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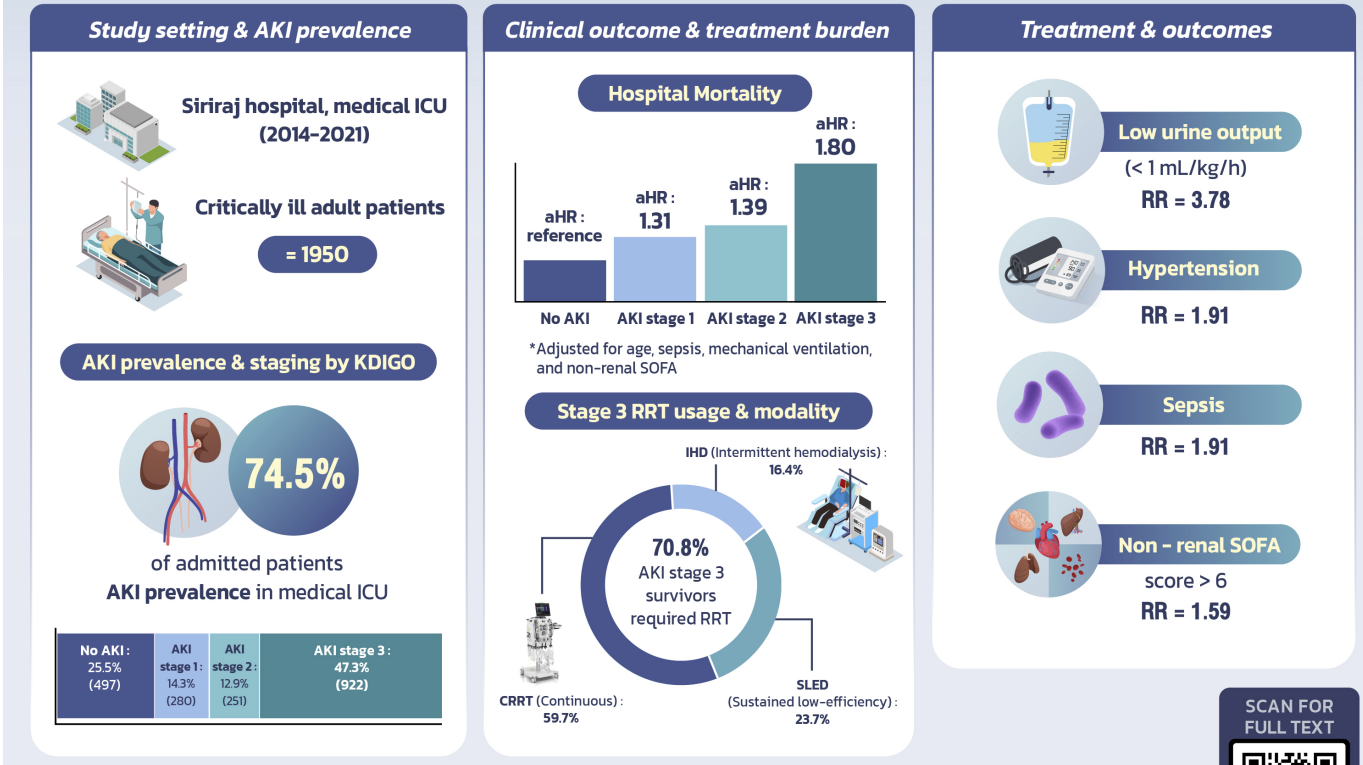
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ORIGINAL ARTICLE

AKI in the Medical ICU : Prevalence and Outcomes



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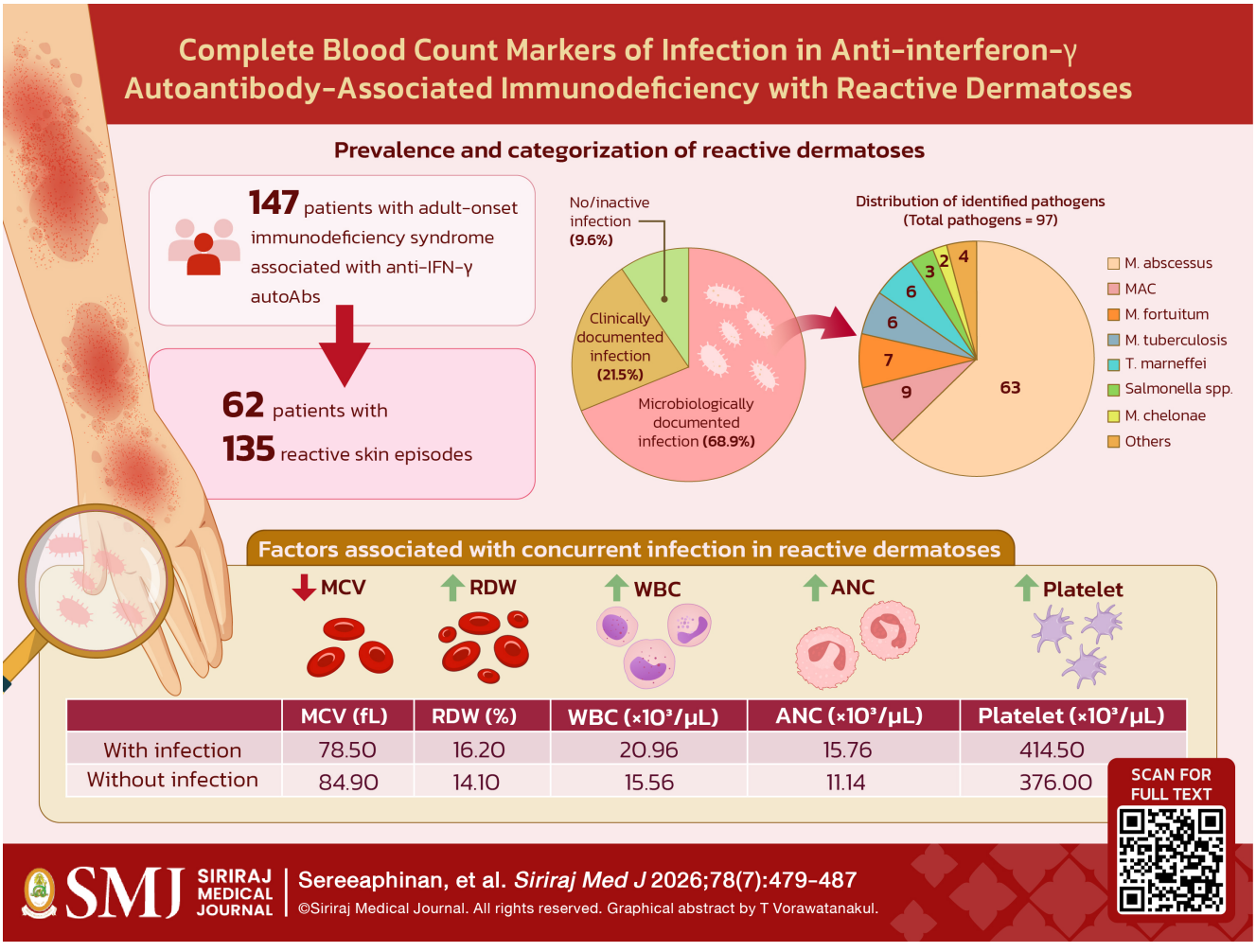
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Complete Blood Count Markers of Infection in Anti-interferon-γ Autoantibody-Associated Immunodeficiency with Reactive Dermatoses

Chudapa Sereeaphinan, M.D.[1], Penvadee Pattanaprichakul, M.D.[1], Sumanas Bunyaratavej, M.D.[1], Pattriya Jirawattanadon, M.D.[1], Nasikarn Angkasekwinai, M.D.[2], Weerapat Owattanapanich, M.D.[3], Charussri Leeyaphan, M.D.[1,*]

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	MCV (fL)	RDW (%)	WBC (×10³/μL)	ANC (×10³/μL)	Platelet (×10³/μL)
With infection	78.50	16.20	20.96	15.76	414.50
Without infection	84.90	14.10	15.56	11.14	376.00

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ABSTRACT

Objective: To identify clinical and laboratory parameters associated with infections in patients with reactive dermatoses.

Materials and Methods: This retrospective study reviewed the medical records of patients diagnosed with adult-onset immunodeficiency syndrome caused by anti-interferon-gamma autoantibodies. Clinical data, laboratory findings, and information on concurrent infections were analyzed.

Results: Of the 147 patients reviewed, 62 (42.2%) presented with reactive dermatoses, accounting for 135 episodes. Patients with concurrent infections had significantly lower mean corpuscular volume (78.5 vs. 84.9 fL; p=0.039). In contrast, red cell distribution width (16.2 vs. 14.1%; p=0.005), white blood cell count (20.96 vs. 15.56 $\times 10^3$/μL; p=0.037), absolute neutrophil count (15.76 vs. 11.14 $\times 10^3$/μL; p=0.038), and platelet count (414.5 vs. 376.0 $\times 10^3$/μL; p=0.023), were significantly higher in infected episodes than in non-infected episodes.

Conclusion: In patients presenting with reactive dermatoses, laboratory parameters derived from the routine complete blood count can serve as valuable indicators of increased risk for concurrent infections, enabling prompt diagnosis and targeted management.

Keywords: Adult-onset immunodeficiency syndrome; anti–interferon-gamma autoantibodies; reactive dermatoses; concurrent infection (Siriraj Med J 2026;78(7):479-487)

INTRODUCTION

Complete blood count (CBC) is a basic laboratory investigation that provides valuable information for prognostic assessment and evaluation of disease severity in various inflammatory conditions, including dermatologic disorders. Systematic review and meta-analyses have demonstrated that red cell distribution width (RDW) and mean platelet volume (MPV) are significantly elevated in dermatologic conditions such as psoriasis compared with healthy controls.[1] Moreover, elevated RDW has been linked to systemic vasculitis in patients presenting with cutaneous vasculitis,[2] while elevations in white blood cell count (WBC), neutrophil count, neutrophil-lymphocyte ratio, and monocyte-to-lymphocyte have been shown to correlate with disease severity in psoriasis patients.[2,3]

In accordance with this concept, this study focuses on adult-onset immunodeficiency syndrome (AOIS) caused by anti-interferon-gamma (IFN-γ) autoantibodies (AIGAs), which is an emerging acquired immunodeficiency that predisposes individuals to severe, difficult-to-treat infections. In addition to infectious manifestations such as lymphadenopathy and fever, affected patients also present with skin lesions, particularly reactive dermatoses. These dermatoses are classified into neutrophilic dermatoses (ND) and non-ND.[4-7] Timely detection of concurrent infections in patients with reactive dermatoses is essential, as management often requires both empirical antimicrobial therapy and anti-inflammatory treatment. According to *Jutivorakool et al.*, NDs are strongly associated with concurrent infections, with an odds ratio of 14.79 compared with patients without NDs.[6] Furthermore, among patients with reactive dermatoses, disseminated concurrent infections are more frequently observed in those with NDs than in those with non-NDs.[8] However, based on a review of existing literature, data on laboratory parameters associated with infections in patients with reactive dermatoses is limited. Therefore, this study aims to investigate potential laboratory predictors of infection in reactive dermatoses, with a particular focus on the CBC panel, which is both cost-effective and readily available.

MATERIALS AND METHODS

Study design and participants

This retrospective cross-sectional study was conducted at a Tertiary center in Thailand, following approval from local ethic committee (COA no. SI 314/2023). Medical records of patients diagnosed with AIGA-associated immunodeficiency syndrome, confirmed by the presence of AIGAs and negative anti-human immunodeficiency virus testing, between January 2003 and December 2022 were reviewed. Patients aged 18 years or older who presented with reactive dermatoses were included in the study. Patients with hematologic diseases, other definite causes, or those receiving medications known to influence CBC results were excluded.

AIGAs were detected using an enzyme-linked immunosorbent assay, based on a modified protocol described by *Ding et al.*[9] The cut-off value was determined by comparing local hospital data from patients with AIGA-associated immunodeficiency syndrome to healthy controls. An average optical density of 1.0 or higher was considered a positive result.

Sample size calculation

The sample size was calculated using a formula for comparing two independent means, based on previously reported laboratory data from patients with reactive neutrophilic dermatoses and concurrent infections. The mean red cell distribution width (RDW) in this group was reported as 16.9 ± 3.2%.[4] As laboratory data for patients without concurrent infection were unavailable, the mean RDW in the non-infected group was assumed to be lower, approximately 13.5 ± 3.2%, representing a 20% difference. Using the two independent means formula with a significance level of 0.05 and 85% statistical power, and assuming an 8:1 ratio of infected to non-infected based on prior data from our hospital, the required sample size was estimated to be 72 infected and nine non-infected patients, respectively. To account for an anticipated 20% rate of missing data, the target enrollment was increased to 86 infected and 11 non-infected patients with reactive dermatoses and anti-IFN-γ autoantibodies.

Study procedure and definition

Data on baseline characteristics, clinical manifestations, concurrent infections, and laboratory findings obtained within two weeks of disease onset were collected. Reactive skin conditions were classified as ND, which included generalized pustular reactions and Sweet syndrome, or as non-ND, comprising erythema nodosum, vasculitis, urticaria, exfoliative dermatitis, and maculopapular eruptions. Definitive dermatologic diagnoses for all episodes were established by consensus between two dermatologists. Among patients with reactive dermatoses, concurrent infections were classified either as microbiologically documented (defined by organism identification from blood cultures, specimens obtained from infection site, or serological testing) or clinically documented (based on clinical presentation and/or histopathological reports). Disseminated infection was defined as either a positive blood or bone marrow culture or involvement of at least two non-adjacent organ systems.

Statistical analysis

All analyses were performed using PASW Statistics for Windows, version 18 (SPSS Inc., Chicago, IL, USA). Categorical variables were summarized as frequencies and percentages, while continuous variables were expressed as means or medians as appropriate. Generalized estimating equations were employed to compare clinical presentations and laboratory findings between reactive skin episodes with and without concurrent infections, as well as between those with and without disseminated infections. Episodes with missing complete blood count data were excluded from the analyses. A p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 147 patients diagnosed with AOIS caused by AIGAs were reviewed. After excluding drug-induced cases, 83 patients with non-drug-related skin episodes were identified, accounting for 211 total skin episodes. Following further exclusion of infectious dermatoses, 62 patients with 135 episodes of reactive dermatoses were included in the final analysis. Overall, the prevalence of reactive dermatoses in this cohort was approximately 42.2%.

Among the 62 patients with reactive dermatoses, females predominated, comprising 72.6% of the cohort. The median age at first skin manifestation was 51.50 years (IQR: 43.00–58.25). In most patients, the initial reactive skin episode occurred prior to the detection of AIGAs, as detailed in Table 1.

The 135 reactive dermatosis episodes were further categorized as ND or non-ND. NDs accounted for 73.3% of reactive dermatoses, with pustular eruptions and Sweet syndrome representing 40.0% and 33.3%, respectively. Non-ND comprised approximately 26.7% of episodes, with erythema nodosum being the most common subtype (Table 2).

Reactive dermatoses were subsequently classified according to the presence of concurrent infection. Microbiologically documented infections (MDI) accounted for 68.9% (93 episodes), while clinically documented infection (CDIs) comprised 21.5% (29 episodes). The remaining 13 episodes did not meet the criteria for either MDI or CDI and were defined as having no active infection. Among MDIs, *Mycobacterium abscessus* was the most frequently identified pathogen, followed by *Mycobacterium avium* complex (Fig 1).

Patients with reactive dermatoses with documented infections — either microbiologically or clinically — showed significant differences in certain blood parameters compared to those without infection. Those with infections had significantly lower mean corpuscular volume (MCV) than those without infections. Additionally, their RDW, WBC, absolute neutrophil counts (ANC), and platelet counts were higher than the non-infected group (Table 3). When these variables were categorized using standard laboratory cutoffs, this study found that anisocytosis (RDW > 14.5%), leukocytosis (WBC > 11,000/μL), and neutrophilia (ANC > 7,700/μL) were each significantly associated with the presence of concurrent infection (Table 4).

Among patients with reactive dermatoses, those

TABLE 1. Demographic data of patients with reactive dermatoses.

Demographic data	Number (%) (n = 62)
Median age at the first reactive episodes	51.50(43.0 – 58.25)
Female	45(72.6)
Underlying diseases	
Hypertension	11(17.7)
Diabetes mellitus	3(4.8)
Chronic kidney disease	0(0.0)
Cardiovascular disease	3(4.8)
Dyslipidemia	4(6.5)
Cirrhosis	1(1.6)
Connective tissue disease	1(1.6)
Others	15(24.2)
Onset of reactive episodes	
Before the detection of AIGAs	26(41.9)
Same visit/admission as the detection of AIGAs	17(27.4)
After the detection of AIGAs	19(30.6)

Abbreviations: AIGAs, Anti–interferon-gamma autoantibodies; IQR, interquatile range

TABLE 2. Classification of reactive dermatoses.

Reactive dermatoses	Number (%) Total n = 135
Neutrophilic dermatoses	99(73.3)
Pustular reaction	54(40.0)
Sweet syndrome	45(33.3)
Non-neutrophilic dermatoses	36(26.7)
Erythema nodosum	23(17.0)
Vasculitis	7(5.2)
Maculopapular rash	2(1.5)
Urticaria	2(1.5)
Thrombophlebitis	1(0.7)
Exfoliative dermatitis	1(0.7)

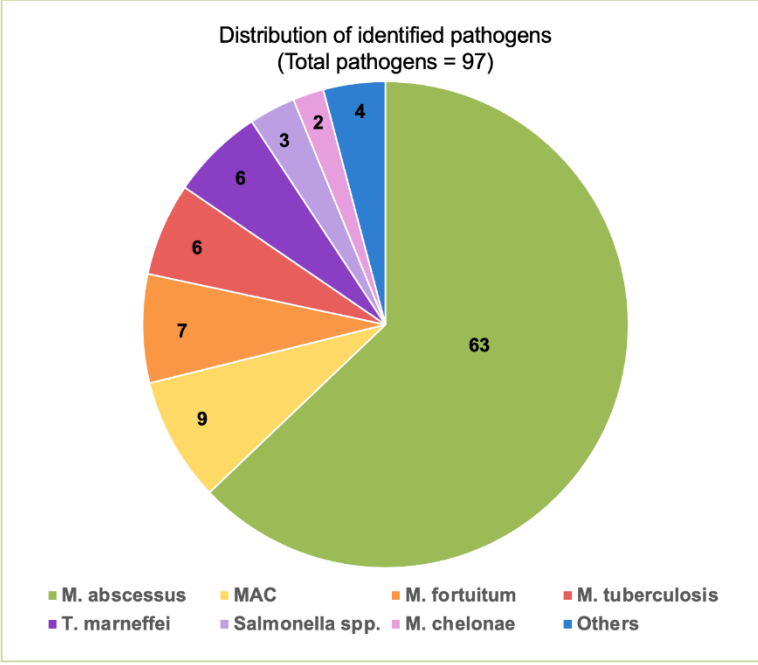


Fig 1. *Mycobacterium abscessus* was the most frequently identified pathogen in reactive dermatoses episodes with microbiologically documented infection.
Note: A total of 97 pathogens were identified across 93 infection episodes, as some episodes involved multiple concurrent pathogens.
Abbreviation: MAC, Mycobacterium avium complex.

TABLE 3. Comparison of reactive dermatoses episodes stratified by concurrent infection status.

Clinical features	No active infection (n = 13)	Concomitant infection (n = 122)	P
Clinical characteristics			
Median age onset	57.0(50.0 - 67.5)	50.50(43.00 – 58.00)	0.075
Male gender	0(0.0)	36(29.5)	-
Presence of co-morbidities	4(30.8)	41(33.6)	0.431
Systemic symptoms	6(46.2)	83(68.0)	0.159
Cutaneous symptoms	7(53.8)	71(58.2)	0.935
Generalized skin lesions	7(53.8)	89(73.0)	0.240
Neutrophilic dermatoses	7(53.8)	92(75.4)	0.074
Laboratory investigation			
Hb (g/dL)	11.50(10.20-13.10)	10.20(8.78 – 11.50)	0.056
MCV (fL)	84.90(78.70 – 90.95)	78.50(66.80 – 85.63)	0.039*
MCH (pg)	27.70(24.8 – 29.35)	24.70(20.88-27.23)	0.085
MCHC (g/dL)	31.80(31.35-32.75)	31.80(30.88-32.70)	0.981
RDW (%)	14.10(13.55-15.50)	16.20(14.90 – 18.40)	0.005*
WBC (×10³/μL)	15.56(6.27 – 21.18)	20.96(16.02 – 29.38)	0.037*
ANC (×10³/μL)	11.14(3.49-16.75)	15.76(11.18-22.00)	0.038*
ALC (×10³/μL)	2.79(1.66-3.38)	3.08(2.35-4.18)	0.098

TABLE 3. Comparison of reactive dermatoses episodes stratified by concurrent infection status. (Continued)

Clinical features	No active infection (n = 13)	Concomitant infection (n = 122)	P
N/L ratio	3.73(1.78 – 4.84)	4.94(3.38 – 7.50)	0.328
Platelet (×10³/μL)	376.00(276.50 – 456.50)	414.50(317.25 – 509.0)	0.023*
ESR (mm/h) (n = 12, 95)	60.50(32.75 – 80.75)	82.00(50.00 – 99.00)	0.144
Cr (mg/dL) (n = 9, 117)	0.67(0.53 – 1.01)	0.80(0.68 – 1.01)	0.794
Albumin (g/dL) (n = 10, 115)	3.50(3.18 – 3.73)	3.30(2.90 – 3.70)	0.143
Globulin (g/dL) (n = 10, 114)	4.15(3.98 – 4.95)	4.70(4.30 – 5.40)	0.464
TB (mg/dL) (n = 10, 111)	0.38(0.32-0.47)	0.43(0.30-0.60)	0.185
AST (U/L) (n = 11, 120)	27.00(22.00-34.00)	24.00(17.00 – 35.75)	0.908
ALT (U/L) (n = 11, 120)	22.00(15.0-38.0)	19.00(12.50 – 38.50)	0.225
ALP (U/L) (n = 11, 116)	132.00(89.00 – 172.00)	181.50(125.00-268.00)	0.058
CRP (mg/L) (n = 10, 83)	62.05(8.81 – 112.50)	71.42(35.88-121.26)	0.680

All continuous data were reported using the median and interquartile range.
*P < 0.05 indicated statistical significance.
Abbreviations: ALC, absolute lymphocyte count; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; Cr, creatinine; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, hemoglobin MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; N/L, neutrophil-to-lymphocyte; RDW, red cell distribution width; TB, total bilirubin; WBC, white blood cell count

TABLE 4. Comparison of reactive dermatoses episodes stratified by concurrent infection status using standard laboratory cut-off values.

Clinical features	No active infection (n = 13)	Concomitant infection (n = 122)	P
MCV < 80 fL	4(30.8)	67(54.9)	0.185
RDW > 14.5 %	5(38.5)	98(80.3)	<0.001*
WBC > 11,000/μL	7(53.8)	112(91.8)	0.005*
ANC > 7,700/μL	7(53.8)	110(90.2)	0.007*
Platelet > 450,000/μL	4(30.8)	46(37.7)	0.211

*P < 0.05 indicated statistical significance.
Abbreviations: ANC, absolute neutrophil count; MCV, mean corpuscular volume; RDW, red cell distribution width; WBC, white blood cell count

with disseminated infections exhibited a significantly higher prevalence of systemic symptoms and were more likely to present with NDs compared with those with localized or no infection. Laboratory analyses revealed that disseminated infection was associated with significantly lower hemoglobin levels, MCV, and mean corpuscular hemoglobin. Conversely, RDW, WBC, ANC, platelet count, and erythrocyte sedimentation rate (ESR) were significantly higher. With respect to liver function tests, albumin levels were lower whereas globulin and alkaline phosphatase (ALP) levels were higher in the disseminated infection group (see Supplementary Table 1 for details).

DISCUSSION

The CBC is a routinely performed laboratory test widely used across various medical conditions, including dermatological diseases.[1-3] Patients with complex skin manifestations, such as reactive dermatoses seen in AOIS, frequently require specialized evaluation. These challenging cases are often encountered during inpatient dermatologic consultations, or they may necessitate teledermatology consultations when clinical presentations are ambiguous and require remote expert diagnostic decision-making.[10,11] Given the diagnostic challenges in these settings, identifying practical, rapid, and accessible markers is crucial. In this study, we evaluated the role of simple laboratory results, particularly those derived from the CBC, in predicting concurrent infections among patients with AOIS caused by AIGAs who presented with reactive dermatoses.

Reactive dermatoses were the focus of this study because they represent a common and distinctive clinical manifestation of AIGA-associated immunodeficiency syndrome. The present study indicates that a significant number of patients with this syndrome exhibit reactive dermatoses, with an overall prevalence of 42.2%, which is consistent with previous reports indicating a prevalence of 39–66%.[4,6] Notably, around 40% of reactive episodes occurred before the diagnosis of the syndrome, suggesting that they may serve as an early clinical indicator of this condition. Sweet syndrome associated with AOIS due to AIGAs appears to represent a distinct condition that differs from Sweet syndrome observed in other clinical contexts.[12]

Among patients with reactive dermatoses, the presence of active infection — defined by microbiologic and clinical documentation, was associated with lower MCV, as well as higher RDW, WBC, ANC, and platelet count. However, when these parameters were analyzed using standard laboratory cut-offs, only RDW of more than 14.5%, WBC of more than 11,000/uL, and ANC of more than 77,000/uL were the only three CBC parameters associated with the presence of concomitant infection.

These findings align with previous studies evaluating laboratory parameters of disease activity in patients with AOIS caused by AIGAs. *N. Angkasekwinai et al.* reported that elevated C-reactive protein, ESR, WBC, and lower hematocrit levels were associated with active disease.[7] Similarly, *Chi et al.* demonstrated that patients with active nontuberculous mycobacteria infection had higher WBC counts, neutrophil percentages, C-reactive protein, and ESR, along with lower lymphocyte percentages and hemoglobin levels.[13] They found that WBC, percentage of neutrophil, C-reactive protein, and ESR were significantly higher. In contrast, *Wongkulab et al.* observed higher hemoglobin levels, WBC, ANC, absolute eosinophil count, and ALP in patients with active infection.[14] Mycobacterium infection—the most frequently isolated pathogen in our cohort—is well-documented to cause deep-seated and difficult-to-treat infections, recognizing these CBC alterations is clinically crucial for prompt management.[15]

Several mechanisms may explain the observed laboratory abnormalities in patients with reactive dermatoses and concurrent infection. Active infection triggers a robust inflammatory response that can disrupt erythropoiesis, resulting in reduced MCV.[16] Additionally, elevated RDW is a recognized marker of systemic inflammation and has been associated with a variety of inflammatory and infections conditions.[17,18] Increased WBC counts, predominantly driven by neutrophilia, are a hallmark of infection, reflecting an ongoing inflammatory or infectious process. Furthermore, platelets often function as acute-phase reactants, increasing in response to inflammatory cytokines such as interleukin-6,[19] making thrombocytosis a potential indicator of ongoing or severe inflammation, aligning with the presence of infection.[19,20]

Our findings further demonstrated that, among patients with reactive dermatoses, those with disseminated infection exhibited more pronounced clinical and laboratory abnormalities. Clinically, disseminated infection was associated with a higher prevalence of systemic symptoms and ND, consistent with prior reports demonstrating a strong association between NDs and risk of infection.[6] Laboratory abnormalities in disseminated infection mirrored those observed in patients with and without infection, as previously described, with more pronounced changes in liver function tests. Specifically, lower albumin levels, along with elevated globulin and ALP, were observed in the disseminated infection group. ALP has been shown to exert anti-inflammatory effects and may increase in response to infection.[21,22] Elevated ALP may be the result of hepatobiliary involvement of

disseminated infection or reflect a biological response to infection, as ALP plays a role in detoxifying bacterial endotoxins and extracellular adenosine triphosphate through dephosphorylation, thereby reducing systemic inflammation.[21,22] Hypoalbuminemia and hyperglobulinemia have also been associated with infectious conditions, such as in prosthetic joint infections.[23] The combination of hypoalbuminemia and hyperglobulinemia could indicate a heightened inflammatory response, which is the nature of the infection.

The main limitation of this study was its retrospective design, which inherently carries the risk of missing data and potential information biases. Also, the generalizability of the findings may be limited, as the study was conducted at a single tertiary care center. Further studies in broader or more diverse populations are needed to confirm these findings in other settings.

CONCLUSIONS

Simple laboratory findings, particularly those derived from the CBC panel, could assist clinicians in identifying patients at higher risk of infection. These factors include lower MCV, higher RDW, WBC, ANC, and platelet counts. Early recognition of these hematological shifts can prompt closer clinical surveillance and timely diagnostic workups in AOIS patients with AIGAs. Given its affordability and accessibility, the CBC panel represents a practical tool for stratifying infection risk and guiding early clinical evaluation.

Data availability statement

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

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Conflict of Interest

The authors declare no conflict of interests.

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Not applicable.

Author Contributions

Conceptualization and methodology, P.P., S.B., P.J., N.A., W.O., and C.L.; Data curation, C.S.; Writing – original draft preparation, C.S. and C.L.; Supervision, P.P., S.B., P.J., N.A., W.O., and C.L. All authors have read and agreed to the final version of the manuscript.

Use of Artificial Intelligence

During the preparation of this work, the authors used Google Gemini in order to improve English language readability and correct grammar throughout the manuscript. After using this tool, the authors thoroughly reviewed and edited the content as needed and take full responsibility for the final content of the publication.

