 structured in-person sessions over 4 weeks in a hospital setting. Session 1 focused on osteoarthritis self-care, goal setting, and joint mobility strategies. Session 2 addressed cognitive restructuring, low-impact exercises, and self-care planning. Session 3 emphasized problem solving, adherence strategies, and peer support.

Online follow-ups were conducted to reinforce adherence and self-monitoring. Participants received weekly virtual check-ins via video or phone calls along with motivational messages through a mobile platform. They also maintained a self-care journal that was reviewed by the research team for feedback and engagement tracking.

In contrast, the control group received standard care, comprising routine nursing consultations, osteoarthritis educational brochures, and verbal guidance on pain and mobility management. They were encouraged to continue regular physical activity and joint mobility exercises according to the general osteoarthritis guidelines.

Statistical Analysis

All statistical analyses were performed using SPSS version 29.0 (IBM SPSS Statistics for Windows, Version 29.0. Armonk, NY: IBM Corp; 2021). Descriptive statistics, including mean (SD), were used to summarize participant characteristics and baseline measurements. Independent *t* tests and chi-square tests were conducted to compare baseline characteristics between the experimental and control groups.

To assess within-group and between-group differences over time for the primary outcomes (self-care behavior, pain, and mobility difficulties), 2-way repeated measures ANOVA was used. Post hoc analyses with Bonferroni correction were conducted to further explore significant interaction effects. All statistical tests were performed at a 95% CI and a P value < .05 was considered statistically significant.

Results

General Characteristics of Participants and Baseline Statistics

The study included 17 participants in the experimental group and 17 in the control group, all of whom were patients with primary knee osteoarthritis receiving treatment at Vajira Hospital. All participants had radiographically confirmed knee osteoarthritis classified as KL grade 3 or 4 and had been on the surgical waiting list for at least 1 year. The majority of participants in both groups were female (94.12%), aged 61-70 years, and had attained a primary level of education. Most were homemakers (76.47%) and had a disease severity classified as KL grade 4.

The chi-square test showed no statistically significant differences in demographics and clinical characteristics between groups, confirming comparability at baseline. The mean (SD) age in the experimental and control groups was 66.06 (4.56) and 66.53 (6.81) years, respectively. The mean (SD) BMI was 26.23 (5.35) kg/m^2 in the experimental group and 24.58 (5.44) kg/m^2 in the control group. Both groups had an identical mean knee osteoarthritis severity score (mean [SD], 3.71 [0.47]).

Effect of the Intervention on Self-Care Behavior

The repeated measures ANOVA results for self-care behavior were determined (Table 1 and Figure 1).

The interaction effect (time x group), a significant interaction effect was observed ($F = 38.581$; $P < .001$; $\eta^2 = 0.547$), indicating that changes in self-care behavior over time varied by group. The experimental group demonstrated a consistent increase in self-care behavior scores post-intervention and at follow-up, while the control group exhibited a decline in scores.

The between-groups effect, the experimental group consistently had significantly higher self-care behavior scores compared to the control group ($F = 24.982$; $P < .001$; $\eta^2 = 0.438$).

The within-groups effect (time), the effect of time alone was not statistically significant ($F = 0.269$; $P = .681$; $\eta^2 = 0.008$), suggesting that observed changes were not solely due to time but rather the impact of the intervention.

These findings indicate that the intervention effectively improved self-care behavior among patients in the experimental group, with significant gains sustained at follow-up.

Effect of the Intervention on Pain and Mobility Difficulty

The repeated measures ANOVA results for pain and mobility difficulty were determined (Table 2 and Figure 2).

Interaction effect (time x group), a significant interaction effect was found ($F = 42.261$; $P < .001$; $\eta^2 = .569$), showing that changes in pain and mobility difficulty varied by group. The experimental group had a substantial decrease in pain and mobility difficulty post-intervention and at follow-up, while the control group remained relatively unchanged.

Between-groups effect while the between-groups difference was not statistically significant at the conventional threshold ($F = 4.060$; $P = .052$; $\eta^2 = 0.113$), the effect size suggests a small to moderate impact of the intervention.

Within-groups effect (time), a significant time effect was observed ($F = 24.866$; $P < .001$; $\eta^2 = 0.437$), indicating that time contributed to changes in pain and mobility difficulty, particularly within the experimental group.

These findings suggest that the intervention effectively reduced pain and mobility difficulty, with sustained improvements in the experimental group at follow-up.

Summary of Findings

The intervention significantly improved self-care behavior, as evidenced by a substantial increase in scores in the experimental group over time. The intervention led to a meaningful reduction in pain and mobility difficulty, with sustained improvements at follow-up. The interaction effects (time x group) were highly significant, underscoring the intervention's impact. Between-group differences in pain and mobility difficulty approached significance, with an effect size suggesting clinical relevance table changes, reinforcing the effectiveness of the intervention.

These results highlight the effectiveness of the intervention in enhancing self-care behavior and reducing pain and mobility difficulty among patients with knee osteoarthritis. The improvements in the experimental group were not solely attributed to the passage of time but rather to the impact of the structured intervention program.

Table 1. Repeated Measures Analysis of Variance for Self-Care Behavior in Patients With Knee Osteoarthritis

Source of Variance	SS	*df*	MS	*F* Test	*P* Value	η^2
Between groups						
Group	3866.510	1.000	3866.510	24.982	< .001	0.438
Error	4952.745	32.000	154.773	NA	NA	NA
Within groups						
Time	8.647	1.374	6.294	0.269	.681	0.008
Time x group	1241.196	1.374	903.505	38.581	< .001	0.547
Error	1029.490	43.960	23.419	NA	NA	NA

Abbreviations: *df*, degrees of freedom; MS, mean square; NA, not applicable; η^2, effect size; SS, sum of squares.

Figures 1. Changes in Self-Care Behavior Scores Over Time

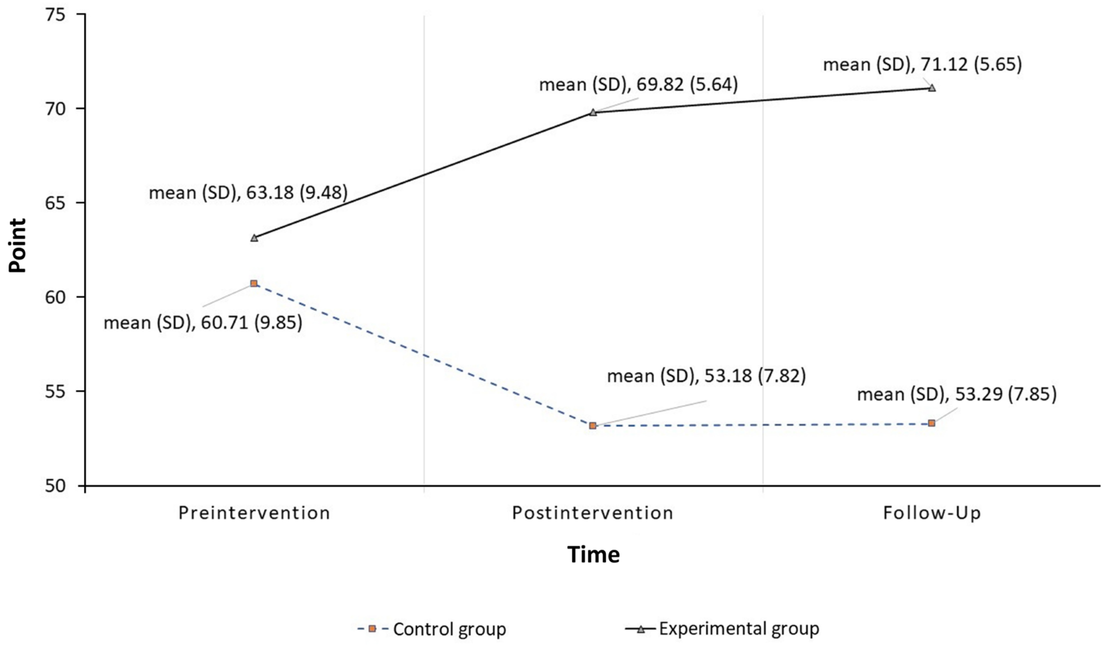
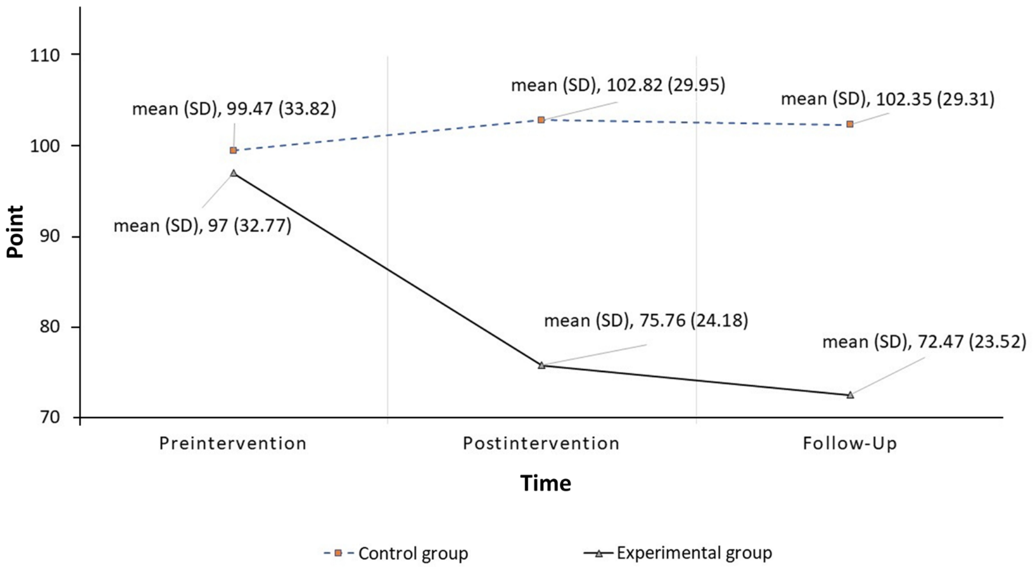


Table 2. Repeated Measures Analysis of Variance for Pain and Mobility Difficulty in Patients with Knee Osteoarthritis

Source of Variance	SS	*df*	MS	*F* Test	*P* Value	η²
Between groups						
Group	10000.980	1.000	10000.980	4.060	.052	0.113
Error	78829.650	32.000	2463.426	NA	NA	NA
Within groups						
Time	2273.882	1.640	1386.702	24.866	< .001	0.437
Time x group	3864.549	1.64	2356.753	42.261	< .001	0.569
Error	2926.235	52.473	55.767	NA	NA	NA

Abbreviations: *df*, degrees of freedom; MS, mean square; NA, not applicable; η², effect size; SS, sum of squares.

Figures 2. Pain and Mobility Difficulty Trends Across Assessment Periods



Discussion

This study evaluated the effects of an integrated intervention combining PsyCap theory and the self-management model on self-care behaviors, pain, and mobility in patients with knee osteoarthritis. The findings indicate that this dual-framework approach significantly enhanced self-care adherence and reduced both pain and mobility difficulties over time. In contrast, participants who received standard care did not show significant improvements, underscoring the added value of structured psychological and behavioral strategies in osteoarthritis management.

The improvements observed in the experimental group likely stemmed from the synergistic effects of the 2 theoretical components. PsyCap — comprising self-efficacy, resilience, optimism, and hope — has been shown to strengthen motivation and commitment to health-related behaviors.[14] Among these, self-efficacy is particularly influential in sustaining activity despite pain, while optimism and hope help patients cognitively reframe limitations and maintain focus on achievable health goals.[23] These findings are consistent with literature linking psychological resilience to greater pain tolerance and better functional outcomes in osteoarthritis populations.[24]

Complementing the psychological component, the self-management model provided participants with concrete tools for behavioral regulation. Strategies such as goal setting, symptom monitoring, and behavior adjustment empowered patients to take an active role in their care. These principles align with Creer's self-management framework, which emphasizes action planning and self-monitoring as essential for sustaining long-term behavior change.[15] Previous studies support these findings, showing that structured self-management interventions can lead to reduced pain severity and improved mobility in patients with osteoarthritis.[25] In particular, elements like joint protection and weight management directly mitigate biomechanical stressors that contribute to osteoarthritis symptoms.[26]

The lack of significant change in the control group highlights the limitations of passive care strategies. While standard consultations and educational brochures provide essential knowledge, they often lack the interactive and reinforcing components necessary to initiate and sustain behavioral change. Without structured guidance and motivational support, patients may find it difficult to adhere to recommended self-care routines.

This integrated intervention offers a comprehensive approach by addressing both psychological resilience and behavioral engagement. PsyCap strengthens the internal capacity for self-regulation, while self-management strategies offer a practical pathway for translating psychological strengths into action. When combined, these frameworks appear to generate more substantial and sustainable health benefits than when used independently.

Physiologically, the intervention likely contributed to symptom improvement through several mechanisms. Encouraging regular physical activity may have enhanced joint stability, muscle strength, and proprioception — all of which are critical in reducing osteoarthritis-related pain.[27, 28] Furthermore, research suggests that psychological resilience can lower inflammatory markers and reduce pain perception, reinforcing the mind–body link in chronic disease management.[17]

Despite these positive outcomes, certain limitations must be acknowledged. The relatively small sample size may limit the generalizability of findings, and conducting the study within a single clinical setting may reduce its applicability to other healthcare contexts. Future studies should include larger and more diverse populations to validate these results and explore subgroup-specific responses.

Additionally, the 12-week follow-up period may not be sufficient to determine the long-term sustainability of the intervention. Further research should investigate the durability of outcomes over longer periods and examine whether digital tools, ongoing peer support, or booster sessions enhance adherence. Exploring the individual contribution of each PsyCap component — such as optimism or self-efficacy — in facilitating specific self-care behaviors could also inform the refinement of future interventions.

From an implementation perspective, adapting this integrated intervention for broader clinical and community use holds promise. It may be incorporated into preoperative care for patients awaiting knee replacement surgery or delivered through digital platforms that combine interactive self-care modules with remote psychological coaching. Blending face-to-face delivery with telehealth approaches may improve both accessibility and scalability. These strategies align with health system goals to support multimodal, patient-centered care and empower individuals to actively manage chronic conditions.

Conclusions

This study underscores the efficacy of integrating positive PsyCap and self-management model strategies in the comprehensive management of knee osteoarthritis. By addressing both the psychological and behavioral dimensions of patient care, the intervention resulted in significant improvements in pain reduction, mobility enhancement, and sustained self-care behaviors. These findings highlight the synergistic interaction between psychological resilience (encompassing self-efficacy, hope, optimism, and resilience) and structured self-management model techniques including goal setting, behavioral monitoring, and patient education. The intervention was developed to empower patients with the necessary psychological and behavioral tools to engage in sustained self-management model practices. The incorporation of positive PsyCap principles fostered motivation, persistence, and adaptive coping mechanisms, whereas the self-management model framework provided structured guidance for symptom regulation and functional maintenance. This dual-faceted approach facilitates both behavioral adherence and psychological adaptation, contributing to long-term self-efficacy and improved disease management outcomes. The adoption of a holistic model of care reflects the recognition that osteoarthritis management extends beyond pharmacological and surgical intervention. By integrating psychosocial and behavioral interventions, this study demonstrates the necessity of a patient-centered, multidimensional strategy that supports physical, psychological, and emotional well-being. The success of this intervention highlights the importance of multimodal approaches to chronic disease management, emphasizing the role of psychological resilience and structured self-care practices in promoting patient autonomy, functional independence, and overall quality of life.

Additional Information

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Exploring Kratom Use in High-Prevalence Areas of Southern Thailand: Attitudes, Knowledge, and Consumption Patterns – A Mixed-Methods Study

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Abstract

Background: Kratom (*Mitragyna speciosa*), a tropical tree native to Southeast Asia, has traditionally been used in Thailand for medicinal and recreational purposes. Although recently legalized for medicinal use, concerns remain regarding its safety and potential for abuse.

Objectives: To investigate kratom consumption patterns and identify demographic, behavioral, and cognitive predictors of current and harmful use in high-prevalence rural communities in southern Thailand.

Methods: A cross-sectional study was conducted among 169 participants from southern Thai communities with high kratom use. A structured questionnaire assessed demographics, attitudes, knowledge, and usage patterns. Harmful use was defined as consumption of more than 20 leaves per day. Multiple logistic regression analysis identified predictors of current and harmful use.

Results: Among participants, 45 (26.6%) were current users, and of those 22 (48.9%) met the criteria for harmful use. Predictors of current use included younger age (adjusted OR [AOR], 0.97; 95% CI, 0.94-0.99), tobacco use (AOR, 16.12; 95% CI, 5.01-51.86), poor mental health (AOR, 8.8; 95% CI, 2.2-35.16), and favorable attitudes toward kratom (AOR, 1.12 per point; 95% CI, 1.06-1.18). Harmful use was associated with long-term consumption (AOR, 10.54; 95% CI, 1.01-109.9), boiling as the method of use (AOR, 80.96; 95% CI, 4.98-1315.6), and lower knowledge scores (AOR, 17.8; 95% CI, 1.57-201.68).

Conclusions: Current and harmful kratom use are linked to specific demographic and behavioral factors. These findings support the need for targeted public health education and regulation in high-risk communities.

Keywords: *Mitragyna speciose*, Kratom, Consumption patterns, Behavioral predictors, Southern Thailand

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Introduction

Kratom (*Mitragyna speciosa*), a tropical evergreen tree native to Southeast Asia — particularly Thailand — has been used for centuries for both medicinal and recreational purposes. Recently, its use has gained global popularity, especially in the United States, as an alternative to opioids for pain management and for its purported health benefits.[1, 2] However, the legal status of kratom remains contentious: some countries have banned it outright, whereas others regulate it as a controlled substance.[3-5]

Traditionally, kratom has been recognized for its analgesic, antipyretic, anti-inflammatory, and stimulant properties. In Thailand, it has been used to treat conditions such as diarrhea, cough, and pain. However, in 1943, the Thai government enacted the Kratom Act, prohibiting its use and possession because of concerns about addiction and social impact.[6] Although the act was repealed in 2019, legalizing kratom for medicinal and traditional use, concerns persist regarding its safety and potential for abuse. Studies have linked kratom to adverse effects, including seizures, liver damage, and withdrawal symptoms.[7-9]

Kratom contains several bioactive compounds, primarily the alkaloids mitragynine and 7-hydroxymitragynine, which interact with the opioid receptors in the brain — mainly the mu-opioid receptor. Mitragynine, a partial agonist, contributes to the analgesic and sedative effects of kratom, whereas 7-hydroxymitragynine, though less abundant, is a more potent analgesic. Both alkaloids also act on adrenergic and serotonergic receptors, producing stimulant effects and mood enhancement. However, these interactions raise concerns about dependence and addiction.[10-12]

In Thailand, kratom remains widely accepted in rural communities, especially in the southern region where it is cultivated and traditionally used to relieve fatigue and boost work endurance. Despite its cultural significance, recent developments in legal status and usage patterns — particularly among younger populations and in combination with other substances — have raised public health concerns. Studies have highlighted both therapeutic potential and risks of dependence, especially with high doses or mixed use.[13, 14] However, research on the social and cognitive factors — such as attitudes, beliefs, and knowledge — that shape real-world consumption patterns remains limited.[6]

This study investigated cognitive and perceptual factors influencing kratom use in high-prevalence rural areas of southern Thailand. Although prior research has addressed attitudes and regulatory opinions,6 few studies have quantitatively assessed how these factors relate to actual use and harmful consumption at the population level. Guided by the concept of knowledge as justified belief, this study explored community-level perspectives shaping kratom-related behavior. Understanding these influences is key to developing effective, culturally appropriate health promotion and harm reduction strategies.

Methods

Study Design and Setting

This cross-sectional study targeted regions with high rates of kratom consumption in southern Thailand, using a purposive sample. Communities were selected based on kratom prevalence and the willingness of local leaders to participate.

Data Collection and Questionnaire Development

The questionnaire was developed through a qualitative exploration grounded in literature review and community engagement. Initial insights were gathered through a civil society forum involving local stakeholders — including healthcare providers, community leaders, and individuals from high-kratom-use communities. Focus group discussions explored perceived benefits, risks, motivations, and sociocultural influences. These sessions were audio-recorded, transcribed, and analyzed using thematic analysis. Key themes — such as functional use (eg, for work), social normalization, concerns about dependence, and mixed perceptions of harm — informed the development of questionnaire items.

In-depth interviews were also conducted during a pilot test with 30 participants from a demographically similar neighboring area. Thematic analysis of the interview data assessed the relevance, clarity, and cultural appropriateness of the questionnaire items. The inclusion criteria for the pilot phase included age 18 years or older and fluency in Thai.

The finalized questionnaire included the following sections: 1) demographic data included age, sex, education, occupation, religion, marital status, insurance status, and health conditions; 2) attitudes toward kratom use included 17 items rated on a 5-point Likert scale (1 = strongly disagree to 5 = strongly agree), with the total score ranged 17-85, with higher scores indicating more favorable attitudes; 3) knowledge of kratom included 11 true/false items scored 1 for correct and 0 for incorrect or "don't know" responses, with the total score ranged 0-11, with higher scores reflecting greater knowledge; and 4) health perception measures included participants rated their health, mental state, and coping abilities using a 5-point Likert scale based on self-perception, and the response options were very poor, poor, fair, good, and excellent.

Participants who reported current or previous kratom use completed an additional section. Patterns of kratom use were determined which included age at first use, frequency and quantity of consumption, duration, methods of use (eg, boiling or chewing), use with other substances, perceived dependence (eg, cravings, increased use), and social, financial, or health-related burdens, as well as quit attempts.

The primary outcome, harmful kratom use, was defined as consumption of more than 20 leaves per day — corresponding to an estimated mitragynine intake exceeding 150 mg/day — based on dependence-associated thresholds reported in literature.[13, 15] In April 2023, trained interviewers administered the finalized questionnaire to all eligible individuals available during the data collection period, using a census-based approach within the constraints of the community project timeline. Eligibility criteria included individuals aged 18 years or older, fluent in Thai, and residing in the selected high-kratom-prevalence communities during the study period. Individuals unable to provide informed consent (eg, due to cognitive or communication impairments) were excluded from participation. Overall, 169 participants were enrolled from an estimated study population of 600, yielding a margin of error of approximately 7%, which is acceptable for prevalence studies which use a 5%-10% range. All respondents completed the demographic, attitude, knowledge, and health perception sections, whereas those with kratom use experience completed the additional section on usage patterns by using questionnaire (Supplementary S1). Data were anonymized and securely stored, with access limited to the principal investigator. No incentives were provided for participation.

Data Analysis

Data were collected via Google Forms and processed in Excel version 16.74 (Microsoft Corp). Statistical analyses were conducted in R version 4.2.3 (R Project for Statistical Computing), using appropriate packages for data analysis and visualization. All questionnaires were fully completed; therefore, no missing data were included in the analysis.

For descriptive statistics, categorical variables, such as demographic characteristics and kratom use patterns, were summarized as frequencies, percentages, and mean (SD). Group comparisons (eg, current vs noncurrent users, harmful vs nonharmful users) were performed using the chi-square test or Fisher exact test as appropriate. Continuous variables were reported as medians with interquartile ranges (IQRs) and compared using the Mann–Whitney *U* test due to nonnormal distribution.

For multivariate analysis, univariate analysis with a significance threshold of $P < .20$

was used to identify potential predictors of kratom use. This threshold, commonly employed in exploratory studies, ensures that relevant variables are not prematurely excluded from multivariate modeling.[16] Logistic regression was then conducted to examine factors associated with attitudes and knowledge regarding kratom use. The final model was refined through backward stepwise regression based on the Akaike Information Criterion. Model fit was assessed using Nagelkerke's pseudo R-squared from the DescTools package[17] and Hosmer-Lemeshow test from the ResourceSelection package[18] to evaluate how well the predicted probabilities aligned with the observed outcomes. To assess the ability of the model to distinguish between harmful and nonharmful kratom use, a receiver operating characteristic (ROC) curve was constructed, and the area under the curve was calculated using the pROC package,[19] which provided a measure of classification accuracy. Statistical significance was set at $P < .05$.

This study was conducted and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cross-sectional studies (Supplementary S2).[20]

Results

Demographic and Baseline Characteristics of Study Participants

This study included 169 participants from regions in southern Thailand with a high prevalence of kratom use. Demographic and baseline characteristics are summarized (Table 1). The sample comprised 52.7% females and 47.3% males, with a mean (SD) age of 47.7 (18.9) years. Fishing was the most common occupation (24.9%), followed by unemployment (24.3%) and temporary employment (16.6%). Most participants were Muslim (93.5%) and had completed only primary school (43.2%), and 79.9% were enrolled in the universal health coverage scheme. Participants rated their overall health as good (37.3%) and their mental state similarly (44.4%). Coping abilities were rated as excellent by 45.6%. Substance use included tobacco (29%), alcohol (7.7%), and cannabis (5.9%). Common underlying health conditions included hypertension (16.6%), diabetes mellitus (9.5%), and dyslipidemia (9.5%). Regarding kratom use, 26.6% were current users, 13.6% were former users, and 59.8% had never used it. The mean (SD) attitude score toward kratom use was 48.5 (12.4), and the mean (SD) knowledge score was 6.5 (2.5). The distribution of total attitude and knowledge scores by kratom use status, illustrated significant differences among the groups (Figures 1 and 2).