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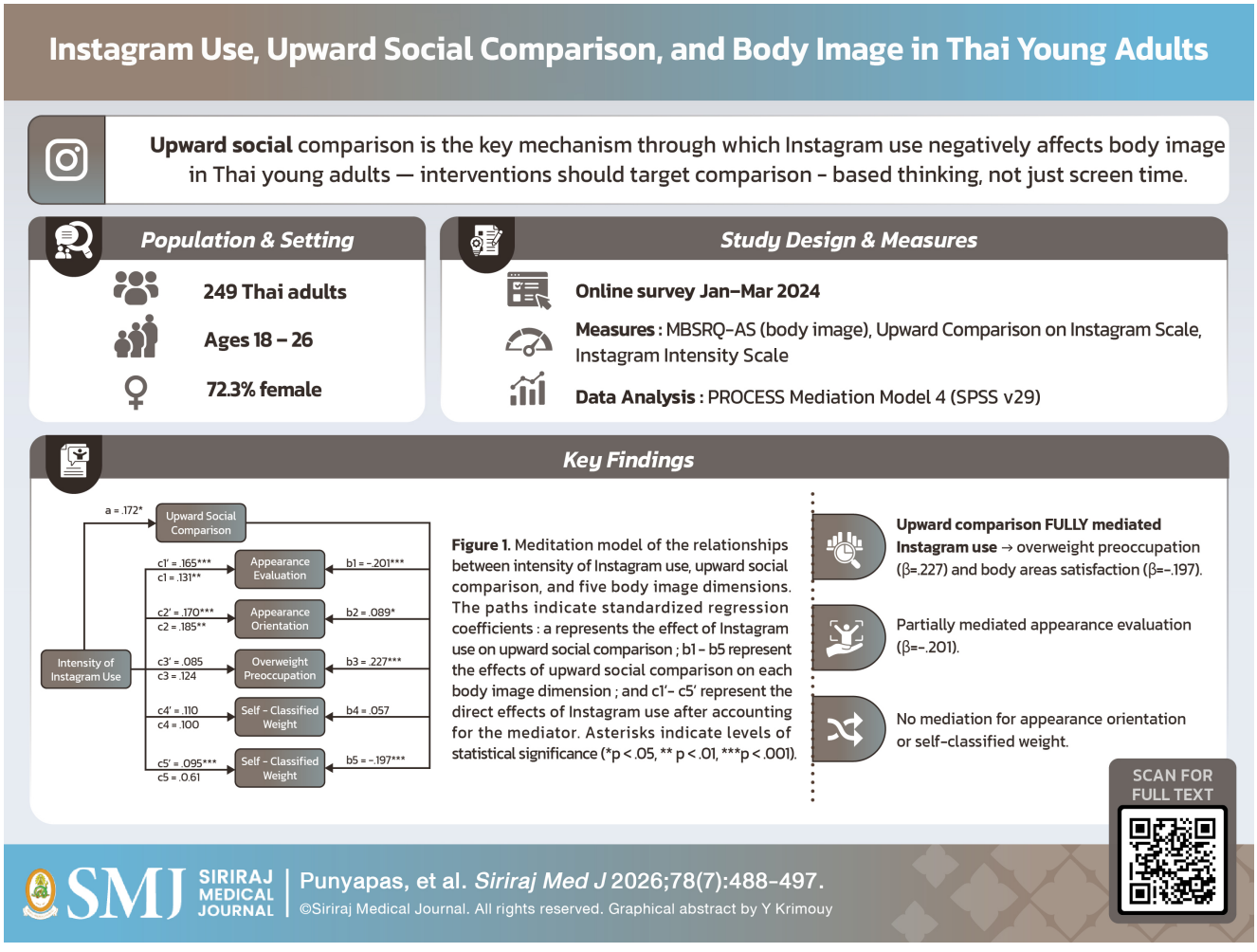
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Upward Social Comparison as a Mediator: Intensity of Instagram Use and Body Image Among Thai Young Adults

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ABSTRACT

Objective: This study examined the correlations among body image, Instagram use intensity, and upward social comparison, and the mediating role of upward social comparison among Thai young adults aged 18–26 years.

Materials and Methods: Following informed consent, 249 Thai young adults aged 18–26 years completed the Multidimensional Body-Self Relations Questionnaire–Appearance Scales (MBSRQ-AS), the Upward Comparison on Instagram Scale, and the Instagram Intensity Scale. Data were analyzed using descriptive statistics, Pearson's correlation, and mediation analysis using PROCESS version 4.2 in SPSS version 29, with bootstrap resampling.

Results: Among eligible participants (72.3% female, 27.3% male; mean age = 22.48, SD = 2.34), Instagram use intensity was very weakly positively correlated with upward social comparison (r = .157), appearance evaluation (r = .174), and appearance orientation (r = .293). Upward social comparison was weakly positively correlated with appearance orientation (r = .249) and overweight preoccupation (r = .249), and weakly negatively correlated with appearance evaluation (r = -.259) and body areas satisfaction (r = -.265). Mediation analysis showed upward social comparison fully mediated the relationships between Instagram use intensity and overweight preoccupation (β = .227) and body areas satisfaction (β = -.197), and partially mediated the relationship with appearance evaluation (β = -.201).

Conclusion: Instagram use intensity, upward social comparison, and body image were significantly associated among Thai young adults. Upward social comparison mediated the relationships between Instagram use intensity and several body image dimensions, suggesting that it is an important mechanism through which Instagram use may influence body image.

Keywords: Body image; Instagram use; mediator; upward social comparison; young adult (Siriraj Med J 2026;78(7): 488-497)

INTRODUCTION

Body image refers to how individuals perceive, think, and feel about their bodies[1] and is widely recognized as a multidimensional construct encompassing aspects such as physical attractiveness, appearance investment, weight concerns, and body satisfaction.[2,3] A negative body image often emerges from a perceived discrepancy between one's actual and ideal body, leading to body dissatisfaction, which can manifest as early as six years of age.[1,4] Such dissatisfaction may lead to an excessive focus on physical appearance and engagement in harmful behaviors, including restrictive dieting, excessive exercise, and the use of supplements as meal substitutes[5,6], and is often associated with the development of eating disorders.[7,8]

Given its strong association with self-concept, body dissatisfaction has been shown to negatively affect psychological well-being, contributing to elevated stress, low self-esteem, and depressive symptoms.[9-11] Epidemiologically, body dissatisfaction affects over 50% of adults in the United States, the United Kingdom, Australia, France, and Germany, and a substantial proportion of adolescents globally across the United States, Spain, and the United Arab Emirates.[12-14]

Theoretical frameworks such as sociocultural theory and the tripartite influence model attribute the development of body dissatisfaction to the internalization of societal appearance ideals, transmitted through media, peers, and family.[1] Social comparison theory further elucidates how individuals evaluate themselves relative to others, with upward comparisons—those made against individuals perceived as superior—being particularly detrimental to well- being.[15-17]

With over 58.4% of the global population actively using social media[18], these platforms have amplified the impact of upward comparisons by exposing users to highly curated and idealized content. Unlike standardized clinical environments where photographic imaging must strictly adhere to unedited, objective guidelines to eliminate environmental bias and document precise anatomical reality[19], social media spaces actively encourage curated digital enhancements that distort real-world proportions. Although some research has identified benefits of social media use, such as enhanced social connectedness and increased self-esteem[20,21], adverse effects are more widely reported. These include increased stress, loneliness, and depressive symptoms, particularly among adolescents and young adults.[22-24]

Instagram, in particular, with its emphasis on visual content and a user base exceeding 2.35 billion globally[25], has emerged as a significant platform influencing body image. In Thailand, Instagram is especially popular among women and youth, with over 21 million users as

of July 2023.[26] Empirical studies have linked Instagram use to various mental health concerns, including body dissatisfaction, depression, anxiety, and low self-esteem.[27-29] Similarly, recent domestic research highlights that body image-focused social media usage (BSMU) significantly elevates the risks of developing inappropriate eating attitudes and behavioral vulnerabilities, such as binging and purging, among high school students in Bangkok.[30] Social comparison and the internalization of idealized body images have been identified as both mediators and moderators in this relationship[31,32], with frequent exposure to idealized images being associated with lower self-rated attractiveness and increased psychological distress.[27,33]

Despite growing scholarly attention, the mediating role of upward social comparison between Instagram use and body image remains underexplored. While most research concentrates on adolescents, young adulthood (ages 18-26) represents a critical developmental period with heightened vulnerability to psychological distress and unique transitional challenges, making them an important demographic.[34-36]

Furthermore, existing literature is predominantly Western and may not generalize to Thai populations, where individuals typically explore broader social environments during university or early employment rather than adolescence. To address these gaps, the present study aims to investigate the associations between Instagram use intensity, body image, and upward social comparison among Thai young adults aged 18-26 years, with a specific focus on examining the mediating role of upward social comparison in these relationships.

MATERIALS AND METHODS

The study examined relationships among Instagram use intensity, body image, and upward social comparison, and assessed whether upward social comparison mediates these associations among Thai young adults aged 18-26. Ethical approval was granted by the Siriraj Institutional Review Board (COA No. Si 029/2024). Data were collected online from January to March 2024.

Population and Sample

Eligible participants were Thai nationals aged 18–26 years residing in Thailand who used Instagram, were able to read and write Thai, and provided informed consent prior to completing an online questionnaire. The calculated sample size was 240, and a 50% allowance for incomplete or randomized responses was added, yielding a target sample of 360. A total of 312 responses were obtained online, of which 249 complete and valid responses were included in the final analysis after exclusion of incomplete and randomized responses.

Research tools

The research tools in this study included a total of four sets of questionnaires with the following details:

1. Demographic information questionnaire collecting gender, age, education, occupation, and residency.

2. The Multidimensional Body-Self Relations Questionnaire Appearance Scales (MBSRQ-AS)[37], a 34-item Likert-scale questionnaire with high reliability ($\alpha = .85$) for assessing individuals' attitudes and concerns regarding body image across five dimensions. The MBSRQ-AS comprises five subscales assessing distinct dimensions of body image.

Dimension 1: appearance evaluation (AE; items 3, 5, 9, 12, 15, 18, and 19) measures feelings of physical attractiveness or unattractiveness, with higher scores indicating greater satisfaction with appearance.

Dimension 2: appearance orientation (AO; items 1, 2, 6, 7, 10, 11, 13, 14, 16, 17, 20, and 21) assesses the extent of investment in appearance, with higher scores reflecting greater attention to and effort devoted to one's looks.

Dimension 3: overweight preoccupation (OP; items 4, 8, 22, and 23) evaluates fat anxiety, dieting, weight vigilance, and eating restraint, with higher scores indicating greater preoccupation with weight.

Dimension 4: self-classified weight (SCW; items 24–25) reflects perceived weight status, with higher scores indicating perception of oneself as heavier.

Dimension 5: body areas satisfaction scale (BASS; items 26–34) measures satisfaction with specific body areas, with higher composite scores indicating greater body-area satisfaction.

Most subscales are rated on a 5-point Likert scale ranging from 1 = definitely disagree to 5 = definitely agree, whereas SCW ranges from 1 = very underweight to 5 = very overweight, and BASS ranges from 1 = very dissatisfied to 5 = very satisfied. Items 11, 14, 16, 18, 19, and 20 are reverse-scored.[38]

3. The Upward Comparison on Instagram Scale[39], a reliable 3-item Likert scale ($\alpha = .878$) assessing frequency of upward comparison on Instagram. Responses range from 1 (never/strongly disagree) to 5 (usually/strongly agree). Higher scores indicate a greater tendency for upward social comparison on Instagram, while lower scores reflect less comparison behavior. Sample items include: "When you compare yourself to others on Instagram, how often do you compare with those whose life is better than yours?", "When I see others' pictures

or videos on Instagram, I usually think that they have better lives than me", and "When I see others' pictures or videos on Instagram, I usually think that they can do things better than me".

4. The Instagram Intensity Scale was used to assess Instagram engagement, with permission. This 8-item scale, rated on a 5-point Likert scale, has demonstrated high reliability (α = .888).[39] Only the first six items, which measure psychological and behavioral connection to Instagram, with statements such as "Instagram is part of my everyday activity" and "I am proud to tell people that I'm on Instagram", were used for results analysis. The final two items, which inquire about the number of people the participant follows and the average time spent on Instagram daily, provide supplementary data. Responses range from 1 (strongly disagree) to 5 (strongly agree). Higher scores on the first six items indicate more intense Instagram use.

Data collection

Data were collected via Google Forms disseminated through "M.Sc.Clipsy" Line groups, the "Clinical Psychology Siriraj" Facebook page, the "psyche.tourlife" Instagram account, and personal networks. After providing consent, participants completed demographic items, the MBSRQ-AS, the Upward Comparison Scale, and the Instagram Intensity Scale. Educational body-image material was provided upon completion.

Statistical analyses

Analyses were performed using SPSS Version 29 and PROCESS Macro version 4.2 by Hayes.[40] Descriptive statistics summarized participant characteristics and variable distributions. Pearson's correlations assessed associations among Instagram use, upward social comparison, and body image variables. Mediation analyses employed PROCESS Model 4 with 5,000 bootstrap resamples and 95% bias-corrected confidence intervals. Statistical significance was set at $p < .05$.

RESULTS

Of the 249 participants, 72.3% were female and 27.3% male, with a mean age of 22.48 years and a standard deviation (SD) = 2.34. Most held a bachelor's degree (74.7%) and were students (65.1%). Nearly half resided in Bangkok (43.4%), as shown in Table 1.

Among the MBSRQ-AS subscales, OP had the highest mean score (mean = 3.98), followed by AO, SCW, BASS, and AE. Participants also reported moderate upward social comparison (mean = 3.06) and moderately high Instagram intensity (mean = 3.57), as shown in Table 2.

Participants were further categorized into three groups based on the number of Instagram accounts they followed: 0-500, 501-1000, and more than 1000 followers. The majority (44.6%) followed 0-500 accounts. The mean number of accounts followed was 684.96 (SD = 546.38), with a range from 2 to 3,267. Based on Alfonso-Fuertes et al.[41], daily Instagram usage was divided into two groups: those who used Instagram for three hours or less and those who used it for more than three hours. Most participants (77.1%) used Instagram for three hours or less per day. The average daily usage was 158.88 minutes (SD = 137.15), equivalent to approximately 2 hours and 38 minutes, with reported usage ranging from 0 to 18 hours per day.

As shown in Table 3, correlation analyses showed a very weak positive association between Instagram use intensity and upward social comparison ($r = .157$, $p < .05$). Instagram use was also positively correlated with AE ($r = .174$, $p < .01$) and AO ($r = .293$, $p < .01$), but not with OP, SCW, or BASS. Upward social comparison was negatively associated with AE ($r = -.259$, $p < .01$) and BASS ($r = -.265$, $p < .01$), and positively associated with AO ($r = .196$, $p < .01$) and OP ($r = .249$, $p < .01$). No significant correlation was found with SCW.

As shown in Fig 1, mediation analyses using PROCESS Model 4 indicated that Instagram use significantly predicted upward social comparison (β = .172, p < .05) in the AE model, and upward comparison predicted lower AE (β = -.201, $p < .001$). Moreover, Instagram use had a direct positive effect on AE (β = .165, $p < .001$). The indirect effect (-.046, 95% CI: -.071 to -.003) indicated partial mediation, with 11.5% of AE variance explained.

In the AO model, upward social comparison showed a small positive effect (β = .089, $p < .05$), and Instagram use remained a significant direct predictor (β = .170, $p < .001$). However, the indirect effect (.024, 95% CI: -.000 to .038) was nonsignificant, indicating no mediation. The model accounted for 10.9% of AO variance.

For OP, upward social comparison significantly predicted OP (β = .227, $p < .001$), whereas Instagram use showed no significant direct or total effects. The indirect effect (.037, 95% CI: .002 to .088) indicated full mediation, with the model explaining 6.9% of OP variance.

For SCW, none of the paths reached significance. Instagram use did not predict SCW either directly or indirectly, and upward social comparison did not significantly predict SCW. The indirect effect (.010, 95% CI: -.010 to .038) was nonsignificant. Although R^2 was .069, the model lacked statistical significance and was not further interpreted.

TABLE 1. Demographic characteristics of the participants ($N = 249$).

Characteristic	*n*	%
Sex		
Male	68	27.3
Female	180	72.3
Missing data	1	0.4
Age (Mean = 22.48, SD = 2.34)		
Highest level of Education		
Lower Secondary	5	2.0
Higher Secondary	45	18.1
Diploma	3	1.2
Bachelor's	186	74.7
Master's	10	4.0
Occupation		
Student	162	65.1
Government Officials	39	15.7
Self-Employed	20	8.0
Freelancer	3	1.2
Unemployed	21	8.4
Missing data	4	1.6
Current Province of Residence		
Bangkok	108	43.4
Central	65	26.1
North	14	5.6
Northeast	7	2.8
East	7	2.8
West	2	0.8
South	45	18.1
Missing data	1	0.4

TABLE 2. Mean scores of MBSRQ-AS subscales, upward social comparison, and Instagram intensity ($N = 249$).

Measures	Mean	*SD*
Body image		
1. Appearance evaluation (AE)	3.150	0.738
2. Appearance orientation (AO)	3.552	0.621
3. Overweight preoccupation (OP)	3.976	1.032
4. Self-classified weight (SCW)	3.436	1.008
5. Body areas satisfaction scale (BASS)	3.254	0.744
Upward social comparison	3.056	1.077
Intensity of Instagram use	3.566	0.984

TABLE 3. Pearson's correlations among Intensity of Instagram Use, Body Image, and Upward Social Comparison on Instagram ($N = 249$).

Measures	1	2	3	4	5	6	7
Body image	(.79)						
1. Appearance evaluation (AE)	(.74)						
2. Appearance orientation (AO)	.089	(.80)					
3. Overweight preoccupation (OP)	-.146*	.461**	(.79)				
4. Self-classified weight (SCW)	-.389**	-.058	.370**	(.88)			
5. Body areas satisfaction scale (BASS)	.659**	-.096	-.177**	-.247**	(.86)		
Upward social comparison	-.259**	.196**	.249**	.044	-.265**	(.87)	
Intensity of Instagram Use	.174**	.293**	.118	-.098	.081	.157*	(.84)

*Note. *p < .05 (2-tailed), **p < .01 (2-tailed), Numbers in parentheses refer to Cronbach's alpha.*

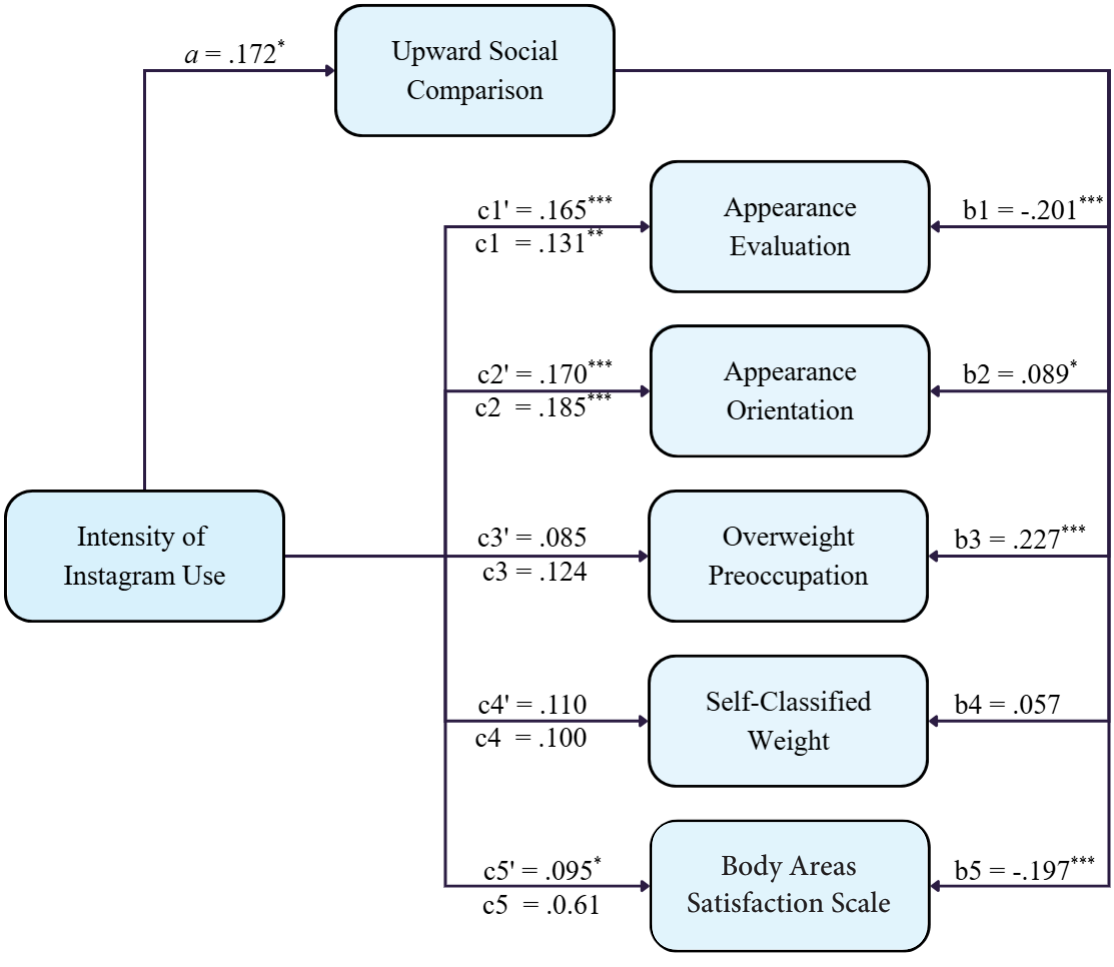


Fig 1. Mediation model of the relationships between intensity of Instagram use, upward social comparison, and five body image dimensions. The paths indicate standardized regression coefficients: a represents the effect of Instagram use on upward social comparison; *b1-b5* represent the effects of upward social comparison on each body image dimension; and *c1'-c5'* represent the direct effects of Instagram use after accounting for the mediator. Asterisks indicate levels of statistical significance (*$p < .05$, **$p < .01$, ***$p < .001$).

For BASS, upward social comparison negatively predicted BASS (β = –.197, $p < .001$). Instagram use had a small direct effect (β = .095, $p < .05$), while the total effect was nonsignificant. The indirect effect (-.045, 95% CI: -.072 to -.002) indicated full mediation, with 8.6% of BASS variance explained.

DISCUSSION

This study addressed concerns that visually driven platforms like Instagram heighten appearance-focused cognition and body dissatisfaction[27,31], risks that are amplified among Thai youth given the platform's local popularity[26] and the vulnerabilities of emerging adulthood.[34,35]

The sample was predominantly female (72.3%) and student-based (65.1%), reflecting our recruitment channels and targeted demographic. Descriptive findings indicated substantial appearance investment and overweight preoccupation, alongside moderate upward social comparison. These trends correspond with multidimensional models of body image[2,3] and may reflect sociocultural appearance ideals and frequent exposure to idealized images on Instagram, which can intensify appearance monitoring and internalization of beauty norms.[1,31]

Instagram use intensity showed a very weak positive association with upward social comparison, consistent with findings that greater engagement on social networking sites slightly increases comparison tendencies.[42] Although modest, this aligns with evidence that curated, idealized content amplifies comparison-based processing.[43] Instagram intensity also demonstrated weak positive correlations with appearance evaluation and appearance orientation, consistent with work showing reciprocal reinforcement between social media use and appearance investment.[44-46] Such patterns may reflect evaluative feedback mechanisms—such as likes and comments—that strengthen appearance-based self-appraisal.[27]

Upward social comparison showed weak negative correlations with appearance evaluation and body areas satisfaction, and weak positive correlations with appearance orientation and overweight preoccupation. These trends are aligned with social comparison theory, which posits that upward comparison evokes feelings of inadequacy and diminished satisfaction when individuals evaluate themselves against those perceived as more successful or attractive.[16,47] Furthermore, these results complement existing empirical evidence that explicitly links weight-focused comparison to dysfunctional dieting cognitions and behaviors.[48] Crucially, this pronounced cognitive preoccupation and anxiety regarding body weight among Thai young adults aligns with clinical observations within the local population, where objective increases in body mass index (BMI) are independently associated with structural changes like left atrial enlargement.[49]

The present findings suggest that Instagram use may not directly influence negative body image across all domains, but rather exerts its effects through comparison-based cognitive processing, whereby individuals evaluate themselves against others perceived as more attractive or successful. This pattern highlights upward social comparison as a key psychological mechanism linking social media engagement to body image outcomes, extending prior research that has identified comparison processes as central to body dissatisfaction in visually saturated online environments.[31,32] Exposure to idealized Instagram content has been associated with poorer mood, lower self-perceived attractiveness, and increased body dissatisfaction.[27,33] From a theoretical perspective, these results further support social comparison theory, suggesting that upward comparisons amplify perceived discrepancies between the actual and ideal self, thereby intensifying dissatisfaction and appearance-related concerns.[1,16,47]

The demographic composition of the sample may also help contextualize these findings. The predominance of female, young and university-educated participants reflects a socially connected group at a developmental stage characterized by heightened concerns regarding appearance, peer evaluation, and identity formation. This may increase vulnerability to appearance-focused comparisons and partly explain why upward social comparison demonstrated stronger associations with appearance evaluation, body areas satisfaction, and overweight preoccupation than with self-classified weight. Furthermore, the overrepresentation of women may have amplified sensitivity to visual beauty standards on Instagram, as previous research indicates that women are more frequently exposed to and affected by thin-ideal and appearance-related social pressures on visual social media platforms.[1,12,27,31] Accordingly, the observed mediation effect may reflect not only the influence of Instagram exposure but also the interaction between platform engagement and the psychosocial characteristics of this population. Taken together, these findings suggest that, among young adults—particularly female university users—the psychological impact of Instagram may depend less on usage intensity alone and more on the extent to which platform content activates upward comparison processes that shape body-related self-evaluation.

Together, these findings indicate that upward comparison represents a key psychological pathway

through which Instagram shapes body image. Moreover, Instagram appears to affect users' experiences primarily when individuals engage in cognitive comparisons with others more attractive or more successful, highlighting the importance of addressing comparison-based processing rather than focusing solely on reducing screen time. This is consistent with theoretical perspectives that emphasize cognitive appraisal as a determinant of emotional and behavioral outcomes when exposed to idealized social information.[1,47]

Despite these contributions, limitations warrant attention. Instagram use was measured as a single construct without distinguishing between specific features or content types. The predominance of women limits generalizability, and the upward comparison scale captured broad lifestyle comparisons rather than appearance-specific comparisons, which may underestimate appearance-focused effects. Variability in mediation effect sizes also suggests the presence of additional unmeasured factors.

Future research should incorporate Instagram-specific features (e.g., stories, reels) and appearance-focused content such as fitness or beauty imagery. Inclusion of clinical samples— particularly individuals with eating disorders— would provide richer insights into pathological processes. Expanding demographic diversity, including LGBTQ+ and male participants, would improve representativeness. Additionally, employing appearance-based comparison measures, such as the Physical Appearance Comparison Scale, may yield more targeted findings. Finally, further work incorporating constructs such as self-esteem, beauty standards, media internalization, and social expectations could deepen understanding of the multiple pathways shaping body image outcomes.

CONCLUSIONS

Instagram use intensity was weakly associated with upward social comparison and some dimensions of body image among Thai young adults. Upward social comparison was negatively associated with appearance evaluation and body areas satisfaction, and positively associated with appearance orientation and overweight preoccupation. It also mediated the relationships between Instagram use and several body image dimensions, suggesting that upward comparison is an important mechanism through which Instagram may influence body image. These findings suggest that interventions for young adults and adolescents should focus not only on reducing time spent on Instagram, but also on helping users recognize and manage comparison-based thinking when viewing idealized online content.

Data Availability Statement

The data supporting the findings of this study are not publicly available due to the inclusion of identifiable and sensitive information from human participants. De-identified summary data may be available from the corresponding author upon reasonable request.

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Conflict of Interest

All authors confirm that they have no personal or professional conflicts of interest.

Registration Number of Clinical Trial

Not applicable.

Author Contributions

Conceptualization and methodology: S.P., T.S. and J.L.; Validation: S.P. and T.S.; Formal analysis: T.S. and J.L.; Investigation, Resources, Data curation, Visualization, Writing—original draft: J.L.; Writing–review and editing: S.P., T.S., N.A. and J.L.; Supervision: S.P., T.S. and N.A. All authors have read and agreed to the final version of the manuscript.

Use of Artificial Intelligence

Parts of the manuscript were drafted and refined using ChatGPT 5.1 (OpenAI), specifically for paraphrasing text, reorganizing sections for clarity, generating alternative wording, and assisting with tightening academic language. All outputs were reviewed, corrected, and validated by the authors. No AI tool was used to analyze data, generate research findings, or replace human interpretation.

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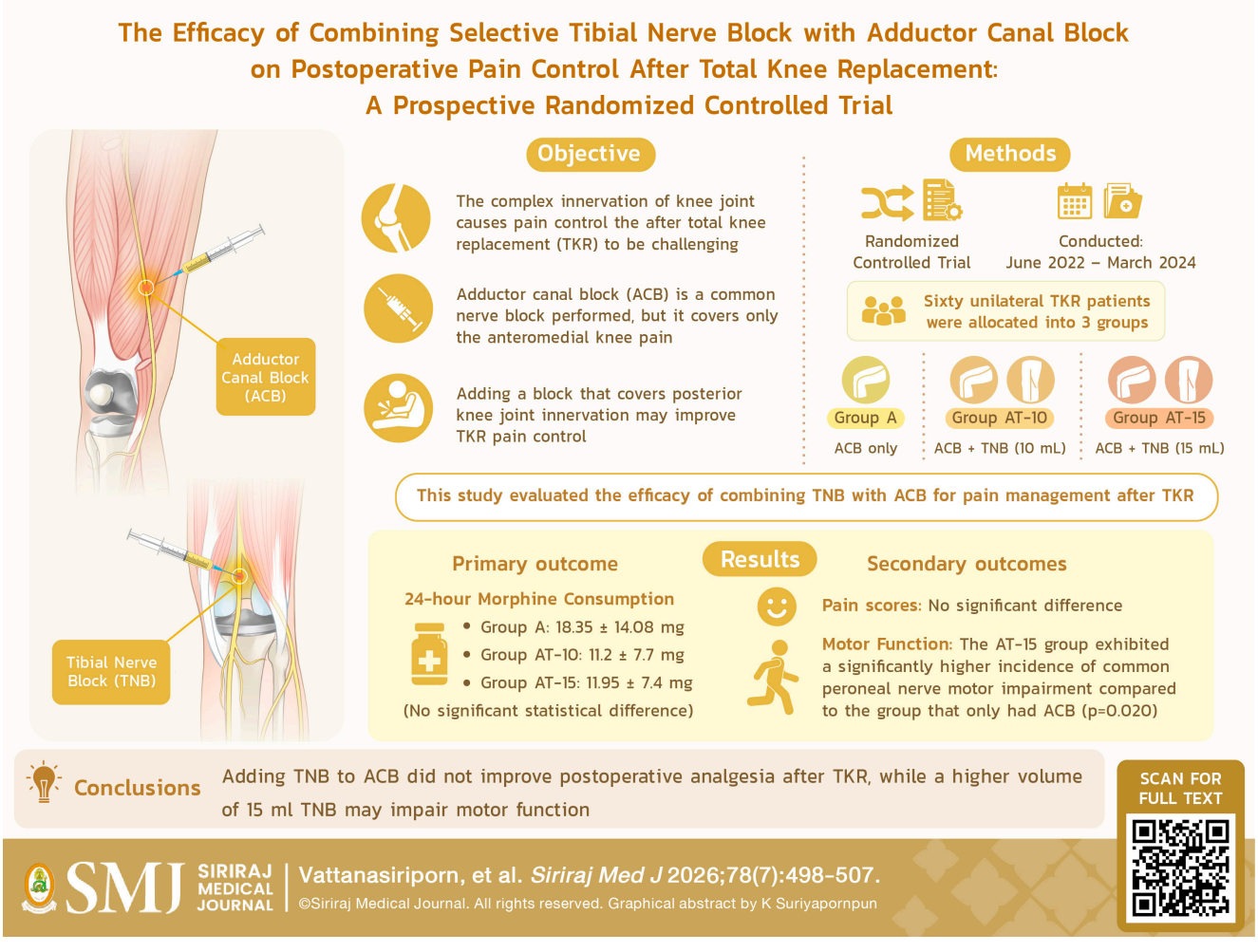
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The Efficacy of Combining Selective Tibial Nerve Block with Adductor Canal Block on Postoperative Pain Control After Total Knee Replacement: A Prospective Randomized Controlled Trial

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ABSTRACT

Objective: Pain control after total knee replacement (TKR) is crucial for early recovery but remains challenging. This study aimed to assess the analgesic efficacy of the combination of tibial nerve block (TNB) and adductor canal block (ACB), the motor-sparing block for TKR.

Material and Methods: This randomized controlled trial was performed from June 2022 to March 2024. Sixty patients undergoing unilateral TKR were recruited and randomly allocated to one of three groups. Group A received the ACB, group AT-10 received ACB and TNB using 10 ml of local anesthetic (LA), and group AT-15 received ACB and TNB using 15 ml of LA. The primary outcome was 24-hour total postoperative morphine consumption. Secondary outcomes included Numeric Rating Scale (NRS) pain scores, sensorimotor function, and adverse events.

Results: The 24-hour postoperative accumulated morphine consumption in groups A, AT-10, and AT-15 was 18.35 ± 14.08 mg, 11.2 ± 7.7 mg, and 11.95 ± 7.4 mg, respectively. There was no statistically significant difference in morphine consumption or NRS pain scores at any time point. Motor function of the common peroneal nerve (CPN) was significantly impaired in group AT-15 compared with group A (P = 0.020), with no significant differences observed between group AT-10 and group A or in group AT-10 and group AT-15. No serious adverse event was observed in any group.

Conclusion: The addition of TNB to ACB does not improve analgesic efficacy following TKR, and 15 ml of TNB is also associated with CPN motor impairment that may delay ambulation.

Keywords: Adductor canal block; motor-sparing block; postoperative pain; tibial nerve block; total knee replacement
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INTRODUCTION

Total knee replacement (TKR) is a widely performed and effective surgical intervention for patients with advanced knee osteoarthritis.[1,2] Despite its success in improving long-term outcomes, TKR is associated with significant postoperative pain; more than 50% of patients experience moderate to severe pain in the early postoperative period.[3,4] This pain can impede early mobilization, delay rehabilitation, and negatively impact overall recovery. Consequently, effective pain management after surgery is a key component of improved recovery.[5,6]

Multimodal analgesia (MMA) has become the standard of care for managing pain following TKR, as it aims to reduce opioid consumption.[7] Among various strategies, the adductor canal block (ACB), the motor-sparing peripheral nerve block (PNB), has gained popularity as it provides effective analgesia and facilitates early rehabilitation by preserving quadriceps motor function.[8,9] However, the ACB covers anteromedial knee pain without involving the pain of the posterior knee.[10] This pain can be reported as high as 72–89%.[11] Theoretically, adding the sciatic nerve block (SNB) that covers the posterior knee pain may provide better analgesia. However, the SNB may cause foot drop due to its effect on the common peroneal nerve (CPN), a branch of the sciatic nerve. A tibial nerve block (TNB), the selective block of another branch of the sciatic nerve, might be a better alternative PNB technique that can preserve the ankle dorsiflexion—a key component of ambulation.[12] This randomized controlled trial study aims to evaluate the analgesic effect of adding the TNB to the ACB after TKR. In addition, we also evaluated the effect of motor blockade in the two different volumes (10 ml vs. 15 ml) of the local anesthetic (LA) used for TNB, which had no prior studies.

MATERIALS AND METHODS

Study and population

This study was an assessor-blind, single-center, randomized controlled trial conducted in a university hospital. The study was first approved by the institutional ethics committee for performing a pilot study of 15 subjects, then amended for changing the number of subjects from 15 to 60 (HE641572). The trial was subsequently registered with the Thai Clinical Trials Registry (TCTR20220622001) prior to the first enrollment.

Patients undergoing elective TKR from June 2022 to March 2024 were eligible for the study. The inclusion criteria were aged between 18 and 75 years and had the American Society of Anesthesiologists physical status (ASA PS) of I–III. The exclusion criteria were those scheduled for bilateral TKR or revision surgery, neurological deficits, a body weight less than 30 kg, contraindications to spinal anesthesia or PNB, and inability to communicate or cooperate.

Study procedure and measurements

Patients who met the criteria were invited to participate in the study. The informed consent was obtained the day before surgery. The computer-generated random sequence (a block size of four) was employed. The random numbers were kept in the sealed opaque envelopes and revealed before performing the block by one of the investigator members, who was the regional anesthesia (RA) specialist who performed the block. All participants were randomly allocated to one of three study groups. Group A received the ACB; Group AT-10 received the ACB and the TNB using 10 ml of LA; Group AT-15 received the ACB and the TNB using 15 ml of LA. An assessor-blind method was applied to this study (a nurse who was the outcomes assessor was unaware of group allocation, while the patients and the PNB performers were unable to be blind). To ensure the block's success, all the PNB (ACB and TNB) were performed under ultrasound (US) guidance by two experienced RA specialists.

All patients received education on self-report pain assessment using the numeric rating scale (NRS), which ranges from 0 to 10, where NRS 0 indicates no pain and NRS 10 represents the worst imaginable pain; they were also educated on how to use the patient-controlled analgesia (PCA) device on the day prior to surgery. On the day of surgery, patients were transported to a block area, and the standard monitoring, including non-invasive blood pressure (NIBP), electrocardiogram (EKG), and pulse oximetry, was applied. Intravenous (IV) fentanyl 25 mcg was administered for patient comfort. The PNB was then performed by US guidance (SONIMAGE HS2, Konica Minolta, Japan) using a high-frequency (11–3 MHz) linear transducer, under strict adherence to sterile technique. A 21G, 100 mm block needle (Ultraplex®, B. Braun, Germany) and 0.25% bupivacaine (Marcain®, AstraZeneca, Sweden) with adrenaline (1:200,000) added were used for all patients.

All patients in any group received the proximal ACB. The block was performed in a supine position with the hip and knee slightly in external rotation. The transducer was placed transversely at the mid-thigh. The sonoanatomy of the femoral triangle apex was identified as the point where the medial border of the sartorius muscle and the adductor longus muscle intersected (Fig 1A). At this point, the block needle was inserted in-plane from the lateral to the medial direction until the tip reached the lateral side of the femoral artery, where the saphenous nerve is located. The 15 ml of LA was then incrementally injected after confirming the tip of the needle and negative aspiration (Fig 1B).

In addition to receiving ACB, patients in group AT-10 and group AT-15 also received TNB. The TNB was performed in a lateral position with the side blocked uppermost. The transducer was placed transversely at the back of the knee. Once the bifurcation of the tibial nerve (TN) and CPN was seen, the transducer was slowly slid distally toward the popliteal crease to where only the TN was clearly identified (Fig 1C). The needle was then inserted in-plane from the lateral to the medial direction, aiming the tip underneath the TN. Once

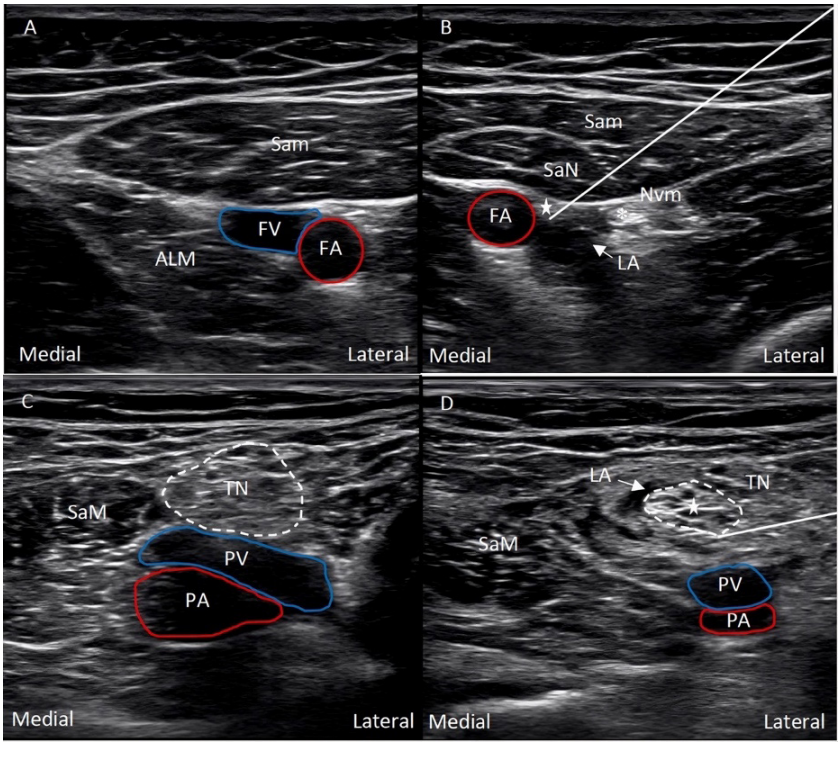


Fig 1. Sonoanatomy of adductor canal block and tibial nerve block. (A) shows the femoral triangle apex. (B) shows the location of the adductor canal block. The star indicates the saphenous nerve, the asterisk indicates the nerve to vastus medialis, the arrow indicates local anesthetic deposition, and the white line indicates the trajectory of the needle. (C) shows the tibial nerve. (D) shows the location of the tibial nerve block. The star indicates the tibial nerve, the arrow indicates local anesthetic deposition, and the white line indicates the trajectory of the needle.
Abbreviations: Sam-Sartorius muscle, ALM-adductor longus muscle, FA-femoral artery, FV-femoral vein, SaN-saphenous nerve, Nvm-nerve to vastus medialis, TN-tibial nerve, SnM-semimembranosus muscle, PA-popliteal artery, PV-popliteal vein, LA-local anesthetic.

confirming the needle position, 10 ml and 15 ml of LA were then incrementally injected for group AT-10 and group AT-15, respectively (Fig 1D).

The dermatomal sensory test on the dorsoplantar surface of the affected foot with an ice pack and the motor strength assessment of the ankle's dorsoplantar flexion were conducted 30 minutes after the block by a nurse anesthetist who was blinded to the group allocation. A grading of sensory loss was defined as grade 0 = no perception of touch nor cold sensation, grade 1 = feeling of a normal touch but no cold perception, and grade 2 = normal sensation. The motor function grading was divided into grade 0 = unable to resist resistance, grade 1 = able to resist some resistance, and grade 2 = normal power.

After the sensorimotor assessment, patients were then transferred to the operating room. The monitoring (NIBP, ECG, and pulse oximetry) was reattached. Standard spinal anesthesia was administered by an attending anesthesiologist using 0.5% bupivacaine to achieve the anesthesia level between thoracic (T) 6 and T10. The TKR was operated on by experienced orthopedists with the same standard medial parapatellar approach technique. Patients were all closely monitored for hemodynamics throughout the surgery in the operating room and also continued to be observed at the post-anesthesia care unit (PACU). In the PACU, a nurse attached an IV PCA morphine device with the setting of 1 mg/ml, a lockout interval of 5 minutes, and a maximum dose of 10 mg/hour. The same postoperative pain regimen was administered to all patients, including oral paracetamol 500–1,000 mg every 6 hours and IV parecoxib 40 mg every 12 hours. The primary outcome of the study was the 24-hour postoperative accumulated morphine consumption. The secondary outcomes were accumulated morphine consumption at 6, 12, and 48 h. The postoperative NRS at rest and during movement at 6, 12, 24, and 48 h. Sensorimotor assessment of CPN and TN at 30 minutes after the block and reassessed in every patient who revealed partial or complete impairment at 24 h after the block until return to normal. LA toxicity and opioid-related complications such as nausea, vomiting, sedation score, and respiratory depression were also recorded.

Statistical analysis

The sample size calculation used the formula for comparing two independent means.[13] Based on the data from our pilot study, the mean and standard deviation (SD) of the 24-hour postoperative morphine consumption after TKR in group A, group AT-10, and group AT-15 were 32.6 (20.38) mg, 12.8 (4.21) mg, and 11.8 (5.89) mg, respectively. The estimated pooled SD was 15.01 mg from the control (group A) and the comparison groups (group AT-10 and group AT-15). Using a two-sided significance level of 1% ($\alpha = 0.01$) and a power of 90% ($\beta = 0.10$), the minimum sample size required to detect a mean difference of 20.8 mg in morphine consumption between groups was 16 per group. To compensate for the 20% possible dropout rate, the final sample size of 60 participants was required.

The categorical data was presented as numbers and percentages. The Pearson's chi-square test or Fisher's exact test was used to compare data between groups. The Shapiro–Wilk test was used to test the normal distribution of the continuous data. Normally distributed data was presented as mean (SD) and analyzed using the analysis of variance (ANOVA), while non-normally distributed data was presented as median and interquartile range (IQR) and analyzed using the Kruskal–Wallis test. The generalized estimating equations (GEE) were employed to compare outcomes between groups at each time point, while considering within-subject correlations in repeated measures. Pairwise comparisons were performed using Bonferroni-adjusted P-values to control for multiple testing. A P-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using STATA version 18.

RESULTS

Seventy-two patients were assessed for eligibility (ten did not meet the inclusion criteria, and two declined to participate). A total of 60 patients were enrolled and randomized into three groups, with 20 in each group. There were no dropouts or losses to follow-up. All enrolled patients were included in the final analysis (Fig 2). The demographic and surgical data of all three groups were comparable (Table 1).

The 24-hour postoperative accumulated morphine consumption was highest in group A, with a similar consumption for group AT-10 and group AT-15 (group A, group AT-10 and group AT-15 = 18.35 ± 14.08 mg, 11.20 ± 7.70 mg, and 11.95 ± 7.40 mg, respectively). However, there was no statistically significant difference in morphine consumption at any time point of measurement and also among any groups of comparison (Table 2). The postoperative NRS pain scores at rest and during movement did not significantly differ among the three groups at any assessed time points (Table 3).

In the distribution of CPN, motor block was observed in 15% and 30% in group AT-10 and group AT-15, respectively. Of these, 5% of the AT-15 group had a complete motor block. The partial TN motor block was

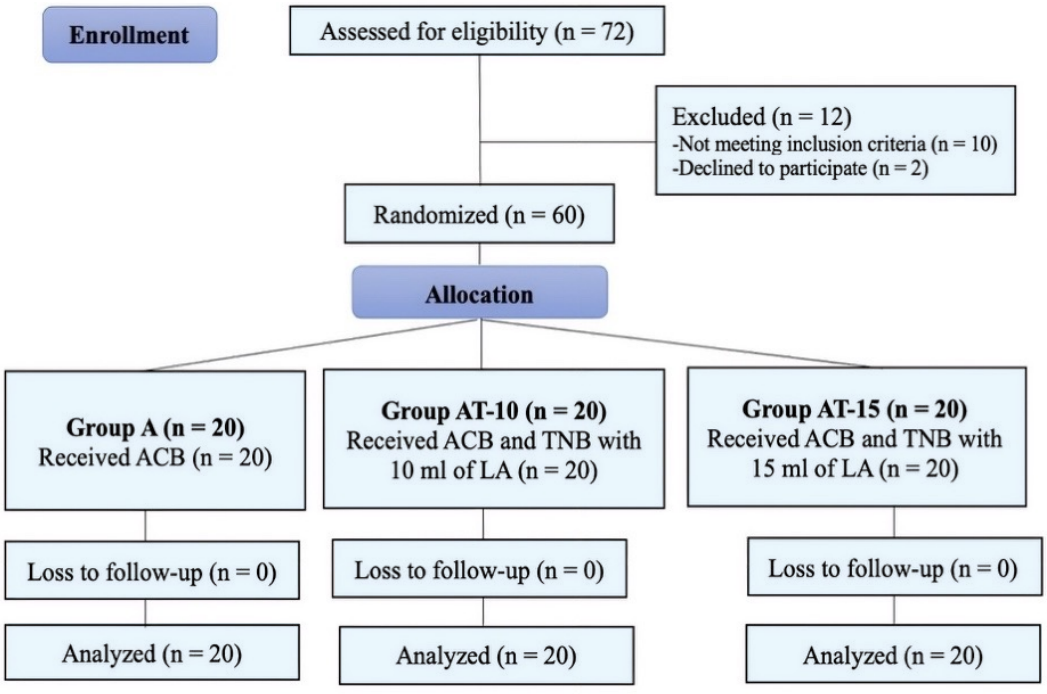


Fig 2. CONSORT diagram.
Abbreviations: ACB; Adductor canal block, TNB; Tibial nerve block, LA; Local anesthetic

TABLE 1. Demographic and surgical data.

Variables	Group A (n = 20)	Group AT-10 (n = 20)	Group AT-15 (n = 20)	P-value
Gender: Male/ Female	5 (25)/ 15 (75)	4 (20)/ 16 (80)	6 (30)/ 14 (70)	0.766
Age (years)	65.6 ± 5.8	64.6 ± 5.9	66.1 ± 7.2	0.763
Weight (kg)	66.1 ± 10.3	65.5 ± 11.2	60.9 ± 9.9	0.242
Height (cm)	156.5 ± 5.3	156.5 ± 6.0	157.5 ± 6.8	0.820
BMI (kg/m^2)	26.9 ± 4.2	26.7 ± 4.5	24.4 ± 3.2	0.103
ASA PS: I/ II/ III	1 (5)/ 19 (95)/ 0 (0)	2 (10)/ 16 (80)/ 2 (10)	2 (10)/ 17 (85)/ 1 (5)	0.667
Surgical time (min)	120.0 (107.5, 150.0)	120.0 (117.5, 147.5)	115.0 (104.0, 135.0)	0.223
Tourniquet time (min)	124.0 (107.5, 148.5)	120.0 (111.5, 141.5)	115.0 (103.5, 131.5)	0.505
Blood loss (ml)	20.0 (10.0, 30.0)	20.0 (10.0, 20.0)	20.0 (12.5, 25.0)	0.794

Gender and ASA PS were presented as a number (percentage). Age, weight, height, and BMI are presented as mean ± standard deviation. Surgical time, tourniquet time, and blood loss were presented as median (IQR).
A P-value < 0.05 was considered statistically significant.
Abbreviations: BMI: body mass index, ASA PS: American Society of Anesthesiologist Physical Status

TABLE 2. Postoperative accumulated morphine consumption.

Time	Group A (n = 20)	Group AT-10 (n = 20)	Group AT-15 (n = 20)	Mean difference (95% confidence interval)	P-value
6 h	4.75 ± 3.09	4.80 ± 3.49	4.90 ± 4.12	0.05 (-2.75, 2.85)[a]	>0.999
				0.15 (-2.94, 3.24)[b]	>0.999
				0.10 (-3.14, 3.34)[c]	>0.999
12 h	12.80 ± 8.47	8.50 ± 5.86	8.15 ± 5.14	-4.30 (10.49, 1.89)[a]	0.460
				-4.65 (-10.61, 1.31)[b]	0.262
				-0.35 (-5.04, 4.34)[c]	>0.999
24 h	18.35 ± 14.08	11.20 ± 7.70	11.95 ± 7.40	-7.15 (-16.79, 2.49)[a]	0.341
				-6.40 (-15.96, 3.16)[b]	0.538
				0.75 (-5.67, 7.17)[c]	>0.999
48 h	25.65 ± 23.71	16.80 ± 11.93	15.75 ± 10.57	-8.85 (-24.80, 7.10)[a]	>0.999
				-9.90 (-25.50, 5.70)[b]	0.662
				-1.05 (-10.63, 8.53)[c]	>0.999

Values were presented with mean ± standard deviation. [a] compared between group A vs. group AT-10, [b] compared between group A vs. group AT-15, and [c] compared between group AT-10 vs. group AT-15. Data were analyzed using the generalized estimating equations (GEE) with Bonferroni adjustment. A P-value < 0.05 was considered statistically significant.

TABLE 3. Postoperative resting and movement pain score.

Pain	Time	Group A (n = 20)	Group AT-10 (n = 20)	Group AT-15 (n = 20)	P-value between groups		
					A vs. AT-10	A vs. AT-15	AT-10 vs. AT-15
Resting	6 h	2.10 ± 2.43	2.00 ± 2.49	1.50 ± 2.26	>0.999	>0.999	>0.999
	12 h	1.70 ± 2.41	2.45 ± 3.20	2.20 ± 2.42	>0.999	>0.999	>0.999
	24 h	1.35 ± 1.46	2.35 ± 2.13	1.85 ± 2.08	0.628	>0.999	>0.999
	48 h	1.05 ± 1.47	1.10 ± 1.55	0.60 ± 1.14	>0.999	>0.999	>0.999
Movement	6 h	4.40 ± 3.03	3.80 ± 3.41	3.30 ± 2.99	>0.999	>0.999	>0.999
	12 h	4.20 ± 2.53	4.85 ± 3.48	4.40 ± 2.23	>0.999	>0.999	>0.999
	24 h	4.00 ± 1.81	4.20 ± 2.63	4.00 ± 2.32	0.695	>0.999	0.953
	48 h	3.65 ± 1.66	3.25 ±2.45	3.25 ± 1.55	>0.999	>0.999	>0.999

Values were presented with mean ± standard deviation. A P-value < 0.05 was considered statistically significant.

observed in 10% and 30% in group AT-10 and group AT-15, respectively. No complete motor block of TN was observed in any group. In addition, the incidence of CPN motor block was similar in group A vs. group AT-10 (P = 0.231) and in group AT-10 vs. group AT-15 (P = 0.451). However, there was a statistically significant impairment of CPN block in group AT-15 compared to group A (P = 0.020). The TN motor block was also similar in group A vs. group AT-10 (P = 0.487) and in group AT-10 vs. group AT-15 (P = 0.235). However, a statistically significant impairment of TN blockade was observed in group AT-15 compared to group A (P = 0.020) (Table 4).

Sensory block in the distribution of the CPN was observed in 90% in group AT-10, and group AT-15. Of these, 5% in both groups had a complete sensory block. The TN sensory block was observed in 95% in group AT-10 and group AT-15. Of these, 5% of patients in group AT-15 had a complete sensory block. Moreover, the CPN and TN sensory block was statistically significant in group A vs. group AT-10 (P < 0.001) and in group A vs. group AT-15 (P < 0.001) without a difference between group AT-10 and group AT-15 (P > 0.999) (Table 4). None of the groups reported any major adverse events, including LA toxicity, severe nausea and vomiting, oversedation, respiratory depression, or prolonged sensorimotor impairment for more than 24 hours.

DISCUSSION

This randomized controlled trial aimed to evaluate the benefit of adding the TNB to the ACB in terms of postoperative pain control following TKR. In addition, we also evaluated the effect of motor block in the two different volumes (10 ml vs. 15 ml) of the LA used for TNB. In this study, we found that adding the TNB to the ACB did not decrease the 24-hour postoperative accumulated morphine consumption or the pain score following TKR. Moreover, the use of 15 ml of LA for TNB was the cause of the CPN block.

Recently PNB has become an important part of MMA for managing pain after TKR, and the femoral nerve block (FNB) was traditionally considered a standard technique

TABLE 4. Motor and sensory block of the common peroneal nerve and tibial nerve.

Motor block	Grade	Group A (n = 20)	Group AT-10 (n = 20)	Group AT-15 (n = 20)	P-value between groups		
					A vs. AT-10	A vs. AT-15	AT-10 vs. AT-15
Dorsiflexion	2	20 (100)	17 (85)	14 (70)	0.231	0.020*	0.451
	1	0 (0)	3 (15)	5 (25)			
	0	0 (0)	0 (0)	1 (5)			
Plantarflexion	2	20 (100)	18 (90)	14 (70)	0.487	0.020*	0.235
	1	0 (0)	2 (10)	6 (30)			
	0	0 (0)	0 (0)	0 (0)			
Sensory block	**Grade**	**Group A (n = 20)**	**Group AT-10 (n = 20)**	**Group AT-15 (n = 20)**	**P-value between groups**		
					A vs. AT-10	**A vs. AT-15**	**AT-10 vs. AT-15**
Dorsum of foot	2	20 (100)	2 (10)	2 (10)	<0.001*	<0.001*	>0.999
	1	0 (0)	17 (85)	17 (85)			
	0	0 (0)	1 (5)	1 (5)			
Plantar of foot	2	20 (100)	1 (5)	1 (5)	<0.001*	<0.001*	>0.999
	1	0 (0)	19 (95)	18 (90)			
	0	0 (0)	0 (0)	1 (5)			

Values were presented as a number (%). A P-value < 0.05 was considered statistically significant.

for achieving analgesia for knee surgery. However, recent evidence favors the ACB, which blocks the terminal branch of the femoral nerve (saphenous nerve), as it provides comparable pain relief and opioid consumption while preserving quadriceps strength compared to the FNB.[9,14,15] Nevertheless, the saphenous nerve mainly supplies the anteromedial aspect of the knee, but lacks coverage of the posterior knee part may cause inadequate knee pain management.[11] Thus, adding the PNB that covers the posterior knee innervation, such as the TNB, might possibly improve the benefit of pain control after knee surgery.

Meanwhile, our study results surprised us; they also contradicted the current evidence that demonstrated the impact of posterior knee pain control. The trial by Abdallah et al.[11] examined whether a single shot subgluteal (proximal) or popliteal (distal) SNB provides superior analgesia in the posterior knee compared with no SNB after TKA; all patients also received continuous FNB. The results indicated that the proportion of patients who experienced moderate-to-severe posterior knee pain was significantly lower in the proximal and distal SNB up to 8 h postoperatively compared with no SNB. Additionally, the proportion of patients who reported significant anterior knee pain was lower in those who received either approach to SNB, which may be explained by the partial innervation of the lateral and anterolateral knees by the articular branches of the CPN. A meta-analysis by Abdallah et al.[16] also quantified the analgesic effects of adding SNB to FNB following TKA and found that both single-shot and continuous SNB significantly reduced the 0–24-hour weighted mean difference in morphine consumption by 10.6 mg and 20.5 mg, respectively. Single-shot SNB reduced pain up to 8 h postoperatively, whereas continuous SNB reduced pain much longer, up to 36 h. Another meta-analysis by Zorrilla-Vaca and Li[17] has also supported the benefits of SNB as a complement to FNB in TKA; the pain score and opioid consumption were shown to be significantly reduced in the patients who received SNB.

The explanation of negative results in our study may be because of the complexity of the innervation of the posterior knee capsule, which is derived from the articular branches originating from the TN, the CPN, and the posterior division of the obturator nerve.[18] Consequently, blocking only the TN may add slightly more analgesia, especially in cases in which the ACB is applied together with other administered systemic analgesic agents such as paracetamol and parecoxib, which are also administered postoperatively in all patients for enhanced pain control in this study.[19] Another reason may be that the surgical technique in our study was the medial parapatellar approach, where ACB plays a major role in the pain for this incision site.[10] Because the ACB targets the saphenous nerve, giving the infrapatellar branch, which innervates the anterior inferomedial part of the knee, and cutaneous tissues of the anteromedial knee. Moreover, as we performed the proximal ACB, which also blocks the nerve to the vastus medialis, it commonly contributes to the innervation of the anterior superomedial part of the knee.[20] Another explanation is the lack of sufficient power to detect the smaller effect size of morphine consumption observed in this study. Nevertheless, the 24-hour morphine reduction in the intervention groups in our study was about 6–7 mg lower than that in the control group, which is below the generally accepted minimal clinically significant difference (MCID) of 10 mg for morphine reduction. Regardless, this trial was unable to determine the actual clinical advantage of including TNB in the ACB for pain management following TKR.[21]

From our results, we did not observe the difference in the postoperative morphine consumption and pain score after performing the TNB with 10 ml or 15 ml of LA. We assumed that a volume of 10 ml is adequate for blocking this single nerve. Although the optimal volume for TNB has not yet been revealed and needs further investigation, the common volume of LA used for TNB in previous studies was 10 ml.[23,24] Moreover, a prospective study was found that only 8.7 ml of 0.5% ropivacaine was enough to enclose the tibial nerve.[12] Thus, using a higher volume of 15 ml for selective TNB may not be necessary. Another important result from our study was that the use of 15 ml of LA for TNB was associated with a significant CPN motor block when compared to the group that did not receive TNB. This phenomenon might be because of cephalad spread of the LA solution from the site of TNB. In a previous study[12], a lower volume of LA than in our study was used for TNB (8.7 ml, 99% CI = 7.9 to 9.4). In their study, no patient in the TNB group developed a complete CPN motor block; however, a partial block was found in 22.5% of the cases. This incidence was similar to ours, where a partial CPN motor block was observed in 15% of cases with 10 ml of LA and in 25% of cases with 15 ml of LA. In addition, 5% of the 15 ml TNB in our study had a complete CPN motor block, which was high because a larger volume of LA could potentially cause more cephalad spreading from the injection site. A cadaveric study by Silverman et al.[25] also confirmed the cephalad spreading of LA in TNB. Although there was no dye observed around the CPN at the level of injection (popliteal crease), dye was observed

at 14.5 cm (range: 8–21 cm) extending proximal to the sciatic nerve bifurcation. While the distance from the bifurcation to the popliteal crease in this study was only 6.6 cm (range: 4.5–9.0 cm), the excess spread beyond the bifurcation was observed in all specimens. Additionally, the clinical observations from 20 patients undergoing TKR in this study revealed that 15% experienced a partial motor block of the CPN, which may have contributed to the occurrence of undesirable foot drop.

The strength of our study was that there was no prior study evaluating the benefit of adding TNB compared with ACB alone. Moreover, no study compares the different volumes of LA used for TNB. Some limitations include biases arising from the inability to apply a sham block; therefore, we can only blind the outcome assessor, not the patient. However, the main outcome of this study was accumulative morphine consumption from the PCA device, which we believe was more reliable and less affected than self-reported pain scores. Our study did not evaluate functional outcomes after surgery, such as time to ambulation and the time-up-and-go test. Another issue is the risk of a Type II error, which we have previously mentioned. For future study, the volume, concentration, and type of LA used for TNB may also influence pain control and the incidence of motor block; these topics are still lacking and should be evaluated. In addition, functional outcomes should be assessed to provide information extending to recovery after the surgery period. Lastly, although we did not demonstrate analgesic benefit from supplementing TNB with ACB, other combinations of newer blocks that address posterior knee pain, such as the infiltration between the popliteal artery and the posterior capsule of the knee (iPACK), the genicular nerve block, or the popliteal plexus block, may yield different results and should be further investigated.

CONCLUSION

Our study found that either 10 ml or 15 ml of 0.25% bupivacaine with adrenaline 1:200,000 for TNB added to the ACB does not decrease postoperative opioid consumption or reduce postoperative pain following TKA. However, this study might be underpowered to detect it statistically. A higher volume (15 ml) of TNB increases the risk of motor impairment, potentially compromising early mobilization. A lower volume (10 ml) TNB appears safer but may need larger and adequately powered trials.

Data Availability Statements

The research data in this study are available from the corresponding author upon reasonable request.

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DECLARATIONS

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This study received no funding from any source.

Conflict of Interest

All authors declare that they have no conflict of interest.

Registration Number of Clinical Trial

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Author Contributions

Conceptualization and methodology, NV, AW, CS, and KW; Investigation, NV, AW, JI, PC, and RC; Formal analysis, NV, and JI; Visualization and writing - original draft, NV; Writing – review and editing, NV, and AW; Supervision, AW. All authors have read and agreed to the final version of the manuscript.

Use of Artificial Intelligence

We used the program QuillBot for English language grammar checking and refinement of this manuscript. All concepts, analyses, and findings presented are the original work and were developed without artificial intelligence (AI) assistance.