Table 1. Demographic and Baseline Characteristics of Study Participants

Baseline Characteristic	No. (%) (N = 169)
Sex	
Female	89 (52.7)
Male	80 (47.3)
Age, mean (SD), y	47.7 (18.9)
Occupation	
Agriculture	12 (7.1)
Temporary employee	28 (16.6)
Fishing	42 (24.9)

Table 1. Demographic and Baseline Characteristics of Study Participants (Continued)

Baseline Characteristic	No. (%) (N = 169)
Government	4 (2.4)
Self-employed	6 (3.6)
Student	17 (10.1)
Merchant	19 (11.2)
Unemployed	41 (24.3)
Religion	
Buddhism	11 (6.5)
Islam	158 (93.5)
Marital status	
Single	43 (25.4)
Married	112 (66.3)
Divorced	14 (8.3)
Education level	
Higher than bachelor	13 (7.7)
Vocational	5 (3.0)
High school	38 (22.5)
Middle school	37 (21.9)
Primary school	73 (43.2)
No education	3 (1.8)
Insurance type	
Cash	5 (3.0)
Disabled	3 (1.8)
Universal health coverage	135 (79.9)
Government	15 (8.9)
Health volunteer	4 (2.4)
Social security	3 (1.8)
Student	4 (2.4)
Health state (self-perception)	
Very poor	10 (5.9)
Poor	12 (7.1)
Fair	45 (26.6)
Good	63 (37.3)
Excellent	39 (23.1)
Mental state (self-perception)	
Very poor	3 (1.8)
Poor	9 (5.3)
Fair	24 (14.2)
Good	75 (44.4)
Excellent	58 (34.3)

Table 1. Demographic and Baseline Characteristics of Study Participants (Continued)

Baseline Characteristic	No. (%) (N = 169)
Coping abilities (self-perception)	
Very poor	1 (0.6)
Poor	5 (3.0)
Fair	27 (16.0)
Good	59 (34.9)
Excellent	77 (45.6)
Other substances used	
Cannabis	10 (5.9)
Smoking	49 (29.0)
Alcohol	13 (7.7)
Underlying diseases	
Hypertension	28 (16.6)
Diabetes mellitus	16 (9.5)
Dyslipidemia	16 (9.5)
Others	18 (10.7)
Kratom use	
Current	45 (26.6)
Former	23 (13.6)
Never	101 (59.8)
Total score, mean (SD)	
Attitude	48.5 (12.4)
Knowledge	6.5 (2.5)

Figure 1. Boxplot of Total Attitude Scores by Kratom Use Status

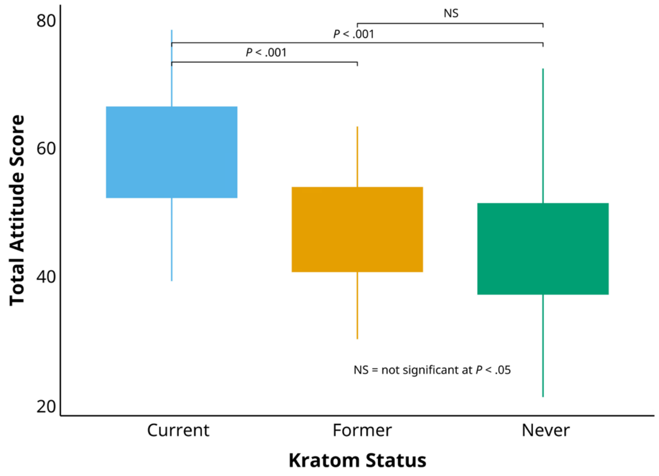
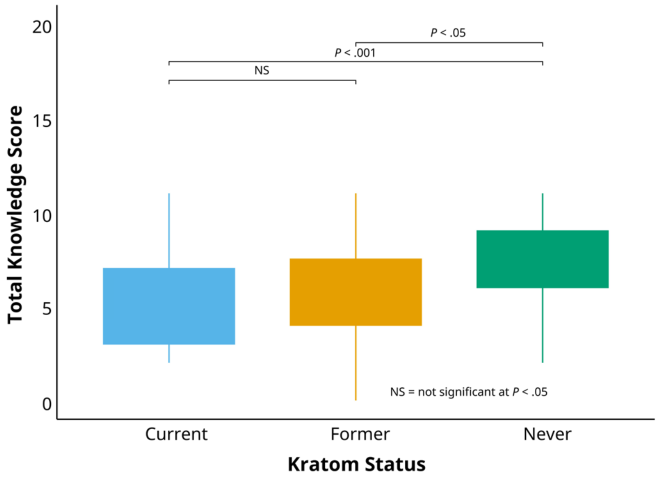


Figure 2. Boxplot of Total Knowledge Scores by Kratom Use Status



Kratom Usage Patterns and Methods

Among the 45 participants who reported current kratom use (Table 2), most were male (86.7%) with a mean (SD) age of 41.8 (14.7) years. On average, kratom use began at the mean (SD) age of 30.1 (15.0) years. Polysubstance use was common: 73.3% smoked tobacco, and 20% used both cannabis and alcohol. Initiation varied, with 44.4% starting on their own, 40% influenced by friends, and 11.1% by neighbors. Reported daily consumption ranged widely: 8.9% used < 1 leaf, 24.4% used 1-5 leaves, 8.9% used 6-10 leaves, 8.9% used 11-20 leaves, 15.6% used 21-30 leaves, and 33.3% used > 30 leaves per day — with the latter 2 categories reflecting harmful use. Current and harmful kratom use patterns by sex and age group, showed that males aged 21-40 had the highest prevalence of both, which indicated the significant involvement of this demographic in kratom use and related risks (Figure 3A and 3B). Long-term use was common, with 60% reporting use for over 5 years. The primary method of consumption was boiling the leaves (62.2%), followed by chewing and spitting them out (31.1%) or swallowing (6.7%). Furthermore, 48.9% reported mixing kratom with other substances — typically a cough suppressant, an amphetamine derivative, or cola.

Participants reported various burdens associated with kratom use, included increased consumption (20%), cravings (20%), social conflicts (6.7%), financial strain (24.4%), and health concerns (15.6%). Motivations for use varied. The most commonly cited reason was recreational use (42.2%), followed by enhanced work capacity (33.3%) and cough suppression (33.3%). Other reported motivations included stress relief (15.6%), muscle relief (20%), and social engagement (20%) (Figure 4).

In the past 3 months, 21 participants (46.7%) were advised to quit kratom, and 26 (57.8%) made independent attempts to stop. Reported reasons for relapse included easy access to kratom (7.7%), withdrawal symptoms (19.2%), social and workplace influences (38.6%), and continued use for cough suppression (7.7%). Motivations for quitting varied: 12 participants (46.2%) reported a loss of interest, 3 cited difficulty obtaining kratom (11.5%), and 4 were influenced by family or societal pressure (15.4%). Additional reasons included fear of side effects, financial strain, peer advice at work, and concerns about cognitive decline.

Table 2. Kratom Usage Patterns and Methods

Baseline Characteristic	No. (%) (N = 45)
Sex	
Female	6 (13.3)
Male	39 (86.7)
Age, mean (SD), y	41.8 (14.7)
Initiation age of kratom use, mean (SD), y	30.1 (15.0)
Other substances used*	
Cannabis	9 (20.0)
Smoking	33 (73.3)
Alcohol	9 (20.0)
Influenced to use kratom by	
Friends	18 (40.0)
Neighbors	5 (11.1)
Themselves	20 (44.4)
Traditional doctor	2 (4.4)
Quantity of use, leaves/day	
< 1	4 (8.9)
1-5	11 (24.4)
6-10	4 (8.9)
11-20	4 (8.9)
21-30 (harmful use)	7 (15.6)
> 30 (harmful use)	15 (33.3)
Duration	
< 6 months	4 (8.9)
6-12 months	3 (6.7)
1-2 years	3 (6.7)
2-5 years	8 (17.8)
> 5 years	27 (60.0)
Consumption method	
Boil leaves to drink	28 (62.2)
Chew leaves without spitting out	3 (6.7)
Chew leaves and spit out	14 (31.1)
Mixing with supplements	
No	15 (33.3)
Cough suppressant	3 (6.7)
Mix (cough suppressant, derivative of amphetamine, cola)	22 (48.9)
Others**	5 (11.1)

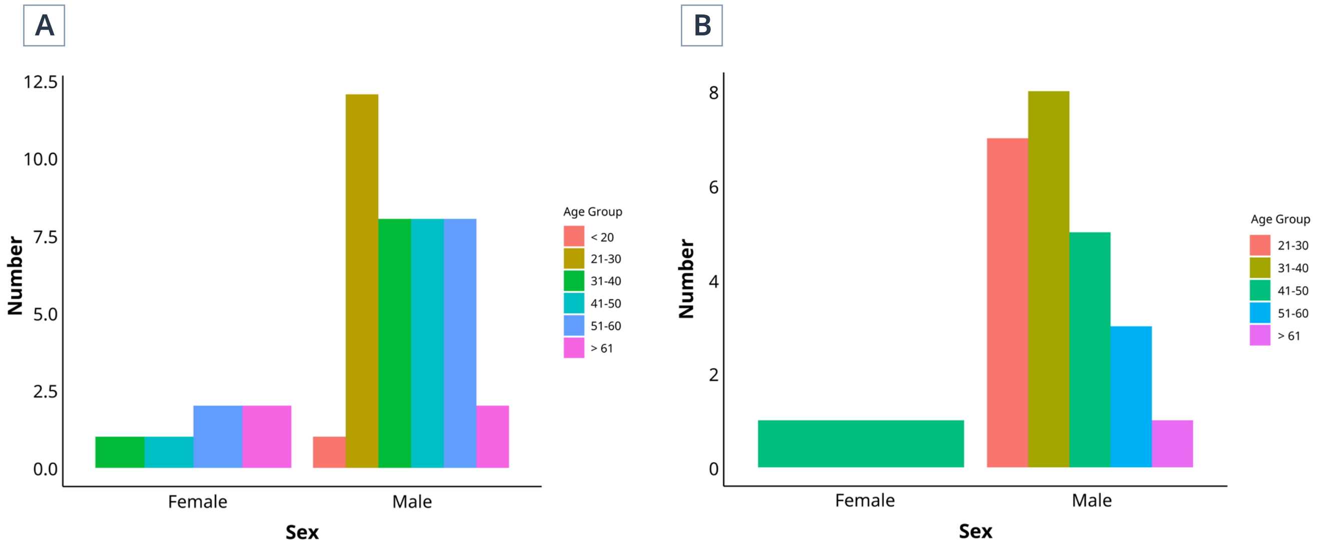
Table 2. Kratom Usage Patterns and Methods (Continued)

Baseline Characteristic	No. (%) (N = 45)
Burden of use (in past 1 month)	
Perceptions of increased consumption	9 (20.0)
Craving to use	9 (20.0)
Social conflicts	3 (6.7)
Financial strain	11 (24.4)
Health concerns	7 (15.6)
Reasons for kratom use	
Muscle relief	9 (20.0)
Cough suppression	15 (33.3)
Enhanced work capacity	15 (33.3)
Recreation	19 (42.2)
Stress relief	7 (15.6)
Withdrawal intolerance	5 (11.1)
Social engagement	9 (20.0)
Believed health benefits	5 (11.1)
Sleep issues	5 (11.1)
Quit attempts (in past 3 months)	
Somebody advised patient to quit	21 (46.7)
Tried to quit	26 (57.8)
Reason for relapse (in participants who tried to quit) (n = 26)	
Easy to purchase kratom	2 (7.7)
Withdrawal symptoms	5 (19.2)
Others	7 (26.9)
Influenced by social environment	2 (7.7)
Taking it for cough	2 (7.7)
Influenced by working environment	8 (30.9)
Reason for trying to quit (in participants who tried to quit) (n = 26)	
Decided to quit by oneself (got bored of using it)	12 (26.7)
Difficulty in purchasing kratom	3 (6.7)
Family, society, religion told to quit	4 (8.9)
Fear of side effects	3 (6.7)
Income insufficient for long-term use	2 (4.4)
Supervisor, coworkers told to quit	1 (2.2)
Thinking, reading slower than before	1 (2.2)

[*] Each participant could select more than 1 option.

[**] Sugar, coffee or lemon.

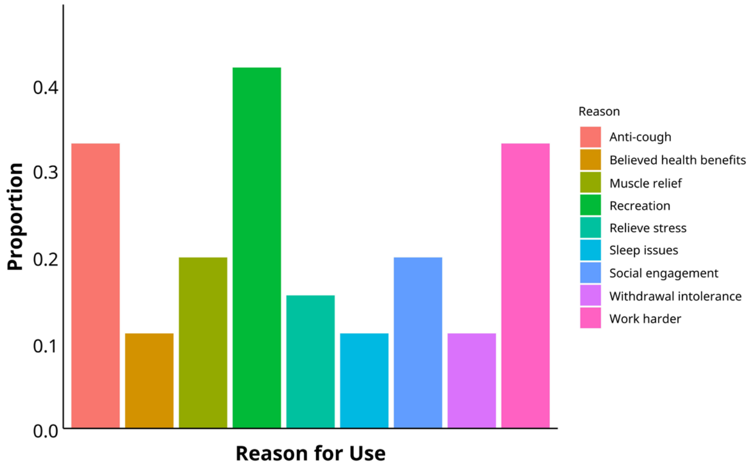
Figure 3. Distribution of Current and Harmful Kratom Use by Sex and Age Group



A, Current kratom use by sex and age group.

B, Current harmful kratom use by sex and age group.

Figure 4. Distribution of Reasons for Kratom Use Among Participants



Univariate Analysis of Factors Associated With Current and Harmful Kratom Use

The univariate analysis was summarized which compared behavioral and demographic characteristics between current kratom users and noncurrent users (including both former and never users), as well as between harmful and nonharmful users among current users.

Attitudes toward kratom use were significantly more favorable among current users, with a mean (SD) score of 59.6 (9.6), compared with 44.4 (10.7) in nonusers (*P* < .001). In contrast, knowledge about kratom was lower among current users, with a median (IQR) score of 4 (3-7) vs 7 (5.8-9) in nonusers (*P* < .001). Sex differences were pronounced, with males comprising the majority of current users (86.7% male vs 13.3% female, *P* < .001). Current users were also younger, with a mean (SD) age of 41.8 (14.7) years compared with 49.8 (19.8) years among nonusers (*P* = .015). Fishermen were significantly overrepresented among current users, accounting for 46.7% (*P* < .001). Lifestyle factors such as smoking and alcohol use were also significantly associated with current kratom use, indicating a pattern of polysubstance use (Table 3).

Harmful kratom use, defined as consuming more than 20 leaves per day, was significantly associated with several factors. Individuals who began using kratom at a younger age were more likely to exhibit harmful usage patterns, with a mean (SD) initiation age of 23.5 (10.8) years compared with 36.4 (15.9) years among less intensive users (*P* = .003). Educational attainment also played a role, as those with only basic or lower education were more likely to exceed safe consumption levels. The method of consumption was a key determinant: individuals who boiled kratom were significantly more likely to engage in harmful use (95.5%, *P* < .001) than those who chewed the leaves. Moreover, mixing kratom with cough suppressants was strongly associated with harmful consumption, with 86.4% of such users exceeding the threshold (*P* < .001) (Table 4).

Multivariate Analysis of Factors Influencing Kratom Usage Patterns

Multivariate logistic regression analysis, identified key predictors of both current and harmful kratom use (Table 5). For current use, each additional year of age was associated with a 3% decrease in the likelihood of use (adjusted OR [AOR], 0.97; 95% CI, 0.94-0.99; *P* = .015). Current smokers had significantly higher odds of kratom use (AOR, 16.12; 95% CI, 5.01-51.86; *P*< .001), and individuals with poorer mental health were also more likely to use it (AOR, 8.8; 95% CI, 2.20-35.16; *P* = .001). A positive attitude toward kratom use was another strong predictor: for every one-point increase in the attitude score, the odds of kratom use rose by 12% (AOR, 1.12; 95% CI, 1.06-1.18; *P* < .001).

For harmful kratom use, the duration of use emerged as a significant predictor, with long-term users facing a higher risk (AOR, 10.54; 95% CI, 1.01-109.90; *P* = .049). The method of consumption also played a key role: individuals who boiled kratom had significantly greater odds of harmful use compared with those who chewed it (AOR, 80.96; 95% CI, 4.98-1315.6; *P* = .002). In addition, lower knowledge scores were associated with more harmful use (AOR, 17.8; 95% CI, 1.57-201.68; *P* = .02). The model fit was strong, with Nagelkerke's pseudo R-squared values of 0.62 for current use and 0.72 for harmful use. Hosmer-Lemeshow tests supported model calibration, and discrimination was confirmed by high area under the curve values (AUC) of 0.92 for current use and 0.94 for harmful use.

Table 3. Univariate Analysis of Factors Associated With Current Kratom Use

Factor	No. (%)			*P* Value
	Noncurrent Use (n = 124)	Current Use (n = 45)	Total (N = 169)	
Total attitude score, mean (SD)	44.4 (10.7)	59.6 (9.6)	48.5 (12.4)	< .001
Total knowledge score, median (IQR)	7 (5.8-9.0)	4 (3.0-7.0)	7 (4.0-9.0)	< .001
Sex				
Female	83 (66.9)	6 (13.3)	89 (52.7)	< .001
Male	41 (33.1)	39 (86.7)	80 (47.3)	

Table 3. Univariate Analysis of Factors Associated With Current Kratom Use (Continued)

Factor	No. (%)			
	Noncurrent Use (n = 124)	Current Use (n = 45)	Total (N = 169)	*P* Value
Age, mean (SD), y	49.8 (19.8)	41.8 (14.7)	47.7 (18.9)	.015
Religion				
Buddhism	9 (7.3)	2 (4.4)	11 (6.5)	.729
Islam	115 (92.7)	43 (95.6)	158 (93.5)	
Education level*				
More than basic education	83 (66.9)	30 (66.7)	113 (66.9)	.974
Below and equal to basic education	41 (33.1)	15 (33.3)	56 (33.1)	
Marital status				
Single	28 (22.6)	15 (33.3)	43 (25.4)	.085
Married	88 (71.0)	24 (53.3)	112 (66.3)	
Divorced	8 (6.5)	6 (13.3)	14 (8.3)	
Insurance type				
Universal health coverage	94 (75.8)	41 (91.1)	135 (79.9)	.075
Government	14 (11.3)	1 (2.2)	15 (8.9)	
Others	16 (12.9)	3 (6.7)	19 (11.2)	
Occupation				
Temporary employee	19 (15.3)	9 (20.0)	28 (16.6)	< .001
Fishing	21 (16.9)	21 (46.7)	42 (24.9)	
Others	33 (26.6)	8 (17.8)	41 (24.3)	
Student	15 (12.1)	2 (4.4)	17 (10.1)	
Unemployed	36 (29.0)	5 (11.1)	41 (24.3)	
Health state				
Very poor/poor/fair	57 (46.0)	10 (22.2)	67 (39.6)	.005
Good/excellent	67 (54.0)	35 (77.8)	102 (60.4)	
Mental health				
Very poor/poor/fair	23 (18.5)	13 (28.9)	36 (21.3)	.147
Good/excellent	101 (81.5)	32 (71.1)	133 (78.7)	
Coping abilities				
Very poor/poor/fair	25 (20.2)	8 (17.8)	33 (19.5)	.730
Good/excellent	99 (79.8)	37 (82.2)	136 (80.5)	
Cannabis				
Nonuser	123 (99.2)	36 (80.0)	159 (94.1)	< .001
User	1 (0.8)	9 (20.0)	10 (5.9)	
Smoking				
Nonuser	108 (87.1)	12 (26.7)	120 (71.0)	< .001
User	16 (12.9)	33 (73.3)	49 (29.0)	

Table 3. Univariate Analysis of Factors Associated With Current Kratom Use (Continued)

Factor	No. (%)			*P* Value
	Noncurrent Use (n = 124)	Current Use (n = 45)	Total (N = 169)	
Alcohol				
Nonuser	120 (96.8)	36 (80.0)	156 (92.3)	1.000
User	4 (3.2)	9 (20.0)	13 (7.7)	
Prior diagnosed hypertension				
No	98 (79.0)	43 (95.6)	41 (83.4)	.011
Yes	26 (21.0)	2 (4.4)	28 (16.6)	
Prior diagnosed diabetes				
No	110 (88.7)	43 (95.6)	153 (90.5)	.241
Yes	14 (11.3)	2 (4.4)	16 (9.5)	

[*] Basic education in Thailand refers to middle school.

Table 4. Univariate Analysis of Factors Associated With Harmful Kratom Use

Factor	No. (%)		*P* Value
	Not Harmful (n = 23)	Harmful (n = 22)	
Sex			
Female	5 (21.7)	1 (4.5)	.187
Male	18 (78.3)	21 (95.5)	
Age, mean (SD), y	47.5 (14.5)	35.8 (12.7)	.006
Initiation age of kratom use, mean (SD), y	36.4 (15.9)	23.5 (10.8)	.003
Health state			
Very poor/poor/fair	8 (34.8)	2 (9.1)	.071
Good/excellent	15 (65.2)	20 (90.9)	
Mental health			
Very poor/poor/fair	8 (34.8)	5 (22.7)	.372
Good/excellent	15 (65.2)	17 (77.3)	
Coping abilities			
Very poor/poor/fair	5 (21.7)	3 (13.6)	.699
Good/excellent	18 (78.3)	19 (86.4)	
Education level[*]			
More than basic education	19 (82.6)	11 (50)	.020
Below and equal to basic education	4 (17.4)	11 (50)	
Cannabis			
Nonuser	20 (87)	16 (72.7)	.284
User	3 (13)	6 (27.3)	

Table 4. Univariate Analysis of Factors Associated With Harmful Kratom Use (Continued)

Factor	No. (%) Not Harmful (n = 23)	No. (%) Harmful (n = 22)	*P* Value
Smoking			
Nonuser	9 (39.1)	3 (13.6)	.053
User	14 (60.9)	19 (86.4)	
Alcohol			
Nonuser	18 (78.3)	18 (81.8)	1.000
User	5 (21.7)	4 (18.2)	
Duration, y			
≤ 5	13 (56.5)	5 (22.7)	.021
> 5	10 (43.5)	17 (77.3)	
Method			
Boil	7 (30.4)	21 (95.5)	< .001
Chew	16 (69.6)	1 (4.5)	
Mixing with cough suppressant			
No	17 (73.9)	3 (13.6)	< .001
Yes	6 (26.1)	19 (86.4)	
Total attitude score			
≤ 50	8 (34.8)	2 (9.1)	.071
> 50	15 (65.2)	20 (90.9)	
Total knowledge score			
≤ 6	10 (43.5)	19 (86.4)	.003
> 6	13 (56.5)	3 (13.6)	

[*] Basic education in Thailand refers to middle school.

Table 5. Multivariate Analysis of Factors Associated With Current Kratom Use and Harmful Use

Factor	Adjusted OR (95% CI)	*P* Value
Current kratom use		
Increase of one year in age (continues variable)	0.97 (0.94-0.99)	.015
Current smoking (reference, do not smoke)	16.12 (5.01-51.86)	< .001
Very poor/poor, or fair mental health (reference, good/excellent)	8.8 (2.20-35.16)	.001
Increase of one point in attitude score (continues variable)	1.12 (1.06-1.18)	< .001
Harmful use		
Duration > 5 years (reference, ≤ 5 years)	10.54 (1.01-109.90)	.049
Method of use is boiling (reference, chewing)	80.96 (4.98-1315.60)	.002
Knowledge toward kratom use less ≤ 6 (reference, > 6)	17.8 (1.57-201.68)	.020

Discussion

This study offers a comprehensive analysis of kratom use in rural communities in southern Thailand, providing key insights into knowledge, attitudes, and usage behaviors. While knowledge about the effects of kratom varied, many users expressed positive attitudes toward its perceived benefits — such as increased stamina and pain relief — despite limited understanding of potential harms. Kratom use was particularly common among males aged 21-40, especially those in fishing and low-skilled occupations. Nearly half of current users engaged in harmful consumption, defined as > 20 leaves per day. Multivariate analysis identified several factors associated with both current and harmful use, including poor mental health, tobacco use, method of consumption, and favorable attitudes toward kratom. These findings highlight the need for targeted, culturally informed interventions.

The diverse reasons for kratom use, which ranged from enhancing work capacity to recreational purposes, reflect the complex motivations underlying its consumption. Many users may be drawn to its stimulant and euphoric effects, which offer temporary relief from the physical and mental demands of their occupations. This finding aligned with previous research in Thailand,[21] which reported that approximately 70% of kratom use was work-related, which is a distinct pattern from Western contexts,[1, 22-24] where kratom is more commonly used for medicinal purposes, such as pain management, mental health conditions, and as an opioid substitute. The usage patterns observed in this study contribute to the ongoing discourse on kratom as both a recreational and self-medicated substance. Although its pain-relieving properties are well-recognized, the potential for recreational use and dependence remains a critical concern. Understanding these contextual factors is essential for informing educational initiatives and developing strategies to mitigate the spread of kratom use.

The demographic specificity of kratom use noted in this study — predominantly among males in physically demanding occupations — was consistent with literature suggesting that manual laborers are at increased risk of initiating substance use as a coping strategy. These patterns also align with global trends, where substance use is strongly influenced by socioeconomic and occupational factors.[2, 23, 25] The significant association between smoking and kratom use points to a broader pattern of polysubstance use, raising significant public health concerns owing to the potential for compounded health risks. This study supports findings from previous research which have indicated that kratom users frequently consume other substances,[9, 23] particularly tobacco.[21] Research in Thailand has demonstrated a strong relationship between tobacco use and kratom consumption. This study also identified patterns involving other substances, such as cannabis which is of particular relevance as cannabis regulations in Thailand are currently undergoing major changes.[26] In the US, kratom use has been linked to multiple substances, including marijuana,[22] alcohol, tobacco, psychedelics, heroin, and prescription drugs.[25] Therefore, legalizing kratom solely on the basis of its potential scientific or medicinal benefits, without addressing its broader social context and potential to facilitate other substance use, may be inadequate.

In addition, this study has highlighted that individuals whose socioeconomic circumstances encourage kratom use often experience significant financial strain and health concerns because of prolonged consumption. These consequences play a critical role in shaping the decision to quit, which is frequently influenced by withdrawal symptoms and social pressures. This underscores the complex interplay between individual experiences and broader social influences.[23]

This study's results have also revealed a strong association between positive attitudes toward kratom and current use, suggesting that individuals who view kratom favorably are more likely to consume it. Conversely, limited knowledge about kratom is significantly linked to harmful use, indicating that misinformation or lack of awareness may lead to riskier consumption behaviors. These findings highlight the urgent need for educational programs that provide accurate information about the effects and risks of kratom.[6, 21]

Mental health status also plays a pivotal role, in which poorer mental health was significantly associated with higher levels of kratom use.[27] This finding emphasizes the importance of integrating mental health support into substance use interventions. By examining these factors, this study offers valuable insights into the demographic and behavioral characteristics linked to kratom use and highlights the need for public health strategies that address both the physical and psychological dimensions of substance use in communities.

A notable concern emerging from this study is the predominant method of kratom consumption, which involves boiling the leaves. This contrasts with earlier research showing that kratom used for work-related purposes was typically consumed by chewing the leaves directly.[6] This study's findings indicate that boiling may lead to the intake of larger — and potentially harmful — quantities. Moreover, this method is often accompanied by mixing kratom with substances such as codeine and amphetamines, a widespread and dangerous practice. This issue is not confined to this study area, and similar patterns are observed in other parts of Thailand, where kratom is commonly mixed into tea and distributed via delivery services, complicating regulation and enforcement.[28] These practices across different regions emphasize the urgent need for robust regulatory oversight by governmental bodies to curb risky consumption behaviors and protect public health.

Implications for Public Health

The patterns of kratom use identified in this study mirror global trends in which substance use is shaped by socioeconomic and occupational factors — particularly in settings where individuals rely on substances to cope with physically demanding work. These findings highlight the need for public health strategies that extend beyond general education, calling for targeted interventions which are tailored to high-risk demographics. Occupational health programs could play a critical role in reducing harmful kratom use by addressing substance use within physically intensive jobs. In parallel, community-based educational initiatives should be implemented to raise awareness of both the perceived benefits and potential risks of kratom, while considering the socioeconomic pressures and occupational stressors that influence substance use. By addressing these factors in the context of local conditions, such interventions can achieve greater relevance, impact, and sustainability.

Strengths, Limitations, and Future Research

A major strength of this study is its use of qualitative methods to inform the development of a culturally and linguistically appropriate quantitative survey. This mixed-methods approach ensured that the quantitative findings were grounded in the lived experiences of the community, enhancing the validity and contextual relevance of the data. Furthermore, active engagement with local communities during the questionnaire development phase strengthened the relevance and applicability of the findings.

Although the initial qualitative insights provided a strong foundation, the cross-sectional design limited the ability to draw causal inferences about the relationships between observed factors and kratom usage patterns. The study relied on self-reported data, which might have been subject to recall bias and social desirability bias. The relatively small sample size (n = 169) might have reduced statistical power to detect weaker associations and has limited the precision of prevalence estimates. In addition, the purposive selection of areas with known high kratom prevalence, might have affected the generalizability of the findings. Although this approach was valuable for identifying usage patterns in high-risk communities, the results may not reflect behaviors in regions with different socioeconomic or cultural contexts.

Future research should explore the dynamics of kratom use over time through longitudinal studies, particularly to assess its long-term health effects across varying social and cultural contexts. Expanding the scope to include more diverse populations and settings will help to clarify how socioeconomic factors influence usage patterns over time. Such studies can provide critical evidence to support the development of culturally informed public health interventions and policies, ultimately enhancing the effectiveness of targeted prevention and harm reduction strategies.

Conclusions

This study identified key demographic and behavioral factors associated with kratom use in high-prevalence areas of southern Thailand. Younger age, male sex, tobacco use, and positive attitudes toward kratom were significantly linked to current use. Harmful consumption — defined as > 20 leaves per day — was more common among long-term users, those who boiled kratom leaves, and individuals with limited knowledge of its effects. These findings highlight the need for evidence-based public health strategies that address both usage patterns and their underlying drivers. Interventions should prioritize knowledge enhancement, particularly among high-risk groups such as young males and manual laborers, and promote regulation of harmful consumption practices. The insights gained from this study may inform local health promotion efforts and support the development of targeted educational and regulatory measures to reduce the risks associated with kratom use.

Additional Information

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Ethics Approval: This study was approved by the Human Research Ethics Committee (HREC), Faculty of Medicine, Prince of Songkla University (REC 64-167-9-2 on 9 June 2021). HREC is the official institutional body responsible for ethical oversight of human research. The study was conducted in accordance with the Declaration of Helsinki. Before the study began — conducted as part of the Community Medicine curriculum — cooperation was sought from local public health authorities and relevant stakeholders in both government and private sectors. Researchers engaged with the community to build trust, which was a critical step considering the sensitive nature of the questionnaire. Informed consent was obtained from all participants. Data confidentiality and secure storage were ensured, with all responses anonymized and managed electronically by the research team.

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Supplementary Material: Download Supplementary S1-S2 from the following link: https://he02.tci-thaijo.org/index.php/ramajournal/article/view/272935/187736

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Original Article

Nursing Students' Perceptions of Spiritual Care Competency: A Qualitative Study

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Abstract

Background: Spiritual care is a crucial component of holistic nursing practice, as it addresses patients' emotional, psychological, and existential well-being. Nursing students play a vital role in providing spiritual support, yet their competencies in this area remain underexplored.

Objectives: To explore nursing students' perceptions of their competencies in providing spiritual care to patients.

Methods: A descriptive qualitative research design was employed in this study. Ten fourth-year nursing students from the Faculty of Nursing at Ubon Ratchathani Rajabhat University were selected using purposive sampling and snowball techniques. Data were collected through in-depth interviews conducted between December 2024 and January 2025. The research instruments included a semi-structured interview guide, field notes, observational tools, and the researcher's reflective journal. Content analysis was used to analyze the data.

Results: The findings revealed that nursing students perceived their spiritual care competencies as encompassing 3 key areas: 1) assessing and diagnosing spiritual issues; 2) planning and implementing spiritual care, which included: maintaining a positive attitude and respecting patients' spiritual beliefs, communication and counseling, empathy and compassion, encouraging patients to practice their faith and beliefs, and referring patients to spiritual care specialists; and 3) evaluating spiritual care practices.

Conclusions: While nursing students show confidence in certain aspects of spiritual care, the study highlights the need for enhanced training. Integrating comprehensive spiritual care education and practical experiences into the curriculum, along with support from spiritual care professionals, is essential for strengthening students' competencies.

Keywords: Nursing students, Spiritual care, Competency, Patients, Holistic nursing

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Introduction

Spirituality is a fundamental dimension of human existence, encompassing a search for meaning, purpose, and connection that becomes particularly significant in times of illness and vulnerability.[1, 2] In healthcare, especially in nursing, addressing patients' spiritual needs is essential for holistic care. Spiritual care involves recognizing and responding to the existential concerns of patients, such as hope, suffering, meaning, and the need for transcendence.[2] Core components of spiritual care nursing include presence, active listening, compassion, and facilitated access to spiritual resources. Competent nurses in this area are trained to assess spiritual distress, incorporate spiritual beliefs into care plans, and support diverse spiritual expressions without imposing their own beliefs.[3]

Research indicates that effective spiritual care enhances patient outcomes by promoting emotional well-being, resilience, and a sense of peace, particularly in palliative and end-of-life settings.[2, 3] Moreover, nurses with strong spiritual care competencies are better equipped to navigate ethical dilemmas and provide culturally sensitive support, ultimately enriching the quality of care and the human experience within healthcare contexts.[3] Nursing students, as future healthcare providers, must acquire the necessary knowledge, skills, and confidence to deliver spiritual care effectively.[3] Their perceptions of spiritual care competency play a crucial role in shaping their attitudes, preparedness, and willingness to integrate spirituality into their professional practice.[3]

Despite the recognized importance of spiritual care, research indicates that nursing students often encounter challenges in developing competence in this area. Factors such as a lack of formal education, limited clinical exposure, and personal uncertainties regarding spirituality contribute to gaps in their ability to provide effective spiritual care.[4, 5] For instance, previous studies have shown that the majority of nursing students possess a moderate level of competency in spiritual care, with scores ranging from 52.40% to 55.22%,[4, 5] and only 34.10% have received training in this domain.[4]

In Thailand, research on the competencies of nursing students in providing spiritual care remains limited, with existing studies primarily focusing on nurses' behaviors in delivering spiritual care. Findings indicate that nurses exhibit moderate levels of spiritual care behaviors.[6] Understanding nursing students' perspectives on spiritual care competency is therefore critical for informing improvements in nursing education and practice.

Given the subjective and experiential nature of spirituality in healthcare, qualitative research is particularly well-suited for investigating nursing students' perceptions of spiritual care competency. A qualitative approach allows for an in-depth exploration of students' lived experiences, beliefs, and challenges, providing nuanced insights that may not be captured through quantitative methodologies.[7] By employing qualitative methods, researchers can better understand the complexities of spiritual care competency and identify strategies to enhance its integration into nursing curricula, ultimately strengthening the delivery of holistic patient care.

Methods

Study Design, Setting, and Participants

A descriptive qualitative study design was employed for this research. The research was conducted at the Faculty of Nursing, Ubon Ratchathani Rajabhat University.

Participants were selected using purposive sampling, ensuring the inclusion of individuals with relevant experiences and insights into spiritual care competency. Additionally, the snowball sampling technique was used, allowing initial participants to refer other potential informants who met the study criteria. This approach facilitated access to a diverse range of perspectives while ensuring that all participants had direct, firsthand experience with spiritual care in clinical settings. For instance, such experience may include engaging in conversations with patients about their spiritual concerns, offering spiritual support through prayer, or assisting patients in connecting with a monk, chaplain, or other spiritual care provider.

The inclusion criteria required participants to be fourth-year nursing students who had experience providing care to patients across all age groups and in various fields, including critical and chronic illness, within both hospital and community settings. Additionally, participants had to be willing to take part in the study.

According to Creswell and Plano Clark,[8] an appropriate sample size for qualitative research typically ranges from 1 to 30 participants or until data saturation is achieved. Data saturation occurs when no new themes, patterns, or insights emerge from further data collection, indicating that the gathered information is sufficient for comprehensive analysis. In this study, data saturation was reached with a total of 10 participants, as additional interviews did not yield new findings. This ensured the depth and richness of the qualitative data while maintaining methodological rigor.

Research Instruments

A semi-structured interview guide was developed to facilitate open-ended discussions and was tested for content validity by 5 experts. It was designed to allow participants to share their perspectives on nursing students' competencies in providing spiritual care to patients. The guide ensured consistency in data collection while maintaining flexibility for participants to elaborate on their experiences. Three key interview questions were included to explore nursing students' perceptions of spiritual care competency: 1) What does spiritual care mean to you in the context of nursing? 2) In your opinion, what core competencies should nursing students have in order to provide effective spiritual care? 3) Can you describe a personal experience during your training or clinical practice in which you provided or witnessed spiritual care?

Field notes and observational tools consisted of three main components: nonverbal cues, contextual factors, and relevant interactions. These aspects included body language, facial expressions, the physical setting, and social dynamics during interviews. A nonparticipant, naturalistic observation approach was used, allowing the researcher to record observations without interference. This method supported a richer interpretation of participants' responses and strengthened the depth and accuracy of the qualitative analysis.[7, 10]

The researcher used a reflective journal to record personal insights and reactions after each interview, focusing on assumptions, emotions, and ethical considerations. This helped maintain reflexivity and reduce bias. A secure digital tool was used for journaling, without including any participant-identifiable data. The process enhanced the credibility and depth of the qualitative analysis.[10]

Data Collection

Data were collected through face-to-face, in-depth interviews to gain a comprehensive understanding of nursing students' perceptions of spiritual care competency. The interviews were conducted after participants had completed either their clinical ward practice or relevant coursework. All interviews took place in a safe and private setting, scheduled at times convenient for the participants to ensure comfort and confidentiality. The interview process began with simple, rapport-building questions and gradually progressed to more complex inquiries. Specific techniques, such as the use of open-ended prompts and encouragement to share personal experiences, were employed to elicit in-depth insights into spirituality. Each interview lasted between 45 and 60 minutes and was conducted 1 to 2 times per participant, depending on the depth of information provided and the need for clarification or further exploration of emerging themes. A total of 10 participants were interviewed between December 2024 and January 2025. This method facilitated rich, detailed responses and enabled a deeper exploration of participants' experiences and perspectives on spiritual care competency.

Data Analysis

Qualitative data analysis was conducted using content analysis based on the framework proposed by Cohen et al.[9] This analytical process involved several key steps to ensure a systematic and rigorous approach to interpreting the data. The process began with data immersion, where the researcher repeatedly reviewed transcripts to develop a deep understanding of the content. This was followed by data reduction or transformation, in which irrelevant or redundant information was eliminated or reorganized to facilitate meaningful analysis. Line-by-line coding was then applied to systematically identify key concepts, patterns, and recurring ideas within the data. The coded data were subsequently grouped into categories, allowing for the formation of broader thematic structures. From these categories, preliminary themes were developed and refined through iterative analysis. Finally, determination of final themes was completed by synthesizing insights into well-defined, overarching themes that captured the essence of the participants' perspectives. In qualitative analysis, disagreements among the researchers verifying the themes were resolved through discussion and consensus. The researchers reviewed the data together, compared interpretations, and collaboratively refined the themes to ensure accuracy, consistency, and alignment with the study's objectives.

To ensure the trustworthiness of the study, Lincoln and Guba's criteria were applied,[10] addressing credibility, transferability, dependability, and confirmability. Credibility was achieved through triangulation by collecting data from multiple sources, including interviews with participants and observational notes. Additionally, member checking was employed, where participants were provided with the opportunity to review and validate the interpretations of their responses, ensuring that their perspectives were accurately represented. Transferability was supported by providing a comprehensive description of the sampling process, participant characteristics, and the research context. This detailed account allows future researchers to assess the relevance and applicability of the study's findings to different settings or populations. Dependability was ensured through meticulous documentation of the research process. This included a clear record of data collection procedures, the coding framework used for analysis, and a step-by-step outline of the data analysis process. Such transparency allowed for consistency and replicability. Confirmability was maintained by engaging in regular consultations with the research team throughout the study to verify findings and interpretations. Additionally, detailed audit trails and supporting records were kept, which minimized researcher bias and ensured that the findings were shaped by the data rather than personal assumptions.[10]

Results

The key informants in this study were 10 fourth-year nursing students (9 females and 1 male), all of whom identified as Buddhists. The key informants identified essential competencies required for nursing students to provide adequate spiritual care for patients, categorized as follows:

Theme 1 Competency in Assessing and Diagnosing Spiritual Issues

Key informants highlighted the critical role of developing core competencies in assessing and diagnosing patients' spiritual needs as a foundation for effective spiritual care. This competency encompasses the observation of nonverbal cues, such as facial expressions and body language, the recognition of spiritually significant objects or individuals, and the use of empathetic communication to explore patients' spiritual concerns. Additionally, the application of appropriate assessment tools was seen as vital for accurately identifying spiritual needs and tailoring individualized care interventions. These findings emphasize the centrality of assessment within the spiritual care process. As key informants stated:

"We must first assess the patient's needs, specifically their spiritual needs or issues. Then, we use that information to diagnose the problem and design appropriate care activities. Each patient requires different care activities, and their issues are not the same. Since we are providing spiritual care, our conversations must be conducted with sincerity. Additionally, we may use appropriate assessment tools to support this process, ensuring that we identify the relevant issues." [KI01]

"In my view, the most important competency that nursing students must develop first is assessment. We need to assess the patient's spiritual issues and identify what they are. Then, we use that information to plan nursing interventions and implement appropriate care." [KI04]

Theme 2 Competency in Planning and Implementing Spiritual Care

Subtheme 2.1 Maintaining a Positive Attitude and Respecting Patients' Spiritual Beliefs

Key informants emphasized that maintaining a positive attitude and showing respect for patients' spiritual beliefs are essential competencies in providing effective spiritual care. This involves not only accepting and valuing patients' faith and spiritual perspectives without prejudice or judgment, but also understanding the deeper meaning these beliefs hold for each individual. Such an approach fosters trust and emotional reassurance, contributing to a supportive care environment. As illustrated by the following statements from the key informants:

"I think it is part of nursing practice, which includes having a positive attitude toward patients and respecting their diverse cultural and religious beliefs." [KI03]

"We should have a positive attitude toward patients' spirituality, which means accepting, respecting, and refraining from making judgments about their spiritual beliefs." [KI02]

Subtheme 2.2 Communication and Counseling for Patients

Key informants explained that building an effective caregiver-patient relationship through open communication, active listening, and counseling is essential for understanding patients' spiritual issues, needs, and perspectives. Such a relationship fosters trust and enables the development of care plans that are truly aligned with patients' spiritual concerns, thereby enhancing the relevance and effectiveness of spiritual care interventions. This is illustrated by the following statements from the key informants:

"We must engage in meaningful communication, which involves active listening and understanding patients' emotions. By building a good relationship and fostering trust, we create a safe space where patients feel comfortable expressing their feelings." [KI02]

"Sometimes, patients hesitate to talk directly to the nurses, but they may feel more comfortable speaking with the student nurses during clinical practice. For example, when I was training in community psychiatric care, I met a patient who had lost a loved one and was struggling to cope. By engaging in conversation and building rapport, I provided a space for the patient to express their emotions. The patient mentioned never having spoken to family members about

their feelings due to fear of being perceived as weak. However, through our interaction, they were able to share their emotions, which brought them comfort and relief." [KI05]

Subtheme 2.3 Empathy and Compassion for Patients

Key informants emphasized that empathy and compassion are essential in addressing patients' spiritual needs. Providing care with genuine kindness and attentiveness helps patients feel valued and understood, fostering a strong therapeutic relationship. Additionally, demonstrating honesty in the care process is vital for building trust between caregivers and patients, which is crucial for spiritual well-being. Prioritizing patient safety is also a reflection of a commitment to holistic care, addressing not only physical and emotional but also spiritual needs. The following statements from key informants illustrate these perspectives:

"For me, I think the most important thing is having compassion for patients. Understanding that those who come for treatment often feel discomfort or distress due to their illness. As nursing students, we have the opportunity to care for these patients, so we should show empathy and understand their suffering. We need to consider how to provide appropriate care and interact with them in a way that respects their condition." [KI06]

"By using our own spirituality — whether it is providing nursing care with gentleness and kindness — we embody the spirit of being a nursing student." [KI04]

Subtheme 2.4 Encouraging Patients to Practice Their Faith and Beliefs

Key informants explained that encouraging patients to practice their religious and spiritual beliefs is a crucial element in addressing their spiritual needs. Examples of practices that support this include meditation, chanting, listening to religious teachings, and reading spiritual books. Involving family members or close individuals in these activities can further enhance their effectiveness. Additionally, providing necessary accommodations, such as prayer rooms, meditation spaces, or other designated areas for religious activities, is essential. For patients with mobility limitations, facilitating spiritual practices at their bedside is also significant. These activities play a vital role in fostering emotional strength, promoting inner peace, and alleviating the suffering of patients. This is reflected in the following statements from key informants:

"We should encourage patients to practice their faith. For example, Buddhist patients may engage in meditation or chanting. If there is a designated space available, we should facilitate their access to it." [KI01]

"Encouraging patients to follow their religious beliefs, such as practicing meditation, chanting, or reading spiritual books. Additionally, providing support by arranging spaces or facilities for religious activities." [KI03]

Subtheme 2.5 Referral of Patients to Spiritual Care Specialists

The key informants explained that referring patients to specialized spiritual care professionals is essential when their spiritual needs exceed the nursing students' capabilities. Such referrals may involve consultations or guidance from clinical instructors, healthcare professionals, monks, clergy members, religious leaders, or individuals with expertise in religion and spirituality. This process ensures that patients receive appropriate and profound care that aligns with their beliefs, faith, and spiritual needs, providing personalized support tailored to each individual. The following statements from key informants illustrate these perspectives:

"Providing patients with access to specialists — if we can facilitate this, it would be highly beneficial." [KI01]

"Giving patients the opportunity to communicate with their spiritual support and ensuring they have access to this resource." [KI02]

Theme 3 Competency in Evaluating Spiritual Care Practices

Key informants emphasized that evaluating spiritual care practices is essential for nursing students, as it allows them to assess whether patients have received adequate spiritual support. This evaluation, a key part of the nursing process, helps determine care effectiveness and identify areas for improvement. It also serves as a reflective tool, enabling nursing students to deepen their understanding of spiritual care and enhance their ability to address patients' spiritual needs in the future. The following statements from key informants illustrate these perspectives:

"The competency in evaluating spiritual care means that after assessing the patient's needs and implementing care, we must evaluate each time. This helps us determine how beneficial our actions have been for the patient and allows us to make improvements." [KI01]

"The competency in evaluating spiritual care is essential for adjusting and improving patient care to better suit their needs." [KI03]

Discussion

Nursing students' perceptions of their competency in providing spiritual care encompass several key areas: assessing and diagnosing spiritual issues, planning and implementing spiritual practices, and evaluating spiritual care interventions. Understanding these perceptions is crucial for improving nursing education and ensuring the integration of spiritual care into clinical practice.

Competency in Assessing and Diagnosing Spiritual Issues

Key informants emphasized the importance of building core competencies in evaluating and identifying patients' spiritual needs as a fundamental aspect of delivering effective spiritual care. The ability to assess and diagnose spiritual issues is a critical competency for nursing students and healthcare professionals in delivering holistic patient care.

Effective assessment involves observing patients' facial expressions, body language, and significant spiritual objects or symbols, such as amulets or sacred threads, which may indicate their spiritual beliefs and needs.

Additionally, engaging in conversations regarding spiritual concerns and utilizing standardized spiritual assessment tools are essential in identifying patients' spiritual distress and requirements. These practices serve as the foundation for planning and implementing appropriate spiritual care interventions.[11-13]

This perspective aligns with the nursing process framework, which emphasizes that assessment and diagnosis are fundamental steps in identifying patient needs and planning appropriate nursing interventions.[14] Empirical studies further support this view, highlighting that assessing patients' spiritual concerns is a core competency required for both nursing students and practicing nurses in providing spiritual care.[15-19]

A recent qualitative study by Matos et al[2] examining spiritual care from the perspective of palliative care specialists in Portugal reinforces the importance of spiritually competent care strategies. The study emphasizes that assessment of patients' spiritual needs is essential for effective spiritual care delivery, particularly in palliative settings. These findings underscore the necessity of integrating spiritual assessment training into nursing education to enhance students' competency in addressing the spiritual dimensions of patient care.

Competency in Planning and Implementing Spiritual Care

- **Maintaining a Positive Attitude and Respecting Patients' Spiritual Beliefs**

Key informants emphasized that maintaining a positive attitude and respecting patients' spiritual beliefs are essential components of effective spiritual care. A fundamental aspect of spiritual care competency in nursing is maintaining a positive attitude and demonstrating respect for patients' spiritual beliefs. This includes acknowledging and valuing patients' faith, religious practices, and spiritual perspectives without bias or judgment. Nurses must be mindful of not imposing their own beliefs on patients, as doing so may compromise trust and emotional comfort. Instead, by fostering an environment of acceptance and respect, healthcare providers can enhance the therapeutic relationship and contribute to holistic patient care.[20]

This approach aligns with previous studies emphasizing the significance of positive attitudes and respect for patients' faith as a core competency for nursing students and professional nurses in delivering spiritual care.[15-19] A study by Bø et al[21] analyzing the strengths and areas for improvement in nursing students' spiritual care competencies found that an open and accepting attitude toward patients plays a crucial role in enhancing students' ability to provide effective spiritual care. Similarly, García-Navarro et al[22] explored nursing students' perceptions of the spiritual needs of terminally ill patients and found that respecting patients' and their families' beliefs is a fundamental aspect of end-of-life spiritual care.

Furthermore, Irajpour et al[23] examined the perspectives of chronically ill Muslim patients on spiritual care, revealing that patients want recognition and treatment that respects their cultural values, personal beliefs, and spiritual traditions. These findings underscore the necessity of integrating cultural sensitivity and respect for diverse spiritual perspectives into nursing education and practice, thereby enhancing nurses' ability to provide patient-centered and spiritually competent care.

- **Communication and Counseling for Patients**

Key informants emphasized that effective communication and patient counseling are fundamental to providing meaningful spiritual care. Effective communication and counseling are essential competencies in spiritual care, enabling caregivers to establish meaningful relationships with patients. Open communication, active listening, and providing counseling facilitate a deeper understanding of patients' spiritual concerns, needs, and perspectives. Establishing such relationships not only fosters trust between caregivers and patients but also enhances the ability to design care interventions that are truly aligned with patients' spiritual needs.[13, 20]

These findings align with previous research emphasizing the critical role of communication and counseling skills in nursing students' and professional nurses' ability to provide spiritual care.[15-19] Moosavi et al[24] further examined the impact of spiritual care on cancer patients, highlighting that effective communication is a key factor in spiritual care. Their findings suggest that nurses who are sensitive to patients' spiritual needs and encourage them to express their feelings can reduce their sense of isolation, foster stronger nurse-patient relationships, build trust, and enhance the overall quality of spiritual care. Thus, integrating effective communication and counseling skills into nursing education and practice is essential for delivering holistic, patient-centered spiritual care. By doing so, nurses can better support patients' emotional and spiritual well-being, ultimately improving their overall healthcare experience.

- **Empathy and Compassion for Patients**

Key informants emphasized that empathy and compassion are vital in meeting patients' spiritual needs and supporting holistic, person-centered care. Providing care with genuine empathy and compassion allows patients to feel valued and acknowledged, fostering effective communication and a trusting caregiver-patient relationship.[20-23] Moreover, demonstrating integrity in the care process plays a crucial role in establishing trust between nursing students and patients. Prioritizing patient safety reflects a nursing student's responsibility and commitment to holistic health, encompassing physical, psychological, social, and spiritual dimensions. These findings align with previous studies indicating that nursing students and professional nurses should be attentive to patients' spiritual needs as part of routine care.[15-19] Similarly, Irajpour et al[25] and Irajpour et al[23] found that compassion and kindness from caregivers are crucial in addressing the spiritual needs of chronically ill Muslim patients. Furthermore, Wang et al26 identified a positive correlation between nursing students' empathy and their perception of spiritual care, indicating that students with higher levels of compassion are more likely to engage in effective spiritual care practices. These findings underscore the necessity of integrating compassion, integrity, and patient safety into nursing education and clinical practice to enhance the delivery of holistic, patient-centered spiritual care.

- **Encouraging Patients to Practice Their Faith and Beliefs**

Key informants emphasized that encouraging patients to practice their faith and beliefs is an important aspect of supporting their spiritual well-being. The primary informants emphasized the importance of supporting patients in maintaining their religious and spiritual practices, such as meditation, prayer, listening to religious teachings, reading sacred texts, and engaging in religious activities with family members or close companions. Additionally, facilitating access to religious spaces, such as prayer rooms or bedside accommodations for those with mobility limitations, plays a vital role in addressing patients' spiritual needs. These practices enhance patients' inner strength, promote peace of mind, and alleviate suffering.[12, 13, 24] This perspective aligns with previous studies by Vogel et al,[15] Daghan et al,[16] Abusafia et al,[17] Seid et al,[18] and Fang et al[19] which highlight the essential role of nurses and nursing students in assisting patients to maintain their spiritual and religious practices. Similarly, studies by Irajpour et al[25] and Irajpour et al[23] found that Muslim patients with chronic illnesses often seek religious practices to cope with their illnesses by fostering inner peace, reducing anxiety and fear, strengthening their connection with religious figures, and enhancing hope, confidence, and a sense of security. Moreover, Cheng et al[27] investigated the spiritual needs of patients with advanced cancer in China and found that many expressed a strong desire to engage in folk religious practices. These included visiting temples to pay homage to Buddha and participating in religious rituals such as incense burning, chanting, and listening to spiritual music. Such practices provided patients with comfort and hope, helping them navigate the challenges of their illness.

- **Referral of Patients to Spiritual Care Specialists**

Key informants emphasized that referring patients to spiritual care specialists is important for ensuring they receive appropriate and personalized support for their spiritual needs. The primary informants emphasized the critical importance of referring patients to specialized spiritual care providers when their spiritual needs exceed the nursing students' capacity. Such referrals may involve consultations with clinical supervisors, healthcare professionals, Buddhist monks, clergy members, religious leaders, or individuals with expertise in religious and spiritual matters. This process ensures that patients receive appropriate and in-depth spiritual care tailored to their individual beliefs, faith, and spiritual needs.[12] This perspective aligns with previous studies by Vogel et al,[15] Daghan et al,[16] Abusafia et al,[17] Seid et al,[18] and Fang et al[19] which highlight that referring patients to spiritual care specialists is a crucial competency for nursing students and nurses in providing spiritual care. Similarly, García-Navarro et al[22] explored the spiritual needs of terminally ill patients from the perspective of nursing students. The findings revealed that nursing students recognized the importance of nurses facilitating access to spiritual care specialists, such as hospital chaplains, priests, or other spiritual leaders who align with the patient's faith and beliefs. This approach ensures that patients receive holistic care that respects and supports their spiritual well-being.

Competency in Evaluating Spiritual Care Practices

Key informants emphasized that evaluating spiritual care is vital for ensuring effectiveness and improving future care. The primary informants emphasized that evaluating spiritual care practices is a crucial process, as it enables nursing students to assess whether patients' spiritual needs have been adequately addressed. This evaluation not only helps determine the effectiveness of the care provided but also serves as a guideline for improving and enhancing the quality of spiritual care for patients.[13] This concept aligns with the nursing process, which identifies nursing evaluation as a critical step in assessing whether nursing interventions achieve the intended outcomes. Through this process, caregivers can measure the success of resolving patient concerns, conduct reassessments, and modify care plans to enhance the quality of care.[13] Furthermore, previous studies Vogel et al,[15] Daghan et al,[16] Abusafia et al,[17] Seid et al,[18] and Fang et al[19] have highlighted that evaluating spiritual care alongside patients and healthcare teams is a key competency for nursing students and professional nurses in providing holistic spiritual care.[15-20] Similarly, a qualitative synthesis by Sarrión-Bravo et al[3] examined learning outcomes related to the assessment of nursing students' competencies in spiritual and emotional care. The findings indicated that monitoring, evaluating, and improving spiritual and emotional care to meet patients' needs are essential indicators for measuring learning outcomes in nursing students' ability to provide spiritual and emotional care.

Recommendations

For nursing education institutions, nursing curricula should incorporate structured training — such as case-based learning, role-play, and simulations — focused on using spiritual assessment tools and developing critical thinking to help students effectively identify and assess patients' spiritual needs. Nursing programs should provide practical training that fosters respect for spiritual diversity, builds communication and empathy skills, and guides students in supporting spiritual practices and making appropriate referrals. Students should be taught to evaluate spiritual care outcomes using feedback and observable signs of well-being, supported by tools like reflective journals, case studies, and input from patients or preceptors.

For further research, building on the findings of this study, future research should focus on developing models or programs specifically designed to improve nursing students' competencies in providing effective spiritual care for patients.

Conclusions

The findings of this study highlight that nursing students recognize their competencies in providing spiritual care across three key areas: assessment and diagnosis of spiritual concerns, planning and implementation of spiritual care, and evaluation of care practices. Despite these competencies, it is evident that further support and training are essential to enhance their confidence and skills in addressing the spiritual needs of patients. These findings emphasize the importance of integrating spiritual care training into nursing education to better prepare students for the holistic care of patients in clinical settings. A limitation of this study is the lack of religious diversity among participants, as all identified as Buddhists. This homogeneity may limit the generalizability of the findings in addressing spiritual care for individuals from diverse religious backgrounds.

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Effects of a Health Literacy Enhancement Programs for COVID-19 Prevention on Health Literacy and COVID-19 Preventive Behaviors Among Caregivers of Dependent Older People

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Abstract

Background: Older people with dependent conditions are highly vulnerable to COVID-19 due to exposure to respiratory droplets from talking, coughing, sneezing, or close contact with caregivers.

Objectives: To evaluate the effectiveness of a health literacy enhancement program on caregivers' health literacy and preventive behaviors.