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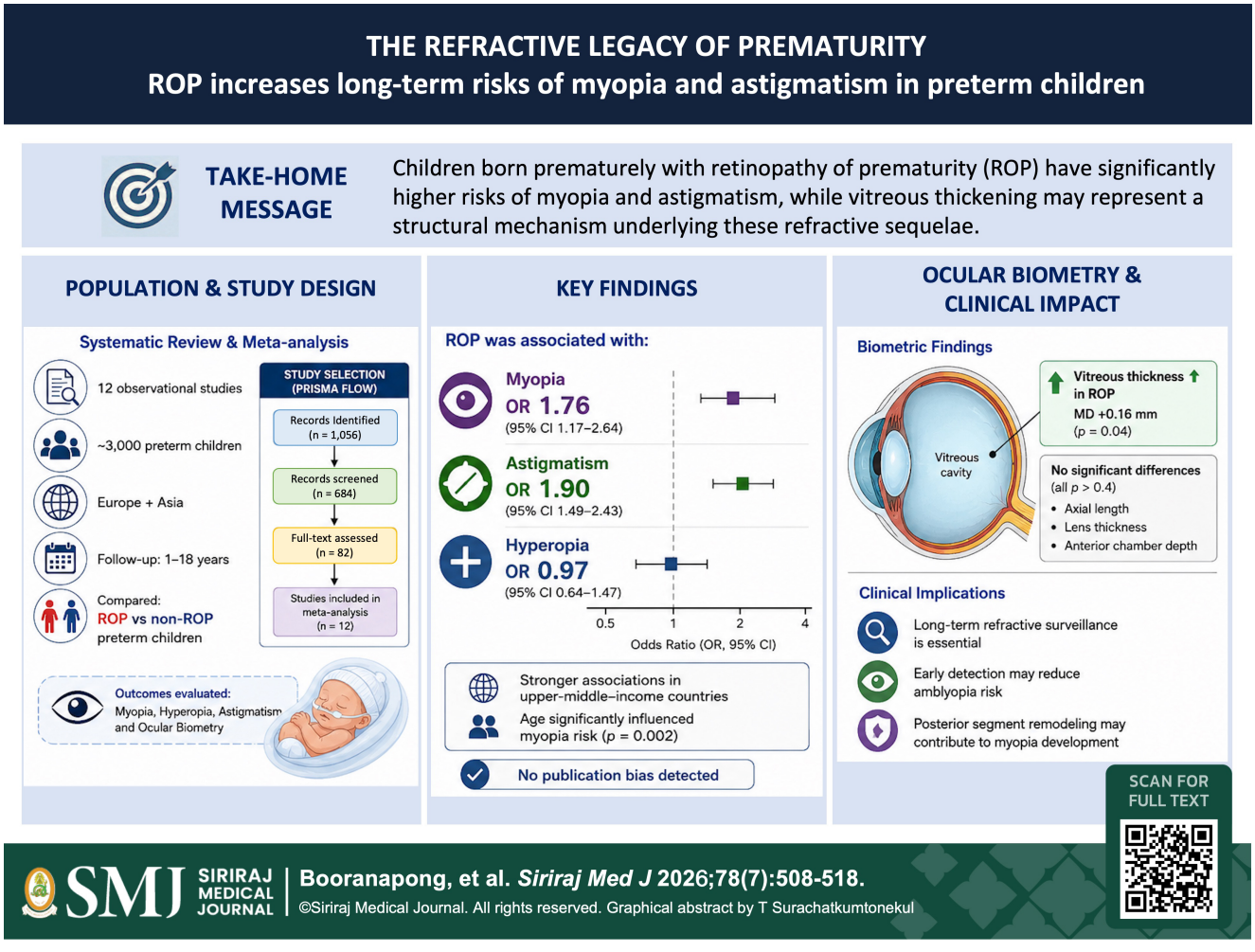
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The Refractive Legacy of Prematurity: A Systematic Review and Meta-Analysis of Refractive Errors and Ocular Biometry in Infants With and Without Retinopathy of Prematurity

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ABSTRACT

Objective: To compare the prevalence of refractive errors in children born prematurely with and without retinopathy of prematurity (ROP) and to identify potential factors contributing to heterogeneity.

Materials and Methods: Relevant literature was systematically searched in PubMed, EMBASE, and CINAHL for studies available through January 2025. Studies were eligible if they used cross-sectional, cohort, or case-control designs and reported refractive outcomes among preterm children stratified by ROP status. Effect estimates were synthesized using random-effects models and expressed as pooled odds ratios and mean differences. Between-study variability was evaluated using Cochran's Q statistic and the I^2 metric. Additional analyses included subgroup comparisons, meta-regression, and assessment of potential publication bias.

Results: Twelve studies were included. ROP was significantly associated with myopia (OR, 1.76; 95% CI, 1.17–2.64; p = 0.01) and astigmatism (OR, 1.90; 95% CI, 1.49–2.43; p < 0.001), but not hyperopia (OR, 0.97; 95% CI, 0.64–1.47; p = 0.89). Strong associations were observed in upper-middle–income countries. Age significantly modified the ROP–myopia association (p = 0.002). Biometric analysis showed greater vitreous thickness in ROP children (mean difference, 0.16 mm; p = 0.04), while axial length, lens thickness, and anterior chamber depth were not significantly different (all p > 0.4). No publication bias was detected.

Conclusions: ROP is associated with increased risks of myopia and astigmatism, with effects influenced by age and socioeconomic context. Vitreous thickness was the only biometric parameter significantly affected, suggesting a potential mechanism underlying refractive sequelae, although this requires further validation.

Keywords: Retinopathy of prematurity; preterm; myopia; hyperopia; astigmatism; meta-analysis; ocular biometry
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INTRODUCTION

Improvements in neonatal medicine over recent decades have markedly increased survival among infants born preterm.[1,2] However, preterm birth remains associated with an elevated risk of various visual and ocular abnormalities.[3,4] Among these, retinopathy of prematurity (ROP) remains a major contributor to visual impairment and blindness in childhood worldwide.[5,6] ROP primarily affects infants born at a gestational age (GA) of less than 32 weeks or with a birth weight (BW) below 1,500 grams, resulting in abnormal retinal vascular development and subsequent retinal ischemia or scarring.[4,7] Beyond these acute retinal changes, children born prematurely frequently develop refractive errors, such as myopia, hyperopia, and astigmatism, later in life.[3,8,9] These refractive anomalies are thought to arise from disrupted postnatal ocular growth, particularly involving anterior segment underdevelopment (e.g., reduced anterior chamber depth) and posterior segment remodeling (e.g., altered axial length and vitreous length).[10,11]

Understanding long-term refractive outcomes in this population is essential for predicting visual prognosis, optimizing early screening, and implementing timely interventions to prevent amblyopia and irreversible vision loss.[9,12]

Despite numerous cohort and population-based studies conducted across Asia and Europe, variations in study design, sample size, and refractive measurement techniques have led to inconsistent findings.[3,8,13] Therefore, a quantitative synthesis is needed to better estimate the prevalence and magnitude of refractive errors among individuals born prematurely and to identify the ocular biometric parameters most strongly associated with these outcomes.

The present study was designed to synthesize available evidence on: (1) the relationship between ROP and refractive errors in children born prematurely; (2) evaluate ocular biometric differences between children with and without ROP, and (3) explore sources of heterogeneity, including age at follow-up and country income classification.

MATERIALS AND METHODS

Study design and Registration

This review followed the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) reporting framework for systematic reviews and meta-analyses. The protocol was registered in PROSPERO under reference CRD42023262977.

Search strategy

We performed a structured database search to identify studies examining refractive outcomes in relation to ROP.

Relevant studies published up to January 2025 were identified through comprehensive searches of PubMed, EMBASE and CINAHL databases.

For PubMed, the following search strategy was utilized:

("Infant, Premature"[Mesh] OR preterm OR prematurity) AND ("Retinopathy of Prematurity"[Mesh] OR "Retinopathy of Prematurity" OR ROP) AND ("Refractive Errors"[Mesh] OR "Refractive errors" OR "Refractive Error").

For EMBASE, the search terms included:

('prematurity'/exp OR prematurity OR preterm) AND ('retrolental fibroplasia'/exp OR 'retrolental fibroplasia' OR 'retinopathy of prematurity'/exp OR 'retinopathy of prematurity' OR ROP) AND ('refraction error'/exp OR 'refraction error' OR 'refractive errors'/exp OR 'refractive errors' OR 'refractive error'/exp OR 'refractive error').

For CINAHL, the search terms included:

(MH "Infant, Premature") OR prematurity OR preterm AND (MH "Retinopathy of Prematurity") OR "retrolental fibroplasia" OR "retinopathy of prematurity" OR "retinopathy of prematurity" OR rop AND (MH "Refractive Errors+") OR "refraction error" OR "refractive errors".

Study eligibility criteria

Studies were considered eligible if they employed cross-sectional, cohort, or case-control designs that reported the prevalence of refractive errors in premature infants with versus without retinopathy of prematurity (ROP). Only studies published between 2000 and 2025 with a sample size greater than 70 eyes were included to ensure adequate statistical power. Eligible studies focused on non-treatment ROP, evaluating the natural progression of refractive outcomes rather than the effects of interventions such as laser photocoagulation or anti-VEGF therapy. Additionally, studies were required to report the prevalence of specific refractive error types, including myopia, hyperopia, and astigmatism, separately. Studies were excluded if they were non-English, unpublished, conference abstracts without full text, or case series lacking a control group of premature infants without ROP. Studies conducted in non-human species were also excluded.

Study selection

All retrieved records from the databases were initially imported into EndNote for reference management and subsequently exported to Covidence for deduplication and systematic screening. The remaining studies were randomly assigned and independently evaluated by two reviewers, both trained in ophthalmology. The screening process involved two stages: initial assessment of titles and abstracts, followed by full-text review, with both stages conducted according to predefined inclusion and exclusion criteria. Each study was categorized within Covidence as "include," "exclude," or "potentially include." Any discrepancies between reviewers were resolved through discussion and consensus, with consultation from a pediatric ophthalmologist when necessary to make a final decision.

Data Extraction

Data from eligible articles were organized in Covidence to support consistent extraction across reviewers. Two reviewers independently identified eligible articles and extracted relevant information into a Microsoft Excel spreadsheet. Extracted variables included study identification code, authors, title, year of publication, study design, total number of patients and eyes, mean age of the study population, country income classification, number of preterm patients with and without ROP, definitions of refractive errors, and biometric parameters, including axial length, anterior chamber depth, lens thickness, and vitreous thickness. Any disagreements between reviewers were addressed through discussion until a consensus was reached, ensuring the reliability of the extracted data.

Risk of Bias Assessment

Methodological quality was evaluated with the Newcastle–Ottawa Scale, which is commonly used for observational research. Each study was rated across three domains (Selection, Comparability, Outcome/Exposure), with total scores ranging from 0 to 9. Studies with scores ≥7 were classified as high quality, those scoring 5–6 as moderate quality, and those with scores ≤4 as low quality.

Statistical Analysis

For binary outcomes (myopia, hyperopia, astigmatism), pooled effect estimates were calculated as odds ratios (ORs) using a random-effects model based on the DerSimonian–Laird approach. Continuous outcomes (biometry) were analyzed using pooled mean differences. Between-study heterogeneity was evaluated using Cochran's Q test and quantified with the I^2 statistic. Subgroup analyses stratified studies by design and World Bank income classification. Meta-regression examined age at follow-up as a potential modifier. Publication bias was examined using Egger's test in conjunction with funnel plot assessment.

RESULTS

Literature search and study characteristics

The database search yielded 1,056 records in total (658 from Embase, 325 from PubMed and 73 from CINAHL), with no additional records obtained from other sources. Following removal of 372 duplicate records, 684 articles proceeded to title and abstract screening, of which 602 were excluded. Eighty-one studies were subsequently assessed for eligibility through full-text review, and all were successfully retrieved. Of these, 69 were excluded due to inappropriate patient population, outcomes, comparator, or study setting, or because full texts were unavailable. Ultimately, 12 studies met the predefined inclusion criteria and were included in the final systematic review (Fig 1).

Characteristics of Included Studies

The included studies comprised both prospective and retrospective cohorts, with the majority being prospective cohort or case-control studies conducted in Europe and Asia. Sample sizes varied considerably, with the number of eyes with retinopathy of prematurity (ROP) ranging from 38 to 153 and comparison groups without ROP ranging from 38 to 434 eyes. In total, 12 observational studies comprising approximately 3,000 premature children were analyzed, with follow-up durations ranging from 1 to 18 years.

The mean or median age at examination ranged from 5.5 to 11 years, reflecting school-aged to early adolescent populations. Definitions of refractive error were relatively consistent across studies, with myopia defined as less than −0.50 D (ranging to −3.00 D in some cohorts), astigmatism defined as cylindrical error greater than 1.00 D (up to 2.00 D), and hyperopia defined as greater than +1.00 D (up to +3.00 D). Criteria for prematurity varied by study but generally included gestational age

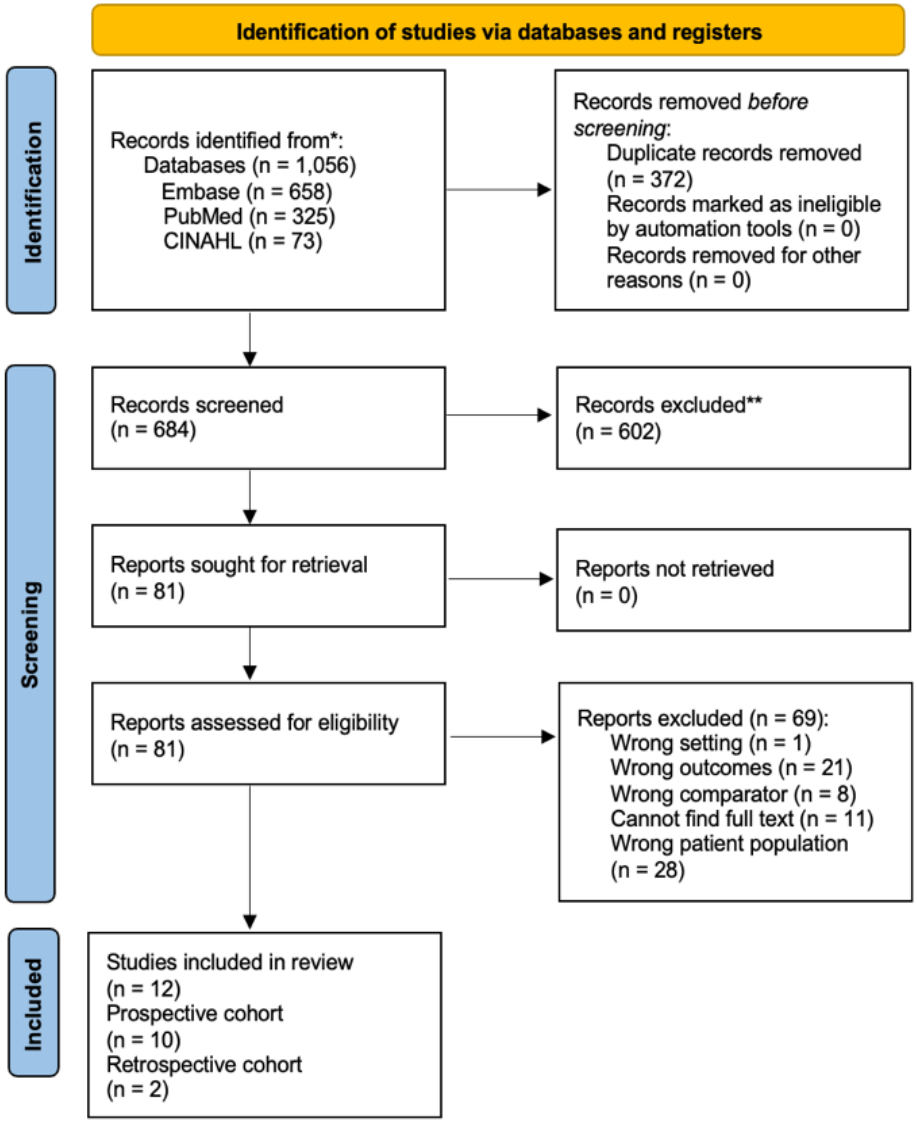


Fig 1. PRISMA 2020 flow diagram of study selection

thresholds between <32 and <37 weeks and/or low birth weight criteria ranging from <1,500 g to <2,500 g (Table 1).

Refractive Outcomes

Myopia Outcomes Pooled analysis showed that children with a history of ROP had significantly greater odds of developing myopia than those without ROP. Using a random-effects model, pooled analysis showed significantly higher odds of myopia among participants with ROP (odds ratio (OR) = 1.76; 95% confidence interval (CI), 1.17–2.64; p = 0.01), with moderate heterogeneity across studies (I^2 = 57%) (Fig 2). Age significantly modified this association (p = 0.002).

Subgroup analysis stratified by country income level revealed differing patterns between ROP and myopia (Fig 3). In high-income countries, the association between ROP and myopia was not statistically significant

TABLE 1. Characteristics of the included studies

Study	Study design	n ROP (eyes)	n non-ROP (eyes)	Age (Yrs)	Myopia (D)	Astigmatism (DC)	Hyperopia (D)	Prematurity criteria	Country
Larsson et al (2003)[9]	Prospective	80	133	10	< -0.50 D	> 1.00 DC	> +1.00 D	BW <1,500g	Sweden
Holmström et al (2005)[8]	Prospective	77	121	10	< -0.50 D	-	> +1.00 D	BW <1,500g	Sweden
O'Connor et al (2006)[3]	Prospective	134	155	11	< -1.00 D	-	> +1.00 D	BW <1,701g	UK
Fieß et al (2017)[17]	Prospective	55	184	6.94	< -3.00 D	> 1.00 DC	> +3.00 D	GA < 32 wk	Germany
Zhu et al (2017)[16]	Prospective	56	104	6.35	< -0.50 D	> 1.00 DC	> +2.00 D	GA < 37 wk, BW < 2,500g	China
Wang et al (2020)[13]	Prospective	50	110	7	< -0.50 D	> 1.00 DC	> +2.00 D	GA < 37 wk, BW < 2,500g	China
Rasoulinejad et al (2020)[18]	Prospective	122	56	5.5	< -3.00 D	> 2.00 DC	> +3.00 D	GA < 34 wk, BW < 2,000g	Iran
Pétursdóttir et al (2022)[21]	Prospective	50	68	10	< -1.00 D	> 1.00 DC	> +1.00 D	GA 24-34 wk, BW < 1,490	Sweden
Xie et al (2022)[19]	Prospective	153	324	7	< -0.50 D	> 1.00 DC	> +2.00 D	GA < 32 wk	China
Genc et al (2023)[22]	Prospective	38	38	9.3	< -0.50 D	> 1.00 DC	> +1.00 D	GA < 34 wk, BW < 1,750g	Turkey
Chen et al (2010)[14]	Retrospective	48	60	8.06	< -0.50 D	-	> +0.50 D	GA < 35 wk, BW < 1,500g	Taiwan
Al Oum Muna et al (2014)[15]	Retrospective	88	434	6	< -0.50 D	> 1.00 DC	> +0.50 D	GA < 32 wk, BW < 1,500g	Italy

Abbreviations: Yrs: Years, D: Diopters, DC: Diopters of Cylinder, BW: Birth weight, GA: Gestational age

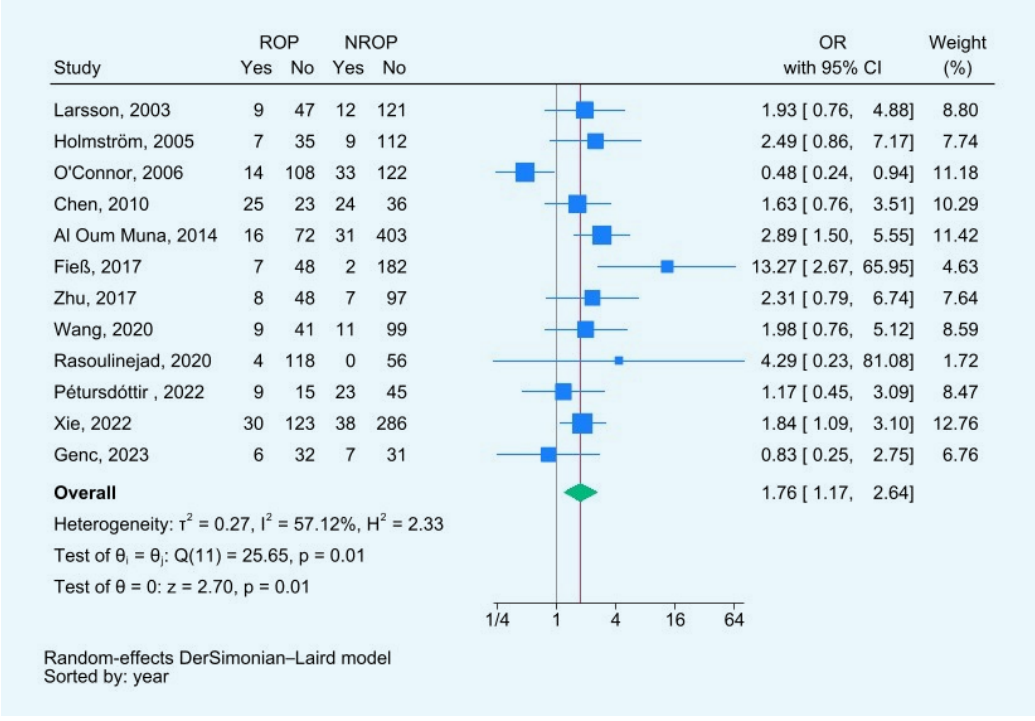


Fig 2. Forest plot comparing the association between myopia in eyes with retinopathy of prematurity (ROP) and those without ROP

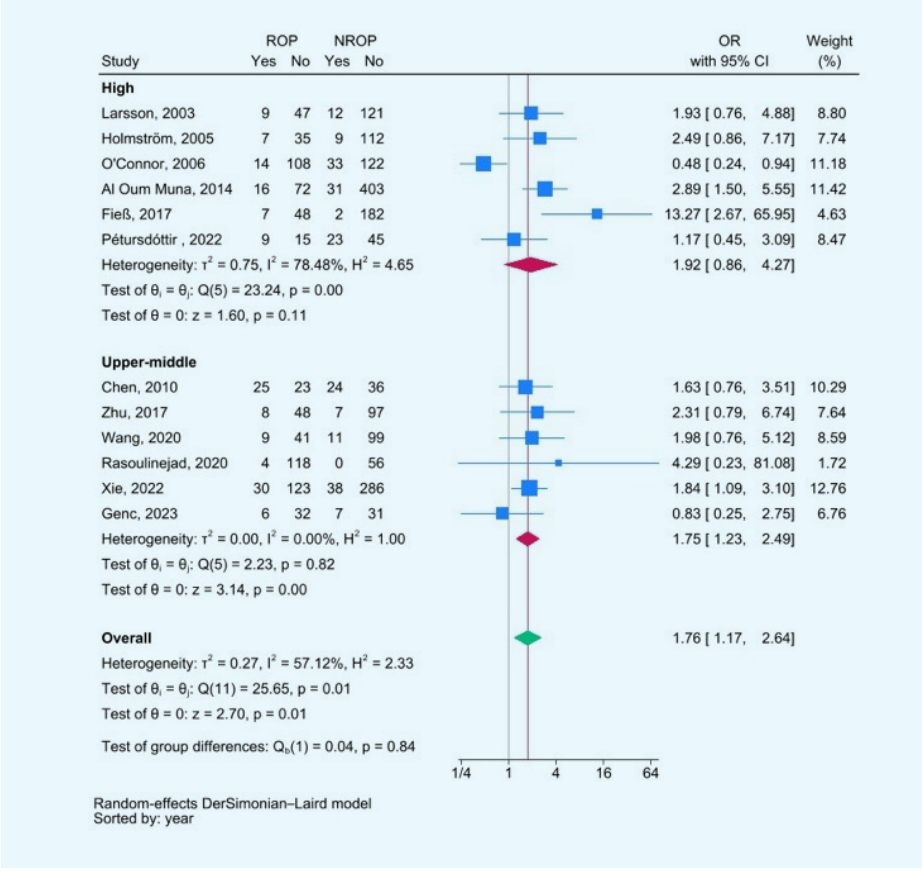


Fig 3. Forest plot of subgroup analysis by country income level for the association between myopia and retinopathy of prematurity (ROP) versus non-ROP

(OR = 1.92; 95% CI, 0.86–4.27), with substantial heterogeneity observed (I^2 = 78.5%). Conversely, studies conducted in upper-middle-income countries demonstrated a significantly increased odds of myopia among individuals with ROP (OR = 1.75; 95% CI, 1.23–2.49), with no observed heterogeneity (I^2 = 0%). However, there was no significant difference between income-level subgroups (p = 0.84).

Astigmatism Outcomes A significant relationship was also observed between ROP and astigmatism, with the pooled estimate indicating nearly two-fold higher odds (95% CI, 1.49–2.43; $p < 0.001$). Between-study heterogeneity for astigmatism was low (I^2 = 3.4%), indicating a high level of consistency among included studies (Fig 4).

Subgroup analysis by country income level showed significant associations in both high-income countries (OR = 1.46, 95% CI 1.02–2.08; p = 0.04) and upper-middle-income countries (OR = 2.35, 95% CI 1.71–3.22; p < 0.001), with negligible heterogeneity (I^2 = 0%). The test for subgroup differences was borderline significant (p = 0.05), suggesting a potentially stronger association in upper-middle-income settings. Overall, the findings support ROP as a significant risk factor for astigmatism across different economic contexts (Fig 5).

Hyperopia Outcomes In contrast, hyperopia prevalence did not differ significantly between the ROP and non-ROP groups (OR, 0.97; 95% CI, 0.64–1.47; p = 0.89) (Fig 6).

Ocular Biometry

Structural ocular parameters were compared between children with and without a history of retinopathy of prematurity (ROP). Meta-analysis demonstrated that vitreous thickness was significantly greater in the ROP group, with a pooled mean difference of 0.16 mm (95% confidence interval [CI], 0.01–0.31; p = 0.04), and no evidence of between-study heterogeneity (I^2 = 0%) (Fig 7). In contrast, axial length, lens thickness, and anterior chamber depth did not differ significantly between the two groups (all p > 0.40).

Risk of Bias

Of the 12 included studies, nine were rated as high quality (≥7 stars on the Newcastle–Ottawa Scale [NOS]), while three were of moderate quality. No studies were classified as low quality.

Selection: Most studies employed validated ophthalmic examination methods, with appropriate control group selection.

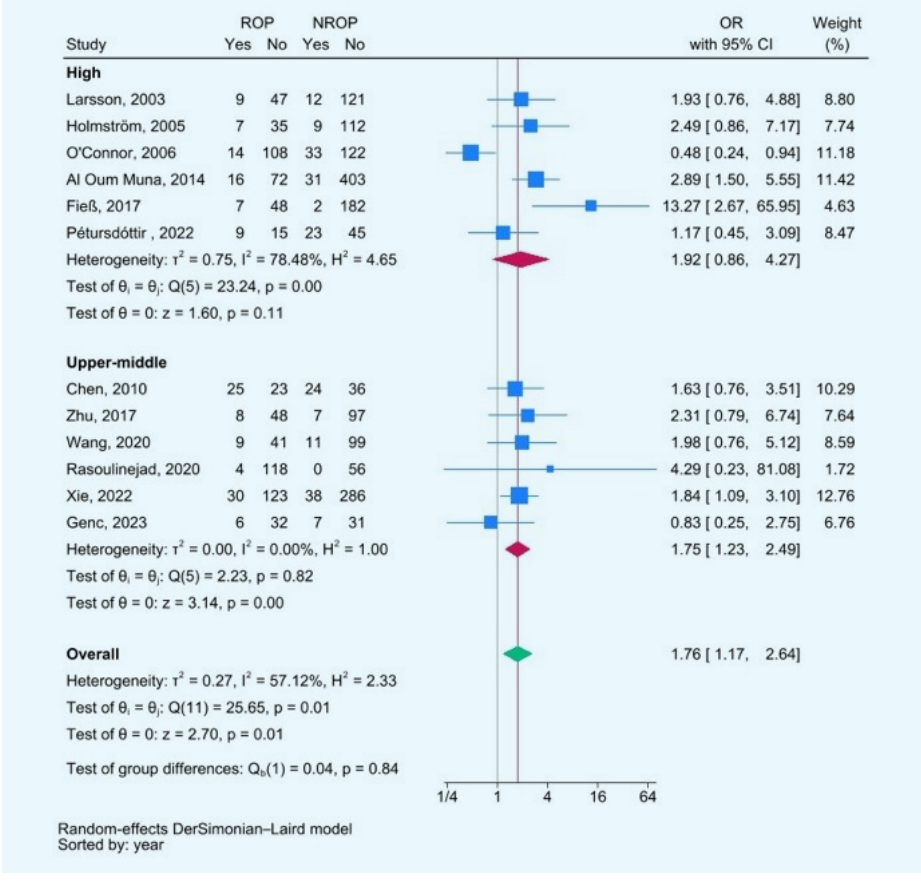


Fig 4. Forest plot comparing the association between astigmatism in eyes with retinopathy of prematurity (ROP) and those without ROP

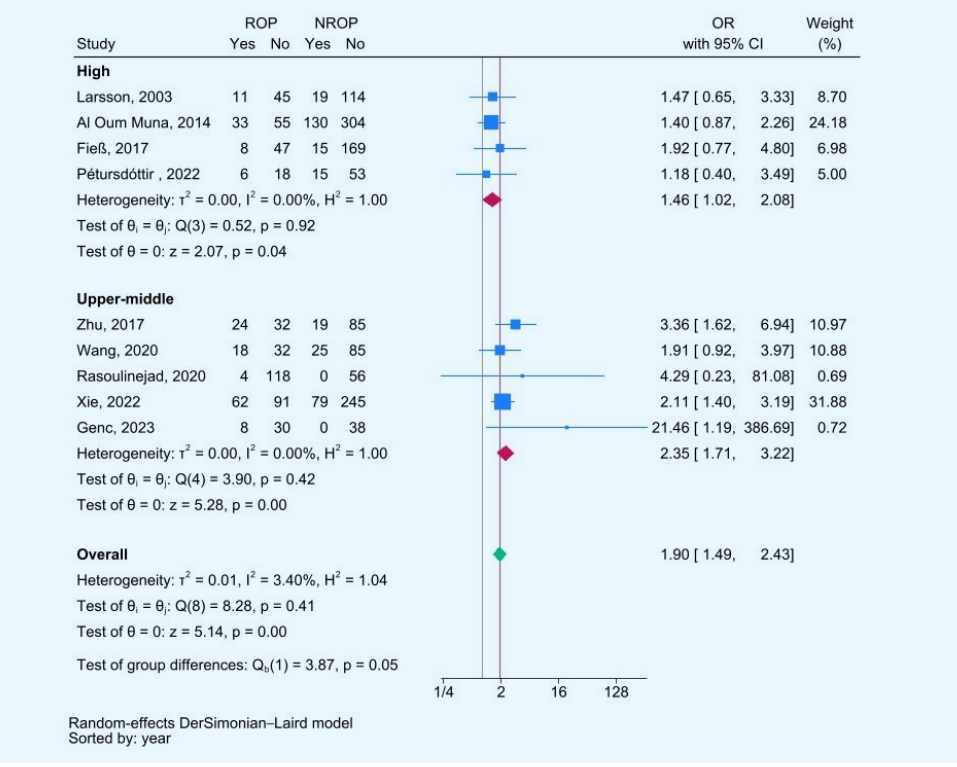


Fig 5. Forest plot of subgroup analysis by country income level for the association between astigmatism and retinopathy of prematurity (ROP) versus non-ROP

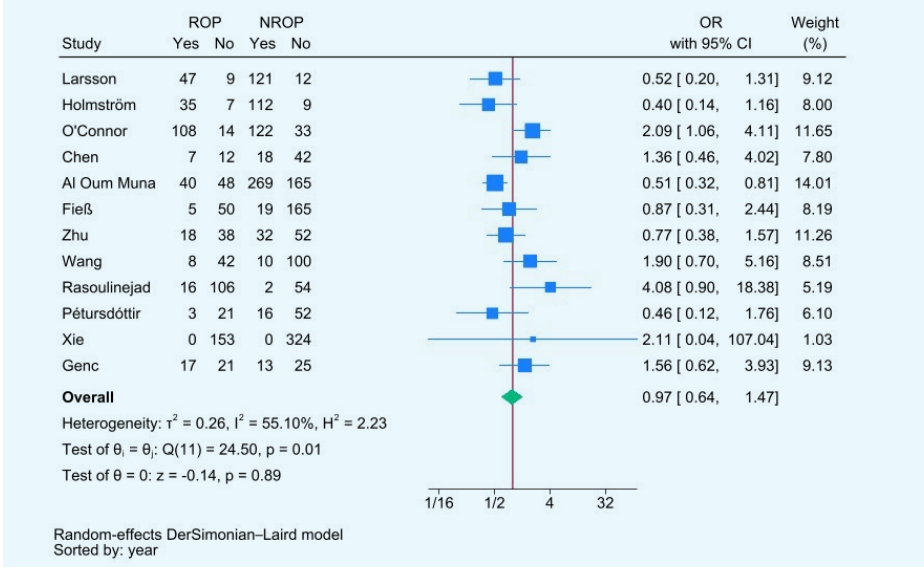


Fig 6. Forest plot comparing the association of hyperopia in eyes with retinopathy of prematurity (ROP) and those without ROP

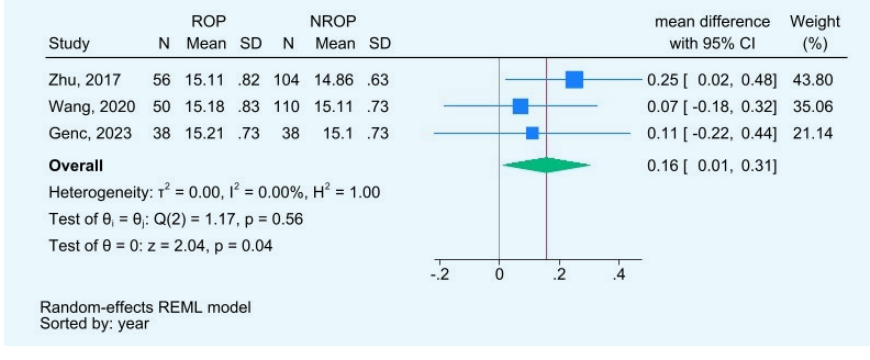


Fig 7. Forest plot comparing vitreous thickness between eyes with retinopathy of prematurity (ROP) and those without ROP

Comparability: Seven studies adequately adjusted for key confounders, including age at follow-up and gestational age.

Outcome/Exposure: Nine studies had follow-up durations exceeding five years, supporting reliable outcome assessment, whereas three had shorter follow-up periods, which may introduce a degree of outcome misclassification.

Sensitivity Analysis and Publication Bias

Leave-one-out sensitivity analyses confirmed robustness. Egger's test showed no evidence of small-study effects (Fig 8).

DISCUSSION

The present synthesis indicates that preterm children with ROP are more likely to develop myopia and astigmatism than their counterparts without ROP, whereas no association was observed with hyperopia. These findings reinforce the concept that ROP exerts selective and long-term effects on refractive development rather than inducing a generalized refractive shift.[8-10] The association between ROP and myopia was significantly modified by age, suggesting that refractive divergence between children with and without ROP evolves over time. This observation is consistent with longitudinal cohort studies indicating altered emmetropization trajectories in preterm children, particularly those with retinal vascular pathology.[8,9,13,16-21] Rather than representing a fixed refractive outcome established in early childhood, myopia in ROP appears to reflect a dynamic process influenced by ongoing ocular growth and remodeling.[9,13] Clinically, this underscores the importance of long-term refractive surveillance beyond early childhood in this population.

Socioeconomic context emerged as a potential effect modifier, with stronger associations between ROP and myopia observed in upper-middle–income countries. Although subgroup differences were not statistically significant, this pattern may reflect disparities in neonatal care quality, survival of more immature infants, variations in ROP screening thresholds, or differences in follow-up adherence.[1,5,6] In higher-income settings, earlier detection and optimized neonatal interventions may mitigate the downstream refractive impact of ROP, whereas in resource-limited contexts, subclinical or untreated retinal changes may exert greater influence on ocular development.[5] These findings highlight the need to interpret refractive outcomes of prematurity within broader healthcare system contexts.

This uniformity suggests a common underlying mechanism, potentially related to altered corneal or anterior segment development secondary to premature birth and retinal disease.[10,11,13,21] The strength and consistency of this association emphasize astigmatism as a key refractive sequela of ROP that warrants early detection and correction to reduce amblyopia risk.[12]

In contrast, hyperopia was not associated with ROP, indicating that posterior segment pathology does not uniformly disrupt refractive development in all directions.[3,10] This finding supports the notion that ROP-related refractive outcomes are not simply a consequence of arrested ocular growth but are instead shaped by specific structural alterations.[10,11]

Biometric analysis further supports this interpretation. Among the evaluated parameters, vitreous thickness was the only biometric measure significantly increased in children with ROP, whereas axial length, anterior chamber depth, and lens thickness did not differ between groups. These findings indicate that posterior segment remodeling may play a central role in the refractive sequelae of ROP, rather than global axial elongation or anterior segment underdevelopment.[10,11,13,21] Increased vitreous thickness may reflect abnormal posterior segment growth following early retinal ischemia and dysregulated vascular development.[11,13,21] This structural alteration provides a plausible explanation for the increased risk of myopia in the absence of axial elongation, a pattern that contrasts with typical school-age myopia.[21,22]

The observed association between ROP and myopia

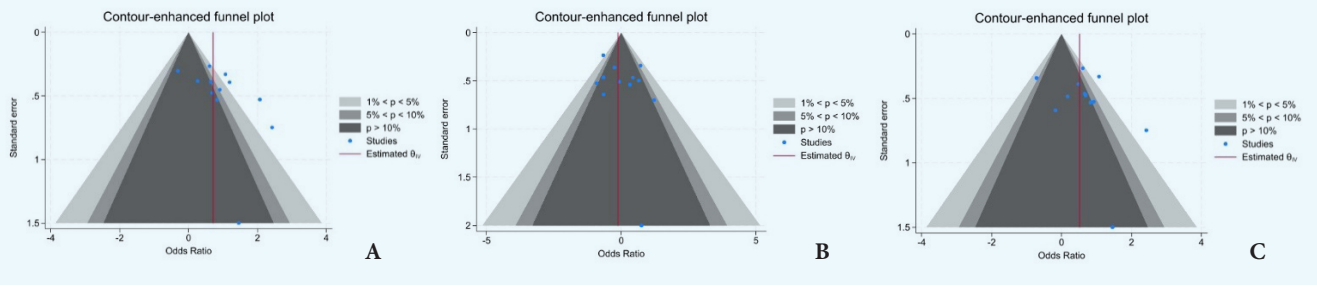


Fig 8. Contour-enhanced funnel plot for myopia (odds ratio) (A), astigmatism (odds ratio) (B), and hyperopia (odds ratio) (C)

may be explained, at least in part, by disruption of the normal emmetropization process. In healthy ocular development, visually guided feedback mechanisms originating from the retina regulate axial growth to achieve emmetropia.[23,24] In preterm infants, particularly those with ROP, retinal immaturity, ischemia, and aberrant vascular development may impair this feedback loop, leading to dysregulated ocular growth.[8,10,25] Rather than a simple increase in axial length, this dysregulation may involve altered coordination between anterior and posterior segment development, resulting in refractive error.[10,14]

The strengths of this study include its comprehensive synthesis of both refractive outcomes and ocular biometry, use of rigorous meta-analytic methods, assessment of effect modifiers through subgroup and meta-regression analyses, and low overall risk of bias across included studies. Importantly, this is one of the first meta-analyses to integrate biometric data into the evaluation of refractive outcomes in ROP.

However, several limitations should be acknowledged. Definitions of refractive errors varied across studies, which may have contributed to residual heterogeneity. The number of studies reporting biometric parameters was limited, restricting more granular analyses of ocular structure. Additionally, most data were derived from high- and upper-middle–income countries, potentially limiting generalizability to low-income settings where ROP epidemiology and care pathways differ substantially. Furthermore, our analysis did not fully account for the severity of ROP due to inconsistent reporting in primary studies. Given that more advanced stages of ROP are typically associated with a higher prevalence of myopia, our findings may partially reflect the influence of more severe disease. Furthermore, the potential impact of ROP treatment also remains an important consideration. Although this study focused on untreated or naturally progressing ROP, contemporary interventions such as laser photocoagulation or anti-VEGF therapy are known to alter refractive development. Specifically, laser treatment has been linked to increased myopic risk, whereas the long-term refractive profile of anti-VEGF therapy is still being elucidated. Therefore, these results may not fully represent refractive outcomes in modern clinical settings where active treatment is standard.

CONCLUSIONS

Preterm children who experienced ROP have a higher long-term likelihood of myopia and astigmatism, whereas hyperopia does not appear to be increased. These associations are influenced by age and socioeconomic context, underscoring the dynamic and multifactorial nature of refractive development following prematurity. Vitreous thickness was the only biometric parameter consistently altered in ROP, suggesting that posterior segment remodeling may underlie these refractive sequelae. Future longitudinal studies using standardized refractive definitions and comprehensive biometric profiling are needed to further elucidate mechanisms and to inform targeted screening and prevention strategies aimed at reducing lifelong visual morbidity in this vulnerable population.

Data Availability Statement

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

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DECLARATIONS

Grants and Funding Information

None

Conflict of Interest

None

Registration number of clinical trial

The protocol was registered in PROSPERO under reference CRD42023262977.

Author Contributions

Conceptualization and methodology, N.B. and T.S. ; Investigation, N.B. and P.J. ; Formal analysis, N.B. and R.K. ; Visualization and writing – original draft, N.B. and P.J. ; Writing – review and editing, N.B. and T.S. ; Supervision, T.S. All authors have read and agreed to the final version of the manuscript.

Use of artificial intelligence

During preparation of the manuscript, the authors used Grammarly and ChatGPT 5.5 to refine grammar and enhance readability.

IRB Approval / COI Disclosure

This systematic review and meta-analysis study was approved by the Siriraj Institutional Review Board, Faculty of Medicine Siriraj Hospital (SIRB Protocol no. 096/2568 Exempt).

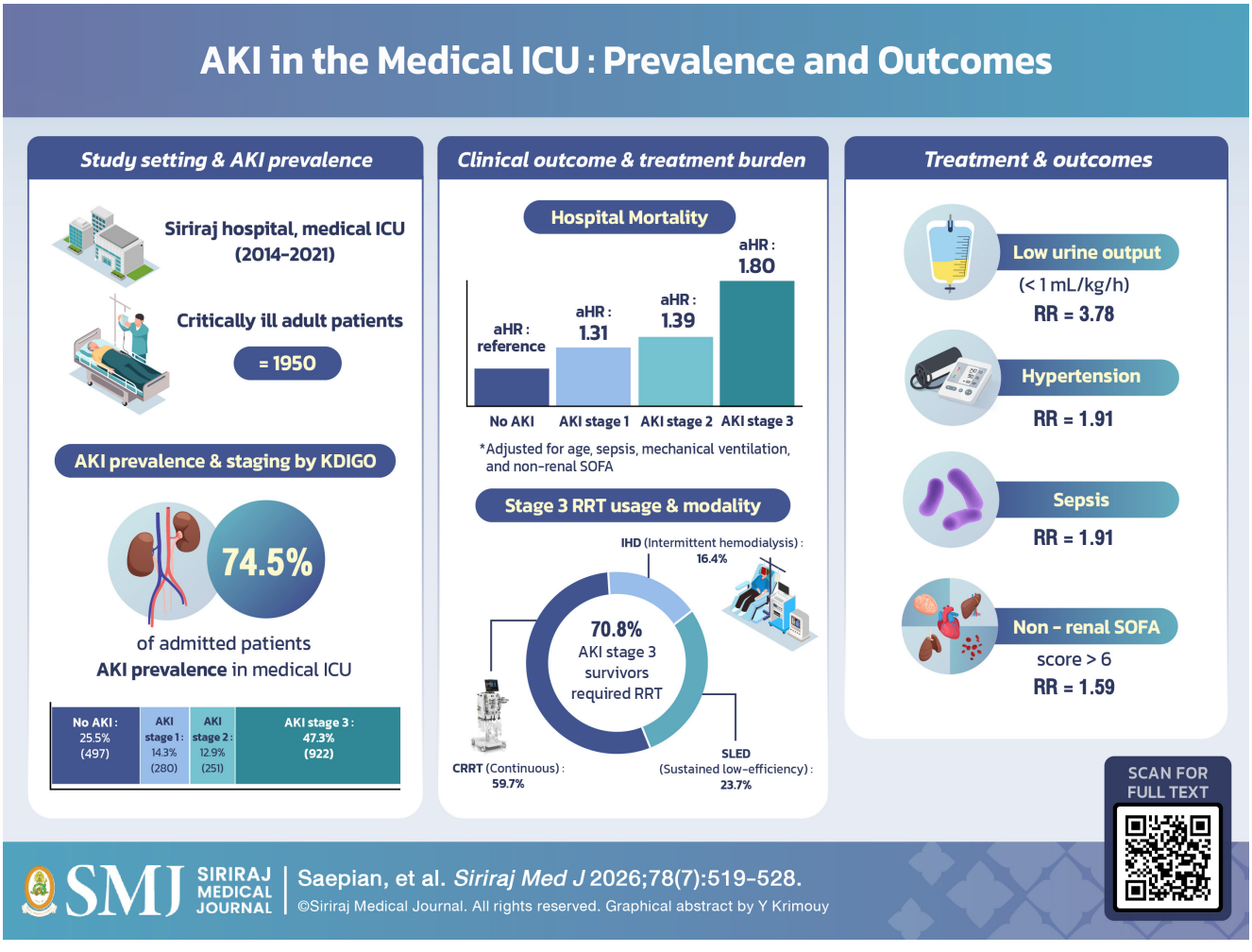
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Clinical Characteristics, Treatments, and Outcomes of Acute Kidney Injury in Critically Ill Patients at Siriraj Hospital

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ABSTRACT

Objective: This study aimed to investigate the prevalence, clinical outcomes, and predictive factors of AKI among intensive care unit (ICU) patients at Siriraj Hospital.

Materials and Methods: We conducted a single-center retrospective study of ICU patients admitted between January 2014 and December 2021. The primary outcome was hospital mortality following ICU admission.

Results: Of the 1,950 patients included, 1,453 (74.5%) developed AKI, with 14.3% classified as stage 1, 12.9% as stage 2, and 47.3% as stage 3. The hospital mortality rate was significantly higher in the AKI group compared to the non-AKI group (49.6% vs. 17.9%, $p < 0.01$). The highest mortality rate was observed in patients with stage 3 AKI (60.6%, $p < 0.001$). Additionally, patients with AKI had longer ICU stays (32 vs. 22 days; $p < 0.001$) and a higher prevalence of nosocomial infections (39.8% vs. 26.6%; $p < 0.001$). Multivariable analysis identified a Non-renal Sequential Organ Failure Assessment (SOFA) score > 6, urine output <1 ml/kg/h, vasopressor use, and hypertension as factors associated with AKI.

Conclusion: AKI was relatively common among critically ill patients in this cohort, and its presence and severity were associated with worse clinical outcomes. High SOFA scores, low urine output, vasopressor use, and hypertension were identified as factors associated with AKI.

Keywords: Acute kidney injury; mortality; intensive care unit; critically ill; Thailand (Siriraj Med J 2026;78(7):519-528)

INTRODUCTION

Acute kidney injury (AKI) is a common and potentially life-threatening complication among critically ill patients. It significantly impacts both short-term morbidity and mortality, as well as long-term adverse outcomes, including reduced quality of life and increased risk of progression to chronic kidney disease (CKD) or end-stage renal disease (ESRD).[1-3] Beyond long-term morbidity and reduced quality of life, the immediate prognosis remains highly critical for the most severe cases. Specifically, patients with Stage 3 AKI requiring acute renal replacement therapy (RRT) represent an exceptionally high-risk cohort with a drastically elevated mortality rate.[32]

The incidence of AKI in this population is substantial but varies across studies[2-5,17], largely due to differences in patient populations, diagnostic criteria and study methodologies.[3,6,16] While some studies report AKI incidence rates exceeding 30% in intensive care units (ICUs)[3,5,7], others report significantly lower rates[1,8,17], emphasizing the influence of study design and patient selection.

In Thailand, the epidemiology of AKI in critically ill patients remains poorly understood. A previous study at Siriraj Hospital's ICU, which used the RIFLE criteria, reported an AKI prevalence as high as 71%, with hospital mortality exceeding 35.7% among affected patients.[9] However, the introduction of Kidney Disease Improving Global Outcome (KDIGO), a newer diagnostic standard, has significantly altered the reported incidence of AKI.[10,11] Additionally, advancements in medical treatment have improved clinical outcomes of AKI.[12,13] Therefore, using earlier diagnostic criteria may not accurately reflect the current clinical landscape.

This study aims to apply the standardized KDIGO criteria to accurately evaluate the burden of AKI in critically ill patients. Specifically, the study investigates the prevalence, clinical outcomes, and predictive factors of AKI among ICU patients at Siriraj Hospital.

MATERIALS AND METHODS

Study design

This retrospective observational study was conducted at a single tertiary care center, Siriraj Hospital, in Bangkok, Thailand. The objective was to compare the mortality rates of patients with or without AKI who were admitted to the ICU between January 2014 and December 2021. The study was approved by the Medical Research Committee for Research Ethics of Siriraj Hospital, Mahidol University, Thailand (approval no. 438/2564).

Patients

Adult patients aged 18 years or older admitted to the medical ICU at Siriraj Hospital were included in this study. Patients were excluded if they met any of the following criteria: (a) ESRD requiring chronic dialysis; (b) ICU stay of less than 48 hours, regardless of cause (i.e., death or discharge); or (c) absence of serum creatinine measurements. For patients with multiple ICU admissions during the study period, only data from the first admission were analyzed.

Data collection

Data were extracted from the hospital's electronic web-based system, SiData+ Center, at Siriraj Hospital through retrospective chart review. Patients' data at admission included demographics, underlying diseases, hemodynamic parameters, Sequential Organ Failure Assessment (SOFA) score, laboratory investigations, fluid balance, and the use of vasopressors and mechanical ventilation. During hospitalization, additional data were collected, including the maximum serum creatinine level, etiology of AKI, development of sepsis or, hospital-acquired infections, initiation and initial modality of renal replacement therapy (RRT), and patient survival status on day 28 after ICU admission.

Definition

AKI was diagnosed and classified according to the KDIGO criteria[11], using the worst value of either serum creatinine or urine output. Baseline serum creatinine was defined using a hierarchical approach, with the lowest value recorded within three months prior to hospital admission, considered the baseline. If no prior creatinine data were available, the first serum creatinine measurement on the day of hospital admission was used. For urine output assessment, total urine output during the first 24 hours of ICU admission was evaluated. Hourly urine output was calculated based on the patient's actual body weight prior to admission. If actual body weight was unavailable, ideal body weight was used instead, calculated as height (cm) minus 110 for females and height (cm) minus 100 for males.

Outcomes

The primary outcome was in-hospital mortality following ICU admission, which was compared between patients with and without AKI, with AKI further stratified by stage. Secondary outcomes included 28-day mortality, ICU and hospital length of stay, and the incidence of hospital-acquired infections. To identify independent risk factors for AKI development, we analyzed data on patient characteristics, SOFA score, urine output, nosocomial infections, vasopressor use, and laboratory results.

Statistical Analysis

Categorical variables were summarized as frequencies and percentages, while non-normally distributed continuous variables were reported as medians with interquartile ranges (IQRs). Categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate. Continuous variables were analyzed using the independent t-test for normally distributed data or the Mann-Whitney U test for non-normally distributed data. Patients with missing data were excluded from the assessment. Kaplan-Meier survival curves were used to assess 28-day mortality, and differences across AKI stages were evaluated using the log-rank test. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated. Time zero for survival analysis was defined as the date of ICU admission, and patients were followed for 28-day and in-hospital mortality outcomes. Multivariate logistic regression analysis was conducted to identify independent risk factors for AKI. All statistical analyses were performed using R software version 4.4.2 (R Foundation, Vienna, Austria), except for multivariate logistic regression analysis, which was conducted using SPSS Statistics version 18 (IBM Corporation, New York, USA). A p-value of <0.05 was considered statistically significant.

RESULTS

Patient Characteristics

From January 2014 to December 2021, a total of 2,685 patients were admitted to the medical ICU at Siriraj Hospital. After excluding 735 patients, the final cohort comprised 1,950 patients. The study flow diagram is shown in Fig 1. The mean patient age was 63 years, and 49% were female. The median body mass index (BMI) was 23.2 kg/m^2. The most common morbidities were hypertension (55.8%), followed by diabetes (35.2%), malignancy (22.9%), coronary artery disease (16.6%), congestive heart failure (14.1%), and chronic liver disease (10.3%). CKD stages 3–5 were present in 41.3% of patients. The mean baseline eGFR was 68.49 mL/min, and the median 24-hour urine output was 0.89 mL/kg/h. Sepsis was diagnosed in 70.3% of patients; 83.4% required mechanical ventilation, and 61.4% received norepinephrine. A severe illness (Non-renal SOFA score >6) was observed in 56.5% of cases. Baseline characteristics and laboratory parameters at ICU admission are presented in Table 1 and Table S1. The mean hemoglobin level was 9.6 g/dL, and platelet counts were within the normal range. The mean arterial blood gas pH was 7.39, and the mean partial pressure of arterial oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) ratio (PaO_2/FiO_2 ratio, or P/F ratio) was 239. The mean lactate level was 3.1 mmol/L, and bilirubin levels were within normal range (0.88 mg/dL).

AKI Prevalence and Clinical characteristics

AKI occurred in 1,453 patients (74.5%). Of these, 47.3% had stage 3, 12.9% had stage 2, and 14.3% had stage 1. There were no significant differences in age, sex,

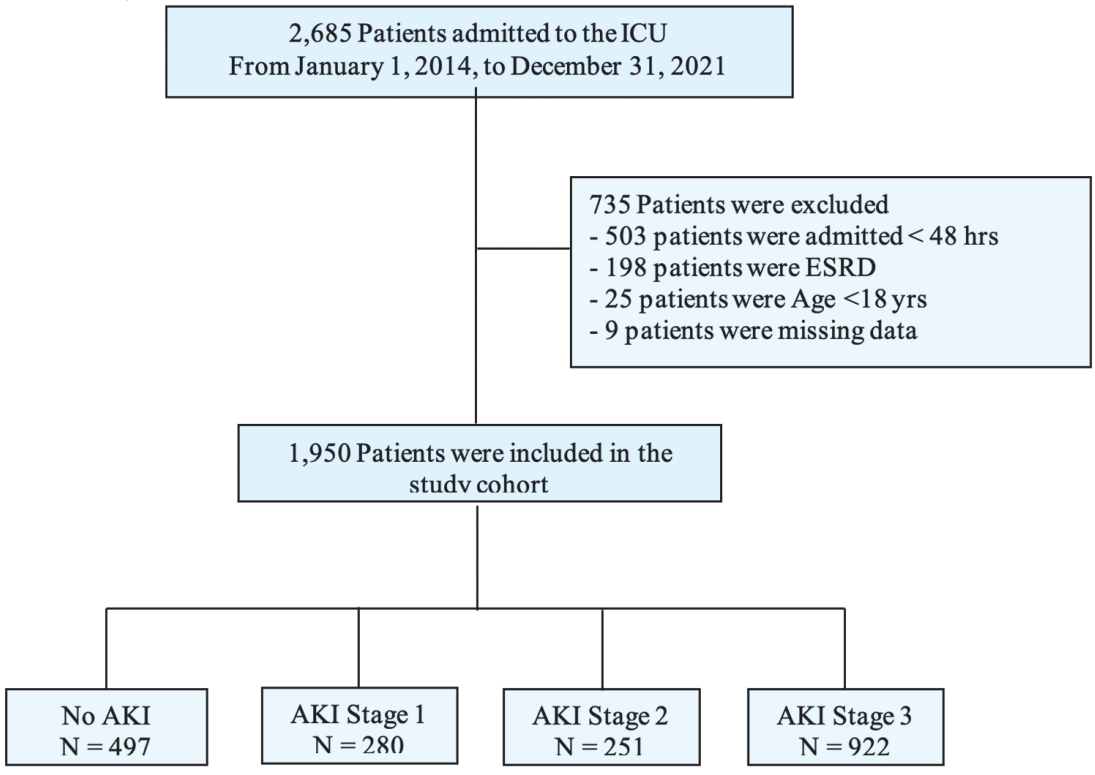


Fig 1. The study flow diagram.

TABLE 1. Baseline Characteristic of Patients in Study Cohort Stratified by Acute Kidney Injury During ICU Admission

Variable	No AKI (n = 497)	AKI Stage 1 (n = 280)	AKI Stage 2 (n = 251)	AKI Stage 3 (n = 922)	p-value
Age, years	59.0 [42.0, 72.0]	66.5 [55.0, 78.3]	66.0 [51.5, 77.0]	64.0 [50.0, 75.0]	< 0.001
Gender (female), %	270 (54.3)	138 (49.3)	117 (46.6)	431 (46.7)	0.044
Weight, kg	57.00 [48.0, 68.4]	58.8 [50.0, 68.0]	61.7 [53.0, 71.0]	61.1 [52.5, 71.9]	< 0.001
BMI, kg/m^2	22.40 [19.1, 25.3]	22.6 [19.6, 25.5]	23.2 [20.5, 26.4]	23.6 [20.5, 26.4]	< 0.001
Co-morbidities					
Diabetes, %	146 (29.4)	111 (39.6)	86 (34.3)	344 (37.3)	0.008
Hypertension, %	212 (42.7)	181 (64.6)	142 (56.6)	553 (60.0)	< 0.001
Chronic liver disease, %	26 (5.2)	22 (7.9)	25 (10.0)	128 (13.9)	< 0.001
Malignancy, %	100 (20.1)	57 (20.4)	69 (27.5)	220 (23.9)	0.083
Coronary artery disease, %	57 (11.5)	59 (21.1)	46 (18.3)	162 (17.6)	0.002
Congestive Heart failure, %	49 (9.9)	48 (17.1)	40 (15.9)	137 (14.9)	0.014
Chronic kidney disease stage 3-5, %	150 (30.2)	128 (45.7)	81 (32.3)	447 (48.5)	< 0.001

TABLE 1. Baseline Characteristic of Patients in Study Cohort Stratified by Acute Kidney Injury During ICU Admission (Continued)

Variable	No AKI (n = 497)	AKI Stage 1 (n = 280)	AKI Stage 2 (n = 251)	AKI Stage 3 (n = 922)	p-value
SOFA Score on ICU admission	6 [4, 8]	7 [5, 9]	8 [5, 10]	10 [8, 12]	< 0.001
Mechanical Ventilator, %	347 (70.0)	213 (76.1)	205 (81.7)	861 (93.4)	< 0.001
Severe sepsis/ septic shock, %	273 (54.9)	190 (67.9)	185 (73.7)	722 (78.3)	< 0.001
MAP, mmHg	69.00 [62.00, 80.00]	68.50 [61.00, 77.00]	69.00 [60.00, 78.00]	65.00 [56.00, 77.00]	< 0.001
Received Norepinephrine, %	246 (49.5)	153 (54.6)	161 (64.1)	637 (69.2)	< 0.001
Dose of norepinephrine, mcg/kg/min	0.09 [0.05, 0.15]	0.09 [0.04, 0.15]	0.08 [0.04, 0.16]	0.11 [0.06, 0.18]	0.001
Baseline creatinine, mg/dL	0.89 [0.65, 1.23]	1.07 [0.79, 1.47]	0.91 [0.72, 1.25]	1.09 [0.82, 1.84]	< 0.001
Baseline eGFR, ml/min	80.08 [53.64, 103.18]	63.09 [43.11, 84.53]	74.70 [54.44, 96.38]	62.05 [33.34, 87.77]	< 0.001
Urine Output in 24 h, ml/kg/hr	1.42 [0.91, 2.21]	1.24 [0.87, 1.94]	0.84 [0.46, 1.53]	0.43 [0.15, 1.04]	< 0.001

Abbreviations: SOFA, Sequential organ failure assessment; MAP, Mean arterial pressure

weight, or BMI between patients with and without AKI. However, patients with AKI had significantly higher rates of hypertension, chronic liver disease, and CKD stages 3–5. They also showed higher SOFA scores, more frequent mechanical ventilation, higher rates of sepsis, and greater norepinephrine use. Compared with non-AKI patients, the AKI group had higher baseline creatinine and lactate levels, and lower 24-hour urine output and platelet counts (Table S1). The most common causes of AKI were sepsis (58.5%) and hypoperfusion (17.1%) (Table S4). Nosocomial infections were most prevalent in stage 3, with pulmonary infections accounting for 75.3% of cases. Between 2014 and 2021 (Table S5), the proportion of non-AKI patients remained relatively stable at approximately 10-15%.

Clinical Outcomes

Patients with AKI had significantly higher hospital (49.6% vs. 17.9%, $p < 0.001$), ICU (34.3% vs. 11.1%, $p < 0.001$), and 28-day mortality rates (38.3% vs. 13.5%, $p < 0.001$) compared to non-AKI patients (Table S2, Fig S1). Mortality rates increased with AKI severity, with stage 3 AKI showing the highest rates (hospital: 60.6%, ICU: 43.9%, 28-day: 46.3%; $p < 0.001$; Table 2). Kaplan–Meier survival curves illustrating 28-day mortality by AKI stage with adjusted HR are shown in Fig 2.

ICU Interventions and RRT Modalities

Among survivors with stage 3 AKI, 70.8% required RRT. Initial RRT modalities included continuous renal replacement therapy (CRRT, 59.7%), sustained low-efficiency dialysis (SLED, 23.7%), hemodialysis (HD, 16.4%), with peritoneal dialysis (PD) use in 0.2% of cases. Among these survivors, 38.7% remained on dialysis on day 28, and 29% were dialysis-dependent at hospital discharge (Table 2).

Factors associated with AKI Development

The demographic characteristics of patients who developed AKI were comparable to those without AKI (Table S3). Univariate analysis was conducted to identify potential risk factors, including age, sex, non-renal SOFA

TABLE 2. Clinical outcomes stratified by stage of acute kidney injury.