Methods: This quasi-experimental study was conducted in Phak Hai district, Phra Nakhon Si Ayutthaya province, from September 2023 to January 2024. The study included 50 caregivers selected through simple random sampling and divided into the experimental group (n = 25) and control groups (n = 25). The experimental group participated in an 8-week COVID-19 prevention program based on Nutbeam's health literacy framework, while the control group received standard care. The instruments used for data collection included 3 components: a personal information questionnaire; the COVID-19 Health Literacy Questionnaire (content validity index [CVI] = 0.88, Cronbach α = 0.84); and the COVID-19 Preventive Behavior Questionnaire (CVI = 0.88, Cronbach α = 0.76). Statistical tests included *t* tests, the Wilcoxon signed rank test, the Mann-Whitney *U* test, and analyses of covariance (ANCOVA).

Results: The experimental group achieved significantly higher postintervention health literacy scores compared to their preintervention scores and the control group ($P < .05$). Improvements were observed in accessing information, decision-making, and health behavior changes ($P < .05$). Also, postintervention preventive behavior scores of the experimental group were significantly higher in the control group, even after adjusting for baseline differences ($P < .05$).

Conclusions: This study has reinforced the importance of health literacy programs in effectively empowering caregivers to prevent COVID-19. Primary healthcare units should implement this program to better protect dependent older people from COVID-19.

Keywords: Caregivers, COVID-19 prevention, Dependent older people, Health literacy enhancement program

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Introduction

COVID-19, caused by the SARS-CoV-2 virus, is primarily transmitted through respiratory droplets produced during speaking, coughing, sneezing, or close contact, particularly in crowded settings. The disease manifests with a wide range of symptoms, from mild to severe, including life-threatening pneumonia. The COVID-19 pandemic has had a profound global impact and has disrupted health systems, mental well-being, societal structures, and economies[1] while incurring significant healthcare expenses and widespread business losses. Between January 2020 and May 2024, approximately 775.48 million cases and over 7.04 million deaths were reported globally.[1] In Thailand, the pandemic resulted in 4.7 million confirmed cases and 34 553 deaths, with widespread community transmission posing substantial challenges to public health management. In 2021, there were 182 950 confirmed cases of COVID-19 among older adults in Thailand, comprising approximately 11% of the total infections reported nationwide that year. Concurrently, 14 597 older adults died due to COVID-19, representing about 70% of all COVID-19-related fatalities during the same period.[2] On 29 February 2020, COVID-19 was officially designated as a dangerous infectious disease under the Communicable Diseases Act, B.E. 2558.[2] Certain regions, such as Phra Nakhon Si Ayutthaya in the fourth health administrative area, experienced continuous increases in cases, particularly among high-risk populations. In this province, significant outbreaks were reported, with 70 866 confirmed cases and 588 deaths recorded between 1 April 2021 and 27 May 2024.[2]

The pandemic disproportionately affected vulnerable groups, including low-income populations, children, individuals with disabilities, and older adults with chronic illnesses. Economic disruptions, such as job losses and reduced work opportunities, exacerbated social vulnerabilities and restricted access to education and healthcare services. Older people faced challenges in self-care, daily activities, and medical access due to these compounded vulnerabilities. Family caregivers encountered heightened burdens, including financial strain, limited personal time, and emotional stress, especially when providing continuous care for older people with disabilities.

Health literacy is critical in enabling caregivers to prevent COVID-19 infections among dependent older people. Caregivers with higher levels of health literacy are better equipped to understand and implement preventive measures, such as frequent handwashing, proper mask usage, and physical distancing.[3, 4] Moreover, health literacy empowers caregivers to assess and validate health information critically, reducing the spread of misinformation and supporting informed decision-making. This knowledge is essential for protecting older people, who are at increased risk of severe COVID-19 complications. Extensive research has highlighted a significant correlation between health literacy and adherence to COVID-19 preventive behaviors. Programs utilizing group-based interventions, individual counseling, and multimedia tools have been effective in enhancing preventive practices.[5-7] However, much of the existing research had focused on community health volunteers, with limited attention to caregivers of dependent older people.

Caregivers were pivotal in safeguarding the health of dependent older people during the pandemic. Improved health literacy enabled caregivers to understand better and implement critical preventive measures, reducing infection risks and alleviating the healthcare burden associated with severe COVID-19 outcomes. Despite its importance, caregiver-specific health literacy research remained underexplored, as most interventions have targeted broader community initiatives rather than addressing the unique challenges faced by caregivers of older adults with dependency.

Promoting health literacy among caregivers has become essential for mitigating COVID-19 infection risks and enhancing the quality of life for dependent older people. By equipping caregivers with accurate information and practical skills, they can adopt effective preventive behaviors, combat misinformation, and make informed decisions. Enhanced health literacy not only benefits dependent older people but also alleviates caregiver stress and improves mental well-being. This study aimed to evaluate the impact of a health literacy promotion enhancement program on caregivers' COVID-19 preventive behaviors, guided by Nutbeam's health literacy framework.[8, 9] Moreover, it aimed to compare the mean scores of COVID-19 health literacy and preventive behaviors within the experimental group (pre- and post-intervention) and between the experimental and control groups postintervention among caregivers of dependent older people. The program emphasized education and skill-building to enhance caregivers' understanding and application of preventive measures. By targeting caregiver health literacy, this study sought to improve health outcomes for dependent older people, reduce hospitalization rates, and alleviate the economic and emotional strain on families.

Methods

Data Collection

This study employed a quasi-experimental, 2-group pretest-posttest control group design to assess the effectiveness of a health literacy promotion enhancement program on COVID-19 prevention among caregivers of older people with dependency in Phak Hai district, Phra Nakhon Si Ayutthaya province. This study used Nutbeam's health literacy framework in a quasi-experimental pretest-posttest design with 44 participants. An effect size of 0.83 indicated a large effect, which required 20 participants per group at 80% power and 0.05 significance. To account for attrition, the sample was increased to 25 per group (total 50). Participants were randomly assigned by subdistrict to experimental and control groups. The sample consisted of 50 caregivers aged 18-59 years who were literate in Thai, without mental health problems, and who had served as primary family caregivers for at least one year. All participants had a close relationship or kinship with the dependent older people. Participants were recruited through community networks and randomly assigned using simple random sampling into the experimental or control group, with 25 participants each. Data collection was conducted in 2 subdistricts: Lat Chit for the experimental group, and Na Khok for the control group.

The 8-week intervention for the experimental group was designed based on Nutbeam's health literacy framework, addressing functional, communicative, and critical health literacy.[8, 9] Weekly activities focused on enhancing caregivers' skills in information comprehension, access, self-management, communication, media literacy, and critical decision-making. The intervention employed a blended approach, including interactive group sessions, practical exercises, and online discussions facilitated via the LINE application. In addition to these activities, validated questionnaires were provided to track participants' progress. The control group also received a handbook containing COVID-19 prevention guidelines and continued with routine caregiving practices.

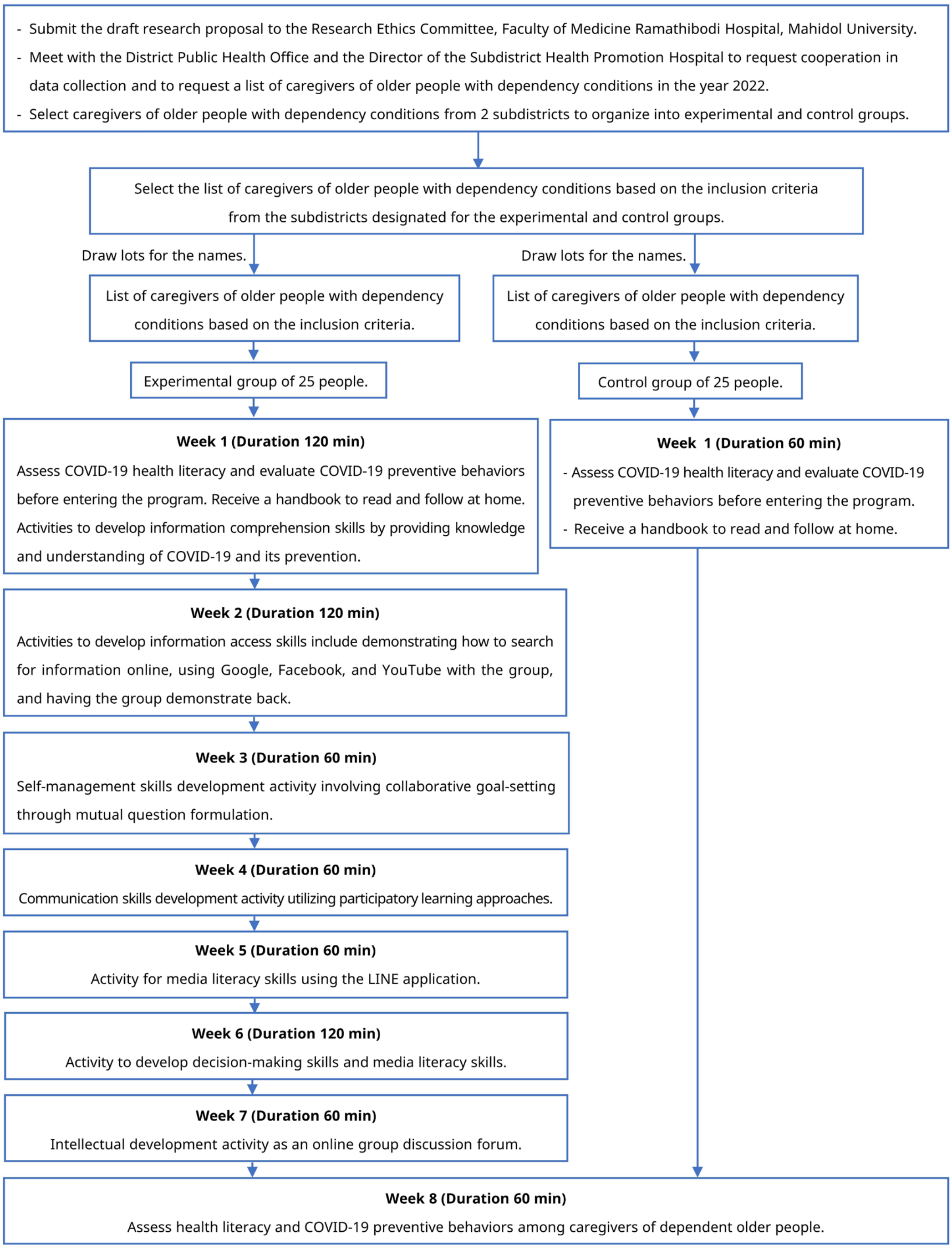
Ethics approval for this study was obtained from the Faculty of Medicine Ramathibodi Hospital, Mahidol University (MURA2023/265). Permissions were also secured from provincial, district, and local health offices. Stakeholders were briefed on the study objectives to ensure alignment and support. Trained research assistants with experience in community health promotion conducted recruitment and data collection to maintain procedural consistency and data quality. Baseline data were collected before the intervention, including the Barthel Index,[10] COVID-19 Health Literacy Questionnaire, and COVID-19 Preventive Behavior Questionnaire, which ask close-ended questionnaires. The responses were rated on a Likert scale. Experts evaluated content validity, language clarity, alignment with research variables, and comprehensiveness of content. Based on the expert feedback, the researcher revised the COVID-19 Preventive Behavior Questionnaire, which demonstrated good content validity (content validity index [CVI] = 0.88) and acceptable internal consistency reliability (Cronbach α = 0.76). Similarly, the COVID-19 Health Literacy Questionnaire demonstrated strong content validity (CVI = 0.88) and high reliability (Cronbach α = 0.84).

A pilot test with 15 family caregivers yielded a reliability coefficient of 0.84. The main study (n = 50) assessed internal consistency using Cronbach α. The COVID-19 Health Literacy Questionnaire showed a reliability coefficient of 0.88, and the COVID-19 Preventive Behavior Questionnaire yielded 0.93, indicating high reliability. The selection of the subdistricts for the experimental and control groups was done using simple random sampling through a lottery draw of subdistricts in Phak Hai district out of a total of 16 subdistricts. The first subdistrict drawn was assigned to the experimental group (Lat Chit subdistrict), and the second subdistrict drawn was assigned to the control group (Na Khok subdistrict). Both subdistricts are in rural communities and are approximately 10 kilometers apart. Lat Chit subdistrict comprises 10 villages, while Na Khok subdistrict comprises 7 villages. The intervention lasted 8 weeks, during which the experimental group participated in weekly health literacy activities targeting COVID-19 prevention. The data collection spanned 8 weeks and involved both experimental and control groups. The experimental group participated in a structured health literacy intervention comprising sessions of varying durations — 120 minutes during Weeks 1, 2, and 6, and 60 minutes in Weeks 3, 4, 5, 7, and 8 — while the control group received standard health information sessions of 60 minutes in Weeks 1 and 8. In Week 1, baseline assessments were conducted, and participants received a self-study handbook along with foundational learning activities to enhance their understanding of COVID-19 related information. Week 2 focused on developing information access skills through training in digital searches using platforms such as Google, Facebook, and YouTube, supplemented by group demonstrations. Week 3 emphasized self-management by facilitating personalized goal setting and the formulation of individual health questions. Week 4 focused on developing communication skills through participatory learning methods, while Week 5 introduced media literacy through practical exercises using the LINE application. In Week 6, decision-making and critical evaluation skills were reinforced through a guided assessment of health information credibility and applicability. Week 7 engaged participants in intellectual development through online discussion forums, and Week 8 concluded with postintervention assessments to evaluate changes in health literacy and COVID-19 preventive behaviors (Figure 1). Postintervention evaluations were conducted to assess changes in health literacy and preventive behaviors. Participants were fully informed about the study objectives, procedures, and their rights, including the option to withdraw at any point without repercussions. Data confidentiality was maintained, and findings were reported transparently to uphold scientific integrity.

Statistical Analysis

Data analysis was performed using SPSS software version 26.0 (IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp; 2019). Descriptive statistics were calculated to summarize demographic and caregiving-related characteristics, including frequency, percentage, mean (SD), and median. Inferential statistics were used to evaluate the intervention's impact. The Shapiro-Wilk test assessed the normality of the data. The Wilcoxon signed rank test was used for within-group comparisons of nonnormally distributed variables, while the Mann-Whitney *U* test compared differences between groups. Additionally, analysis of covariance (ANCOVA) was applied to adjust for baseline differences and compare postintervention COVID-19 preventive behavior scores between groups. This rigorous analytical approach ensured the reliability and validity of the study's findings, offering robust insights into the effectiveness of the health literacy promotion program.

Figure 1. Flow Diagram of Intervention Between Experimental and Control Group



- Submit the draft research proposal to the Research Ethics Committee, Faculty of Medicine Ramathibodi Hospital, Mahidol University.
- Meet with the District Public Health Office and the Director of the Subdistrict Health Promotion Hospital to request cooperation in data collection and to request a list of caregivers of older people with dependency conditions in the year 2022.
- Select caregivers of older people with dependency conditions from 2 subdistricts to organize into experimental and control groups.

Select the list of caregivers of older people with dependency conditions based on the inclusion criteria from the subdistricts designated for the experimental and control groups.

Draw lots for the names.

List of caregivers of older people with dependency conditions based on the inclusion criteria.

Experimental group of 25 people.

Week 1 (Duration 120 min)

Assess COVID-19 health literacy and evaluate COVID-19 preventive behaviors before entering the program. Receive a handbook to read and follow at home. Activities to develop information comprehension skills by providing knowledge and understanding of COVID-19 and its prevention.

Week 2 (Duration 120 min)

Activities to develop information access skills include demonstrating how to search for information online, using Google, Facebook, and YouTube with the group, and having the group demonstrate back.

Week 3 (Duration 60 min)

Self-management skills development activity involving collaborative goal-setting through mutual question formulation.

Week 4 (Duration 60 min)

Communication skills development activity utilizing participatory learning approaches.

Week 5 (Duration 60 min)

Activity for media literacy skills using the LINE application.

Week 6 (Duration 120 min)

Activity to develop decision-making skills and media literacy skills.

Week 7 (Duration 60 min)

Intellectual development activity as an online group discussion forum.

Draw lots for the names.

List of caregivers of older people with dependency conditions based on the inclusion criteria.

Control group of 25 people.

Week 1 (Duration 60 min)

- Assess COVID-19 health literacy and evaluate COVID-19 preventive behaviors before entering the program.
- Receive a handbook to read and follow at home.

Week 8 (Duration 60 min)

Assess health literacy and COVID-19 preventive behaviors among caregivers of dependent older people.

Results

The study involved 50 older people with dependency and their 50 primary caregivers, equally divided into experimental and control groups (n = 25 each) from 2 subdistricts in Phak Hai district, Phra Nakhon Si Ayutthaya province. Among the older participants, most were female, aged between 73 and 78 years, and moderately dependent for daily activities. The majority were single, widowed, divorced, or separated, and they had at least a primary education, identified as Buddhist, and lived with family members. Hypertension was the most common chronic illness. Most were related to their caregivers. In terms of income, a greater proportion of the experimental group reported adequate income without savings or debt, whereas the control group showed more variability. Access to communication technology was generally limited, particularly in the experimental group. Nearly all participants were covered under Thailand's universal health coverage scheme. Statistical analysis revealed no significant differences between the groups in baseline characteristics (*P* > .05) (Table 1).

The results showed that almost all primary caregivers were children or grandchildren, predominantly female and married, with both groups mainly identifying as Buddhist. Educational attainment differed, with the experimental group having more caregivers with at least a high school education, while the control group had more with elementary education or below. Common chronic conditions include hypertension and diabetes. Family roles varied, with the experimental group evenly split between heads of families and members, while most in the control group were family members. Universal health coverage was the main welfare benefit, which was more common in the control group. Caregivers had varied proficiency in using phones and digital applications, with differences analyzed using chi-square tests (Table 2).

Table 1. Characteristics of Older People With Dependency

Personal Information	**No. (%)**		**Statistics**	***P* Value**
	Experimental Group	**Control Group**		
Barthel ADL Index				
Severe and complete dependence (0-8)	9 (36)	12 (48)	0.74[b]	.390
Moderate dependence (9-11)	16 (64)	13 (52)		
Gender				
Male	12 (48)	8 (32)	1.33[b]	.248
Female	13 (52)	17 (68)		
Education level				
No formal education	4 (16)	4 (16)	NA	1.00[a]
Primary education and above	21 (84)	21 (84)		
Marital status				
Marital status/partner/single/widowed	5 (20)	6 (24)	0.12[b]	.733
Divorced/separated	20 (80)	19 (76)		

Table 1. Characteristics of Older People With Dependency (Continued)

Personal Information	No. (%)		Statistics	*P* Value
	Experimental Group	Control Group		
Living arrangements				
Living independently with spouse/family including children/grandchildren	24 (96)	2 (8)	NA	1.00[a]
Living with family, including children/grandchildren occasionally	1 (4)	23 (92)		
Family membership				
Householder	2 (8)	2 (8)	NA	1.00[a]
Family member	23 (92)	23 (92)		
Ability to use the telephone to communicate				
Yes	3 (12)	10 (40)	5.10[b]	.024
No	22 (88)	15 (60)		

Abbreviations: ADL, activities of daily living; NA, not applicable.

[a] Fisher exact test.

[b] Chi-square test.

Table 2. Characteristics of Primary Caregivers

Personal Information	No. (%)		Statistics	*P* Value
	Experimental Group	Control Group		
Relationship				
Child/grandchild	16 (64)	18 (72)	0.37[b]	.544
Spouse/sibling	9 (36)	7 (28)		
Gender				
Male	4 (16)	2 (8)	NA	.667[a]
Female	21 (84)	23 (92)		
Education level				
Primary education or below	7 (28)	13 (52)	NA	NA
Secondary education or higher	18 (72)	12 (48)		
Marital status				
Single/widowed	6 (24)	7 (28)	0.10[a]	.747
Divorced/separated/married	19 (76)	18 (72)		
Family membership				
Head of the family	13 (52)	3 (12)	9.20[b]	.002
Family member	12 (48)	22 (88)		

Abbreviation: NA, not applicable.

[a] Fisher exact test.

[b] Chi-square test.

Participants in the control group had a higher average monthly income (mean [SD], ฿4124 [฿3455.22]) compared to the experimental group (mean [SD], ฿5720 [฿2614.38]), though income variability was greater in the control group. Older people in the control group were also older on average (mean [SD], 77.96 [10.31] years) compared to the experimental group (mean [SD], 72.88 [7.89] years). Despite these differences, statistical analysis indicated no significant differences in income or age between groups ($P > .05$). Analysis using the Mann-Whitney U test revealed no significant differences in age ($Z = -0.058$, $P = .954$). Chi-square tests indicated no significant differences in caregiver characteristics, except for education and welfare benefit use.

The analysis comparing the mean rank scores for health literacy on COVID-19 among caregivers of older people with dependency in the experimental and control groups before the intervention revealed no statistically significant difference ($Z = -1.084$, $P = .278$). In contrast, comparing the mean scores of COVID-19 prevention behaviors between the experimental and control groups before the intervention showed a statistically significant difference ($t = -5.643$, $P < .001$), from which the mean preventive behavior in the experimental group was higher than the control group, which showed notable variations (Table 3).

The hypothesis was that the health literacy and COVID-19 prevention behavior scores would improve post-program and be higher in the experimental group. The Shapiro-Wilk test assessed normalities. Most variables were normally distributed, except for specific pre- and post-program health literacy scores. The Wilcoxon signed-rank test showed significant improvements in health literacy scores for the experimental group postintervention ($Z = -2.40$, $P = .016$). No significant differences were observed in the control group ($Z = -0.701$, $P = .483$). COVID-19 prevention behavior scores using paired t tests revealed no significant changes in either group (experimental: $t = -0.712$, $P = .483$; control: $t = -0.097$, $P = .923$) (Table 4).

Comparative analysis of preintervention health literacy scores between groups showed no significant differences ($Z = -1.084$, $P = .278$). However, postintervention scores were significantly higher in the experimental group ($Z = -2.09$, $P < .05$). ANCOVA confirmed that postprogram COVID-19 prevention behavior scores were significantly higher in the experimental group than in the control group ($P < .05$) (Table 5).

Table 3. Comparison of Scores for Health Literacy on COVID-19 and COVID-19 Preventive Behaviors Between Control and Experimental Groups Before and After the Program

Study Variable	Possible Scores	Control Group (n = 25)		Experimental Group (n = 25)		Z	*t*	*P* Value
		Min-Max	Mean (SD)	Min-Max	Mean (SD)			
Before received the program								
Scores of COVID-19 health literacy	0-40	27-38	33.04 (3.28)	23-38	33.56 (4.25)	-1.084	NA	.278
Scores of COVID-19 preventive behaviors	0-80	46-72	58.16 (7.67)	51-80	70.44 (7.71)	NA	-5.643	< .001
After received the program								
Scores of COVID-19 health literacy	0-40	17-40	31.08 (7.18)	31-40	35.52 (2.63)	-2.09	NA	< .05

Abbreviation: NA, not applicable.

Table 4. Comparison of Average Scores of COVID-19 Preventive Behaviors Among Caregivers of Older People With Dependency Before and After the Intervention in Each Group With Paired *t* Test

Study Variable	Status	No.	Min-Max	Mean (SD)	*t*	*df*	*P* Value
Experimental group							
COVID-19 preventive behaviors	Before the experiment	25	51-80	70.44 (7.71)	-0.712	24	.483
	After the experiment	25	61-80	71.48 (5.92)			
Control group							
COVID-19 preventive behaviors	Before the experiment	25	27-38	58.16 (7.67)	-0.097	24	.923
	After the experiment	25	17-40	58.40 (11.57)			

Abbreviations: *df,* degree of freedom; NA, not applicable.

Table 5. Comparison of Mean Scores of COVID-19 Prevention Behaviors Between Control and Experimental Groups at Pretest (Week 1) and Posttest (Week 8) Using Parametric ANCOVA

Study Variable	SS	*df*	MS	*F*	*P* Value
Prevention Behaviors Pretest	349.097	1	349.900	4.418	.041
Group	578.097	1	578.097	7.299	.010
Error	3722.340	47	79.199	NA	NA

Abbreviations: *df,* degree of freedom; MS, mean square; NA, not applicable; SS, sum of squares.

Discussion

Data collection was conducted on the same day in both settings to control for potential variation from participant interaction across study sites. The personal information of dependent older people included factors such as their ability to perform daily living activities (Barthel ADL Index),[10] gender, age, education, marital status, chronic diseases, family membership, income, and use of communication technologies. Most dependent older people were female, with the average age in the experimental and control groups being 72.88 and 77.96 years, respectively. This aligned with global trends, as older females generally live longer than males.[11] Both groups exhibited moderate dependency on the Barthel ADL Index, consistent with previous research.[12, 13] Many participants were widowed, divorced, or separated, supporting findings from other studies.[13, 14] Most participants had primary education or higher, and most were Buddhists. The study revealed that most lived with family members, and many had multiple chronic conditions, particularly hypertension, in line with earlier studies.[13, 14] Regarding income, most participants reported sufficient income but no savings or debt, consistent with economic challenges faced by older Thai people.[15]

Caregivers of dependent older people were predominantly female and in late adulthood, typically children or grandchildren, reflecting traditional caregiving roles in Thai culture[16, 17] Most caregivers were married, with spousal support critical in caregiving effectiveness.[16, 18] Caregivers with higher education levels demonstrated better caregiving outcomes, which aligned with previous research.[19] The health status of caregivers varied, with some reporting chronic conditions, particularly hypertension, which could impact caregiving capacity. The role of family members, particularly heads of the family, differed between the experimental and control groups, with the former demonstrating better caregiving awareness, which may enhance care quality.[19] Both groups were covered under universal health coverage and were proficient in using mobile phones and communication applications, which was crucial for staying connected and accessing information. These findings highlight the importance of educational and health interventions for caregivers, particularly those with lower education or chronic health issues. Further research should examine the long-term impact of caregiving on physical and mental health and the role of spousal support.

The findings of this study supported the hypothesis, which posited that primary caregivers of older people with dependency in the experimental group would demonstrate enhanced health literacy and improved COVID-19 preventive behaviors postintervention. The results revealed a significant increase in the mean health literacy score related to COVID-19 among participants in the experimental group following the program. In addition, the caregivers exhibited a marked improvement in their COVID-19 preventive behaviors. This improvement can be attributed to the structured health literacy promotion activities incorporated in the program, which focused on 6 key skills: information access, comprehension, communication, self-management, decision-making, and media literacy. These activities facilitated caregivers' acquisition of knowledge about COVID-19 and engaged them in online platforms that supported knowledge sharing and self-monitoring, which were essential for mitigating risk behaviors. The program's emphasis on communication, media literacy, decision-making, and cognitive skills empowered caregivers to understand and apply COVID-19-related information, promoting safer practices in their caregiving.

The program's success aligned with Nutbeam's framework for health literacy, which emphasizes developing social and analytical skills to motivate and enable individuals to access, understand, and apply health information. In this context, caregivers gained functional health literacy by learning about COVID-19 prevention practices, and their ability to communicate effectively was enhanced through group discussions and online exchanges. Communicative health literacy was also advanced by engaging caregivers in online discussions and sharing knowledge within a LINE application group, which fostered social skills necessary for effective participation in health-related activities. Moreover, critical health literacy was promoted through activities that required caregivers to analyze and solve problems related to COVID-19 risks. This process contributed to their ability to make informed decisions and effectively manage health behaviors. The expectation that the experimental group's caregivers would exhibit more significant health literacy and COVID-19 preventive behaviors than the control group, was also supported. After completing the program, the experimental group showed significantly higher mean health literacy scores than the control group. This improvement was primarily due to the program's focus on enhancing 6 essential health literacy components: access skills, cognitive skills, communication skills, self-management, decision-making skills, and media literacy. These components were reinforced through various activities, including demonstrations of reliable information sources, video presentations, group discussions, and simulated caregiving scenarios that allowed caregivers to practice decision-making and problem-solving. Integrating the LINE application to track and monitor COVID-19 preventive behaviors was crucial in ensuring continuous learning and caregiver engagement with the program.[20, 21] The findings of this study were consistent with those of Choojai et al,[22] who demonstrated that a structured health literacy promotion program significantly improved COVID-19-related health literacy among village health volunteers. Similarly, following a comparable intervention, Srithongpim[23] reported enhanced health literacy and preventive behaviors among individuals with chronic diseases. These studies have supported the efficacy of skill-based health literacy programs in promoting preventive behaviors. Education level was also a significant factor in determining the program's success. The experimental group mainly consisted of participants with higher education levels than the control group, who had only completed primary education. Higher education levels are known to correlate with better health literacy, as shown by studies which have found that individuals with higher education levels exhibited better health literacy and more effective health behaviors.[24-28] Although the control group received general COVID-19 prevention information from public health officials and media, their lack of participation in the health literacy enhancement program resulted in lower health literacy and preventive behaviors than the experimental group.[29] This was consistent with Bloom's Taxonomy[30] learning theory, which highlights the cognitive domains involved in learning and applying information, suggesting that the experimental group benefited from structured learning and ongoing support through the LINE application, which facilitated self-assessment and sustained behavior change.

Conclusions

Based on the results, a health literacy enhancement program significantly improved caregivers' health literacy and COVID-19 prevention behaviors. Adapting the program to fit caregivers' schedules and incorporating follow-up measures, such as information exchange via the LINE application, will enhance adherence, build confidence, and ensure consistent application of preventive practices. These improvements will better safeguard older adults with dependencies, promoting their health and well-being.

Additional Information

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Ethics Approval: This study was approved by the Human Research Ethics Committee, Faculty of Medicine Ramathibodi Hospital, Mahidol University (MURA2023/265 on 1 April 2023). The researchers initially gave the participants a full explanation of the research and its aims and obtained verbal informed consent from the participants. All data remained confidential, and the data were kept as encrypted files in computers which were only available to the study researchers. Study researchers asked for permission to use the secondary data before conducting the research. Additionally, the study was conducted in accordance with the Declaration of Helsinki.

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RMJ Original Article

Vitamin D Deficiency and Bone Turnover in People Living With HIV Switching to Tenofovir Disoproxil Fumarate/Lamivudine/Dolutegravir Versus Continuing Nonnucleoside Reverse Transcriptase Inhibitor or Protease Inhibitor Regimens in Thailand

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Abstract

Background: People living with HIV (PLWH) frequently have low bone mineral density, with vitamin D deficiency as a key risk factor. Recently, World Health Organization (WHO) and Thai national HIV guidelines recommend dolutegravir as first-line therapy, replacing nonnucleoside reverse transcriptase inhibitor (NNRTI)-based regimen.

Objectives: To compare vitamin D levels and bone changes in PLWH switching from NNRTI- or boosted protease inhibitor (PI)-containing regimens to DTG-based therapy versus those continuing NNRTI- or PI-based therapy.

Methods: This post hoc analysis used data from a randomized controlled trial (2020-2022) at Suddhavej Hospital, a university-affiliated tertiary care hospital in Maha Sarakham, Thailand. PLWH aged 18 years or older without virologic failure were randomized to either continue current NNRTI/boosted PI-containing combined antiretroviral therapy (control group, CG) or switch to tenofovir disoproxil fumarate/lamivudine/dolutegravir (TDF/3TC/DTG) (switch group, SG). The primary outcome was vitamin D deficiency at 48 weeks; secondary outcomes assessing changes in bone metabolism markers.

Results: Thirty-nine patients completed follow-up (20 CG, 19 SG). After 48 weeks, vitamin D deficiency prevalence increased in both groups (CG: 15% to 35%; SG: 15.8% to 31.6%) with no significant difference ($P = .905$). Osteocalcin increased in SG but decreased in CG ($P = .036$). Beta-crosslaps increased in both groups ($P = .461$ between groups). Procollagen type 1 amino-terminal propeptide showed a nonsignificant decrease in both ($P = .960$).

Conclusions: Switching to TDF/3TC/DTG had minimal impact on vitamin D status but was associated with increased osteocalcin, suggesting a possible positive effect on bone formation. No significant differences were seen in bone resorption or other formation markers.

Keywords: HIV, Dolutegravir, Vitamin D deficiency, Bone turnover, Bone resorption

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Introduction

In 2023, approximately 39.9 million people living with HIV (PLWH) worldwide included 1.4 million children and 38.6 million adults. An estimated 1.3 million new HIV infections occurred globally.[1] In Thailand, approximately 580 000 PLWH in 2023 represented a prevalence of about 1.1% among adults aged 15 to 49. Additionally, around 9100 new adult HIV infections were reported in the same year.[1] As the population of PLWH continues to increase, so too does the prevalence of aging-related comorbidities, such as osteoporosis and fragility fractures. PLWH are at a significantly higher risk for fragility fractures — 35% to 68% greater than that of HIV-negative individuals.[2, 3] Concurrently, vitamin D deficiency is highly prevalent among PLWH, with rates reported as high as 80%, even in sun-rich regions.[2]

Although several studies have documented the high prevalence of vitamin D deficiency and low bone mineral density in PLWH, limited data are available on the burden of vitamin D deficiency specifically among those with confirmed fragility fractures.[3] Furthermore, while the impact of various antiretroviral therapies on bone health has been explored, the bone-specific effects of newer regimens — particularly those containing integrase strand transfer inhibitors (INSTIs) — remain inadequately characterized, especially in real-world settings.[3, 4] This lack of data poses a challenge for optimizing antiretroviral therapy (ART) regimens to minimize bone-related complications.

The etiologies of low bone mineral density in PLWH are multifactorial, involving the direct effects of HIV infection, traditional risk factors for osteoporosis, chronic illness (eg, malnutrition and low body weight), tobacco and alcohol use, vitamin D deficiency, and the effects of ART.[4-6] HIV infection itself may contribute to impaired bone health through chronic systemic inflammation and immune activation, which disrupt the balance between bone formation and resorption. Furthermore, certain ART agents — particularly efavirenz (EFV) and tenofovir disoproxil fumarate (TDF) — have been shown to interfere with vitamin D metabolism by enhancing catabolism via induction of cytochrome P450 enzymes and impairing renal tubular function, respectively, thereby contributing to lower serum vitamin D levels and altered bone turnover.

INSTIs have been recommended as the preferred backbone of combined antiretroviral therapy (cART) in international treatment guidelines.[7-9] Among these, dolutegravir (DTG) and bictegravir (BIC) have demonstrated efficacy equal to or greater than that of nonnucleoside reverse transcriptase inhibitor (NNRTI) and protease inhibitor (PI)-based regimens in numerous randomized controlled trials (RCTs).[10-12] According to the 2020 Thai national HIV treatment guidelines, DTG in combination with 2 nucleoside reverse transcriptase inhibitors (NRTIs) is recommended as first-line therapy for individuals newly diagnosed with HIV-1 infection, based on its well-established durability, efficacy, and safety.[13] The guidelines also support switching from older NNRTI-based fixed-dose combinations — such as TDF/lamivudine (3TC) or emtricitabine (FTC)/EFV — to the preferred DTG-based regimen.[13]

This study aimed to evaluate the clinical outcomes associated with the implementation of the national guideline recommending a switch to the TDF/3TC/DTG fixed-dose combination, with a particular focus on bone metabolism markers.

Methods

Study Design, Setting, and Participants

This study serves as a post hoc analysis of an open-label, RCT conducted at Suddhavej Hospital, Maha Sarakham, Thailand, from December 2020 to December 2022. The study included PLWH aged 18 years or older without evidence of virologic failure, recruited from the outpatient clinic. Following the provision of written informed consent, participants were randomly assigned in a 1:1 ratio to either switch to a regimen of TDF/3TC/DTG or continue their current cART, using a computer-generated block randomization method with a block size of 4. The current cART group (CG) consisted of patients who continued to receive an NNRTI or boosted PI-containing regimen, while the switch group (SG) comprised patients who switched from an NNRTI or boosted PI-containing regimen to a fixed drug combination including 300 mg of TDF, 300 mg of 3TC, and 50 mg DTG. The exclusion criteria included: 1) women of childbearing age who intended to conceive within the next 52 weeks or refused contraception; 2) pregnant women; 3) presence of documented ART-resistant-associated mutations; 4) virologic failure, defined as an HIV viral load at least 200 copies/mL; 5) creatinine clearance less than or equal to 60 mL/min/1.73 m^2; 6) cirrhosis Child-Turcotte-Pugh score of B to C; 7) current antituberculous therapy; 8) current metformin use at a dose exceeding 1000 mg/day; 9) history of DTG hypersensitivity; 10) alanine aminotransferase (ALT) levels exceeding 5 times the upper limit of normal or total bilirubin levels exceeding 1.5 times the upper limit of normal; and 11) current use of vitamin D supplementation.

The study assessed 210 participants for eligibility, of whom 48 participants were included in the study. The remaining individuals were excluded because 130 did not meet the inclusion criteria, 17 declined to participate, 13 women of childbearing age declined contraception, and 2 were on antituberculous therapy. The 48 eligible participants were randomized, with 23 assigned to the TDF/3TC/DTG group and 25 assigned to the NNRTI or boosted-PI-containing regimen group. The intention-to-treat-exposed analysis included all participants in their assigned groups, while the per-protocol analysis included 19 participants in the TDF/3TC/DTG group and 20 in the NNRTI/boosted-PI group after accounting for discontinuations and loss to follow-up (Figure 1).

Outcomes

The primary outcome measure of this study was the proportion of patients with vitamin D deficiency, defined as a serum 25(OH) vitamin D level below 20 ng/mL at 48 weeks. Secondary outcomes included changes in biological markers of bone health assessed at the 48-week follow-up, specifically beta-crosslaps (bCTx), N-MID (N-midfragment) osteocalcin, and total procollagen type 1 amino-terminal propeptide (P1NP). Beta-crosslaps (bCTx), degradation products of type I collagen, serve as sensitive indicators of bone resorption and reflect the rate of bone turnover. N-MID osteocalcin, synthesized by osteoblasts during the bone mineralization process, is a marker of bone formation and indicative of osteoblastic activity. Total P1NP, another bone formation marker, reflects the synthesis of type I collagen, the principal structural protein in the bone matrix. Collectively, these markers provide insights into the dynamic balance between bone formation and resorption.

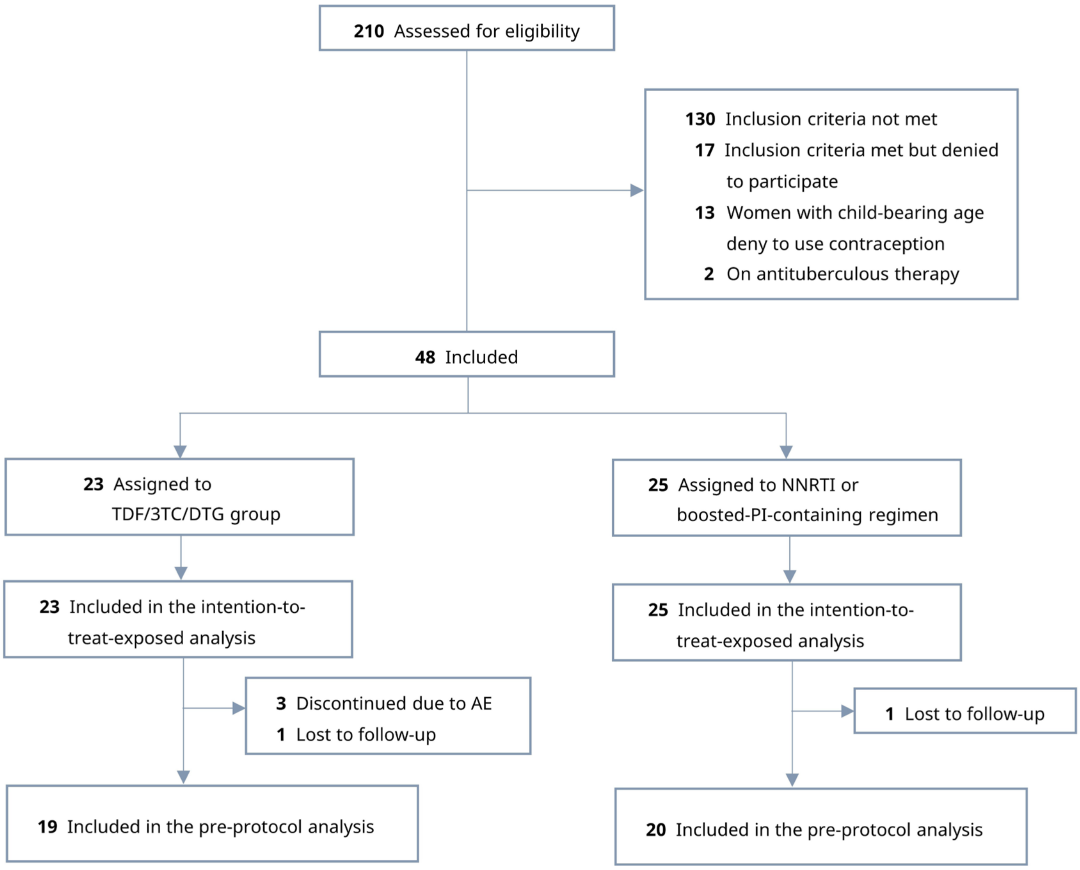
Demographic data and routine laboratory tests were also collected. Blood samples were obtained at baseline and at the 48-week follow-up to measure serum 25(OH)D and the aforementioned bone turnover markers. These samples were collected concurrently with routine blood chemistry evaluations, including renal and liver function panels, as part of the preliminary RCT protocol. All specimens were processed and analyzed in a certified central laboratory using standardized procedures.

Statistical Analysis

Statistical analysis involved expressing categorical data as frequencies and percentages, which were compared using the chi-square test. If exceed 20% of expected cell counts were less than 5, Fisher exact test was used instead. Continuous variables were analyzed using Student’s *t* test or the Wilcoxon rank sum test, depending on data distribution. A mixed model was used to analyze changes in bone turnover markers between groups. The McNemar test was applied to categorical dichotomous data. The primary outcome of the study was achieving a viral load of less than 50 copies/mL at the end of week 24 (with a 4-week window on either side) in the intention-to-treat population, which included all patients who received at least 1 dose of the trial medication. Patients with missing RNA results at week 24 were considered as not having reached an undetectable level of plasma HIV-1 RNA for the primary efficacy measure.

Sample size was calculated based on a noninferiority assumption to demonstrate that the new treatment is not clinically inferior to the standard therapy within a prespecified margin, ensuring adequate power to confirm comparable efficacy. To determine the noninferior efficacy of the DTG-based regimen compared to the standard-of-care regimen, we estimated a sample size of 75 patients per group, providing 80% power. The calculations were based on a noninferiority margin of -10 percentage points and an assumed efficacy of 79% in the standard-of-care group. The analysis also included a minimum of 20 patients per group from the pilot study. Statistical analyses were conducted using SPSS version 24.0 (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp; 2016) with a significance level set at $P \leq .05$ (2-sided). The efficacy and safety results of the main pilot study were published in an abstract presented at IDWeek 2023.[14]

Figure 1. Flow Diagram of Eligible Patients



Abbreviations: AE, adverse event; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TDF/3TC/DTG, tenofovir disoproxil fumarate/lamivudine/dolutegravir.

Results

The study population consisted of 48 PLWH, with 25 patients in the CG (continuing their current ART, either NNRTI or boosted-PI regimen) and 23 patients in the SG who had switched to the DTG-based regimen. All baseline characteristics were similar between groups (Table 1).

A total of 39 patients completed the 48-week follow-up period (20 in the CG and 19 in the SG). The prevalence of vitamin D deficiency in this population was 33.33% (13 out of 39 at the final follow-up). The proportion of patients with vitamin D deficiency showed a tendency to increase in both groups after the 48-week follow-up period (from 15.78% to 31.58% in the SG and from 15% to 35% in the CG; *P* = .268 and .186, respectively). However, there was no statistical difference between the 2 groups (*P* = .428). In the SG, mean serum 25(OH) vitamin D levels tended to minimally decrease from baseline at the final follow-up period, but the difference was not statistically significant (*P* = .321). Conversely, in the CG, mean serum 25(OH) vitamin D levels remained steady (*P* = .983). Furthermore, there was no statistical difference between the 2 groups (*P* = .505) (Table 2).

At 48 weeks, after switching to DTG, the osteocalcin level significantly increased (mean [SD], 23.85 [13.92] to 30.21 [13.92]; *P* = .025). In the CG, which maintained the NNRTI or boosted PI-containing regimen, there was a slight but insignificant decrease from 23.95 (7.58) to 22.74 (8.15) (*P* = .570). There was a significant difference in osteocalcin level changes between the 2 groups, corresponding to a 7.57 ng/mL difference in the SG compared to the CG (*P* = .036). Beta-crosslaps significantly increased in both groups (mean [SD], 0.48 [0.34] to 0.73 [0.34]; *P* = .019 in the switch group and from 0.45 [0.25] to 0.61 [0.27]; *P* = .030 in the current cART group). However, there was no statistical difference between the 2 groups (*P* = .461). Total P1NP showed a tendency to decrease in both groups after the 48-week follow-up, but there was no statistical difference between the 2 groups (*P* = .960) (Figure 2).

Table 1. Baseline Characteristics and Laboratory Markers in the 2 Groups

Baseline Characteristic	No. (%)	
	DTG-Based Regimen (n = 19)	**NNRTI or Boosted-PI-Containing Regimen (n = 20)**
Age, mean (SD), y	28.94 (11.20)	29.45 (9.57)
Sex		
Male	16 (84.21)	17 (85.00)
Female	3 (15.78)	3 (15.00)
Body weight, mean (SD), kg	60.67 (12.97)	63.06 (10.19)
Waist circumference, mean (SD), cm	76.44 (10.60)	78.82 (8.88)
Body mass index, mean (SD), kg/m^2	21.46 (3.55)	21.85 (3.32)
Duration since HIV diagnosis, median (IQR), mo	24 (10.00-47.00)	22 (18.00-39.50)
Nadir CD4, median (IQR), %	407 (168.50-562.00)	337 (219.00-449.00)

Table 1. Baseline Characteristics and Laboratory Markers in the 2 Groups (Continued)

Baseline Characteristic	No. (%) DTG-Based Regimen (n = 19)	No. (%) NNRTI or Boosted-PI-Containing Regimen (n = 20)
Preswitch ART		
TDF + FTC + EFV	12 (63.15)	15 (75.00)
TDF + 3TC + EFV	4 (21.05)	4 (20.00)
TDF + 3TC or FTC + RPV	2 (10.52)	1 (5.00)
TDF + 3TC or FTC + LPV-r	1 (5.26)	0
Laboratory profiles		
Vitamin D deficiency*	3 (15.78)	3 (15.00)
Serum 25(OH) vitamin D, mean (SD), ng/mL	30.75 (10.80)	26.79 (8.10)
N-MID osteocalcin, mean (SD), ng/mL	23.85 (13.92)	23.95 (7.58)
Beta-crosslaps , mean (SD), ng/mL	0.48 (0.34)	0.45 (0.25)
Total P1NP, mean (SD), ng/mL	66.04 (24.47)	57.35 (15.77)
CD4, mean (SD), cells/mm^3	518.78 (191.76)	506.25 (229.70)
CD4, mean (SD), %	21.94 (7.52)	21.52 (8.32)

Abbreviations: ART, antiretroviral therapy; DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; IQR, interquartile range; LPV-r, lopinavir-ritonavir; N-MID, N-midfragment; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; P1NP, procollagen type 1 amino-terminal propeptide; RPV, rilpivirine; TDF, tenofovir disoproxil fumarate; 3TC, lamivudine.

* Vitamin D deficiency referred to serum 25(OH) vitamin D level less than 20 ng/mL.

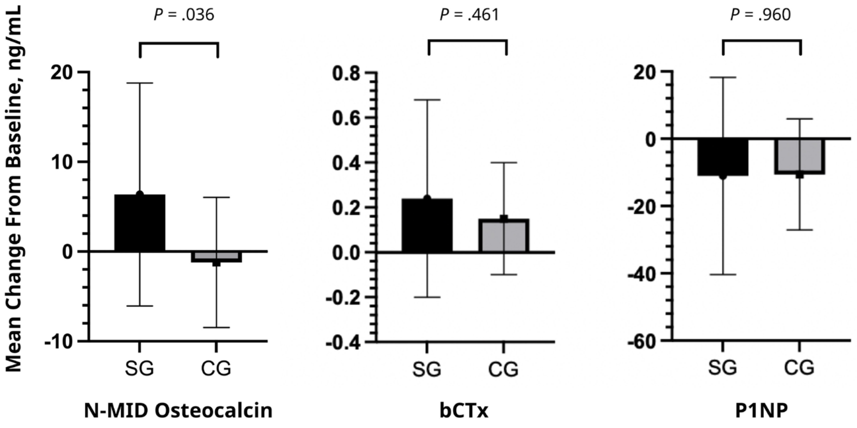
Table 2. Laboratory Markers After 48-Week Follow-Up Period in the 2 Groups

Laboratory Profile	DTG-Based Regimen (n = 19)			NNRTI or Boosted-PI-Containing Regimen (n = 20)		
	Baseline	48-Week	*P* Value	Baseline	48-Week	*P* Value
Vitamin D deficiency, No. (%)*	3 (15.78)	6 (31.58)	.268	3 (15.00)	7 (35.00)	.186
Serum 25(OH) vitamin D, mean (SD), ng/mL	30.75 (10.80)	28.46 (14.13)	.321	26.79 (8.10)	26.74 (11.93)	.983
N-MID osteocalcin, mean (SD), ng/mL	23.85 (13.92)	30.21 (13.92)	.025	23.95 (7.58)	22.74 (8.15)	.570
Beta-crosslaps, mean (SD), ng/mL	0.48 (0.34)	0.73 (0.34)	.019	0.45 (0.25)	0.61 (0.27)	.030
Total P1NP, mean (SD), ng/mL	66.04 (24.47)	54.98 (24.47)	.100	57.35 (15.77)	46.73 (17.11)	.029

Abbreviations: DTG, dolutegravir; N-MID, N-midfragment; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; P1NP, procollagen type 1 amino-terminal propeptide.

* Vitamin D deficiency referred to serum 25(OH) vitamin D level less than 20 ng/mL.

Figure 2. Bone Markers Change After 48-Week Follow-Up Period



Abbreviations: CG, current cART group; bCTx, beta-crosslaps; N-MID, N-midfragment; P1NP, procollagen type 1 amino-terminal propeptide; SG, switch group.

Discussion

Low vitamin D levels, defined as a serum 25(OH) vitamin D level below 30 ng/mL, have been reported to range from 60% to 75% in the literature.[15, 16] The prevalence of vitamin D deficiency in PLWH in Thailand has been reported to be between 10% and 25%,[17, 18] whereas in this study, it was 33%. There was a tendency for the proportion of vitamin D deficiency to increase in both groups at the 48-week follow-up, but this difference was not statistically significant. Interestingly, low vitamin D levels, vitamin D insufficiency, and vitamin D deficiency showed different effects in this population.

Occupational factors likely influence vitamin D status, as individuals working indoors or night shifts have reduced sunlight exposure, limiting cutaneous vitamin D synthesis. In contrast, outdoor workers may have higher serum vitamin D levels due to greater sun exposure.[19] In this study, the majority of participants in both treatment groups were young adult males (84%-85%) with a mean age of approximately 29 years. As most participants were of working age, it is likely that a significant proportion engaged in the indoor work, limiting their UVB exposure and consequently their vitamin D synthesis. This finding aligns with previous studies indicating that occupational sun exposure is a key determinant of vitamin D status, even in the tropical regions.[19] These differences suggest that occupation should be considered a relevant factor when evaluating vitamin D status in PLWH.

Switching to the DTG-containing regimen led to a nonsignificant increase in the proportion of individuals with low vitamin D levels, while those who received NNRTI or boosted PI-containing regimens showed a nonsignificant decrease. It is worth noting that there was a difference in the proportions of low vitamin D levels between the 2 groups at baseline, rendering the interpretation of these changes invalid. These findings align with the results from a larger observational study, which demonstrated a significant increase in bone mineral density of the lumbar spine (+1.6%) after approximately 2 years of DTG-based ART, particularly among participants with baseline osteopenia or those receiving vitamin D supplementation.[20] These data support the potential favorable effect of DTG-containing regimens on the bone health in PLWH. Additionally, low vitamin D levels may occur in the general population without significant clinical implications; however, factors such as the use of sunblock lotion — which reduces UVB radiation needed for cutaneous vitamin D synthesis — may further contribute to lower serum vitamin D levels, particularly in individuals with limited sun exposure.[19] It is noteworthy that the CG had persistently lower baseline vitamin D levels compared to the SG. This can be explained by the mediation of EFV through cytochrome P24 (CYP24) induction. Upregulation of CYP24, a 25-hydroxyvitamin D3-24-hydroxylase, may accelerate the catabolism of vitamin D, thereby decreasing the level of 25(OH) vitamin D.[21]

Initiation of ART induces a significant loss of bone mineral density by 2% to 6%, regardless of the choice of ART.[8, 22, 23] Underlying pathogenesis includes HIV-related inflammation after immune reconstitution and ART-related toxicity.[21, 22] Tenofovir (TNV), a NRTI, may indirectly affect bone health through proximal renal tubulopathy, leading to renal phosphate wasting and increased bone resorption, commonly known as renal osteomalacia.[24] However, chronic renal phosphate loss from TNV-induced proximal renal tubulopathy can result in osteoporosis and subsequent fractures.[23] EFV and PIs may also indirectly affect bone metabolism through vitamin D metabolism.[25-27] Boosted PIs can increase TNV exposure and the risk of renal and bone adverse events.[22, 23] In a rat model, EFV was shown to have a negative effect on bone tissue by affecting bone microarchitecture and impairing biomechanical properties.[24]

In terms of clinical evidence, switching to a TDF-sparing DTG-based regimen has previously been associated with increased bone turnover rates, manifesting as reductions in bone formation markers (P1NP, osteocalcin) with minimal changes in bone resorption markers (beta-crosslaps).[28] In contrast, this study demonstrated a significant increase in N-MID osteocalcin in the SG compared to the CG, with no significant differences in P1NP or bCTx between groups. Interestingly, total P1NP was significantly reduced only in the CG. These findings suggest enhanced bone formation activity following the switch to the DTG-based regimen. This observation appears more pronounced than what was reported in the STRIIVING trial, which also observed increased bone turnover and formation after switching to a DTG-based regimen, even when TDF remained a part of the regimen.[27] Regarding bone metabolism, this data supports the phase-out strategy endorsed by the 2020 Thai national HIV guidelines, which advocate switching to TDF/3TC/DTG. Given that NNRTI- or PI-based regimens remain widely used in the resource-limited settings, and with the increasing availability of fixed-dose combination TDF/3TC/DTG, transitioning to DTG-based regimens may mitigate long-term bone toxicity.

PLWH with compromised bone health should be managed with a comprehensive care strategy incorporating routine screening, lifestyle optimization, ART regimen selection, and nutritional support. Improved dietary intake of calcium-, vitamin D-, and protein-rich foods — such as dairy products, fortified cereals, eggs, fatty fish, and leafy green vegetables — along with safe sun exposure and regular weight-bearing exercise, may enhance bone metabolism and lower fracture risk.

However, several limitations must be acknowledged. The small sample size may have reduced the statistical power to detect significant differences across some parameters. Additionally, the study population primarily comprised of young male PLWH, limiting generalizability to the older individuals and postmenopausal women, who are at greater risk of bone-related complications. This study was limited by its relatively short follow-up period and modest sample size. Moreover, bone mineral density was not assessed using dual-energy x-ray absorptiometry, the gold standard for evaluating bone health and diagnosing osteoporosis. Future studies with larger, more diverse populations and longitudinal assessment are essential to clarify the long-term skeletal effects of DTG-based regimens in PLWH.

Conclusions

In this study, switching to TDF/3TC/DTG had a minimal impact on vitamin D status. Bone turnover markers indicated an increase in bone formation compared to continuing NNRTI or PI-based cART. These findings suggest a potential beneficial effect of the TDF/3TC/DTG regimen on bone metabolism within the 48-week follow-up period.

Further research with longer-term follow-up is necessary to assess the impact of switching to TDF/3TC/DTG on bone mineral density and fracture incidence, particularly in aging populations of PLWH. Such studies would provide more comprehensive insights into the clinical implications of bone metabolism changes observed in this study.