Variable	No AKI (n = 497)	AKI Stage 1 (n = 280)	AKI Stage 2 (n = 251)	AKI Stage 3 (n = 922)	p-value
Hospital Morality, %	89 (17.9)	79 (28.2)	83 (33.1)	559 (60.6)	< 0.001
ICU Mortality, %	55 (11.1)	42 (15.0)	52 (20.7)	405 (43.9)	< 0.001
28-Day mortality from ICU admission, %	67 (13.5)	61 (21.8)	68 (27.1)	427 (46.3)	< 0.001
Creatinine on day 28	0.71 [0.52, 0.85]	0.97 [0.69, 1.33]	1.00 [0.69, 1.42]	1.62 [0.95, 2.92]	< 0.001
Hospital LOS, days	17.0 [10.0, 33.0]	21.00 [11.0, 43.0]	26.00 [14.0, 42.0]	25.00 [14.0, 45.0]	< 0.001
ICU LOS, days	6.0 [4.0, 12.0]	7.00 [4.0, 13.0]	9.00 [5.0, 15.5]	11.00 [6.0, 20.0]	< 0.001
RRT				653 (70.8)	
First RRT modality					
- CRRT				390 (59.7)	
- SLED				155 (23.7)	
- HD				107 (16.4)	
- PD				1 (0.2)	
RRT dependence day 28 among survival				127 (38.7)	
RRT dependence hospital discharge among survival				74 (29.0)	
Nosocomial infection	130 (26.2)	90 (32.1)	95 (37.8)	393 (42.6)	< 0.001
Source of nosocomial infection					0.056
Gastrointestinal tract	3 (2.3)	8 (8.7)	6 (6.5)	31 (7.9)	
Genitourinary	12 (9.1)	13 (14.1)	5 (5.4)	17 (4.3)	
Respiratory system	109 (82.6)	65 (70.7)	73 (78.5)	297 (75.6)	
Skin and soft tissue	1 (0.8)	2 (2.2)	2 (2.2)	15 (3.8)	
Others	7 (5.3)	4 (4.3)	7 (7.5)	33 (8.4)	

Abbreviations: LOS, Length of stay; RRT, Renal replacement therapy; CRRT, Continuous renal replacement therapy; SLED, Sustained low-efficiency dialysis; HD, Hemodialysis; PD, Peritoneal dialysis

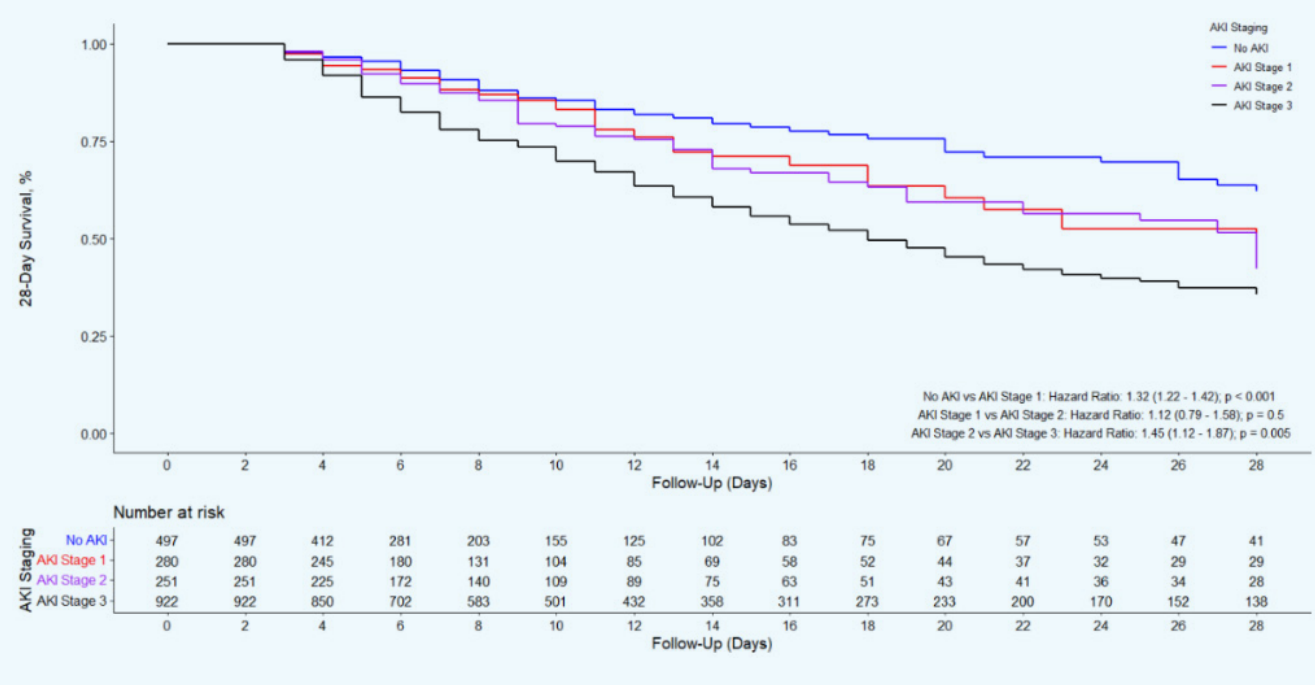


Fig 2. *Kaplan–Meier estimates of 28-day survival.* The curves depict survival probabilities within 28 days of ICU admission, stratified by the stage of acute kidney injury (AKI). The adjusted Hazard Ratios (aHR) were calculated using a multivariable Cox proportional hazards model, adjusting for baseline age, presence of sepsis, mechanical ventilation requirements, and the non-renal SOFA score to ensure independent associations.

score, comorbidities, sepsis, nosocomial infection, urine output, vasopressor use, and mechanical ventilation requirements. In multivariate analysis, a urine output <1 mL/kg/h (RR = 3.78, p < 0.001) emerged as the strongest independent factor associated with AKI, followed by a non-renal SOFA score >6 (RR = 1.59, p < 0.001). Sepsis was also significantly associated with AKI development (RR = 1.91, p = 0.001). Among comorbidities, hypertension was the only independent predictor (RR = 1.91, p < 0.001). Interestingly, while adrenaline and dopamine use were associated with an increased risk of AKI in univariate analysis, multivariate analysis showed a reduced risk (RR = 0.43, p < 0.001 and RR = 0.43, p = 0.03, respectively).

DISCUSSION

Key findings

In this cohort study of 1,950 critically ill patients admitted to the medical ICU at Siriraj Hospital between 2014 and 2021, AKI occurred in 74.5% of patients, with a high proportion developing stage 3 AKI. The presence of AKI and its severity were associated with a significantly higher rate of hospital, ICU, and 28-day mortality compared to non-AKI patients, with mortality increasing alongside AKI severity. Sepsis and hypoperfusion were identified as the leading causes of AKI. Among survivors with AKI stage 3, over 70% required RRT. Multivariate analysis identified a high non-renal SOFA score (>6), low urine output (<1 mL/kg/h), sepsis, and hypertension as independent predictors for the development of AKI.

Comparison with previous studies

The prevalence of AKI in this cohort was notably higher than global averages.[4,5] This finding is likely due to the high severity of illness in patients at our tertiary care center, where 56.5% had non-renal SOFA scores greater than 6. However, similar AKI rates were reported by a previous study at the same institution a decade earlier[9], suggesting that despite advances in medical treatment, AKI remains a persistent complication in critically ill patients.[16,17]

The high burden of comorbidities observed in this cohort, including hypertension (55.8%) and diabetes mellitus (35.2%), aligns with known AKI risk factors.[15,24] Additionally, 41.3% of patients had pre-existing CKD stages 3–5.[18] Sepsis, identified in 70.3% of patients, was the leading cause of AKI, responsible for 58.5% of cases, consistent with previous reports on sepsis-induced AKI.[19,20] Our findings reinforce that AKI significantly worsens clinical outcomes linked to hospital, ICU, and 28-day mortality, with mortality rates rising progressively with

AKI severity. The highest mortality rate (60.6%) was observed in patients with stage 3 AKI, which is consistent with previous studies.[1–3,9,14] This underscores the critical need for early detection and aggressive management of AKI in critically ill patients.

A high rate of RRT usage was observed among patients with stage 3 AKI, with 70.8% of survivors requiring dialysis. The majority of these patients received CRRT, which is often favored for hemodynamically unstable patients.[21] These results indicate that, despite advancements in critical care, a significant proportion of patients with severe AKI still require dialysis, highlighting the substantial renal burden in this population. Furthermore, a notable proportion of stage 3 AKI survivors experienced persistent renal dysfunction, with 38.7% remaining dialysis-dependent at day 28 and 29% at hospital discharge. This prolonged impairment may significantly affect long-term outcomes and quality of life.[22]

Several significant independent factors associated with AKI were identified through multivariate analysis. A non-renal SOFA scores greater than 6 emerged as the factor associated with AKI. As a well-established measure of organ dysfunction, higher SOFA scores correlate with increased risk of multi-organ failure and, in this study, significantly predicted AKI development, reinforcing its prognostic value in ICU settings.[24] Reduced urine output (<1 mL/kg/h) also strongly predicted AKI, underscoring the importance of close monitoring as an early indicator of renal dysfunction.[25] Sepsis was another major factor significantly associated with AKI development. The strong link between sepsis and AKI is well-documented, with sepsis-associated AKI contributing substantially to renal dysfunction.[26,27] These results highlight the need for early identification and aggressive management of sepsis to prevent or mitigate AKI in critically ill patients. Interestingly, our multivariable analysis found that vasopressor use (adrenaline and dopamine) was associated with a reduced risk of AKI, a finding that may reflect the complex hemodynamic effects of these agents. While vasopressors improve perfusion by managing hypotension[28], they also carry potential nephrotoxic risks. In this cohort, vasopressor use may have enhanced renal perfusion and mitigated AKI risk in some patients. However, this finding contrasts with several meta-analyses that have concluded that 'renal-dose' dopamine does not prevent or ameliorate AKI in critically ill patients.[29,30]

Strengths and limitations

The study's strengths include its large retrospective cohort of over 2,000 patients and its use of the KDIGO guidelines, which incorporate both creatinine and urine output criteria for a more precise definition of AKI. This makes our findings robust and more relevant to current clinical practice.

The study has several limitations. First, as a single-center study conducted at a tertiary hospital, patient characteristics and therapeutic approaches may differ from those in general hospitals across Thailand, which could limit the generalizability of the findings. Nevertheless, the study highlights the significant impact of AKI on patient outcomes. Second, the retrospective design relies on previously recorded data, which may be incomplete and subject to confounding factors that could introduce bias. Despite this, the study represents one of the larger ICU cohorts reported in Thailand. Third, in some patients, the absence of serum creatinine measurements from the preceding three months necessitated the assumption that day-one serum creatinine represented baseline levels, potentially affecting the accuracy of AKI diagnosis and staging. However, the use of urine output criteria in the methodology likely enhanced early and precise identification of AKI. Fourth, the exclusion of patients with an ICU stay of less than 48 hours may have led to an underestimation of the true prevalence and mortality of AKI, as it removes patients with the highest severity of illness or those with a rapid recovery. However, this approach allowed for a more precise interpretation of outcomes for patients who survived beyond the initial period of instability. Fifth, the exclusion of patients with missing data could have introduced selection bias and affected the representativeness of the cohort. Finally, because this was an observational study, it cannot establish a causal relationship between the identified factors associated with AKI development. For example, the finding that vasopressor use was associated with a reduced risk of AKI may be influenced by complex and unmeasured confounding factors. Moreover, we acknowledge that the high prevalence of AKI (74.5%) in our cohort may lead to an overestimation of the associations reported in our regression model.

CONCLUSION

AKI remains a significant challenge in Thai ICUs, with a high incidence and a major impact on patient outcomes. This study identified high non-renal SOFA scores (>6), reduced urine output (< 1 ml/kg/h), vasopressor use, and hypertension as key independent risk factors.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its supplementary-materials files. Further enquiries can be directed to the corresponding author.

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DECLARATIONS

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The authors did not receive any research funding.

Conflict of Interest

The authors declare no potential conflicts of interest.

Registration Number of Clinical Trial

None.

Author Contributions

Conceptualization and methodology, T.N. and D.S. ; Investigation, all authors. ; Formal analysis, T.N. and D.S.; Visualization and writing – original draft, T.N. and D.S. ; Writing – review and editing, T.N. and D.S. ; Supervision, T.N. All authors have read and agreed to the final version of the manuscript.

Use of Artificial Intelligence

None.

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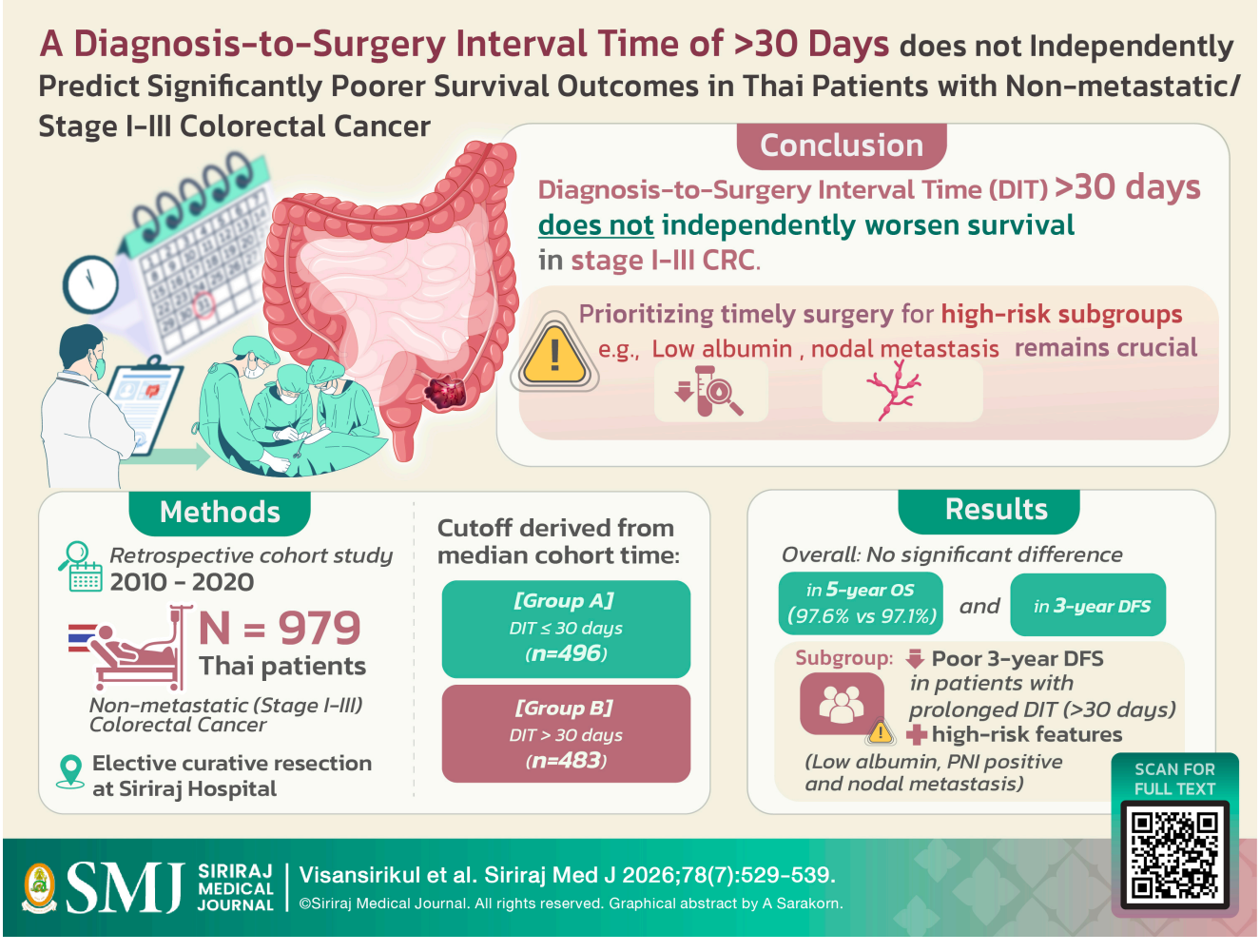
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A Diagnosis-to-Surgery Interval Time of >30 Days Does Not Independently Predict Significantly Poorer Survival Outcomes in Thai Patients with Non-metastatic/stage I-III Colorectal Cancer

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ABSTRACT

Objective: To identify the cutoff value for the optimal number of days to surgery, and to investigate the independent association between the diagnosis-to-surgery interval time (DIT) and survival outcome in Thai patients with non-metastatic/stage I-III colorectal cancer.

Materials and Methods: A chart review of patients diagnosed with and operated upon for stage non-metastatic/stage I-III colorectal cancer at Siriraj Hospital (Bangkok, Thailand) during January 2010-December 2020 was conducted. The primary outcome was the survival rate compared between two different DITs. Multivariate regression was used to identify independent predictors of decreased survival.

Results: A total of 979 patients (median age: 65 years) were included. Of those, 18.4% had stage I, 38.6% had stage II, and 43.0% had stage III disease. The calculated median DIT of 30 days (IQR: 19-47) was used as the cutoff value to categorize patients into the ≤30-days or >30-days group. The 5-year overall survival rate was 97.6% and 97.1% (p=0.536), and the median survival time was 59.4 and 58.9 months - both respectively. The 3-year disease-free survival (DFS) rate was 86.9% and 85.7%, respectively (p=0.523). The independent predictors of decreased 3-year DFS among all patients were lymph node metastasis (p=0.037), adjuvant chemotherapy (p=0.005), and lymphovascular invasion (p=0.051). Further multivariate analysis in the DIT >30-days group found low preoperative albumin level (p=0.035), perineural invasion (p=0.011), and adjuvant chemotherapy (p<0.001) to independently predict significantly poorer 3-year DFS.

Conclusions: A DIT >30 days was not found to independently predict significantly poorer survival outcomes in Thai patients with non-metastatic/stage I-III colorectal cancer.

Keywords: Diagnosis-to-surgery interval time >30 days; significantly poorer survival outcomes; Thai patients; non-metastatic/stage I-III colorectal cancer (Siriraj Med J 2026;78(7):529-539)

INTRODUCTION

Colorectal cancer (CRC) is currently ranked as the third most prevalent cancer in Thai men, and the fourth most prevalent cancer in Thai women, based on data from the Thailand National Cancer Institute covering the years 2013 to 2015. The incidence of CRC resulted in 17,534 newly diagnosed cases, comprising 10.3% of all newly diagnosed cancer cases during the same period. The incidence rate of CRC among Thai men was estimated to be 16.2 new cases per 100,000 Thai men, and the incidence rate of CRC among Thai women was estimated to be 11.2 new cases per 100,000 Thai women.[1]

The primary treatment for CRC is surgical intervention[2], and delays in surgical intervention can lead to disease progression. Factors reported to be associated with delayed surgery include low educational attainment, small tumor size, and asymptomatic presentation at diagnosis.[3] In Thailand, more than 25% of CRC patients experience surgical delays exceeding one month despite national guidelines recommending surgery within four weeks following clinical or radiological staging. This recommendation is part of the Thailand Ministry of Public Health's Cancer Service Plan, which sets a 28-day benchmark as a key performance indicator for timely access to care. For our analysis, the 30-day cutoff was determined post hoc based on the median diagnosis-to-surgery interval time (DIT) of our patient cohort. This data-driven threshold was utilized to ensure a balanced statistical comparison, while also holding clinical significance as it closely aligns with the 28-day national standard.[4]

The relationship between the diagnosis-to-surgery interval time (DIT) and survival rates has yielded inconclusive findings in previous studies. While some studies have failed to establish a correlation between time and survival rates[5-11], others have identified a negative correlation between longer wait times and lower survival rates.[12,13] Moreover, a few studies have reported a U-shaped relationship between the duration and survival rates.[14-16] However, no studies on this topic have been conducted in Thailand.

This study aims to examine the factors affecting DIT and its impact on survival rates. The findings of this study can be applied to treatment planning and serve as a valuable source of information to enhance the healthcare system.

MATERIALS AND METHODS

This retrospective cohort study included adult patients with stage I–III CRC who underwent elective surgery at Siriraj Hospital, Thailand, from January 2010 to December 2020. DIT was calculated from the date the

pathological report was issued to the date of definitive surgery. This specific point was chosen as it reflects the practical onset of definitive surgical decision-making and scheduling. We excluded patients with a second primary cancer, emergency conditions (e.g., bowel obstruction or perforation), or who received neoadjuvant chemoradiation, or had tumors in the middle or lower rectum (≤10 cm from the anal verge). Emergency cases were excluded because they typically undergo urgent surgery, have poorer prognosis, and shorter DITs, which could bias survival estimates in the short DIT group. Middle and lower rectal tumors were excluded due to the high likelihood of neoadjuvant therapy, which could confound the impact of DIT.[2] To minimize confounding and improve comparability, we included only patients with nonmetastatic colon and upper rectal cancer. The data employed in this research were extracted from the SIIT Enterprise patient database, the Ecliar laboratory test result database, and the E-portfolio surgical database. The study was approved by Siriraj Institutional Review Board, SIRB Protocol No. 058/2564 (IRB3).

The primary outcome of this study was to demonstrate an association between the 30-day cut-off DIT and survival for non-metastatic CRC. The secondary outcome was to identify risk factors associated with disease free survival for non-metastatic CRC.

A descriptive analysis using either mean and standard deviation or median and range based on the distribution of data. The study reported the 5-year overall survival (OS) rate and 3-year disease-free survival (DFS) rate, the Kaplan-Meier method was used. The log-rank test was used to compare the survival time of patients who underwent surgery for CRC within less than 30 days after diagnosis with those who underwent surgery after 30 days. Simple Cox regression analysis was used to explore the association with various factors such as comorbidities, cancer stage, cancer location, and surgical method. Multiple Cox regression analysis was conducted to adjust for significant independent factors from the analysis of simple Cox regression and survival time. Adjusted hazard ratios (HRs) were calculated to signify the magnitude and direction of the relationship between independent factors and survival time. Data was recorded and analyzed using IBM SPSS Statistics 21.0. with a p-value < 0.05 considered statistically significant for all analyses.

RESULTS

A total of 979 patients (526 male, 53.7%) were included with a median age of 65 (IQR 57-74). Median DIT was 30 days (IQR 19-47). The DIT for non-metastatic CRC in this study were divided into two groups: ≤ 30 days and > 30 days. Four hundred ninety-six patients (50.7%) patients received surgery within 30 days after diagnosis. Demographics of both groups were displayed in Table 1. In DIT within 30 days group, age, Charlson Comorbidity Index (CCI), American Society of Anesthesiologists (ASA) Classification and depth of invasion were significantly higher than another group.

The 5-year OS was 96.1% and 3-year DFS was 84.6%. Among patients who underwent surgery within 30 days of diagnosis, the 5-year OS was 97.6%, compared to 97.1% in those with DIT >30 days. Similarly, the 3-year DFS was 86.9% in the ≤30 days group and 85.7% in the >30 days group, respectively. Delayed DIT > 30 days was not associated with 5-year OS (p value 0.536) and 3-year DFS (p value 0.523). The survival curves were demonstrated in Fig 1 and 2.

Risk factors of 3-year DFS in non-metastatic CRC were displayed in Table 2. The independent risk factors were higher preoperative carcinoembryonic antigen (CEA) level (HR 2.206; 95%CI 1.500-3.243), lower preoperative albumin level (HR 0.662; 95%CI 0.484-0.906), lymph node metastasis (HR 3.492; 95%CI 2.418-5.043), presence of perineural invasion (PNI) (HR 2.597; 95%CI 1.845-3.656), presence of lymphovascular invasion (LVI) (HR 2.144; 95%CI 1.504-3.055) and received adjuvant chemotherapy (HR 6.601; 95%CI 3.969-10.980), which serves as a surrogate marker for high-risk disease (Stage II/III). In addition, lymph node metastasis and received adjuvant chemotherapy were independent factors of 3-year DFS.

In the subgroup analysis of patients with a DIT within 30 days, clinical parameters were significantly associated with a 3-year DFS, as displayed in Table 3. Notably, higher preoperative CEA levels (HR 2.333; 95%CI 1.327-4.103), lymph node metastasis (HR 2.411; 95%CI 1.450-4.008), the presence of PNI (HR 1.809; 95%CI 1.102-2.971), the presence of LVI (HR 2.387; 95%CI 1.438-3.962) and receiving adjuvant chemotherapy (HR 4.585; 95%CI 2.268-9.269) were identified as dependent factors of the 3-year DFS. However, multivariate analysis revealed that only higher preoperative CEA levels (HR 2.146; 95%CI 1.218-3.780) and receiving adjuvant chemotherapy (HR 3.825; 95%CI 1.863-7.855) remained as independent factors.

In another group of patients with a DIT more than 30 days, clinical factors were associated with 3-year DFS, as displayed in Table 4. Specifically, higher preoperative CEA levels, lower preoperative albumin levels, laparoscopic surgery, lymph node metastasis, the presence of PNI, the presence of LVI, and receiving adjuvant chemotherapy were identified as dependent factors. However, multivariate

TABLE 1. Patient demographic and clinical characteristics among all patients, and compared between the DIT ≤30 days and >30 days groups.

Patient characteristics	Overall patients (n=979)	DIT ≤30 days (n=496)	DIT >30 days (n=483)	*p-value*
Age (years), median [IQR]	65 [57-74]	65 [56-74]	67 [58-75]	***0.003***
Male sex, n (%)	526 (53.7%)	270 (54.4%)	256 (53.0%)	0.700
Body mass index, median [IQR]	23.4 [20.6-25.6]	23.2 [20.5-25.5]	23.6 [20.8-25.8]	0.159
Charleson Comorbidity Index, mean±SD	5.85±1.953	5.65±1.914	6.05±1.974	***0.002***
ASA classification, n (%)				***0.001***
Class I	242 (24.7%)	147 (29.6%)	95 (19.7%)	
Class II	507 (51.8%)	247 (49.8%)	260 (53.8%)	
Class III	230 (23.5%)	102 (20.6%)	128 (26.5%)	
Preoperative CEA level (ng/mL), median [IQR]	3.91 [2.21-8.69	3.91 [2.12-9.22]	3.87 [2.24-8.28]	0.814
Preoperative albumin level (g/dL), median [IQR]	4.1 [3.8-4.4]	4.1 [3.8-4.4]	4.1 [3.8-4.3]	0.236
DIT (days), median [IQR]	30 [19-47]			
Type of surgery, n (%)				
Open	482 (49.2%)	242 (48.8%)	240 (49.7%)	0.828
Laparoscopic	497 (50.8%)	254 (51.2%)	243 (50.3%)	
Conversion, n (%)	20 (4.0%)	10 (3.9%)	10 (4.1%)	1.000
Depth of invasion, n (%)				***<0.001***
T1	102 (10.4%)	12 (4.7%)	47 (19.3%)	
T2	146 (14.9%)	38 (15.0%)	44 (18.1%)	
T3	615 (62.8%)	176 (69.3%)	135 (55.6%)	
T4	116 (11.8%)	28 (11.0%)	17 (7.0%)	
Lymph nodes collected (n), median [IQR]	20 [15-28]	19 [15-26]	19 [15-29]	***0.047***
Lymph node status, n (%)				0.286
0	572 (58.5%)	142 (55.9%)	151 (62.1%)	
1-3	283 (28.9%)	84 (33.1%)	67 (27.6%)	
≥4	123 (12.6%)	28 (11.0%)	25 (10.3%)	
Grade, n (%)				0.365
Well-differentiated	72 (7.4%)	14 (5.5%)	25 (10.3%)	
Moderately-differentiated	852 (87.1%)	226 (89.0%)	208 (86.0%)	
Poorly-differentiated	15 (1.5%)	2 (0.8%)	1 (0.4%)	
Undifferentiated/anaplastic	39 (4.0%)	12 (4.7%)	8 (3.3%)	
Presence of PNI, n (%)	260 (26.9%)	72 (28.3%)	52 (21.4%)	0.253
Presence of LVI, n (%)	220 (22.6%)	59 (23.2%)	51 (21.0%)	0.700
Positive margin, n (%)	15 (1.5%)	4 (1.6%)	5 (2.1%)	0.958

TABLE 1. Patient demographic and clinical characteristics among all patients, and compared between the DIT ≤30 days and >30 days groups. (Continued)

Patient characteristics	Overall patients (n=979)	DIT ≤30 days (n=496)	DIT >30 days (n=483)	*p-value*
Location, n (%)				0.491
Right-side colon	228 (23.3%)	60 (23.6%)	57 (23.5%)	
Left-side colon	127 (13.0%)	33 (13.0%)	31 (12.8%)	
Sigmoid colon	504 (51.5%)	136 (53.5%)	121 (49.8%)	
Upper rectum	95 (9.7%)	21 (8.3%)	28 (11.5%)	
Synchronous lesion	25 (2.5%)	4 (1.6%)	6 (2.5%)	
Adjuvant chemotherapy	519 (53.0%)	151 (59.4%)	114 (46.9%)	***<0.001***
AJCC stage, n (%)				***<0.001***
I	180 (18.4%)	33 (13.0%)	71 (29.2%)	
II	378 (38.6%)	108 (42.5%)	79 (32.5%)	
III	421 (43.0%)	113 (44.5%)	93 (38.3%)	

A *p*-value<0.05 indicates statistical significance

Abbreviations: AJCC, American Joint Committee on Cancer; ASA, American Society of Anesthesiologists; CEA, carcinoembryonic antigen; DIT, diagnosis-to-surgery interval time; g/dL, grams per deciliter; IQR, interquartile range; LVI, lymphovascular invasion; n, number; ng/mL, nanograms per milliliter; PNI, perineural invasion; *p*-value, probability value; SD, standard deviation; T, tumor

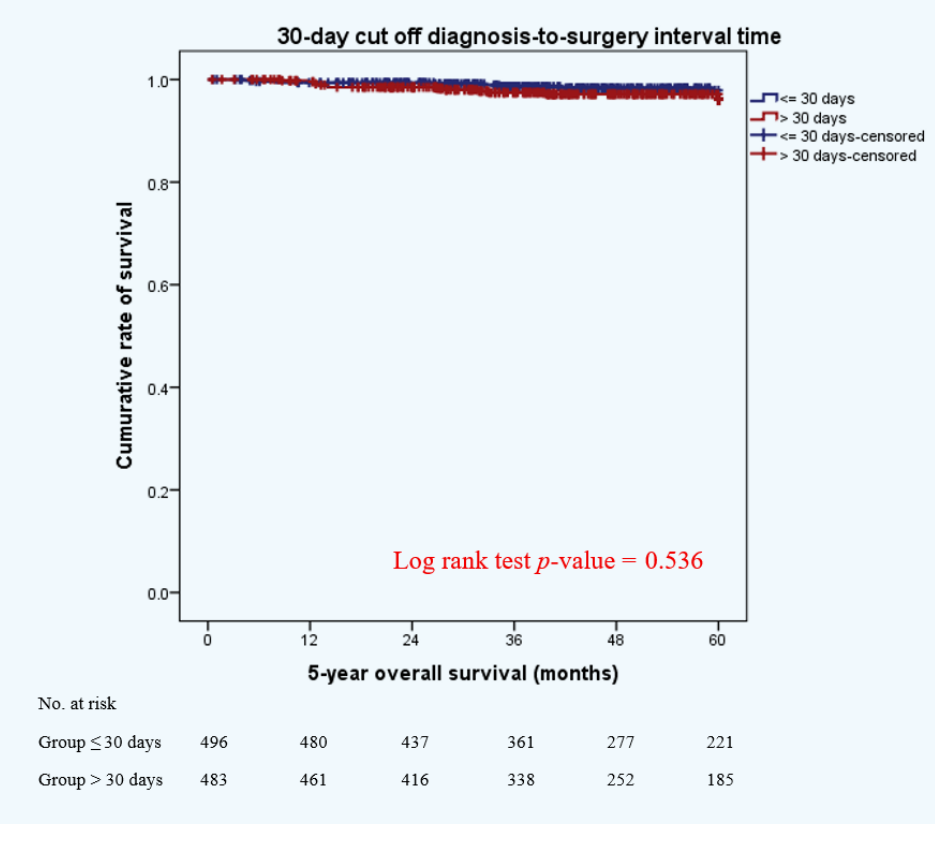


Fig 1. Kaplan-Meier survival analysis to determine the 5-year overall survival rate compared between the DIT ≤30-days group and the DIT >30-days group (p=0.536).