Additional Information

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Clinical Trial Consideration: The study was registered in the Thai Clinical Trials Registry (TCTR20210409003) and received approval on 24 December 2020.

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Original Article

Pleural Fluid Volume for Cytological Diagnosis of Malignancy: How Much Is Optimum

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Abstract

Background: Pleural fluid cytology is essential for evaluating effusions and detecting atypical and malignant cells. However, the optimal fluid volume for accurate diagnosis remains unclear.

Objective: To determine the optimal pleural fluid volume for detecting atypical to malignant cells by analyzing diagnostic yield across different volume groups.

Methods: This retrospective study analyzed pleural fluid samples collected between 2020 and 2021, correlating to cases with confirmed malignancy in pleural cavities. Samples were categorized into volume groups and classified using the International System for Serous Fluid Cytopathology: nondiagnostic (ND), negative for malignancy (NFM), atypia of undetermined significance (AUS), suspicious for malignancy (SFM), and malignant (MAL).

Results: Of 1794 pleural fluid samples, the detection rates of atypical to malignant cells in the samples were < 25 mL (35.87%), 25-49 mL (40.77%), 50-74 mL (45.38%), 75-99 mL (37.89%), 100-249 mL (29.67%), 250-499 mL (21.99%), and ≥ 500 mL (40.97%). Considering the samples with evidence of pleural involvement by malignancy (n = 497), detection rates of atypical to malignant cells in the samples were < 25 mL (83.72%), 25-49 mL (91.67%), 50-74 mL (90.41%), 75-99 mL (93.33%), 100-249 mL (72.06%), 250-499 mL (44.17%), and ≥ 500 mL (82.14%). The proportion of AUS and SFM categories among the atypical and malignant samples were low (< 20%) in the 50-74 mL and 75-99 mL volume groups.

Conclusions: Intermediate volumes (50-100 mL) provide adequate cellular material while maintaining manageable sample processing. Implementing this volume range in clinical practice may enhance diagnostic accuracy.

Keywords: Pleural fluid, Volume, Malignancy, Cytology

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Introduction

Pleural fluid accumulation is a common manifestation of malignancy within the pleural cavities. This condition can stem from both benign and malignant etiologies, including heart failure, parapneumonic effusion, primary malignant tumors of the pleura (eg, mesothelioma, primary effusion lymphoma) or metastatic malignant neoplasms.[1, 2] The cytological analysis of pleural effusion is pivotal for the clinical management and prognosis of patients with malignancy.[1, 2]

In 2020, the International System for Serous Fluid Cytopathology (TIS) introduced 5 diagnostic categories to enhance the clarity of serous fluid cytology results and mitigate variability.[3, 4] These categories are nondiagnostic (ND), negative for malignancy (NFM), atypia of undetermined significance (AUS), suspicious for malignancy (SFM), and malignancy (MAL).

This system standardizes the terminology used in clinical practice guidelines, improving patient management and the quality of clinical care.[4]

Nevertheless, the sample volume may be insufficient in certain instances, potentially resulting in false negatives for malignancy. Within the TIS framework, ND is characterized as a specimen that yields no diagnostic information, typically due to being acellular, highly degenerated, or hemorrhagic.[4]

Some studies have suggested a minimal volume threshold for pleural fluid samples. The suggested volume vary from 25 to 75 mL, which aids in reducing potential false negatives and optimizing test sensitivity.[4, 5] A comprehensive study by Rooper et al[5] involving over 2500 samples indicated that a threshold volume of at least 75 mL significantly enhances the detection of malignancy with malignant fraction 22.1% over 17.0% in volumes of less than 75 mL. The study by Thomas et al[6] suggested that a minimal volume of 25 mL fluid decreased false negative results to detect the malignant cells from 48% (in samples < 25 mL) to 22%; however, the sensitivity did not improve further when the volume was more than 50 mL. These findings highlight the potential impact of specimen volume on diagnostic accuracy and underscore the need to define an optimal volume threshold, particularly in the context of the recently implemented TIS reporting system.

At our institute, TIS has been adopted for the cytological diagnosis of serous fluid cytopathology since 2020. The objective of this study was to ascertain the optimal volume required to effectively detect abnormal cells in pleural fluid following the implementation of TIS.

Methods

Data Collection and Study Process

This retrospective cross-sectional study analyzed all pleural fluid cytologic samples collected from 2020 to 2021. All samples were retrieved from our institute's laboratory information system, developed by the institute's health information technology unit.

This study was conducted in 2 steps. In the first step, all pleural fluid samples were reviewed to collect general data, including demographic information (age and gender), volume of received fluid, cytologic diagnosis of the pleural fluid samples, primary tumor site, and evidence of pleural involvement by malignancy. The samples without recorded volume were excluded from this study.

In the second step, a focused analysis was performed on the subset of samples with confirmed pleural involvement by malignancy. Pleural involvement was defined based on the following criteria: 1) the presence of malignant cells identified by cell blocks (based on cytomorphology and/or immunocytochemistry), histopathologic examination of pleural biopsy, or by malignant pleural fluid cytology in preceding or subsequent cytologic samples within a 6-month interval; and 2) histopathologic evidence of visceral pleural invasion by malignant tumors in lung resection specimens. All data were gathered and processed anonymously to ensure patient confidentiality.

Specimen Processing

Regarding the processing of each pleural fluid sample, specimens were prepared using ThinPrep Liquid Based Preparation (Hologic, Inc, Marlborough, MA, USA). Two conical tubes containing up to 50 mL of fluid were centrifuged at 2500 rpm for

20 minutes. The entire sample was centrifuged if the fluid volume was less than 100 mL. Post-centrifugation, the sediments were transferred to PreservCyt vials, processed by the ThinPrep 2000 processor, and the resulting slides were stained using the Papanicolaou method. Cell blocks were prepared from residual pleural fluid at the request of a pathologist or referring physician, primarily using the sedimentation technique. The Shandon Cytoblock Cell Block Preparation System (Thermo Fisher Scientific, Waltham, MA, USA) was used in cases with limited sediment, following the manufacturer's instructions.

Data Categorization

Pleural fluid volumes were categorized into 7 volume groups: less than 25 mL, 25-49 mL, 50-74 mL, 75-99 mL, 100-249 mL, 250-499 mL, and equal or more than 500 mL. The cytologic diagnosis of pleural fluid was based on the 5 categories of TIS: ND, NFM, AUS, SFM, and MAL. These diagnoses relied solely on cytologic slides.

Statistical Analysis

In the first step, all pleural fluid samples were reported according to the number of samples in each diagnostic category. The detection rate of atypical and malignant cells in each volume group was calculated based on the number of samples reported as AUS, SFM, and MAL categories, divided by the total number of samples in that group. The fraction of AUS and SFM among atypical or malignant cell samples was determined in each volume group.

After filtering samples with evidence of pleural involvement, the detection rate of atypical or malignant cells and the fraction of AUS and SFM among atypical or malignant cell samples in each volume group in the second step were calculated the same way as in the first step.

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated using all available samples. In this study, true positive (TP), false positive (FP), false negative (FN), and true negative (TN) cases were defined. TP were samples classified as AUS, SFM, and MAL in the second step (samples with evidence of pleural involvement). FN were samples categorized as NFM in the second step (samples with evidence of pleural involvement). FP were samples diagnosed as AUS, SFM, and MAL in the first step but not confirmed as TP cases in the second step (samples without evidence of pleural involvement). TN were samples reported as ND and NFM in the first step, excluding those identified as FN in the second step (samples without evidence of pleural involvement).

These definitions were applied to evaluate the diagnostic performance of cytological categorization relative to confirmed pleural involvement.

Statistical analysis was performed using Excel version 2021 (Microsoft Corp) and PASW Statistics version 18.0 (PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc; 2009). A one-way ANOVA test was employed to compare volume groups, with a *P* value < .05 considered statistically significant.

Results

All Pleural Fluid Samples

A total of 1794 pleural fluid cytology specimens collected between 2020 and 2021 were included in this study. The mean patient age was 65.83 years (range 1-99 years).

The sample comprised 784 men (43.7%) and 1010 women (56.3%), with a male-to-female ratio of 1:1.3.

All pleural cytology specimens' diagnostic categories and volumes are detailed (Table 1 and Figure 1). Most of the samples were NFM (1175 cases, 65.50%). The remaining samples were diagnosed as follows: 12 cases (0.67%) of ND material, 191 cases (10.64%) of AUS, 50 cases (2.79%) of SFM, and 366 cases (20.40%) of MAL.

The samples were categorized into volume groups as follows: 315 cases (17.56%) with less than 25 mL of fluid, 130 cases (7.25%) with 25-49 mL of fluid, 238 cases (13.27%) with 50-74 mL of fluid, 95 cases (5.29%) with 75-99 mL of fluid, 246 cases (13.71%) with 100-249 mL of fluid, 482 cases (26.87%) with 250-499 mL of fluid, and 288 cases (16.05%) with 500 mL or more of fluid.

The average volume of the pleural fluid samples was 232.5 mL (range 0.2-1500 mL). The average fluid volume for each TIS category was as follows: ND had 57.6 mL, NFM had 242.40 mL, AUS had 250.97 mL, SFM had 210.64 mL, and MAL had 199.81 mL.

The detection rate of atypical to malignant cells was highest in the 50-74 mL group (45.38%). The remaining groups showed detection rates of 35.87% (< 25 mL), 40.77% (25-49 mL), 37.89% (75-99 mL), 29.67% (100-249 mL), 21.99% (250-499 mL), and 40.97% (≥ 500 mL). The ANOVA *F* statistics were 4.25, indicating a significant difference in pleural fluid volume across TIS categories (*P* = .002).

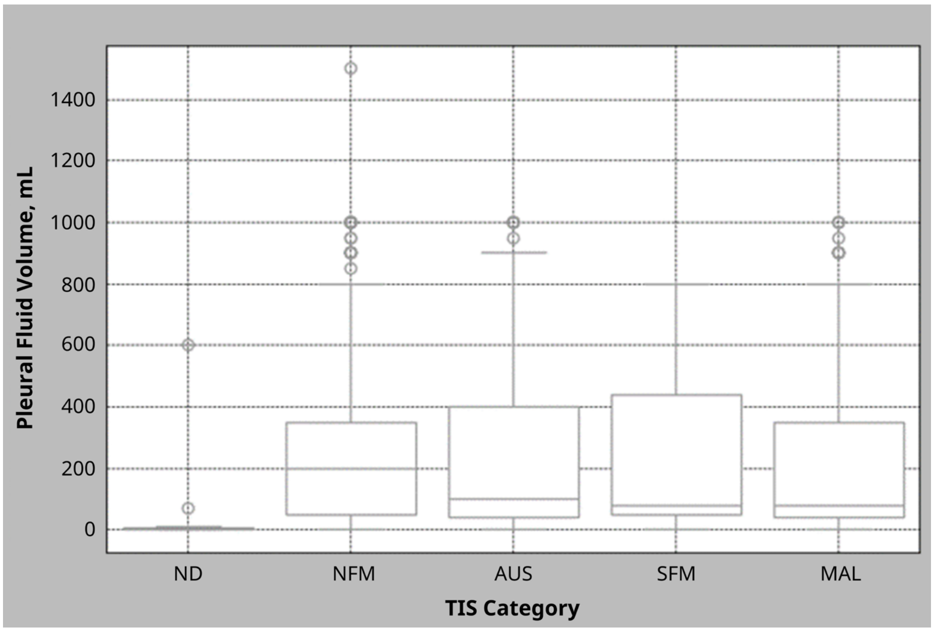
Proportion of the samples reported as AUS and SFM categories among those with atypical to malignant cells in each volume group was as follows: 41.59% (< 25 mL), 33.96% (25-49 mL), 35.19% (50-74 mL), 36.11% (75-99 mL), 34.25% (100-249 mL), 44.34% (250-499 mL), and 44.92% (≥ 500 mL).

Table 1. Correlations Between Diagnostic Categories (Based on the International System for Serous Fluid Cytopathology) and Volume (mL) Groups of All Pleural Fluid Samples

Diagnostic Category	No. of Samples							Total, No. (%)
	Volume Group, mL							
	< 25	25-49	50-74	75-99	100-249	250-499	≥ 500	
ND	10	0	1	0	0	0	1	12 (0.67)
NFM	192	77	129	59	173	376	169	1175 (65.50)
AUS	38	15	26	10	18	43	41	191 (10.64)
SFM	9	3	12	3	7	4	12	50 (2.79)
MAL	66	35	70	23	48	59	65	366 (20.40)
Total, No. (%)	315 (17.56)	130 (7.25)	238 (13.27)	95 (5.30)	246 (13.71)	482 (26.87)	288 (16.05)	1794 (100.00)
Detection rate of atypical to malignant cells, %	35.87	40.77	45.38	37.89	29.67	21.99	40.97	NA

Abbreviations: AUS, atypia of undetermined significance; MAL, malignancy; NA, not applicable; ND, nondiagnostic; NFM, negative for malignancy; SFM, suspicious for malignancy.

Figure 1. Box Plot of Pleural Fluid Volume by the International System for Serous Fluid Cytopathology Category in All Samples



Abbreviations: AUS, atypia of undetermined significance; MAL, malignancy; ND, nondiagnostic; NFM, negative for malignancy; SFM, suspicious for malignancy, TIS, the International System for Serous Fluid Cytopathology.

Pleural Fluid Samples With Evidence of Pleural Involvement by Malignancy

Among the materials with confirmed evidence of pleural involvement, 497 pleural fluid samples were included for analysis. The primary sites of malignancy are summarized (Table 2), with the most common origin being the lung (66.60%), followed by the breast (13.28%) and gynecologic organs (3.22%).

When stratified by sex, notable differences in tumor origin were observed. In male patients, the most common primary site was the lung (79.80%), followed by mesothelioma (5.42%) and hematologic malignancies (3.45%). In female patients, lung cancer also predominated (57.48%), followed by breast cancer (22.45%) and gynecologic malignancies (5.44%).

These pleural cytology specimens' diagnostic categories and volumes are detailed (Table 3 and Figure 2). Most of these samples were diagnosed as MAL (281 cases, 56.54%). The remaining samples were diagnosed as follows: 127 cases (25.55%) of NFM, 59 cases (11.87%) of AUS, and 30 cases (6.04%) of SFM.

The samples were divided into volume groups as follows: 86 cases (17.30%) with less than 25 mL of fluid, 36 cases (7.24%) with 25-49 mL of fluid, 73 cases (14.69%) with 50-74 mL of fluid, 30 cases (6.04%) with 75-99 mL of fluid, 68 cases (13.68%) with 100-249 mL of fluid, 120 cases (24.14%) with 250-499 mL of fluid, and 84 cases (16.90%) with 500 mL or more of fluid. No sample with ND category was included.

The mean (range) volume was 222.82 (1-1000) mL. The average fluid volume for each TIS category was as follows: NFM had 295.21 mL, AUS had 257.31 mL, SFM had 215.93 mL, and MAL had 183.60 mL.

The detection rate of atypical to malignant cells was highest in the 75-99 mL group (93.33%). The remaining groups showed detection rates of 83.72% (< 25 mL), 91.67% (25-49 mL), 90.41% (50-74 mL), 72.06% (100-249 mL), 44.17% (250-499 mL), and 82.14% (≥ 500 mL). The ANOVA *F* statistics was 7.84, indicating a significant difference in pleural fluid volume across TIS categories (*P* = .00004).

The proportion of samples reported as AUS and SFM categories among those with atypical to malignant cells in each volume group was 30.56% (< 25 mL), 21.21% (25-49 mL), 15.15% (50-74 mL), 17.86% (75-99 mL), 16.33% (100-249 mL), 26.42% (250-499 mL), and 33.33% (≥ 500 mL).

The detection rates of atypical to malignant cells in pleural fluid samples by primary tumor site are presented (Table 4). The highest detection rates (100%) were observed in samples from gynecologic organs and the thyroid gland. These were followed by the breast (90.91%), upper gastrointestinal tract (90.91%), and hematologic malignancies (86.67%). Other primary sites with relatively high detection rates included the pancreatobiliary tract and liver (83.33%), bone and soft tissue (80.00%), and lung (71.30%). In contrast, lower detection rates were observed in head and neck malignancies (25.00%) and colorectal cancers (27.27%).

Table 2. Primary Sites of Pleural Fluid Samples With Evidence of Pleural Involvement by Malignancy

Primary Site	No. (%)		
	Male	Female	Total
Lung	162 (79.80)	169 (57.48)	331 (66.60)
Breast	0	66 (22.45)	66 (13.28)
Gynecologic organs	0	16 (5.44)	16 (3.22)
Involvement by hematologic malignancy*	7 (3.45)	8 (2.72)	15 (3.02)
Mesothelium	11 (5.42)	2 (0.68)	13 (2.62)
Colorectum	3 (1.48)	8 (2.72)	11 (2.21)
Upper gastrointestinal tract	5 (2.46)	6 (2.04)	11 (2.21)
Bone and soft tissue	3 (1.48)	7 (2.38)	10 (2.01)
Pancreatobiliary tract and liver	3 (1.48)	3 (1.02)	6 (1.21)
Head and neck	1 (0.49)	3 (1.02)	4 (0.80)
Thyroid gland	1 (0.49)	0	1 (0.20)
Unknown**	7 (3.45)	6 (2.04)	13 (2.62)
Total	203 (100.00)	294 (100.00)	497 (100.00)

* Cases involving hematologic malignancy are under ‘involvement by hematologic malignancy’. No cases of primary effusion lymphoma were identified in this cohort.

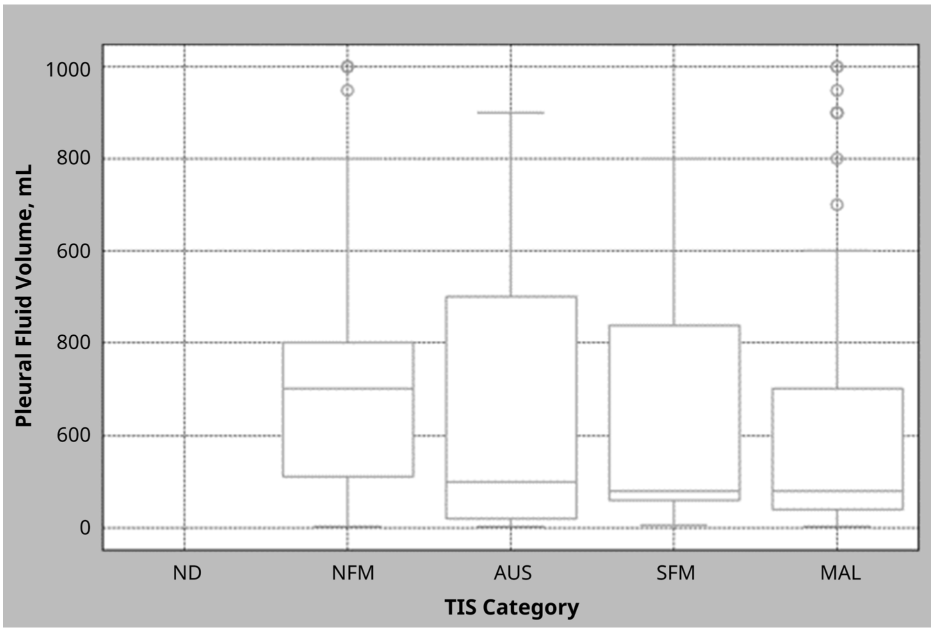
** Unknown primary site is defined as cases without further investigation, caused by loss of follow-up, referring hospital, or death; or cases with inconclusive clinical, radiologic, and histopathologic findings to definitively determine the primary site.

Table 3. Correlations Between Diagnostic Categories (Based on the International System for Serous Fluid Cytopathology) and Volume (mL) Groups of Pleural Fluid Samples With Evidence of Pleural Involvement by Malignancy

Diagnostic Category	No. of Samples							Total, No. (%)
	Volume Group, mL							
	< 25	25-49	50-74	75-99	100-249	250-499	≥ 500	
NFM	14	3	7	2	19	67	15	127 (25.55)
AUS	17	6	3	2	4	11	16	59 (11.87)
SFM	5	1	7	3	4	3	7	30 (6.04)
MAL	50	26	56	23	41	39	46	281 (56.54)
Total, No. (%)	86 (17.30)	36 (7.24)	73 (14.69)	30 (6.04)	68 (13.68)	120 (24.14)	84 (16.90)	497 (100)
Detection rate of atypical to malignant cells, %	83.72	91.67	90.41	93.33	72.06	44.17	82.14	NA

Abbreviations: AUS, atypia of undetermined significance; MAL, malignancy; NA, not applicable; NFM, negative for malignancy; SFM, suspicious for malignancy.

Figure 2. Box Plot of Pleural Fluid Volume by the International System for Serous Fluid Cytopathology Category in Samples With Proven Pleural Involvement



Abbreviations: AUS, atypia of undetermined significance; MAL, malignancy; ND, nondiagnostic; NFM, negative for malignancy; SFM, suspicious for malignancy, TIS, the International System for Serous Fluid Cytopathology.

Table 4. Detection Rates of Atypical to Malignant Cells in the Pleural Fluid Samples According to Primary Sites

Primary Site	No. of Samples		Detection Rate of Atypical to Malignant Cells, %
	With Evidence of Pleural Involvement by Malignancy	With Atypical to Malignant Cells in Cytology	
Lung	331	236	71.30
Breast	66	60	90.91
Gynecologic organs	16	16	100.00
Involvement by hematologic malignancy*	15	13	86.67
Mesothelium	13	9	69.23
Colorectum	11	3	27.27
Upper gastrointestinal tract	11	10	90.91
Bone and soft tissue	10	8	80.00
Pancreatobiliary tract and liver	6	5	83.33
Head and neck	4	1	25.00
Thyroid gland	1	1	100.00
Unknown**	13	8	61.54
Total	497	370	NA

Abbreviation: NA, not applicable.

* Cases involving hematologic malignancy are under ‘involvement by hematologic malignancy’. No cases of primary effusion lymphoma were identified in this cohort.

** Unknown primary site is defined as cases without further investigation, caused by loss of follow-up, referring hospital, or death; or cases with inconclusive clinical, radiologic, and histopathologic findings to definitively determine the primary site.

Diagnostic Performance

As outlined in the Methods section, the numbers of TP, FN, FP, and TN were 370, 127, 237, and 1060, respectively. Sensitivity was 74.45%, calculated as TP divided by the total number of cases with confirmed pleural involvement by malignancy (TP+FN). Specificity was 81.73%, determined by comparing TN to all cases without pleural involvement by malignancy (TN+FP). The PPV was 60.96%, based on the proportion of TP among all cytologic samples diagnosed as atypical to malignant cells (TP+FP). The NPV was 89.30%, calculated by TN divided by the total number of cytologic samples without atypical to malignant cells (TN+FN). Overall diagnostic accuracy was 79.71%, based on the proportion of summation of TP and TN cases among all samples. The corresponding confusion matrix is presented (Figure 3).

Figure 3. Confusion Matrix Demonstrates Pleural Cytology's Diagnostic Performance in Detecting Atypical to Malignant Cells

	Positive evidence of pleural involvement by malignancy	Negative evidence of pleural involvement by malignancy	
Positive for atypical to malignant cells in cytology	True Positive 370	False Positive 237	Positive Predictive Value (PPV) = 60.96%
Negative for atypical to malignant cells in cytology	False Negative 127	True Negative 1060	Negative Predictive Value (NPV) = 89.30%
	Sentivity = 74.45%	Specificity = 81.73%	Accuracy = 79.71%

The confusion matrix compares cytology results (positive or negative for atypical/malignant cells) with the reference (positive or negative evidence of pleural involvement by malignancy).

Discussion

Pleural fluid is a common cytologic specimen collected to evaluate the cause of effusion, particularly for detecting atypical and malignant cells in pleural metastasis. In metastatic disease, detecting malignant cells can alter the patient's cancer stage, impacting clinical management. However, the fluid volume appears to influence the detection rate of atypical/malignant cells and sample adequacy.

This retrospective study aimed to evaluate our institute's 2-year experience with TIS in pleural cavity fluid and to determine the optimal fluid volume for detecting atypical and malignant cells. The study defines the detection rate for each volume group in overall specimens and those with confirmed pleural involvement by malignancy, as well as the diagnostic accuracy.

A total of 1794 pleural fluid samples were included, of which 497 were from cases with confirmed malignancy in the pleural cavity. The most common primary site was lung carcinoma (66.60%), followed by breast carcinoma (13.28%). These findings are consistent with previous studies, which indicate that primary lung carcinoma is the most common cause of malignant effusion,[7-11] with mammary carcinoma being the second most common.[7, 8, 11]

For the overall samples, the highest detection rates were observed in the 50-74 mL volume group at 45.38%, suggesting that this volume range is optimal for cytological analysis. Interestingly, volumes equal or greater than 500 mL also showed a relatively high detection rate, while the 250-499 mL group had a notably lower detection rate. This discrepancy may be due to the dilution effect or more non-diagnostic material in larger volumes. Among the samples with confirmed pleural involvement by malignancy, the highest detection rate was observed in the 75-99 mL volume group (93.33%), followed by the 25-49 mL (91.67%) and 50-74 mL (90.41%) volume groups. When examining the reporting of indeterminate categories (AUS and SFM) within all atypical/malignant cytologic samples in each volume group, the 50-74 mL volume group had the lowest proportion at 15.15%, followed by the 75-99 mL volume group at 17.86%. These 50-74 mL and 75-99 mL groups were optimal for detecting malignant cells while minimizing the reporting of indeterminate categories in pleural fluid.

The optimal volume of pleural fluid for cytological analysis has been debated for several years (Table 5). Abouzgheib et al[12] analyzed 44 pleural fluid samples and found no significant difference in malignant cell detection between 50 mL and high-volume samples. Thomas et al[6] who studied among 2155 pleural fluid samples, suggested that 25-50 mL of pleural fluid is adequate for assessment of malignant cells in pleural effusion. Rooper et al[5] studied 2540 cases of pleural effusion and suggested that a volume of 75 mL or more is optimal. A study by Torous[13] involving 226 pleural fluid samples, suggested that more than 50 mL might be sufficient. However, low-volume specimens could still be valuable in cases of strong clinical suspicion of malignancy Coconubo et al[14] compared 8530 pleural and peritoneal fluid samples across various volume groups and found that the 75-100 mL group had a significantly higher percentage of malignant diagnoses. Beg et al[15] suggested that the minimum volume of 70 mL was optimal for malignant detection. Christofidis et al[11] analyzed 2340 serous fluid samples from pleural, peritoneal, and pericardial cavities, recommending a 10-100 mL medium volume range for optimal diagnostic yield. This study's findings support that intermediate volumes — particularly in the 50-74 mL and 75-99 mL range groups — are optimal for detecting malignant cells while minimizing indeterminate results.

Table 5. Comparison of Suggested Optimal Pleural Fluid Volume in Different Studies

Study	Source of Specimen	Sample Size	Cytologic Preparation Techniques	Suggested Optimal Volume Range/Volume Group, mL
Abouzgheib et al,[12] 2009	Pleural fluid	44	Centrifugation with liquid-based preparation	No significant difference between 50 mL and high-volume
Thomas et al,[6] 2011	Pleural fluid	2155	Centrifugation with conventional smear and cytospin method	25-50
Rooper et al,[5] 2014	Pleural fluid	2540	Centrifugation with the cytospin method	> 75
Torous,[13] 2021	Pleural fluid	226	Centrifugation with liquid-based preparation	> 50 (low-volume still valuable in some cases)
Coconubo et al,[14] 2022	Pleural fluid and peritoneal fluid	8530	Centrifugation with the cytospin method and liquid-based preparation	75-100
Beg et al,[15] 2023	Pleural, pericardial, and peritoneal fluid	1597	Centrifugation with liquid-based preparation	≥ 70 (except pericardial fluid)
Christofidis et al,[11] 2024	Pleural, pericardial, and peritoneal fluid	2340	Centrifugation with conventional smear and liquid-based preparation	10-100
Current study	Pleural fluid	1794	Centrifugation with conventional smear and liquid-based preparation	50-74 and 75-99

This volume range appears to offer a practical balance between obtaining adequate cellular material and ensuring efficient sample processing, making it a feasible recommendation for routine clinical practice. The cytologic techniques employed — centrifugation followed by both conventional smear and liquid-based preparation — are consistent with those used in several recent large-scale studies. Notably, Christofidis et al[11] and Coconubo et al[14] also utilized a combination of conventional smear and liquid-based methods, with optimal volume ranges overlapping with our findings (10-100 mL and 75-100 mL, respectively). This alignment suggests that the methodology in our study not only reflects other current studies but could reinforce the reliability and clinical applicability in detecting malignancy in cytology of pleural fluid.