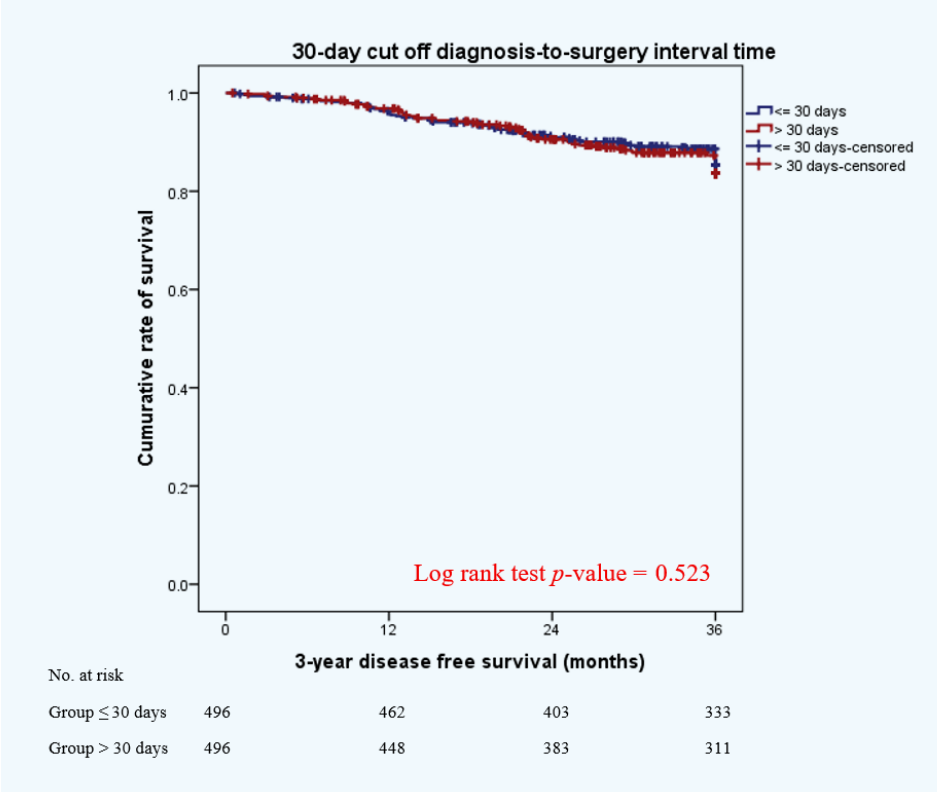


Fig 2. Kaplan-Meier survival analysis to determine the 3-year disease-free survival rate compared between the DIT ≤30-days group and the DIT >30-days group (p=0.523).

analysis revealed that only higher preoperative albumin levels (hazard ratio [HR]: 0.611; 95% confidence interval [CI]: 0.387-0.965) remained as an independent protective factor, while the presence of PNI (HR: 1.904; 95%CI: 1.160-3.124) and receiving adjuvant chemotherapy (HR: 5.444; 95%CI: 2.178-13.606) were the only independent risk factors.

DISCUSSION

This retrospective cohort study evaluated the prognostic impact of DIT on oncological outcomes in patients with non-metastatic CRC undergoing curative resection. Our analysis demonstrated favorable long-term survival outcomes with 5-year OS of 96.1% and 3-year DFS of 84.6%. Notably, DIT exceeding 30 days did not demonstrate a statistically significant association with either 5-year OS or 3-year DFS. Subgroup analysis identified several clinicopathological variables associated with impaired 3-year DFS in patients with prolonged DIT (>30 days), including hypoalbuminemia, nodal metastases, perineural invasion, and receipt of adjuvant chemotherapy. However, multivariate Cox regression analysis confirmed that DIT >30 days did not retain statistical significance as an independent predictor of survival outcomes, while hypoalbuminemia, perineural invasion, and adjuvant chemotherapy administration remained independent prognostic factors for 3-year DFS. Importantly, to prevent misinterpretation, it is crucial to note that adjuvant chemotherapy administration acts as a surrogate marker for high-risk disease characteristics—such as advanced stage (Stage II/III) or aggressive tumor biology—rather than being the underlying cause of decreased survival.

The absence of significant association between 30-day surgical delay and survival outcomes can be explained by established tumor biology principles and Gompertzian growth dynamics. Colorectal adenocarcinomas typically exhibit Gompertzian growth kinetics, characterized by exponential proliferation during early carcinogenesis followed by growth deceleration as tumor volume increases and nutrient supply becomes limiting.[17] Since DIT represents the interval following clinical detection, when tumors have already achieved substantial size and entered the plateau phase of growth, brief delays of 30 days are unlikely to significantly alter tumor burden or metastatic potential. This biological rationale supports our finding that moderate DIT thresholds may not independently influence long-term oncological outcomes in non-metastatic colorectal carcinoma.

Our findings are consistent with modeling studies that demonstrate the critical distinction between moderate and prolonged surgical delays. Sud et al. projected that

TABLE 2. Multivariate analysis for independent predictors of decreased 3-year DFS among all Thai non-metastatic colorectal cancer patients included in this study.

Factors	HR (95%CI)	*p*-value	aHR (95%CI)	*p*-value
Age	1.002 (0.990-1.019)	0.568		
Male sex	1.058 (0.753-1.488)	0.744		
Body mass index	0.977 (0.935-1.021)	0.300		
Charleson Comorbidity Index	1.024 (0.939-1.118)	0.588		
ASA classification				
Class I	**Reference**			
Class II	1.101 (0.713-1.699)	0.664		
Class III	1.362 (0.835-2.222)	0.215		
Preoperative CEA level >3.4	2.206 (1.500-3.243)	***<0.001***	1.164 (0.638-2.123)	0.621
Low preoperative albumin level	0.662 (0.484-0.906)	***0.010***	0.586 (0.321-1.070)	0.082
Delayed DIT >30 days	1.003 (0.999-1.007)	0.150		
Laparoscopic surgery	0.709 (0.504-0.999)	***0.049***	NA	NA
Conversion	2.658 (1.057-6.685)	***0.038***	1.804 (0.637-5.109)	0.267
Depth of invasion				
T1	**Reference**			
T2	NA	NA		
T3	NA	NA		
T4	NA	NA		
Lymph node metastasis	3.492 (2.418-5.043)	***<0.001***	2.252 (1.052-4.820)	***0.037***
Lymph node harvested <12 nodes	1.081 (0.550-2.127)	0.821		
Grade				
Well-differentiated	**Reference**			
Moderately-differentiated	2.203 (0.900-5.390)	0.084	0.554 (0.126-2.439)	0.435
Poorly-differentiated	NA	NA	NA	NA
Undifferentiated/anaplastic	3.953 (1.35-11.567)	***0.012***	0.702 (0.127-3.885)	0.685
Presence of PNI	2.597 (1.845-3.656)	***<0.001***	1.470 (0.826-2.615)	0.190
Presence of LVI	2.144 (1.504-3.055)	***<0.001***	1.754 (0.997-3.086)	***0.051***
Positive margin	1.065 (0.148-7.680)	0.950		
Location				
Right-side colon	**Reference**			
Left-side colon	1.386 (0.778-2.472)	0.268		
Sigmoid colon	1.281 (0.824-1.993)	0.271		
Upper rectum	0.958 (0.464-1.979)	0.907		
Synchronous lesion	1.535 (0.537-4.389)	0.424		
Adjuvant chemotherapy	6.601 (3.969-10.980)	***<0.001***	5.485 (1.690-17.804)	***0.005***

A *p*-value<0.05 indicates statistical significance

Abbreviations: 95%CI, 95% confidence interval; aHR, adjusted hazard ratio; ASA, American Society of Anesthesiologists; CEA, carcinoembryonic antigen; DFS, disease-free survival; DIT, diagnosis-to-surgery interval time; HR, hazard ratio; LVI, lymphovascular invasion; NA, not applicable/available; PNI, perineural invasion; *p*-value, probability value; T, tumor

TABLE 3. Multivariate analysis for independent predictors of decreased 3-year DFS in the DIT ≤30 days group.

Factors	HR (95%CI)	*p*-value	aHR (95%CI)	*p*-value
Age	1.002 (0.981-1.023)	0.872		
Male sex	1.061 (0.651-1.727)	0.813		
Body mass index	0.974 (0.916-1.036)	0.405		
Charleson Comorbidity Index	1.027 (0.903-1.168)	0.683		
ASA				
Class I	**Reference**			
Class II	1.212 (0.656-2.237)	0.540		
Class III	1.831 (0.923-3.634)	0.084		
Preoperative CEA level >3.4	2.333 (1.327-4.103)	***0.003***	2.146 (1.218-3.780)	***0.008***
Low preoperative albumin level	0.701 (0.433-1.137)	0.150		
Laparoscopic surgery	0.503 (0.520-1.378)	0.503		
Conversion	2.197 (0.518-9.320)	0.286		
Depth of invasion				
T1	**Reference**			
T2	NA	NA		
T3	NA	NA		
T4	NA	NA		
Lymph node metastasis	2.411 (1.450-4.008)	***0.001***	1.087 (0.607-1.946)	0.779
Lymph node harvested <12 nodes	0.688 (0.276-1.714)	0.422		
Grade				
Well-differentiated	**Reference**			
Moderately-differentiated	1.514 (0.474-4.836)	0.484		
Poorly-differentiated	NA	NA		
Undifferentiated/anaplastic	2.618 (0.625-10.955)	0.188		
Presence of PNI	1.809 (1.102-2.971)	***0.019***	1.143 (0.685-1.907)	0.608
Presence of LVI	2.387 (1.438-3.962)	***0.001***	1.707 (1.012-2.880)	***0.035***
Positive margin	1.065 (0.148-7.680)	0.950		
Location				
Right-side colon	**Reference**			
Left-side colon	1.376 (0.580-3.266)	0.469		
Sigmoid colon	1.636 (0.856-3.124)	0.136		
Upper rectum	0.737 (0.208-2.610)	0.636		
Synchronous lesion	2.161 (0.483-9.657)	0.313		
Adjuvant chemotherapy	4.585 (2.268-9.269)	***<0.001***	3.825 (1.863-7.855)	***<0.001***

A *p*-value<0.05 indicates statistical significance

Abbreviations: 95%CI, 95% confidence interval; aHR, adjusted hazard ratio; ASA, American Society of Anesthesiologists; CEA, carcinoembryonic antigen; DFS, disease-free survival; DIT, diagnosis-to-surgery interval time; HR, hazard ratio; LVI, lymphovascular invasion; NA, not applicable/available; PNI, perineural invasion; *p*-value, probability value; T, tumor

TABLE 4. Multivariate analysis for independent predictors of decreased 3-year DFS in the DIT >30 days group.

Factors	HR (95%CI)	*p*-value	aHR (95%CI)	*p*-value
Age	1.005 (0.986-1.025)	0.595		
Male sex	0.841 (0.523-1.354)	0.477		
Body mass index	0.978 (0.917-1.044)	0.502		
Charleson Comorbidity Index	1.017 (0.902-1.146)	0.787		
ASA				
- Class I	**Reference**			
- Class II	0.947 (0.512-1.751)	0.861		
- Class III	0.978 (0.486-1.967)	0.950		
Preoperative CEA level >3.4	2.105 (1.241-3.570)	***0.006***	1.412 (0.822-2.424)	0.211
Low preoperative albumin level	0.637 (0.423-0.958)	***0.030***	0.611 (0.387-0.965)	***0.035***
Laparoscopic surgery	0.594 (0.366-0.963)	***0.035***	0.700 (0.425-1.152)	0.161
Conversion	2.868 (0.858-9.521)	0.087		
Depth of invasion				
- T1	**Reference**			
- T2	NA	NA		
- T3	NA	NA		
- T4	NA	NA		
Lymph node metastasis	5.137 (3.001-8.795)	***<0.001***	1.789 (0.964-3.322)	0.065
Lymph node harvested <12 nodes	1.644 (0.599-4.513)	0.335		
Grade				
- Well-differentiated	**Reference**			
- Moderately-differentiated	3.296 (0.806-13.478)	0.097		
- Poorly-differentiated	NA	NA		
- Undifferentiated/anaplastic	6.224 (1.208-32.086)	***0.029***		
Presence of PNI	3.788 (2.353-6.098)	***<0.001***	1.904 (1.160-3.124)	***0.011***
Presence of LVI	1.925 (1.173-3.161)	***0.010***	0.844 (0.494-1.441)	0.534
Positive margin	2.071 (0.507-8.459)	0.311		
Location				
- Right-side colon	**Reference**			
- Left-side colon	1.413 (0.649-3.076)	0.384		
- Sigmoid colon	1.007 (0.548-1.848)	0.983		
- Upper rectum	1.064 (0.434-2.611)	0.891		
- Synchronous lesion	1.121 (0.256-4.901)	0.880		
Adjuvant chemotherapy	9.662 (4.623-20.194)	***<0.001***	5.444 (2.178-13.606)	***<0.001***

A *p*-value<0.05 indicates statistical significance

Abbreviations: 95%CI, 95% confidence interval; aHR, adjusted hazard ratio; ASA, American Society of Anesthesiologists; CEA, carcinoembryonic antigen; DFS, disease-free survival; DIT, diagnosis-to-surgery interval time; HR, hazard ratio; LVI, lymphovascular invasion; NA, not applicable/available; PNI, perineural invasion; *p*-value, probability value; T, tumor

extended delays of 3-6 months in colorectal cancer surgery could generate approximately 3,000 excess deaths annually, with significant reduction in quality-adjusted life-years.[18] This temporal threshold of 3-6 months represents a duration substantially longer than our 30-day cutoff, supporting our hypothesis that brief delays may not compromise survival while extended deferrals pose significant oncological risks. The concordance between our empirical findings and these predictive models validates the concept that there exists a critical time threshold beyond which surgical delay becomes clinically detrimental, and that 30-day intervals fall below this threshold for non-metastatic colorectal carcinoma.

Yung-Heng Lee et al. conducted a retrospective cohort study of 39,000 patients and found that delaying treatment for more than 30 days resulted in a lower 5-year OS rate. The study included patients with stage IV CRC who underwent surgery, chemotherapy, and radiation.[12] Fabian Grass et al. conducted a study involving 118,504 patients who underwent elective surgery for colon cancer stage I-III and observed an increased mortality rate in the group of patients who delayed surgery for more than 40 days.[13] In another retrospective cohort study by Maria Theresa Redaniel et al. involving 46,511 patients, a U-shaped relationship was observed between the time from diagnosis to surgery and 5-year OS. Patients who underwent surgery between 25-38 days had the highest survival rate, while those who delayed surgery for more than 38 days had a higher risk of death (HR 1.16; 95%CI 1.04-1.29), and those who had surgery less than 25 days had an even higher risk of death (HR 1.5; 95%CI 1.37-1.66).[14] These findings suggest that a large population may be affected by the delay in treatment, leading to an overpowered effect.

These findings have direct implications for surgical triage and hospital resource management. Although a short delay beyond 30 days may not adversely affect survival in low-risk patients, identifying high-risk individuals—such as those with nodal metastasis or hypoalbuminemia—can help prioritize surgical scheduling to minimize further delay. Implementation of a structured preoperative risk stratification model may facilitate optimal case allocation and enhance efficiency without compromising oncological outcomes. For instance, a recent study from our institution demonstrated that integrating histopathologic markers, such as lymphovascular invasion, with transcriptomic profiling can accurately predict lymph node metastasis19. Utilizing such predictive models could further refine preoperative triage and prioritize surgical scheduling for these high-risk patients. Furthermore, integrating these insights into national cancer care policies could support the development of performance indicators that balance clinical urgency with real-world logistical constraints. Importantly, these clinical implications specifically apply to patients with colon and upper rectal cancer and should not be generalized to rectal cancer patients requiring neoadjuvant therapy, as their treatment paradigms and prognostic profiles are distinct.

Limitations

Study limitations include selection bias from retrospective design, limited sample size constraining statistical power, and unmeasured confounding variables affecting DIT associations. Exclusion of emergency presentations and middle/lower rectal cancers limits generalizability, as these populations have distinct prognostic profiles and treatment paradigms including neoadjuvant therapy. Specifically, contemporary approaches like total neoadjuvant therapy for locally advanced rectal cancer represent a separate clinical entity aimed at improving complete pathologic response rates and mitigating distant metastases.[20] The cause of surgical delays was not documented, precluding identification of patient-, system-, or provider-related factors that could inform quality improvement initiatives. Furthermore, although a formal a priori power analysis was conducted to determine the target sample size, our final cohort comprised the entire eligible population available at our institution during the study period. Because this final number fell slightly short of the predetermined target, our statistical power to detect clinically meaningful differences in disease-free survival is restricted, risking a Type II error. This limited sample size also precludes definitive proof of causality in our subgroup analysis. Despite this limitation, our recommendation to prioritize patients with low albumin or lymph node metastasis is based on practical clinical principles; their inherently aggressive tumor biology and propensity for rapid progression strongly argue against any surgical delay. Prospective multicenter studies with larger cohorts, comprehensive covariate adjustment, and documentation of delay causation are needed to establish optimal DIT thresholds in non-metastatic CRC.

CONCLUSION

This retrospective cohort analysis demonstrated no significant association between diagnosis-to-surgery intervals exceeding 30 days and survival outcomes in non-metastatic colorectal cancer patients, though subgroup analysis revealed diminished disease-free survival among patients with nodal involvement and hypoalbuminemia experiencing delays. These findings suggest that short surgical delays beyond 30 days may be clinically acceptable

in selected low-risk patients; however, timely surgery remains paramount, particularly for vulnerable subgroups, and prospective studies are needed to validate optimal timing thresholds and inform clinical triage protocols.

Data Availability Statement

All data used in this study is shown within the manuscript. However, any inquiries or requests for clarification about the data should be directed by the journal editor to the corresponding author.

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DECLARATIONS

Grants and Funding Information

This was an unfunded study.

Conflict of Interest

All authors hereby declare no personal or professional conflicts of interest relating to any aspect of this study.

Registration Number of Clinical Trial

None

Author Contributions

Conceptualization and methodology, A.T, K.T. and V.L. ; Investigation, A.T. and K.T. ; Formal analysis, A.T. and K.T. ; Visualization and writing – original draft, K.T. ; Writing – review and editing, A.T, K.T. ; Supervision, A.T. All authors have read and agreed to the final version of the manuscript.

Use of Artificial Intelligence (AI)

AI technology was not employed to develop any aspect of this study.

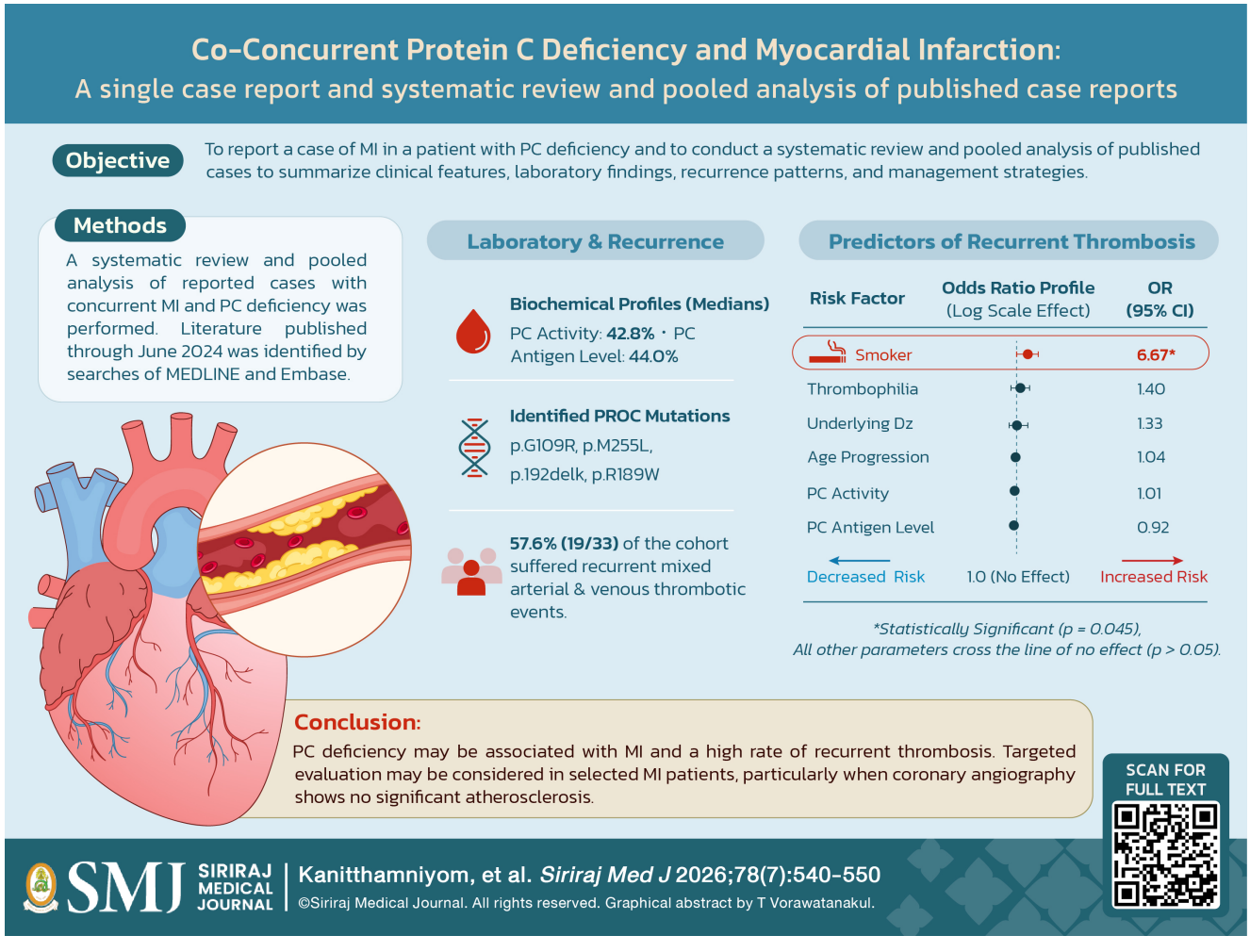
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Myocardial Infarction in a Patient with Coexisting Protein C Deficiency: A Single Case Report and Systematic Review and Pooled Analysis of Published Case Reports

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ABSTRACT

Objective: To report a case of MI in a patient with PC deficiency and to conduct a systematic review and pooled analysis of published cases to summarize clinical features, laboratory findings, recurrence patterns, and management strategies.

Materials and Methods: A systematic review and pooled analysis of reported cases with concurrent MI and PC deficiency was performed. Literature published through June 2024 was identified by searches of MEDLINE and Embase.

Results: Thirty-three patients, including the present case, were analyzed. Median age at presentation was 37 years (IQR 26.5–44). Traditional atherosclerotic risk factors were reported in 6 patients (18.2%). Recurrent arterial and/or venous thrombosis occurred in 19 patients (57.6%). Median PC activity and antigen levels were 42.8% (IQR 32.3–50.5%) and 44.0% (IQR 39.7–52.2%), respectively. Four distinct PROC mutations were described. Coronary angiography most often showed thrombotic occlusion without clear atherosclerotic disease. Combination anticoagulant and antiplatelet therapy was the most common treatment approach. Active smoking was associated with recurrent thrombosis (odds ratio 6.667, 95% CI 1.047–42.431; p=0.045).

Conclusions: PC deficiency may be associated with MI and a high rate of recurrent thrombosis. Targeted evaluation may be considered in selected MI patients, particularly when coronary angiography shows no significant atherosclerosis.

Keywords: Myocardial infarction; patient; coexisting protein C deficiency; single case report; systematic review (Siriraj Med J 2026;78(7):540-550)

INTRODUCTION

Protein C (PC) is an endogenous anticoagulant protein that works together with protein S (PS) to downregulate coagulation by inactivating clotting factors V and VIII.[1] Deficiency of PC has been consistently linked to an increased risk of venous thromboembolism (VTE), as demonstrated across multiple clinical studies.[1-4] In a prospective cohort, Mahmoodi et al. estimated the annual incidence of VTE among individuals with hereditary deficiencies of natural anticoagulants to be about 1%, corresponding to an approximately fourfold higher risk than that observed in the general population.[5]

In contrast to venous thrombosis, the association between PC deficiency and arterial thrombotic events remains less clearly defined.[6] A recent systematic review and meta-analysis reported that PC-deficient individuals had roughly double the risk of ischemic stroke compared with controls.[6] However, information regarding recurrence patterns and implications for treatment decisions in arterial events is still limited. Evidence relating specifically to myocardial infarction (MI) is even more sparse. Prior investigations of inherited thrombophilia in arterial disease have largely focused on factor V Leiden and prothrombin gene variants, with heterogeneous and sometimes conflicting findings.[7-10] Given these uncertainties, some experts propose that thrombophilia evaluation may be considered in selected younger patients (younger than 50–55 years) with arterial thrombosis after other causes have been carefully excluded.[11] Conversely, the British Society for Haematology notes insufficient supporting evidence and does not recommend routine inherited thrombophilia testing in patients with arterial thrombosis.[12]

Because hereditary anticoagulant deficiencies, including PC deficiency, are uncommon, robust observational data examining their relationship with arterial thrombosis—particularly MI—are lacking. To address this knowledge gap, the present study had two primary objectives: first, to describe a patient with PC deficiency who developed cerebral venous sinus thrombosis followed by MI at our center; and second, to perform a systematic review and pooled analysis of published cases of MI occurring in the setting of PC deficiency, with emphasis on clinical features, laboratory characteristics, treatment approaches, and factors associated with recurrent thrombosis.

MATERIALS AND METHODS

Data retrieval for the index case

Clinical information for the patient described in this report was obtained from the institutional electronic medical record system at our center. According to local policy, single case reports are not required to undergo institutional review board evaluation; therefore, formal ethics approval was not requested. Written informed consent for use and publication of clinical data was obtained from the patient. The case description was prepared in accordance with the CAse REport (CARE) reporting guideline.[13] (Supplementary Data 1).

Search strategy for the systematic review and pooled analysis of published case reports

A systematic literature search was performed in the MEDLINE and Embase databases from database inception through June 2024. No language restrictions were applied. The objective was to identify case reports and case series describing patients with both protein C deficiency and myocardial infarction. The core search terms included "Protein C" and "Myocardial infarction". Detailed database-specific search strategies are provided in Supplementary Data 2. The review process followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.[14] (Supplementary Data 3). The study protocol was prospectively registered in the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY202480047).

Eligibility criteria and data extraction

Publications were considered eligible if they met all of the following criteria: (1) involved adult patients aged 18 years or older; (2) documented confirmed protein C deficiency; (3) reported myocardial infarction as a clinical outcome; (4) were designed as case reports or case series without a control group; and (5) contained sufficient clinical detail for data extraction. Studies that did not fulfill these criteria were excluded.

Article screening and data extraction were performed independently by three investigators (CK, TL, and WO). Any uncertainties regarding study eligibility were resolved by consultation with TR1. Baseline characteristics and outcome variables from included reports were independently reviewed by CK, WO, and TR1. Extracted datasets were subsequently cross-verified among these reviewers to improve accuracy and consistency.

Quality assessment

Methodological quality and risk of bias of the included reports were evaluated independently by two reviewers (CK and TR1) using the Joanna Briggs Institute critical appraisal checklist for case reports.[15] (Table 1). Differences in assessment were resolved through discussion with WO.

To evaluate the certainty of exposure and diagnostic accuracy across the pooled cases, we performed a quality assessment using the JBI checklist. We identified that 14 patients, including the current case, were not receiving anticoagulation therapy at the time of testing, strengthening the reliability of the protein C (PC) deficiency diagnosis. Conversely, in six cases, PC levels and functional assays were measured while patients were on warfarin or heparin, which may mask or confound the results. Only two reports (Wypasek et al. and Yaarubi et al.) explicitly confirmed the deficiency through repeat testing. In the remaining cases, the specific timing and conditions of the PC assays were not reported. Regarding outcome ascertainment, the diagnosis of myocardial infarction (MI) was robustly confirmed in all 33 cases through clinical presentation, electrocardiographic changes, cardiac enzyme kinetics, and coronary angiography. Finally, we identified several potential confounders, including smoking, concurrent thrombophilias, family history, and underlying comorbidities, which may contribute to atherosclerotic risk alongside PC deficiency.

Statistical methods

The pooled analysis comprised 33 patients: 29 derived from individual case reports, 3 from a single case series, and 1 from the present case. For statistical analysis, individual patients from published reports were combined and analyzed as a single observational cohort, following the approach described by Sampayo-Cordero et al.[16]

Associations between selected variables (age, smoking status, family history, protein C mutation status, and protein C activity level) and the presence of concurrent thrombosis were evaluated using binomial logistic regression with SPSS Statistics software (SPSS Inc., Chicago, IL, USA). Sensitivity analyses for heterogeneity, as proposed in the reference methodology, were not conducted because no prior meta-analysis addressing this specific outcome was available for comparison.

Categorical variables are presented as counts and percentages. Continuous variables with non-normal distribution are summarized as median and interquartile range (IQR). A two-sided p-value <0.05 was considered to indicate statistical significance.

RESULTS

The single case report given in the present study

A 47-year-old Thai man presented to the emergency department of our tertiary referral center in March 2016 with a seizure. He had no known comorbid conditions and reported no regular medication use, substance abuse, smoking, or alcohol intake. Computed tomography venography demonstrated extensive cerebral venous sinus thrombosis involving multiple sites, including cortical veins in the right frontoparietal and left parietal regions, the superior sagittal and confluence sinuses, the right transverse and sigmoid sinuses, the right internal jugular vein, and part of the left transverse sinus.

Given a family history of venous thrombosis in a sibling and the absence of other provoking factors, an

TABLE 1. Characteristics of the patients included in this systematic review.