Primary tumor origin likely influences the detection rate of atypical to malignant cells in pleural fluid. In this study, high detection rates (over 90%) were observed in malignancies originating from gynecologic organs, thyroid, breast, and upper gastrointestinal tract. In contrast, low detection rates were noted in head and neck (25.00%) and colorectal (27.27%) primary tumors. Primary thoracic malignancies, including those of the lungs and mesothelium, demonstrated intermediate detection rates (71.30% and 69.23%, respectively). These variations may be attributed to several factors, including characteristics of pleural fluid sample, particularly cellular compositions,[15] and natures of tumor cells (anatomical proximity, metastatic potential, and tumor cell cohesiveness).

The diagnostic performance of detecting atypical to malignant cells in pleural fluid cytology demonstrated a sensitivity of 74.45% and specificity of 81.73%, indicating a reasonable ability to detect true positives while reliably excluding nonmalignant cases. The PPV of 60.96% suggests that positive cytology results should be interpreted cautiously and might be confirmed by additional diagnostic methods due to the risk of false positives. In contrast, the high NPV of 89.30% supports cytology as a reliable tool for ruling out malignancy. With an overall accuracy of 79.71%, cytology remains a valuable, minimally invasive diagnostic method, particularly when integrated with clinical, radiological, and histopathological data to improve diagnostic confidence.

This study focused solely on pleural fluid specimens, and it was a retrospective study in a single tertiary care center. Further interesting research should aim to standardize volume collection protocols for other serous fluids, such as peritoneal and pericardial fluids, and evaluate their diagnostic yield across different malignancies and tumor subtypes.

Conclusions

Pleural fluid cytology is essential for evaluating effusions and detecting atypical and malignant cells, impacting cancer staging and management. This retrospective study suggests that intermediate volumes (50-100 mL) are optimal for cytological analysis, balancing adequate cellular material and manageable sample processing. Implementing this volume range in clinical practice may improve diagnostic accuracy and yield for detecting atypical to malignant cells in pleural fluid.

Additional Information

Ethics Approval: This study protocol was reviewed and approved by the Human Research Ethics Committee, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand (MURA2022/273 on 5 May 2022).

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Factors Associated With Transitional Stress Among Relatives During Transferring Critically Ill Patients From ICU-to-Ward

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Abstract

Background: The intensive care unit (ICU) provides effective care for critically ill patients and can significantly reduce mortality rates. However, ICU hospitalization is not only a crisis for patients, but also for their relatives, who often experience high levels of transitional stress. This stress can negatively impact their ability to provide loving care to the patient after the transfer to a general ward.

Objectives: To describe the level of transitional stress and determine the relationship between uncertainty, hope, and preparedness with transitional stress among relatives during transferring critically ill patients from ICU-to-ward.

Methods: This study used a descriptive correlational cross-sectional research design. A total of 112 participants were recruited during December 2022 to September 2023 by selecting participants randomly, following the inclusion criteria. The research instruments included a demographic questionnaire, the Herth Hope Index, the Family Relocation Stress Scale, the Care Preparedness Scale, and the Parents' Perception of Uncertainty in Illness Scale-Family Member. The reliability of the scales was 0.87, 0.88, 0.82, and 0.86, respectively. Descriptive statistics and Pearson product moment correlation were used to perform data analysis.

Results: The mean (SD) score of transitional stress was 36.5 (6.2), indicating a moderate level of stress. Uncertainty was positively correlated with transitional stress ($r = 0.75$, $P < .001$). However, hope and preparedness were negatively correlated with transitional stress ($r = -0.40$, $P < .001$; $r = -0.44$, $P < .001$ respectively).

Conclusions: Clinical nurses should develop nursing interventions to reduce transitional stress among a patient's relatives by promoting their preparedness and hope, and communicate effectively to reduce the relatives' uncertainty about the patient's illness.

Keywords: Hope, Intensive care unit, Preparedness, Relative, Transitional stress, Uncertainty

Introduction

The intensive care unit (ICU) serves as a critical setting for the effective management and care of critically ill patients. However, due to the acute onset and severity of patients' conditions, their relatives often experience confusion, anxiety, or depression and may be at risk for posttraumatic stress.[1] Some family members also experience stress simply from being in the ICU environment, which can be perceived as aggressive, intimidating, and threatening. The ICU is frequently associated with death or permanent disability.[2-4] Therefore, the hospitalization of a critically ill patient in the ICU represents not only a crisis for the patient, but also for their relatives, both during the ICU stay and when the patient is transferred to a general ward.[4]

The transfer of patients from the ICU to a general ward is one of the most challenging, and high-risk transitions of the healthcare system.[1, 2] This vulnerable period carries increased risk of medical errors, adverse events, readmission,[3] dissatisfaction with care, and death.[4] In addition, patient transfer from the ICU to the general ward manifests as an anxiety-inducing scenario for the accompanying relatives[2] because 50%-70% of ICU survivors suffer long-term physical, cognitive, and psychological impairment.[5]

However, the relatives can have both positive and negative responses when hearing that the patient can be transferred from the ICU to the general ward. They may experience relief, excitement, and encouragement since the transfer from the ICU as a marker of clinical improvement or stable medical conditions, allows them to reunite with and personally care for their loved one, often generating feelings of relief and optimism. Conversely, during the ICU stay, the closed management model typically restricts family visitation, limiting their ability to observe the patient's condition and understand the disease progression and prognosis. This asymmetry of information between clinicians and families fosters uncertainty. Upon transfer from the ICU to a general ward, some families may experience fear and anxiety related to unfamiliar care protocols, reduced patient monitoring, potential complications in the general ward setting, an unfamiliar environment, and a lack of knowledge about the illness during the rehabilitation phase. These factors may hinder the family's ability to provide effective support which may negatively impact the patient's recovery and prognosis.[6, 7] Disruptions of the patient environment and continuity of interpersonal relationships, in addition to the nature of the transfer itself, have been identified as a stressful situation for the patient and relatives, and this is called 'transitional' or 'relocation' stress.[8] Transitional stress has been defined as a state in which an individual experiences physiological and/or psychosocial disturbance as a result of transfer from one environment to another, and is also referred to as 'transfer stress' or 'transfer anxiety'.[9]

Furthermore, during the transition period of the patient from the ICU to the general ward, medical staff primarily focus on the patient, but disregard the physical and/or psychological changes among the patient's relatives, which increases the psychological pressure on the relatives.[6] Some studies have found that more than 75% of relatives reported transitional stress when transferring patients out of the ICU.[10] A qualitative study found that, after the ICU patient was transferred to the general ward, some relatives became alarmed by the patient's vulnerability.[5] They realized that transferring from the ICU to the ward was not the end of risk. While they knew that patients tend to get better when they leave the ICU, they do not fully understand the recovery progress, and this may exacerbate anxiety. Oh et al[11] found that the relatives of ICU-transferred patients exhibited a medium-to-high level of transitional stress.

A meta-analysis found that the psychological health of a patient's relatives was positively correlated with the patient's psychological reactions.[12] However, transitional stress may undermine the ability of relatives to care for the patient after transfer from the ICU to the general ward.[13] Schröder et al[14] suggested that if the nurses paid more attention to the relatives' physical and psychological health, the patient's disease outcomes would be better. For this reason, it is important to consider the relative's transitional stress and the factors that correlate with it and help to achieve a reduction of transitional stress, so that patients can make a smooth and safe transition.

Based on Meleis's transition theory, transitional stress refers to a response pattern that can be influenced by transition conditions. Higher transitional stress is an outcome indicator, suggesting an unsuccessful transition. The dimensions of the transition include the shift from technical and individual care to general care; from a secure environment inside the ICU to a vulnerable and unpredictable environment; and the transition from despair to independence.[1] Moreover, coming from an environment of safety in the ICU where the patient-to-nurse ratio was one-to-one and going to a ward where it is one-to-many patients, increases the relative's transitional stress.[10] Therefore, researchers should evaluate and understand the transitional stress experienced by the relatives of critically ill patients. Understanding the transition condition could help hospital staff mitigate the transitional stress experienced by a patient's relatives and help healthcare providers achieve a successful transition by managing the transition conditions to reduce the ICU transfer pressure experienced by the patient's relatives.

Uncertainty is an adverse manifestation of patient transition that is often perceived by the relative(s). During the ICU stay, a patient's relatives may feel disconcerted or insecure, which can trigger fear, anxiety, anger, or depression.[8] The stark difference between the ICU and a general ward can also cause uncertainty.[5] In China, studies found that some relatives felt uncertain about the patient's disease, which could be exacerbated by transitional stress.[15, 16] The uncertainty and the psychological burden of relatives of ICU patients were at a high level, which were the main influencing factors of transitional stress.[17]

Hope, another variable emotion during patient transition, is a concept belonging to positive psychology. Hope is described as an experience, emotion, or need.[18] As a psychological resource, hope can help individuals to respond to trauma with resilience.[19] Meanwhile, Folkman has revealed the importance of hope for people who are coping with serious and prolonged psychological stress. Furthermore, other studies have found that higher levels of hope are associated with fewer stress symptoms in the relatives of critically ill patients.[20, 21] Moreover, Zhang et al,[22] found that perceived stress was negatively correlated with each dimension of hope.

Preparedness is a condition that can affect the transition process and response. Preparedness is defined as perceived readiness for multiple domains of the caregiver role. Preparation includes preparing and planning about individual knowledge, meaning, experience, and the environment in transition.[23] The patient's relative acts as the main carer of a patient after transfer out of the ICU. There is a significant negative correlation between the preparation of the main relatives of the ICU patient and transitional stress. If the relatives are not ready to take care of and deal with the transition, it may lead to anxiety, uneasiness, and other emotions from transitional stress.[24] When it is time to transfer the patient out of the ICU, if the preparation of the relative is successful, the stress and anxiety of the transition can be reduced.[25, 26] More and more scholars pay attention to the preparation of patients before transfer from the ICU to the ward. However, there have been few reports on the relationship between preparedness and the transitional stress of the patient's relatives, which is worthy of in-depth study.

In conclusion, transferring a patient from the ICU is an important and significant potential trigger of transitional stress that can reach extreme levels.[27] From the above literature review, the researcher found that nursing services during the transition period when patients are transferred from the ICU to the general ward have been receiving more and more attention. For patients and their families, transferring out of the ICU is a positive step for managing the disease. However, the transition is also a new challenge, and that could mean that the relatives face a new set of obstacles and experiences, such as changing the frequency of the medical and nursing team visit and changing of treatment.[28, 29] However, in China, the investigation of transitional stress among relatives who take care of a critically ill patient is limited, and there have been few studies on the relationship between transitional stress, uncertainty, hope, and preparedness. Under the guidance of Meleis's transition theory, the purpose of this research was to explore the relative's transitional stress and to examine whether preparedness, uncertainty, and hope were associated with transitional stress. The results of this research should be useful for nurses and healthcare providers to attain a better understanding of transitional stress and the factors that correlate with stress, so that they can develop appropriate nursing interventions to reduce transitional stress among patients' relatives, and facilitate the process for a successful transition, thus helping to meet the ultimate goal of patient safety and recovery after moving from the ICU to general ward.

This study aimed to describe transitional stress among relatives during the transfer of critically ill patients from the ICU to the general ward, and to determine the relationship between uncertainty, hope, preparedness and transitional stress among the relatives when transferring critically ill patients from the ICU to the general ward.

Methods

Study Design and Setting

This study employed a descriptive correlational research design. The study was conducted in the general ICU of the Second Affiliated Hospital of Wenzhou Medical University, in Wenzhou, China. The ICU has 26 beds. During the patient's admission in the ICU, their relatives communicated with the patients and medical staff every day for 10 to 20 minutes, they could see the current state of the patient, and the surrounding environment only online by video call. At the same time, the relatives could get some information about caring for patients through the network, there was an official account on WeChat, and there were some videos and pictures to educate how to take care of the patient, which the relatives studied by themselves.

Participants

The study sample was the relatives of critically ill patients who were transferred from the ICU to the general ward at the Second Affiliated Hospital of Wenzhou Medical University in Wenzhou, China. After identifying eligible participants based on the inclusion criteria, a simple random sampling technique was used to recruit the study sample. The inclusion criteria for the relatives were as follows: 1) being the patient's spouse, son/daughter, or parent(s) who continuously visited and made medical decisions when the patient was admitted to ICU; 2) being the carer during the patient's stay in the general ward; 3) being at least 18 years old; 4) having the ability to read and speak Chinese; 5) willingness to participate in the study; and 6) no history of a psychological disorder such as clinical anxiety, depression, or sleep disorder.

The inclusion criteria for critically ill patients were as follows: 1) being at least 18 years old; 2) having the Acute Physiology and Chronic Health Evaluation II (APACHE II) score of at least 15 on the day of admission; 3) had stayed in the ICU for at least 72 hours; 4) having hemodynamic stability and readiness for transferring from ICU to general ward.

(stable blood pressure, regular heart rate, no mechanical ventilation, and no other special physiological monitoring instruments).

The G*Power 3.1.9.7 program for correlational design was used to calculate the sample size for this study. The significance level was .05, statistical power was 0.90 and estimated medium effect size was 0.30. Accordingly, the study sample was 112 participants.

Instruments

In total, 5 instruments were utilized for data collection, all of which were authorized by the original authors and the Chinese version author. The demographic questionnaire was developed by the researcher, and was divided into 2 parts: information on the patient (sex, marital status, education, monthly income, payment method of medical expenses, diagnosis, length of ICU stay, pretransfer Barthel Index score, APACHE II score during the first 24 hours of ICU stay and the scores before transferring to ward, whether the first time in the ICU, feeding method, and indwelling catheter), and information of the relatives (sex, age, marital status, education, religion, relationship with the patient, monthly income, history of caring for a critically ill person, health status, and chronic illness).

The Family Relocation Stress Scale (FRSS) was used to measure the level of transitional stress. Oh et al[8] had adapted the FRSS for the relatives of patients in the ICU. This scale was back-translated into Chinese and revised by Wang et al.[30] The Chinese version of the FRSS has 14 items with 4 dimensions, including the recognition of the patient who remains critically ill (3 items), the recognition of separation anxiety (3 items), the recognition of general ward environment and care (6 items), and the recognition of transfer (2 items). Each item is rated on a 4-point Likert scale, with 1 indicating 'completely disagree', 2 indicating 'disagree', 3 indicating 'agree', and 4 indicating 'completely agree'. Items 2, 5, 6, 7, 8, 10, and 11 are scored in reverse. The total potential score of this scale is 56, with a higher score indicating more stress. A score of less than or equal to 15 is classified as 'low' stress, 16-40 is 'moderate' stress, and 41-56 is 'high' stress.[11, 17] The Chinese version of the FRSS has been tested in the Chinese population, with a Cronbach α value of 0.86. In this study, the internal consistency reliability of the FRSS was 0.88.

The Care Preparedness Scale (CPS) was used to measure the level at which relatives of the patient perceived that they were prepared for the tasks and demands in the caregiving role. The CPS was originally developed by Archbold et al.[31] Liu et al[32] translated the CPS into Chinese. The CPS comprises 8 items, with each item rated on a 5-point rating scale ranging from not at all prepared (0) to very well prepared (4). A total score of 0-32 is calculated by summing the responses for all items, with a higher score indicating feeling more prepared. The scale had exhibited good validity and reliability among relatives of patients in palliative care. The Chinese version of the CPS has been tested in the Chinese population, with a Cronbach α value of 0.90. In this study, the internal consistency reliability of the CPS was 0.82.

The Parents' Perception of Uncertainty in Illness Scale-Family Member (PPUS-FM) was used to measure the level of uncertainty. It is a self-rating scale compiled by Mishel.[33] The Chinese version of this scale was back-translated by Chuang.[34] This scale demonstrates good reliability and validity in the research of critically ill adult patients.[34, 35] The scale primarily comprises 31 items in 4 dimensions: ambiguity, complexity, lack of information, and unpredictability. Among them, 13 items are in the dimension of uncertainty, 9 items in the dimension of complexity, 5 items in the dimension of lack of information, and 4 items in the dimension of unpredictability. All items were scored using a 5-point Likert scale, ranging from 'strongly disagree', 'disagree', 'don't know', 'agree', and 'strongly agree' as 1 to 5 points, respectively. Eleven items were scored in reverse. The potential total scale score was 31-155 points, with a higher score indicating a stronger sense of uncertainty about the disease. A 'low' illness uncertainty score was below 59 points, a 'medium' score was from 59-87 points, and 'high' score was above 87 points.[36] In this study, the internal consistency reliability of the PPUS-FM was 0.86.

The Herth Hope Index (HHI) was used to measure the level of hope among the relatives of critically ill patients. HHI was developed by Herth[37] and translated into Chinese by Zhao.[38] The scale comprises 12 items, with each item being rated on a 4-point Likert-type scale (1 = strongly disagree to 4 = strongly agree). The potential total score ranges from 12-48. A higher score indicates greater hope, scores of 12-23 indicate low hope, scores of 24-35 indicate medium hope, and scores of 36-48 indicate high hope. The Chinese version of the HHI was tested in the Chinese population, with a Cronbach α value of 0.85. In this study, the internal consistency reliability of the HHI was 0.87.

Data Collection

The researcher explained the data collection procedures to the ICU staff and obtained their cooperation. The ICU nurse assisted in identifying potential participants from the patient registry based on the inclusion criteria. The researcher met each participant and informed them about the study's purpose, ethical issues, and human protections, and invited them to participate in the study. Finally, consent process, and data collection were conducted by the researcher.

The ICU has approximately 2-3 patients, with age at least 18 years who are transferred from the ICU to the general ward every day. The data for this study were collected by the onsite researcher every day between December 2022 and September 2023. It took approximately 30 minutes for each participant to complete the self-reported questionnaires in a private room.

Statistical Analysis

Data analysis was performed using IBM SPSS 26.0 software (IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp; 2019). Descriptive statistics were used to analyze demographic characteristics. Pearson correlation coefficient was used to determine the relationship between uncertainty, hope, preparedness and transitional stress among the relatives of critically ill patients during the transition from the ICU to the general ward. All relevant assumptions for using Pearson correlation were fulfilled.

Results

The description of demographic characteristics (both of relatives and patients) and health information of the 112 participants was determined (Table 1 and Table 2).

Among the patients enrolled, 64.3% of the patients underwent surgery, with 89.3% of the patients being admitted to the ICU for the first time. Over three-fifths (63.4%) of the patients stayed in the ICU for 3-7 days. On the transfer day, 67.0% of the participants had activities in daily living (ADL) scores of 0-20, whereas 92% of the patients had APACHE II scores of 15-24. Most patients (62.5%) were fed through a nasogastric tube, 99.1% of the patients had a venous catheter, and 58% had a central venous catheter. A surgical drainage tube was present in 44.6% of the patients, and 90.2% of the patients had a urinary catheter. Most patients (59.8%) had nasal oxygen when they were transferred to the general ward (Table 3).

Table 1. Demographic Characteristics of the Relatives

Characteristic	No. (%)
Gender	
Male	41 (36.6)
Female	71 (63.4)
Age, y	
20-39	41 (36.6)
40-59	59 (52.7)
60-75	12 (10.7)
Religion	
No religion	63 (56.3)
Buddhism	38 (33.9)
Christian	11 (9.8)
Educational attainment	
None	5 (4.5)
Primary school	23 (20.5)
Junior high school	38 (33.9)
Senior high school	28 (25)
Bachelor's degree	18 (16.1)
Marital status	
Unmarried	6 (5.4)
Married	106 (94.6)
Occupation	
No occupation	55 (49.1)
Employed	49 (43.8)
Civil servant/government staff	3 (2.7)
Laborer (builder, factory worker, sanitation worker, driver, farmer)	35 (31.3)
Businessperson	11 (9.8)
Retired	8 (7.1)
Relationship with the patient	
Spouse	26 (23.2)
Child	60 (53.6)
Parent	9 (8.0)
Brother/sister	15 (13.4)
Nephew/niece	2 (1.8)
Frequency of visit	
Once a day	96 (85.7)
Every 2 days	8 (7.1)
Every 3 days	5 (4.5)
Twice a day	3 (2.7)

Table 1. Demographic Characteristics of the Relatives (Continued)

Characteristic	No. (%)
Experience in caring for a critically ill person	
No	101 (90.2)
Yes	11 (9.8)
Health status	
Unhealthy	2 (1.8)
Healthy	110 (98.2)
Chronic disease (hypertension/diabetes)	
No	105 (93.8)
Yes	7 (6.3)
Received some medical information about the patient when admitted to the ICU	
No	28 (25.0)
Yes	84 (75.0)
Received some information about how to take care of the patient when visiting the patient	
No	41 (36.6)
Yes	71 (63.4)
Need some information or some help after patient was transferred to the general ward	
No	64 (57.1)
Yes	48 (42.9)

Abbreviation: ICU, intensive care unit.

Table 2. Demographic Characteristics of the Patients

Characteristic	No. (%)
Gender	
Male	80 (71.4)
Female	32 (28.6)
Age, y	
18-39	20 (17.9)
40-59	30 (26.8)
60-75	39 (34.8)
75-91	23 (20.5)
Religion	
No religion	69 (61.6)
Buddhism	34 (30.4)
Christian	9 (8.0)
Educational attainment	
Primary school or below	72 (64.3)
Junior high school	22 (19.6)
Senior high school	15 (13.4)
Bachelor's degree	3 (2.7)

Table 2. Demographic Characteristics of the Patients (Continued)

Characteristic	No. (%)
Marital status	
Unmarried	6 (5.4)
Married	106 (94.6)
Divorced	1 (0.9)
Widowed	5 (4.5)
Occupation	
No occupation	33 (29.5)
Employed	59 (52.6)
Healthcare personnel	1 (0.9)
Civil servant/government staff	6 (5.3)
Laborer	47 (42.0)
Businessperson	5 (4.4)

Table 3. Health Information of the Patients

Characteristic	No. (%)
Had surgery	
No	40 (35.7)
Yes	72 (64.3)
History of admission to the ICU	
1st	100 (89.3)
2nd	11 (9.8)
4th	1 (0.9)
Length of stay in the ICU, d	
3-7	71 (63.4)
8-14	30 (26.8)
15-28	8 (7.1)
> 28	3 (2.7)
ADL score (admission day)	
0-20 (completely dependent; extremely severely/severely impaired)	106 (94.6)
21-40 (severely dependent; moderately impaired)	4 (3.6)
41-60 (moderately dependent)	2 (1.8)
ADL score (transferring day)	
0-20 (completely dependent; extremely severely/severely impaired)	75 (67.0)
21-40 (severely dependent; moderately impaired)	20 (17.8)
41-60 (moderately dependent)	17 (15.2)
APACHE II score (admission day)	
15-24	86 (76.8)
≥ 25	26 (23.2)

Table 3. Health Information of the Patients (Continued)

Characteristic	No. (%)
APACHE II score (transferring day)	
15-24	103 (92.0)
≥ 25	9 (8.0)
Feeding method	
Oral eating	34 (30.4)
Tube feeding	70 (62.5)
Treatment for nothing per oral	8 (7.1)
Indwelling catheter*	
Venous catheterization	
None	1 (0.9)
Central venous catheter	65 (58.0)
Peripheral venous catheter	46 (41.1)
Surgical associated drainage tube	
No	62 (55.4)
Yes	50 (44.6)
Urinary catheter	
No	11 (9.8)
Yes	101 (90.2)
Respiratory	
Normal breathing	11 (9.8)
Nasal oxygen	67 (59.8)
Mask oxygen	13 (11.6)
Intubation tube	16 (14.3)
Tracheotomy	5 (4.5)
Comorbidity	
No	106 (94.6)
Yes	6 (5.4)

Abbreviations: ADL, activities in daily living; APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit.

* A patient can have multiple different types of tubes at the same time.

All relatives suffered from transitional stress, with 83.9% suffering a 'moderate' level and 16.1% experiencing 'high' stress. The mean (SD) score of transitional stress was 36.5 (6.2) and ranged 28-51 (Table 4).

The mean (SD) score of hope of the sample was 27.5 (5.1), indicating a 'moderate' level. The mean (SD) score for the preparedness of relatives was 16.1 (4.4), which was also at a 'moderate' level. The mean (SD) score for uncertainty was 83.0 (10.0), which was also at a 'moderate' level (Table 5).

Relatives' hope and preparedness was moderately negatively correlated with transitional stress when the critically ill patient was transferred from the ICU to the general ward (r = -0.40, $P < .001$; r = -0.44, $P < .001$) respectively. Furthermore, uncertainty exhibited a high positive correlation with transitional stress (r = 0.75, $P < .001$) (Table 6).

Table 4. Transitional Stress Among the Relatives

Transitional Stress Score	No. (%)
Low stress (≤ 15)	0
Moderate stress (16-40)	94 (83.9)
High stress (41-56)	18 (16.1)

Table 5. Hope, Uncertainty, and Preparedness Among the Relatives

Variable	Range		Mean (SD)	Level
	Possible Score	Actual Score		
Hope	12-48	18-43	27.5 (5.1)	Moderate
Uncertainty	31-155	65-101	83.0 (10.0)	Moderate
Preparedness	0-32	9-28	16.1 (4.4)	Moderate

Table 6. Pearson's Correlation Coefficients Between Hope, Uncertainty, and Preparedness and Transitional Stress

Variable	Transitional Stress	*P* Value
Hope	-0.40	< .001
Uncertainty	0.75	< .001
Preparedness	-0.44	< .001

Discussion

In this study, the mean (SD) score for transitional stress among the relatives when transferring the critically ill patient from the ICU to the general ward was 36.5 (6.2). This score was considered to be at a moderate level, and was consistent with the studies of Luo et al[39] in 2022 on the transitional stress of relatives when transferring a critically ill patient from the ICU to general ward (mean [SD], 34.5 [6] and 32.3 [3.8], respectively).

According to Meleis's transition theory, transitional stress refers to a response pattern that can be influenced by various conditions during a transition. These conditions encompass personal, community, and societal factors. In the present study, the relatives' transitional stress may be explained based on these aspects.

The first determinant is the severity of the condition of the patient. In this study, the patients had a low ADL score and a high APACHE II score, with 67.0% of patients having an ADL score of 0-20 and 92% having an APACHE II score of 15-24 on the transition day. This indicated that the patient was still at risk of being transferred back to the ICU.[40] Furthermore, the body of the patient was extremely severely or severely impaired, and being severely dependent on others. Seo et al[41] have reported a negative correlation between good ADL scores and stress, ie, the lower the ADL score, the greater the stress of the patient's relatives. In addition, some researchers have reported that as a patient's self-care ability decreases, their relatives face more difficulty in taking care of them. This means that the patient will be more dependent on the care of others, suggesting evident transitional stress among relatives.[42]

Based on transition theory, knowledge of the transition process affects transitional stress. When patients are transferred to the general ward, intensive care is interrupted, and the patients' relatives need to take care of the patients by themselves in the general ward. Furthermore, some studies have found that relatives with caregiving experience suffered from less transitional stress, because they might have more knowledge and could better adapt to the role transition from family relatives to caregivers.[43, 44] In the present study, 90.2% of the relatives had no experience in caring for a critically ill person. This change in role may also contribute to transitional stress among the relatives of patients transferred from the ICU.[45]

Regarding formal schooling, previous studies have found that lower educational attainment was associated with depression, anxiety, and stress.[46-48] Furthermore, a patient whose relatives had lower education would exhibit higher stress.[49] In the present study, 75% of relatives had high level of education, and they could access telehealth support or the relevant online information.[50] In contrast, low education level was an independent factor for low family readiness, potentially affecting their ability to effectively communicate with medical professionals.[43, 44] Therefore, their ability to obtain the needed information was poor. Collectively, these findings have indicated that the low educational attainment of relatives in this study might have affected their transitional stress.

The frequency of patient visits may also be a reason for relatives to perceive transitional stress. More frequent visits may lessen a relative's stress. The primary needs of the relatives of the ICU patient are medical information, reassurance, and being near the patient.[51, 52] Studies have found that the less the ICU visit time, the higher the transitional stress among relatives. This is because when patients are transferred out of the ICU, relatives with fewer visits are not physically and psychologically prepared to care for the patient, who may have various catheters and instrument connections, leading to a higher level of transitional stress.[53] When the relatives visit the patient, the medical staff may give medical information to them. However, in the present study, 85.7% of participants visited patients once a day, which indicated that relatives had insufficient access to medical information when outside the hospital setting, increasing the stress of transfer.

In the present study, 71% of the relatives were female. Studies have found that female relatives of ICU transfer patients experience higher levels of transitional stress. This is because women are more emotionally sensitive and psychologically more susceptible to another's suffering. Furthermore, females have weaker coping ability than males. In particular, when a loved one's condition is critical, women are more likely to experience anxiety, depression, and other negative psychological reactions. While female relatives feel encouraged when their loved one is transferred from the ICU to the general ward, they also experience a higher level of stress, including worry and uncertainty.[54]

In the present study, uncertainty of the participants had a positive significant and high correlation with transitional stress ($r = 0.75$, $P < .001$). This finding was consistent with the study hypothesis. Uncertainty is a transition condition perceived by relatives. A sustained high level of uncertainty is associated with higher stress, poor mental health outcomes, and impaired coping ability.[55] Similarly, the ICU contains monitoring equipment and advanced treatment options. As a result, the medical staff configuration is sufficient for most patient needs. However, in the general ward, monitoring equipment is significantly less, the predictive ward environment is removed, and the care mode changes from 'one-to-one' to 'one-to-many'. Therefore, patients and their families may feel insecure, and even question the treatment effect.[56] In this way, the differences between the ICU and general ward result in uncertainty.[5] In China, some studies have found that some relatives felt uncertain about the patient's disease, potentially increasing the transitional stress.[15, 16]

In the present study, hope was negatively associated with transitional stress among the relatives of critically ill patients ($r = -0.40$, $P < .001$). The mean (SD) score for the hope was 27.5 (5.1). This indicated that relatives had a moderate level of hope. This finding was consistent with many studies.[21, 22, 57, 58] According to Meleis's transitions theory, hope is an important facilitator of the transition condition, and can decrease stress.[59] Hope may serve as a moderating resource at the individual level to decrease negative impacts.[60] Furthermore, hope is a prerequisite for effective coping and decision-making, with a protective function against stress. Hope-based therapy interventions can decrease depressive symptoms and stress.[61] Therefore, helping relatives to have a higher level of hope can decrease transitional stress.

In the present study, there was a negative significant correlation between preparedness and transitional stress ($r = -0.44$, $P < .001$). This finding was consistent with that of other studies.[24, 25] Caregiver preparedness is a key factor in the physical and psychological well-being of caregivers.[25] Preparedness refers to the preparation for transition in a way that can affect the transition process and response. Preparation includes preparing and planning about an individual's knowledge, meaning, experience, and environment in transition.[23] In a study involving 87 family caregivers during patients' cancer treatment, increased caregiver preparedness was associated with decreased fatigue and mood disturbance. Furthermore, preparedness interacts with mutuality (relationship quality) in buffering stress responses to high caregiver demands.[62] Therefore, a higher level of hope among relatives was associated with lower transitional stress, consistent with the results of the present study.

The findings from this study provide a basis for predicting the influencing factors for relatives of patients with transitional stress. Accordingly, clinical nurses can formulate nursing interventions to reduce transitional stress. Specifically, nurses can help mitigate transitional stress by enhancing relatives' preparedness and fostering a sense of hope. Additionally, reducing uncertainty through clear, consistent communication and providing timely information and psychological support can better equip family members for the transition from ICU to general ward. Such nursing practices not only support the emotional well-being of relatives but may also contribute to improved outcomes for patients during the recovery process.

Conclusions

In this study, there was a moderate level of transitional stress among the relatives when transferring critically ill patients from the ICU to the general ward in a hospital in Wenzhou. Hope and preparedness were negatively correlated with transitional stress, whereas uncertainty was positively correlated with transitional stress. Understanding the dynamic relationship among these factors can help nursing staff develop specific interventions to reduce transitional stress among relatives when transferring critically ill patients from the ICU to the general ward.

Additional Information

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Ethics Approval: The study protocol was approved by the Ethics Committee of Burapha University (G-HS082/2565 on 21 November 2022) and the Second Affiliated Hospital of Wenzhou Medical University (2022-K-165-02 on 16 December 2022). Before data analysis, details of the objectives, procedures, and right to withdraw were explained by the researcher, with no effect on the quality of service for each candidate. The confidentiality and anonymity of the participants were ensured throughout the study. A consent form was signed by the participants before collecting data.

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RMJ

Bilateral Third Nerve Palsies Secondary to Pituitary Apoplexy: A Case Report

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Abstract

Background: Bilateral third cranial nerve palsies resulting from pituitary apoplexy with bilateral lateral expansion compressing bilateral third cranial nerves at the cavernous sinuses walls are uncommon.

Case Presentation: A 31-year-old healthy male complained of an acute severe headache, bilateral ptosis, and binocular horizontal diplopia for about 4 days. Eye examinations revealed incomplete ptosis, partial limitation of supraduction, infraduction, complete limitation of adduction, and dilated pupils in both eyes associated with bitemporal hemianopia. A brain computerized tomography (CT) scan with contrast revealed an intra- and suprasellar pituitary mass. Brain magnetic resonance imaging (MRI) reported a heterogenous mass measuring 3.0 × 3.1 × 3.8 cm involving the sphenoid sinus, sella turcica, and suprasellar cistern. Hormonal workup revealed the first diagnosis of type 2 diabetes mellitus, hyperprolactinemia, central hypothyroidism, and hypogonadotropic hypogonadism. The patient received hormonal supplements and the tumor was successfully treated by endoscopic surgery. Pathological confirmation of pituitary hemorrhage was found. All ocular and neurological deficits were completely resolved within 6 months postsurgery. Follow-up MRIs at 3 months and 1 year showed no residual tumor; however, hypogonadotropic hypogonadism and postoperative diabetes insipidus persisted for 4 months.

Conclusions: Localization of the third cranial nerve palsy was significant in determining the possibility of a lesion and detecting an emergency condition causing potential life-threatening complications. Most cases of third cranial nerve palsy from pituitary tumors effect one side, but this case is unusual because it involved both sides, showing a rare pattern of tumor growth and compression.

Keywords: Third cranial nerve palsy, Pituitary apoplexy, Pupil involvement

Introduction

Pituitary apoplexy is a neuro-ophthalmological emergency caused by infarction or hemorrhage within the pituitary gland, requiring prompt and accurate diagnosis.[1] Patients may present with visual loss from optic chiasm compression, ocular motor nerve palsies, and severe headache due to rapid tumor expansion affecting the dura or hemorrhage extending into the subarachnoid space.[2] More than 50% of individuals experience visual impairments (caused by pressure on the optic chiasm or optic nerve from

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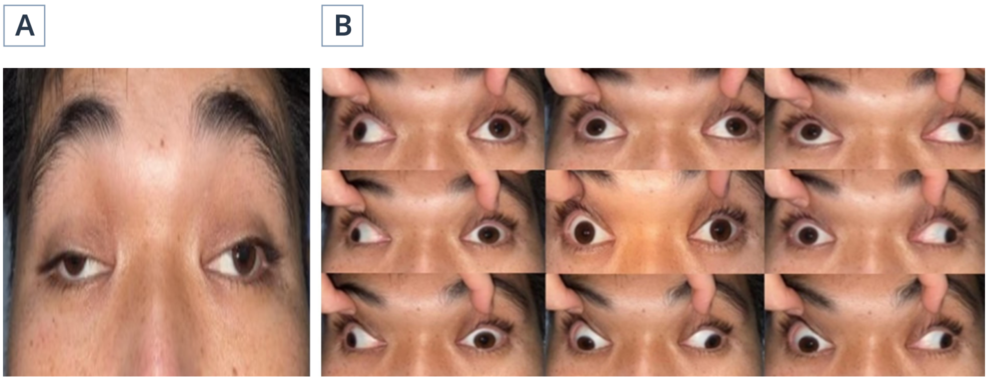
upward growth) and ophthalmoplegia, with the third cranial nerve being the most commonly affected due to intracavernous expansion.[3] However, nearly all reported cases are unilateral third cranial nerve palsy.[4] This report highlights a rare case of bilateral third cranial nerve palsies due to intracavernous expansion of pituitary apoplexy, serving as an example for diagnosis and management.

Case Presentation

A 31-year-old healthy male complained of an acute severe headache for 4 hours. There were no neurological deficits during the initial physical examination at the emergency department. A brain computerized tomography (CT) scan without contrast was unremarkable. The patient was given pain meditation and was then discharged. Four days following the new-onset headache, he had a more severe headache and developed bilateral ptosis and binocular horizontal diplopia. Initial visual acuity was 20/60 in the right eye and 20/50 in the left eye. The intraocular pressure was 12 mmHg in the right eye and 13 mmHg in the left eye. External eye examination revealed bilateral incomplete ptosis (Figure 1A). Krimsky test revealed a 100 prism-diopter exotropia at near. Ocular motility examination revealed a partial limitation of supraduction, infraduction, and complete limitation of adduction in both eyes (Figure 1B). Slit-lamp examinations revealed a normal anterior segment and fixed and dilated pupils 6 mm in size in both eyes. The relative afferent pupillary defect (RAPD) cannot be evaluated. Fundus examination showed a normal optic disc, macula, fovea, and background retina in both eyes. The patient's color vision was normal and the visual field revealed bitemporal hemianopia (Figure 2A). Optical coherence tomography (OCT) showed a normal average peripapillary retinal nerve fiber layer (RNFL) thickness in both eyes. Neurological examinations revealed neither focal deficits nor other cranial nerve involvement. Because the patient had bitemporal hemianopia, a parasellar lesion was suspected. The decreased visual acuity was likely due to involvement of the visual pathway.

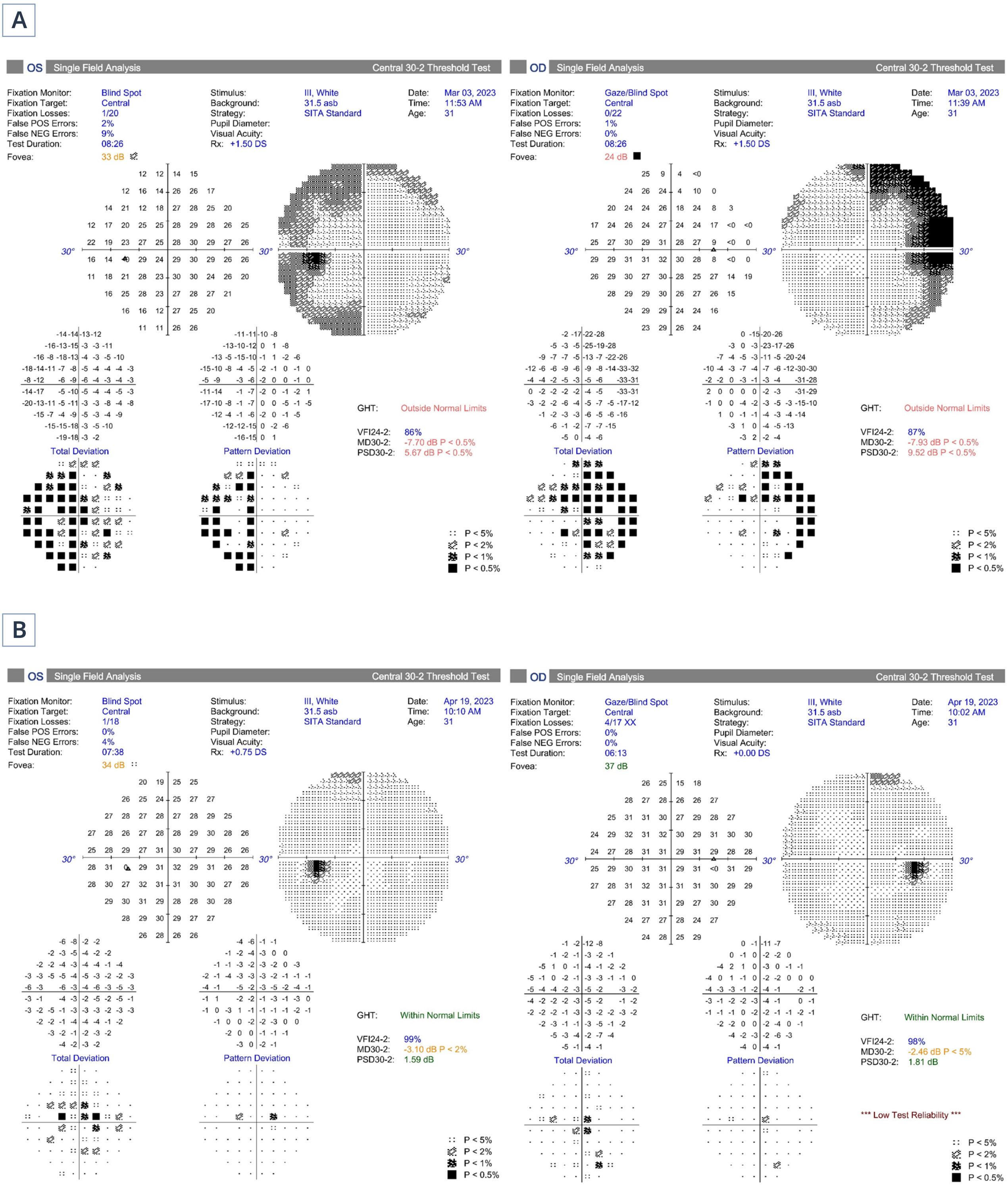
Figure 1. Color Photo Demonstrated Bilateral Ptosis



A, Bilateral ptosis at the initial visit.

B, Nine diagnostic gazes of bilateral incomplete third cranial nerve palsies with pupil involvement.

Figure 2. Computerized Visual Field 30-2 Test



A — OS Single Field Analysis — Central 30-2 Threshold Test

Fixation Monitor: Blind Spot
Fixation Target: Central
Fixation Losses: 1/20
False POS Errors: 2%
False NEG Errors: 9%
Test Duration: 08:26
Fovea: 33 dB
Stimulus: III, White
Background: 31.5 asb
Strategy: SITA Standard
Pupil Diameter:
Visual Acuity:
Rx: +1.50 DS
Date: Mar 03, 2023
Time: 11:53 AM
Age: 31

GHT: Outside Normal Limits
VFI24-2: 86%
MD30-2: -7.70 dB P < 0.5%
PSD30-2: 5.67 dB P < 0.5%

A — OD Single Field Analysis — Central 30-2 Threshold Test

Fixation Monitor: Gaze/Blind Spot
Fixation Target: Central
Fixation Losses: 0/22
False POS Errors: 1%
False NEG Errors: 0%
Test Duration: 08:26
Fovea: 24 dB ■
Stimulus: III, White
Background: 31.5 asb
Strategy: SITA Standard
Pupil Diameter:
Visual Acuity:
Rx: +1.50 DS
Date: Mar 03, 2023
Time: 11:39 AM
Age: 31

GHT: Outside Normal Limits
VFI24-2: 87%
MD30-2: -7.93 dB P < 0.5%
PSD30-2: 9.52 dB P < 0.5%

B — OS Single Field Analysis — Central 30-2 Threshold Test

Fixation Monitor: Blind Spot
Fixation Target: Central
Fixation Losses: 1/18
False POS Errors: 0%
False NEG Errors: 4%
Test Duration: 07:38
Fovea: 34 dB ::
Stimulus: III, White
Background: 31.5 asb
Strategy: SITA Standard
Pupil Diameter:
Visual Acuity:
Rx: +0.75 DS
Date: Apr 19, 2023
Time: 10:10 AM
Age: 31

GHT: Within Normal Limits
VFI24-2: 99%
MD30-2: -3.10 dB P < 2%
PSD30-2: 1.59 dB

B — OD Single Field Analysis — Central 30-2 Threshold Test

Fixation Monitor: Gaze/Blind Spot
Fixation Target: Central
Fixation Losses: 4/17 XX
False POS Errors: 0%
False NEG Errors: 0%
Test Duration: 06:13
Fovea: 37 dB
Stimulus: III, White
Background: 31.5 asb
Strategy: SITA Standard
Pupil Diameter:
Visual Acuity:
Rx: +0.00 DS
Date: Apr 19, 2023
Time: 10:02 AM
Age: 31

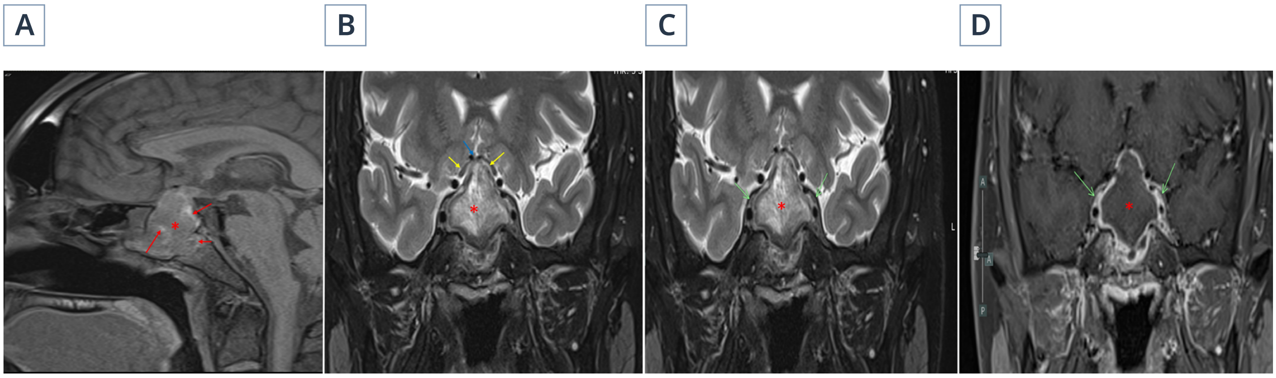
GHT: Within Normal Limits
VFI24-2: 98%
MD30-2: -2.46 dB P < 5%
PSD30-2: 1.81 dB
*** Low Test Reliability ***

A, Preoperative bitemporal hemianopia visual field defect.

B, Marked improvement at the 1-month postsurgery.

A brain CT scan with contrast revealed an intra- and suprasellar heterogenous pituitary mass. Contrast-enhanced brain MRI reported a heterogenous mass measuring 3.0 × 3.1 × 3.8 cm involving the sphenoid sinus, sella turcica, and suprasellar cistern with associated bony destruction of the sellar floor and clivus. The mass demonstrated hyperintensity areas in T1-weighted suggestive of hemorrhagic components (Figure 3A) with visual pathway (Figure 3B) and cavernous expansion (Figure 3C and 3D). Hormonal workup revealed the first diagnosis of type 2 diabetes mellitus, hyperprolactinemia, central hypothyroidism, and hypogonadotropic hypogonadism. The patient was diagnosed with pituitary apoplexy with optic chiasm involvement, bilateral third cranial nerve palsies, and hormonal dysfunction. The patient received hormonal supplements, and the tumor was successfully removed by endoscopic endonasal approach (EEA) surgery at 9 days after onset of symptoms. Pathological confirmation of pituitary hemorrhage with extensive tumor necrosis was found (Figure 4). All ocular and neurological deficits were completely resolved within 6 months postsurgery (Figure 5). The patient developed central diabetes insipidus following pituitary tumor surgery, which persisted for about 4 months and required treatment with desmopressin. At the 1-month postoperative follow-up, the patient demonstrated improved visual acuity, measuring 20/30 in the right eye and 20/20 in the left eye. Bilateral ptosis had resolved, visual field defects had improved (Figure 2B), and both pupils measured 4 mm in size with sluggish reaction to light. Follow-up MRIs at 3 months and 1 year showed no residual tumor, yet hypogonadotropic hypogonadism and diabetes insipidus persisted for 4 months.

Figure 3. Magnetic Resonance Imaging



A, T1-weighted sagittal view of a 3.0 × 3.1 × 3.8 cm mass (red asterisk) with hyperintense areas (red arrows) involving the sphenoid sinus, sella turcica, and suprasellar cistern with bony destruction.

B, T2-weighted coronal view showed optic nerves (yellow arrows) and chiasm compression (blue arrow).

C, T2-weighted view demonstrated cavernous sinus expansion with third cranial nerves compression (green arrows).

D, T1-weighted gadolinium-enhanced coronal view demonstrated cavernous sinus expansion with third cranial nerves compression (green arrows).

Figure 4. Histopathologic Findings Demonstrated Pituitary Hemorrhage With Extensive Tumor Necrosis

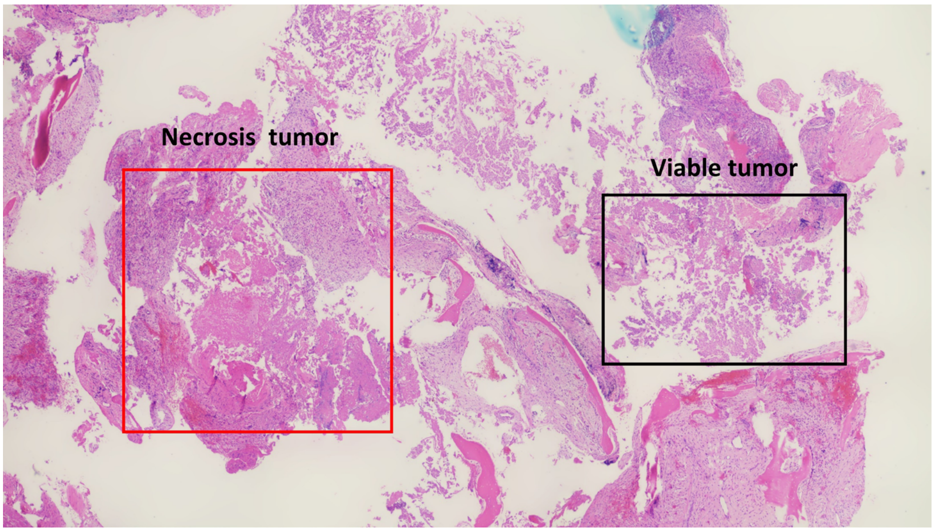
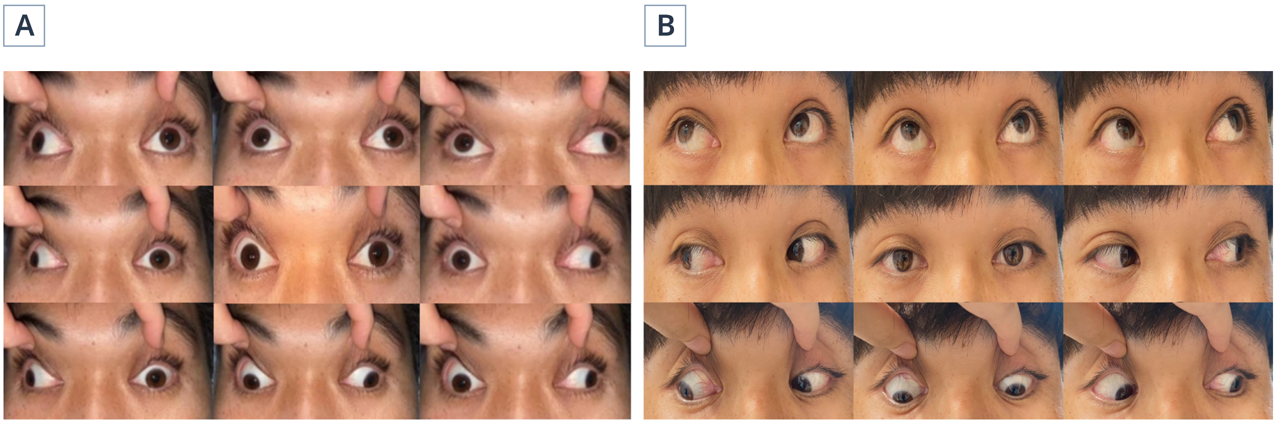


Figure 5. Color Photo Demonstrated Ocular Motility Deficits From Bilateral Incomplete Third Cranial Nerve Palsies With Pupil Involvement



A, At the initial visit.

B, Improved at the 6-month follow-up.

Discussion

Previous studies found that the causes of acquired third cranial nerve palsy were microvascular ischemia (42%), followed by trauma (12%), tumors (11%), aneurysm compression (6%), and pituitary apoplexy (2%).[5, 6] Although in cases of third cranial nerve palsy, only 2% are caused by pituitary apoplexy, it is still an emergency condition that should not be overlooked, as it can lead to patient death. This case presented with severe acute headache along with symptoms of bilateral third cranial nerve palsies with pupil involvement, and bitemporal hemianopia. Anatomically, both the third cranial nerve and optic chiasm could be injured in the sellar region. The cavernous part of the third cranial nerve is located lateral to the interclinoid ligament at the level of the pituitary gland and may be affected by lateral expansion of the sellar mass.[7] The optic chiasm, situated above the sellar region, may be damaged if the mass expands upward. Painful third cranial nerve palsy can implicate acute processes such as apoplexy.[8] Previous reports have described bilateral third cranial nerve palsies in pituitary apoplexy due to sudden hemorrhagic expansion, as seen in this case. However, this patient also exhibited blurred vision and visual field defects, which were occasionally masked by bilateral ptosis. Therefore, assessment of afferent visual function is crucial in all cases of bilateral third cranial nerve palsies.[9-12] A brain MRI scan showed a heterogenous T1 pituitary mass with lateral expansion affecting the bilateral cavernous sinus and upward expansion damaging the optic chiasm, correlating with the clinical presentation, confirming a diagnosis of pituitary apoplexy.

For treatment, the optimal timing of surgery is not yet defined. A previous multicenter observational study indicated that early surgery (within 4 days) did not significantly affect outcomes.[13] The Pituitary Apoplexy Score (PAS), ranging from 0 to 10, is a clinical score used to assess the severity of pituitary apoplexy. It considers factors such as level of consciousness, visual acuity, visual field defects, and ocular motility. Higher scores indicate more severe neurological and visual impairment and may suggest the need for surgical intervention, while lower scores may suggest conservative treatment.[14] There is no consensus regarding surgery versus conservative treatment. But in more severe cases (PAS ≥ 3) are more likely to undergo surgery than patients with PAS 0 to 2 ($P = .03$).[13] This patient (PAS = 6) received tumor removal with EEA 9 days after the onset of symptoms. Visual field defect was improved at 1 month after surgery followed by improvement of ophthalmoplegia at 6 months. However, the patient still requires long-term hormonal therapy.

In summary, bilateral third cranial nerve palsies resulting from pituitary apoplexy with bilateral lateral expansion compressing bilateral third cranial nerves at the cavernous sinuses walls are uncommon. Localization of the third cranial nerve palsy was significant in determining the possibility of a lesion and detecting an emergency condition causing potentially life-threatening complications in this case. While most reported cases of third cranial nerve palsy secondary to pituitary tumor present with unilateral involvement, this case demonstrates a rare presentation of bilateral third nerve palsies, highlighting an uncommon pattern of tumor expansion and compression rarely documented in the literature.

Conclusions

This case emphasizes the clinical manifestations, characteristic radiological features, and presentation of pituitary apoplexy, presenting as painful bilateral third cranial nerve palsies with bitemporal hemianopia.

Additional Information

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Ethics Approval: This study was conducted with the approval of the Medical Ethics Committee of Thammasat University (MTU-EC-OP-0-166/67) from 19 July 2024 in accordance with the tenets of the Declaration of Helsinki. Prior to participating in the study, the patient provided informed consent.

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Visualization: Suntaree Thitiwichienlert
Writing – Original Draft: Supangpa Chuengtanacharoenlert
Writing – Review & Editing: Suntaree Thitiwichienler

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