First author (Year of publication)	Age/ gender	Concurrent thrombosis	Comorbidity	Current smoker	Concomitant thrombophilia	Protein C mutation	Protein C activity (%)	Protein C level (%, IU/dL)	Family	OAC	Antiplatelet	QA
Coller (1987)[17]	23/M	Yes (DVT/PE)	No	Yes	No	N/A	33%	20%	Yes	Warfarin	Dipyridamole	8/8
Hacker (1991)[18]	28/M	No	Asthma	Yes	No	N/A	51%	N/A	Yes	Warfarin	ASA	8/8
Kario (1992)[19]	29/M	No	No	Yes	N/A	N/A	51%	N/A	Yes	Warfarin	ASA	8/8
Bux-Gewehr (1999)[20]	35/F	Yes (DVT/PE)	No	No	No	N/A	57%	N/A	Yes	Phenprocoumon	No	7/8
Ninomiya (2001)[21]	76/M	Yes (DVT)	N/A	N/A	No	N/A	48%	41%	N/A	Warfarin	ASA & dipyridamole	7/8
Ninomiya (2001)[21]	64/M	Yes (MI)	N/A	N/A	No	N/A	15%	49%	N/A	Warfarin	ASA & dipyridamole	6/8
Ninomiya (2001)[21]	60/F	No	N/A	N/A	No	N/A	26%	60%	N/A	Warfarin	ASA	6/8
Sadiq (2001)[22]	22/F	No	Asthma	Yes	No	N/A	33%	N/A	No	Warfarin	No	7/8

Abbreviations: ASA, aspirin; AT, antithrombin; BID, twice daily; CVST, cerebral venous sinus thrombosis; DLD, dyslipidemia; DM, diabetes mellitus; DVT, deep vein thrombosis; F, female; FV Leiden; factor V Leiden; HT, hypertension; IJV, internal jugular vein; IU/dL, international units per deciliter; M, male; mg, milligram; MI, myocardial infarction; MTHFR, methylenetetrahydrofolate reductase; N/A, not available; OAC, oral anticoagulant; PAD, peripheral artery disease; PAI-1, plasminogen activatable inhibitor-1; PE, pulmonary embolism; PROC gene – Protein C, Inactivator Of Coagulation Factors Va and VIIIa gene; PS, protein S; QA, quality assessment (evaluated using the Joanna Briggs Institute checklist); QD, once daily; SVC, subclavian vein; SVT, superficial vein thrombosis

inherited thrombophilia evaluation was performed. Protein C activity was reduced to 40% (reference range 70–140%), whereas free protein S and antithrombin levels were within normal limits. Testing for antiphospholipid syndrome was negative, including lupus anticoagulant and antiphospholipid antibodies. Next-generation sequencing identified a pathogenic homozygous PROC variant, c.565C>T (p.R189W) at exon 7, with a variant allele frequency of 99.62%.

Long-term anticoagulation with a vitamin K antagonist (warfarin) was initiated with ongoing risk–benefit counseling. The patient later discontinued warfarin on his own. One week after treatment interruption, he returned with acute chest pain and was diagnosed with inferoposterolateral ST-elevation myocardial infarction based on electrocardiographic ST elevation in leads II, III, aVF, and V4–V6. Coronary angiography demonstrated complete thrombotic occlusion of the left anterior descending and left circumflex arteries without evidence of underlying atherosclerotic disease. Thrombus aspiration and balloon angioplasty were performed without stent placement. Clopidogrel was started but discontinued after two weeks because of concern regarding thrombophilia-related thrombosis. Warfarin was resumed with a plan for indefinite therapy due to recurrent thrombotic events.

Systematic review and pooled analysis of published case reports

Study selection

The database search identified 15,210 records from MEDLINE and Embase through June 2024. After removal of 1,247 duplicates, 13,963 titles and abstracts were screened by three reviewers. A total of 13,871 records were excluded because they did not report the outcome of interest, were reviews/editorials/commentaries, or involved non-eligible populations. Ninety-two full-text articles underwent detailed assessment. Sixty were excluded because of insufficient protein C–related data or lack of relevant outcomes. Thirty-two published case reports, together with the present case, were included in the final analysis (N=33).[17-46] The selection process is illustrated in Fig 1. Extracted variables included demographic features, laboratory findings, thrombotic manifestations, coronary angiographic patterns, and treatment strategies (Tables 1 and 2).

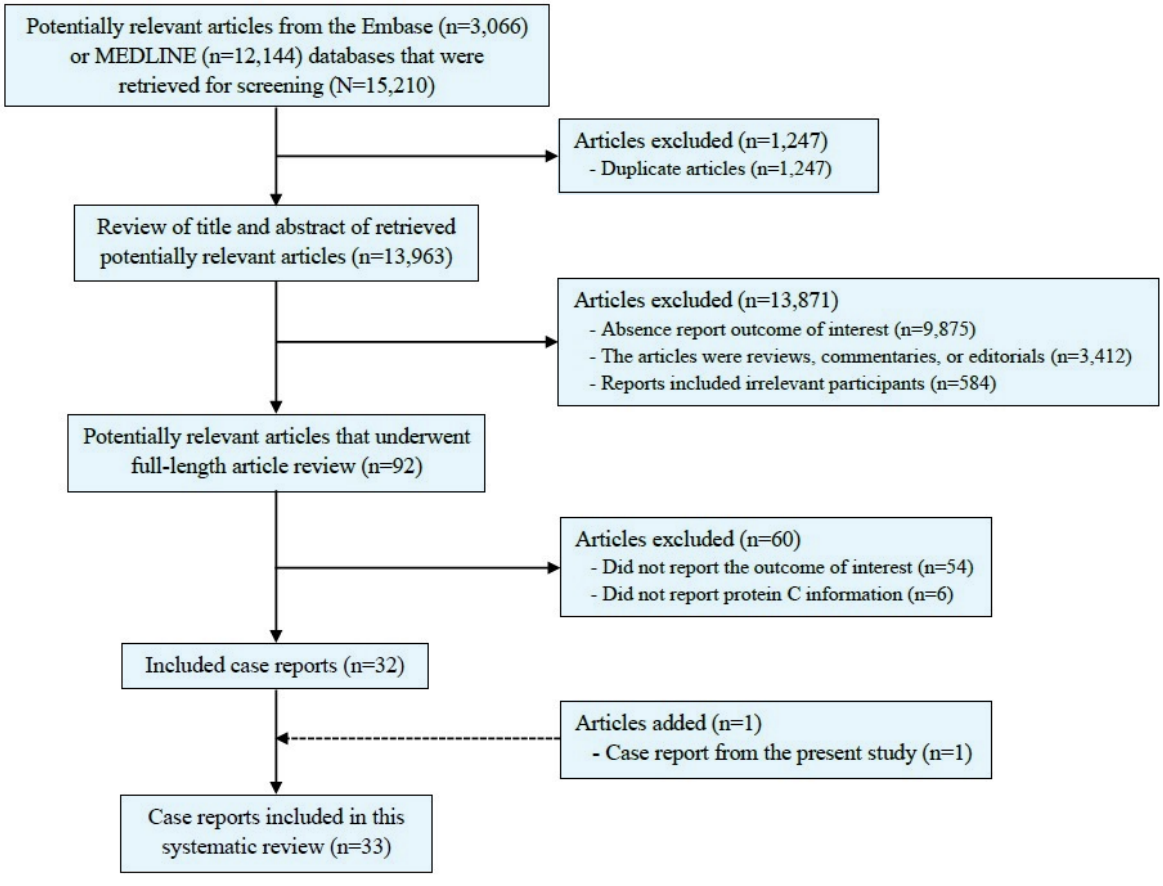


Fig 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart describing the literature review procedure.

TABLE 2. Coronary angiography findings of the patients included in this systematic review.

First author (Year of publication)	Coronary angiography findings
Coller (1987)[17]	Occluded left anterior descending coronary artery without evidence of coronary artery atherosclerosis
Hacker (1991)[18]	Thrombus in the left main coronary artery, large normal right coronary artery, and normal left circumflex coronary
Kario (1992)[19]	Slight stenosis of the left anterior descending coronary artery (25% diameter reduction)
Byux-Gewehr (1999)[20]	Occlusion of the left anterior descending coronary artery but no evidence of arteriosclerosis
Ninomiya (2001)[21]	Repeated thrombo-occlusion of coronary artery bypass grafts (5 recurrences)
Ninomiya (2001)[21]	Repeated occlusion of the left anterior descending coronary artery
Ninomiya (2001)[21]	Repeated complete thrombo-occlusion of the graft
Sadiq (2001)[22]	Total occlusion of the left proximal anterior descending artery by a thrombus, and 70-80% occlusion at the origin of the first diagonal branch by a thrombus
Cakir (2002)[23]	Occlusion of the proximal left anterior descending artery
Peterman (2003)[24]	Total occlusion of the distal left anterior descending coronary artery without collaterals
Tiong (2003)[25]	Acute thrombotic occlusion at the junction of the distal right coronary artery and the posterior descending artery with a normal left coronary system
Cakir (2007)[26]	Occlusion of the left anterior descending coronary artery
Ahmed (2009)[27]	Ectatic epicardial coronary arteries with no flow-limiting stenosis
Yokoyama (2009)[28]	Thrombus localized at the right coronary cusp and occluded right coronary artery
Eshtehardi (2011)[29]	Total thrombotic occlusion of the left anterior descending coronary artery at the bifurcation of the first diagonal branch with no evidence of atherosclerosis
D'Angelo (2011)[30]	Thrombus in proximal left anterior descending artery with no atherosclerotic

Patient characteristics

Baseline characteristics of the 33 included patients are summarized in Table 1. Most were male (25/33, 75.8%). The median age at MI presentation was 37 years (IQR 26.5–44). Traditional atherosclerotic risk factors, such as diabetes mellitus, hypertension, or dyslipidemia, were reported in 6 patients (18.2%). Recurrent thrombotic events at arterial and/or venous sites other than the index MI were documented in 19 patients (57.6%), including 11 with venous events, 7 with arterial events, and 1 with both. In a cohort of 11 patients with concurrent venous thromboembolism (VTE) and myocardial infarction (MI), 5 patients (46%) developed VTE prior to their MI, mostly presenting with deep vein thrombosis (DVT) and/or pulmonary embolism (PE). The remaining 6 patients (54%) experienced MI before the onset of VTE. Fourteen patients were described as current smokers.

PC deficiency-specific information

Median protein C activity across reported cases was 42.8% (IQR 32.3–50.5%), and the median antigen level was 44% (IQR 39.7–52.2%). Genetic data were incompletely reported; only nine cases specified mutation status, comprising eight heterozygous variants and one homozygous variant (the present case). Four reports included detailed *PROC* gene analyses identifying the following variants: c.325G>A (p.G109R), c.764T>A (p.M255L), c.577_579delAAG (p.192delK), and c.565C>T (p.R189W).

These variants are known to reduce protein C function and are consistent with a thrombophilic phenotype. Coexisting inherited thrombophilia was described in nine patients, including protein S deficiency (n=6), methylenetetrahydrofolate reductase mutation (n=1), factor V Leiden (n=1), and combined abnormalities involving antithrombin, plasminogen activator inhibitor-1, and MTHFR (n=1). A family history of protein C deficiency was noted in ten cases.

Coronary angiography (CAG) findings

In most reports, coronary angiography demonstrated thrombotic occlusion, most frequently involving the left anterior descending artery, without clear angiographic evidence of atherosclerotic plaque. Less common findings included recurrent graft thrombosis and thrombosis at atypical arterial locations, such as the aorta and the coronary sinus of Valsalva.

Management

Antithrombotic treatment approaches varied. Combination therapy with an antiplatelet agent plus an oral anticoagulant was reported in 15 patients (45.5%). Anticoagulant monotherapy was used in 9 patients (27.3%), including warfarin (n=6), rivaroxaban (n=2), and phenprocoumon (n=1). Antiplatelet therapy alone was described in 6 patients (18.2%), consisting of dual antiplatelet therapy with aspirin and clopidogrel (n=3), aspirin alone (n=2), or clopidogrel alone (n=1).

Association between variables and recurrent thrombosis

Among evaluated variables—age, smoking status, family history, protein C mutation status, and protein C activity—current smoking was the only factor significantly associated with recurrent thrombosis. Active smokers had more than a sixfold higher odd of recurrent thrombotic events compared with non-smokers (odds ratio 6.667, 95% confidence interval 1.047–42.431; p=0.045) (Table 3).

DISCUSSION

This combined case report and systematic review with pooled analysis of published case reports highlights a group of patients with protein C (PC) deficiency who developed myocardial infarction (MI), a presentation less commonly described than venous thromboembolism. The median age at MI onset in the collected cases was 37 years, which is substantially lower than the reported average age of MI in the general population (approximately 68.6±12.6 years).[47] A proportion of patients also had conventional cardiovascular risk factors, including smoking, diabetes, dyslipidemia, and hypertension. These coexisting factors may contribute to arterial thrombosis when superimposed on an inherited prothrombotic background, suggesting a possible contributory interaction rather than a single direct cause.

With respect to genetic findings, several PROC variants identified in this review have previously been described in association with venous thrombosis but not arterial events. The G109R substitution and the in-

TABLE 3. Analysis for factors significantly associated with recurrent thrombosis.

Factors	Odds ratio	95%CI	p-value
Age	1.038	00980-1.098	0.202
Family history	0.429	0.073-2.500	0.346
Male gender	0.059	0.082-3.0142	0.467
Protein C activity	1.007	0.941-1.076	0.845
Protein C level	0.917	0.822-1.023	0.122
Current smoker	6.667	1.047-42.431	0.045
Thrombophilia	1.400	0.290-6.769	0.676
Underlying disease	1.333	0.2696-0.606	0.725

A p-value<0.05 indicates statistical significance
Abbreviation: 95%CI, 95% confidence interval

frame deletion c.577–579delAAG (p.192delK) have been reported in patients with venous thrombotic disease.[48,49] The c.565C>T (p.R189W) variant at exon 7, which was also detected in our index case, has been described in prior reports from our center and appears relatively frequent in the Thai population.[50] Another variant, c.764T>A (p.M255L), has been documented only once previously in a patient with both MI and superficial vein thrombosis.[37] Taken together, these observations broaden the clinical spectrum associated with PROC mutations and indicate that arterial manifestations, including MI, may occur in selected cases.

Current recommendations do not strongly support routine testing for natural anticoagulant deficiencies in patients with arterial thrombosis.[11,12] Nevertheless, selective testing may be appropriate in younger individuals or in cases lacking an alternative explanation after comprehensive evaluation.[11,12] Also, the timing and clinical context of testing are critical for accurately diagnosing protein C deficiency. Specifically, testing during acute thrombotic events or active anticoagulation therapy can interfere with assays, leading to misinterpretation.[60] The entity of myocardial infarction with normal coronary arteries (MINCA) describes patients with coronary thrombosis in the absence of angiographic atherosclerosis.[51] Several prothrombotic disorders, including antiphospholipid syndrome and myeloproliferative neoplasms, have been reported in this setting.[52,53] A related concept, myocardial infarction with non-obstructive coronary arteries (MINOCA), refers to MI with less than 50% coronary stenosis despite evidence of atherosclerosis.[54] A pooled analysis estimated that approximately 14% of MINOCA patients have an underlying thrombophilic disorder.[55] In our review, most cases demonstrated thrombotic occlusion without clear atherosclerotic lesions on coronary angiography, consistent with a MINOCA-like pattern.[56] In such scenarios, evaluation for thrombophilia, including PC deficiency, may be considered when no other cause is identified.

Optimal management of MI occurring in the context of PC deficiency remains uncertain because evidence-based treatment guidance is lacking. In the cases reviewed, combination therapy with an oral anticoagulant and antiplatelet agent was the most frequently used approach, often with warfarin as the anticoagulant. However, the appropriate intensity and duration of antithrombotic therapy in this population are not well defined and require further study.

While smoking appeared to be associated with recurrent thrombosis (OR 6.667), the extremely wide 95% confidence interval (1.047–42.431) and the biased nature of self-selected case reports render this finding exploratory. Additionally, the small sample size restricts our ability to perform subgroup analyses to differentiate arterial from venous recurrence. These results do not provide a definitive measure of risk for the broader population but instead serve as a basis for future hypothesis-driven research.

Limitations

This study has several limitations that should be acknowledged. First, because protein C deficiency is uncommon, the number of eligible cases was limited, which reduces statistical power and the precision of estimates. Second, published case reports often lack complete clinical and laboratory details, and unreported coexisting risk factors or thrombophilic conditions may have been present. Third, the absence of a control group prevents firm conclusions regarding the magnitude of association between PC deficiency and MI. Furthermore, the reliance on case reports and small case series introduces significant publication bias, as unusual or severe clinical presentations are more likely to be reported. Consequently, applying regression models to non-consecutive, self-selected cases is subject to severe statistical limitations; such data lack a defined population denominator and are not representative of the general patient population. Despite these constraints, the compiled data provide clinically useful descriptive information regarding this rare presentation.

CONCLUSIONS

In summary, the present analysis indicates a possible association between protein C deficiency and myocardial infarction, supported by the observed frequency of recurrent thrombotic events and the predominance of non-atherosclerotic coronary findings. Screening for PC deficiency may be considered in a select subgroup of MI patients—specifically young individuals presenting with no significant atherosclerosis. In this population, testing should be pursued only after coronary angiography confirms the absence of obstructive coronary artery disease and other common thrombophilia etiologies (e.g., antiphospholipid syndrome) have been excluded.

Data Availability Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request from the Editor-in-Chief of Siriraj Medical Journal.

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DECLARATIONS

Grants and Funding Information

This was an unfunded study.

Conflict of Interest

The authors declare that they have no competing interests.

Registration Number of Clinical Trial

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Author Contributions

CK, KT, WO, and TR1 designed the study. CK, WO, and TR1 collected the data for the single case reported in this study. CK, TR1, TL, and WO collected the case report data for the systematic review. WO performed the statistical analyses. CK and TR1 drafted the manuscript, TR1 prepared the final version, and WO made critical revisions to the manuscript. CK and TR1 are co-first authors, and WO is the corresponding author. TR2, BS, and YC critically reviewed the manuscript for important intellectual content. All authors have read and approved the final version of the manuscript to be submitted for journal publication.

Use of Artificial Intelligence

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Ethics Approval and Consent to Participate

In Thailand, a case report does not require institutional review board approval; however, the protocol for the systematic review and pooled analysis of published case reports was approved by the Siriraj Institutional Review Board (SIRB) of the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand. Written informed consent to participate was obtained from the patient profiled in the single case report part of this study.

Consent for Publication

Written informed consent was obtained from the patient profiled in the single case report part of this study permitting us to submit details specific to his case for journal publication. A copy of that signed consent form is available upon reasonable request from the Editor-in-Chief of Siriraj Medical Journal.

INPLASY registration number: INPLASY202480047

List of Abbreviations

95%CI, 95% confidence interval; ASA, aspirin; AT, antithrombin; BID, twice daily; BS, Bundarika Suwanawiboon; CAG, coronary angiography; CARE, CAse REport; CK, Chanakarn Kanitthamniyom; CVST, cerebral venous sinus thrombosis; DLD, dyslipidemia; DM, diabetes mellitus; DVT, deep vein thrombosis; F, female; FV Leiden; factor V Leiden; HT, hypertension; IJV, internal jugular vein; IL, Illinois; Inc., incorporated; INPLASY, International Platform of Registered Systematic Review and Meta-Analysis Protocols; IQR, interquartile range; IU/dL, international units per deciliter; JBI, Joanna Briggs Institute; KT, Korakoth Towashiraporn; M, male; mg, milligram; MI, myocardial infarction; MINCA, Myocardial Infarction with Normal Coronary Arteries; MINOCA, Myocardial Infarction with Non-Obstructive Coronary Arteries; MTHFR, methylenetetrahydrofolate reductase; N/A, not available; NL, Nattawut Leelakanok; OAC, oral anticoagulant; OR, odds ratio; PAD, peripheral artery disease; PAI-1, plasminogen activatable inhibitor-1; PC, protein C; PE, pulmonary embolism; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROC gene – Protein C, Inactivator Of Coagulation Factors Va and VIIIa gene; PS, protein S; QA, quality assessment; QD, once daily; SPSS, Statistical Package for the Social Sciences; SVC, subclavian vein; SVT, superficial vein thrombosis; TL, Thanaphat Lalitrojwong; TR1, Tarinee Rungjirajittranon; TR2, Theera Ruchutrakool; USA, United States of America; VTE, venous thromboembolism; WO, Weerapat Owattanapanich; YC, Yingyong Chinthammitr

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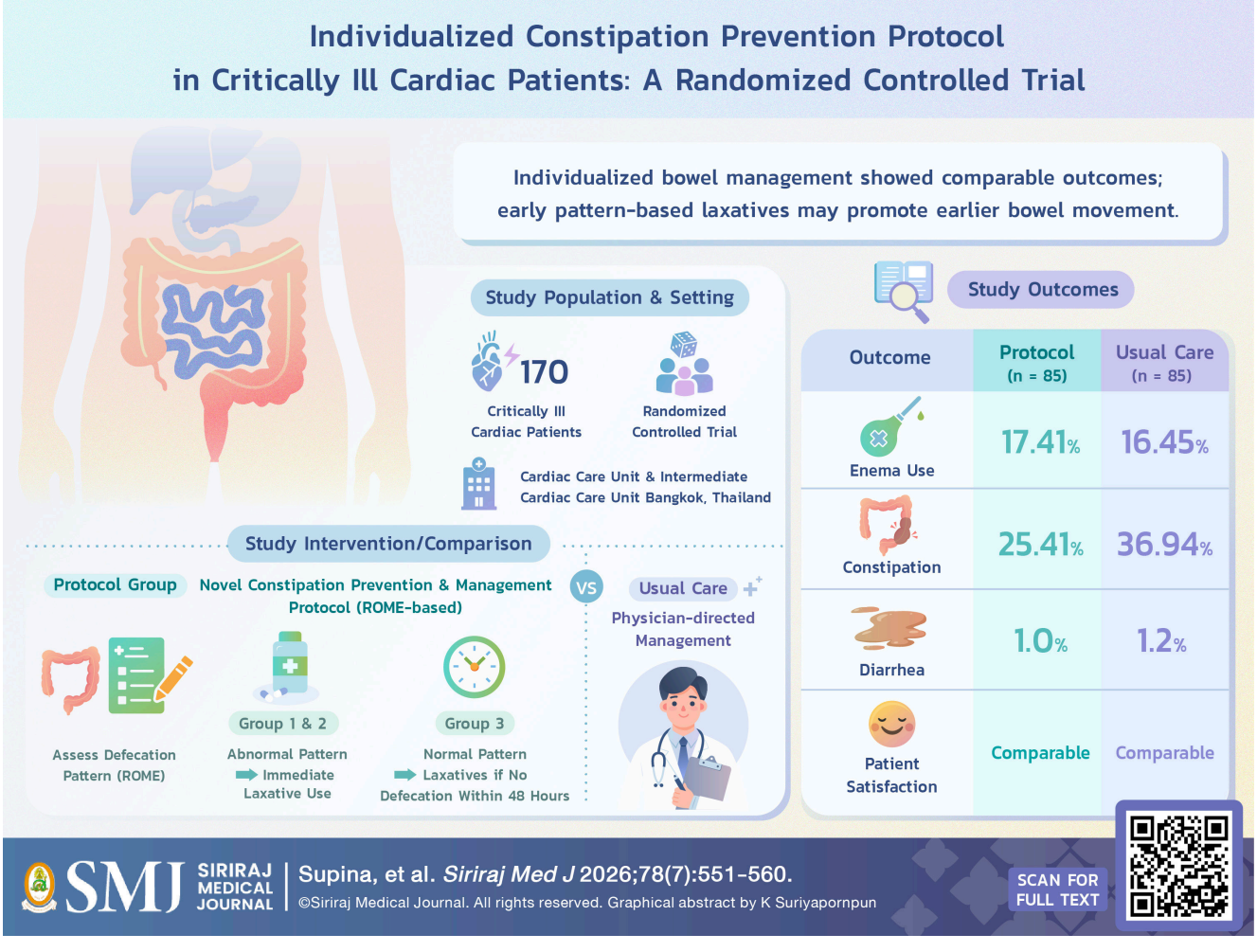
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A Novel Constipation Prevention and Management Protocol Versus Physician-Directed Management of Constipation in Critically Ill Cardiac Patients: A Randomized Controlled Study

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ABSTRACT

Objective: To compare the efficacy of a novel constipation prevention and management protocol with that of routine physician-directed management of constipation in critically ill cardiac patients.

Materials and Methods: This randomized controlled trial was conducted in the cardiac care unit and intermediate cardiac care unit of a tertiary hospital in Bangkok, Thailand. A total of 170 patients were randomized and analyzed according to the intention-to-treat principle. Missing outcome data were handled using multiple imputation. The protocol group was further subdivided using the ROME criteria into Group 1 and Group 2 (abnormal patterns; received immediate laxatives) and Group 3 (normal pattern; received laxatives only if no defecation occurred within 48 hours). The primary outcome was enema use. Secondary outcomes included the incidence of constipation and diarrhea, and patient satisfaction. Data were analyzed using appropriate statistical methods.

Results: The incidence of enema use was 17.41% in the protocol group and 16.45% in the usual care group. Constipation occurred in 25.41% and 36.94% of patients, respectively, while diarrhea occurred in 1.0% and 1.2%. Patient satisfaction was comparable between groups ($p = 0.221$).

Conclusion: The individualized bowel management protocol did not significantly reduce enema use, constipation, or diarrhea compared with usual care. Exploratory findings suggest that early laxative administration based on defecation patterns may facilitate earlier bowel movement.

Keywords: Clinical protocols; defecation behavior; heart diseases; intensive care unit; laxative (Siriraj Med J 2026;78(7):551-560)

INTRODUCTION

Constipation is a common issue among patients in the cardiac care unit and is influenced by factors such as hemodynamic instability, electrolyte imbalances, fluid restriction, immobility, medication side effects, and loss of privacy. Because the healthcare team often prioritizes acute crisis management, constipation is often overlooked. The reported prevalence of constipation ranges from 51% to 83% in other countries[1-4] and is approximately 73% in Thailand.[5] Constipation can prolong the duration of mechanical ventilation, complicate ventilator weaning, and extend hospital length of stay.[3,4,6,7] Straining during defecation can increase blood pressure and lead to cardiovascular events, including congestive heart failure and arrhythmias.[8]

Both nonpharmacological and pharmacological methods are available for the prevention and management of constipation. Nonpharmacological approaches include promoting healthy bowel habits, encouraging physical activity, and ensuring adequate fiber and water intake.[9] However, these measures are often limited in critically ill patients, making laxatives a common management strategy. In critically ill patients, the initial treatment of constipation typically involves stimulant laxatives (e.g., bisacodyl or senna) or osmotic laxatives (e.g., lactulose or polyethylene glycol). Osmotic laxatives, however, may induce gas formation, resulting in abdominal distension, discomfort, and fluid shifts.[10] If patients do not respond to laxatives, more invasive methods, such as manual evacuation or the use of an enema, may be required. In critically ill patients with heart disease, particularly older adults or those with comorbidities, certain medications may complicate constipation management. These medications, such as angiotensin-converting enzyme inhibitors, antiplatelets, and anticoagulants, may increase the risk of adverse effects and complications related to laxatives or enemas.[11]

Several institutions, including the Royal Free Hospital in London and the Cardiff Critical Care Department at the University Hospital of Wales, have developed protocols for constipation management in intensive care units. Warren and Kent designed a bowel management protocol in a cardiac intensive care unit in which all patients received laxatives upon admission; however, the protocol group demonstrated a higher incidence of constipation within the first 96 hours compared with the control group.[12] Similarly, *Knowles et al.* reported no significant differences in the incidence of constipation or diarrhea before and after protocol implementation.[13] However, the findings remain inconclusive. *Guardiola et al.* reported that administration of polyethylene glycol on the first day after initiation of mechanical ventilation resulted in a significantly lower rate of defecation failure compared with initiation on day 4 (8.6% vs. 25%, $p < 0.01$).[14]

In Thailand, constipation management in critically ill patients remains inconsistent and largely depends on individual physicians' judgment. Given the limitations of

existing protocols, particularly their lack of consideration for individual defecation patterns, this study developed a novel constipation prevention and management protocol and compared its efficacy with that of routine physician-directed constipation management in critically ill cardiac patients.

MATERIALS AND METHODS

Study design and participants

This prospective randomized controlled trial investigated the effects of a constipation prevention and management protocol in critically ill cardiac patients. The study was conducted in the cardiac care unit and intermediate cardiac care unit of a tertiary hospital in Bangkok, Thailand. Patients were randomly assigned in a 1:1 ratio to either the protocol group or the usual care group. Ethical approval was obtained from the Institutional Review Board (Approval No. Si 539/2021). Written informed consent was obtained from all participants prior to enrollment. For patients who were unable to provide consent due to impaired consciousness or clinical instability, consent was obtained from their legally authorized representatives. The trial was retrospectively registered with the Thai Clinical Trials Registry (TCTR) under the identification number TCTR20241114002.

This study included patients admitted to the cardiac care unit and intermediate cardiac care unit between October 2021 and June 2023.

The inclusion criteria were:

1. Diagnosis of cardiovascular disease
2. Age ≥18 years
3. Glasgow Coma Scale (GCS) score > 8

The exclusion criteria were:

1. Diarrhea within 1 day prior to randomization
2. Nil by mouth for more than 24 hours
3. Daily laxative use within the previous week
4. Contraindications to laxatives, including allergies, coagulopathy, or rectal perforation
5. History of chronic constipation, irritable bowel syndrome, inflammatory bowel disease, intestinal ileus or obstruction, gastrointestinal bleeding, cirrhosis, or prior bowel surgery
6. Pregnancy at admission
7. Presence of a colostomy, ileostomy, or jejunostomy

Patients were screened and enrolled by co-authors (PS, CD and SK). The primary cardiac diagnoses leading to CCU admission (e.g., acute myocardial infarction, heart failure and other acute cardiovascular conditions) were recorded from the medical records as baseline clinical characteristics. The sample size was calculated based on the primary outcome of enema use during hospitalization. Using the n4Studies program, the calculation assumed a reduction in the proportion of patients requiring an enema from 20% to 5%. With a two-sided alpha of 0.05 and a power of 80% ($\beta = 0.20$), the required sample size was 76 patients per group. To account for a potential 10% dropout rate, the final sample size was increased to 85 patients per group, resulting in a total of 170 participants. Eligible patients were randomized into a control group (usual care) and an intervention group (protocol group) (Fig 1). Randomization codes were generated by PW using a computer-generated randomization scheme with a 1:1 allocation ratio. Allocation concealment was ensured using sequentially numbered, opaque, sealed envelopes prepared by PW, who was not involved in patient recruitment or outcome assessment. The envelopes were opened only after participants had been enrolled in the study. Due to the nature of the intervention, blinding of clinical staff and participants was not feasible; however, outcome data were collected from nursing records by investigators (PS, CD, and SK) according to predefined criteria. Bowel movement status was assessed and summarized daily at 8:00 a.m.

Study protocol

The control group received usual care, defined as physician-directed management of constipation (Fig 2). This included the administration of laxatives on the first day of admission or only after constipation developed. No formal assessment using the ROME criteria was performed in this group. The intervention group was assessed for bowel habits using the ROME criteria, and patients were categorized into three subgroups based on their defecation patterns:

- **Group 1**: Patients exhibiting at least one of the following characteristics:
  - Straining during defecation
  - Hard or lumpy stools
  - Sensation of incomplete evacuation
- **Group 2**: Patients exhibiting at least one of the following characteristics:
  - Sensation of anorectal obstruction during defecation
  - Need for manual maneuvers to facilitate defecation
  - Patients meeting criteria for both Group 1 and Group 2
- **Group 3**: Patients who did not exhibit any characteristics described in Groups 1 or 2.

Patients were classified into the usual care group and three intervention groups based on the aforementioned characteristics, after which tailored interventions were

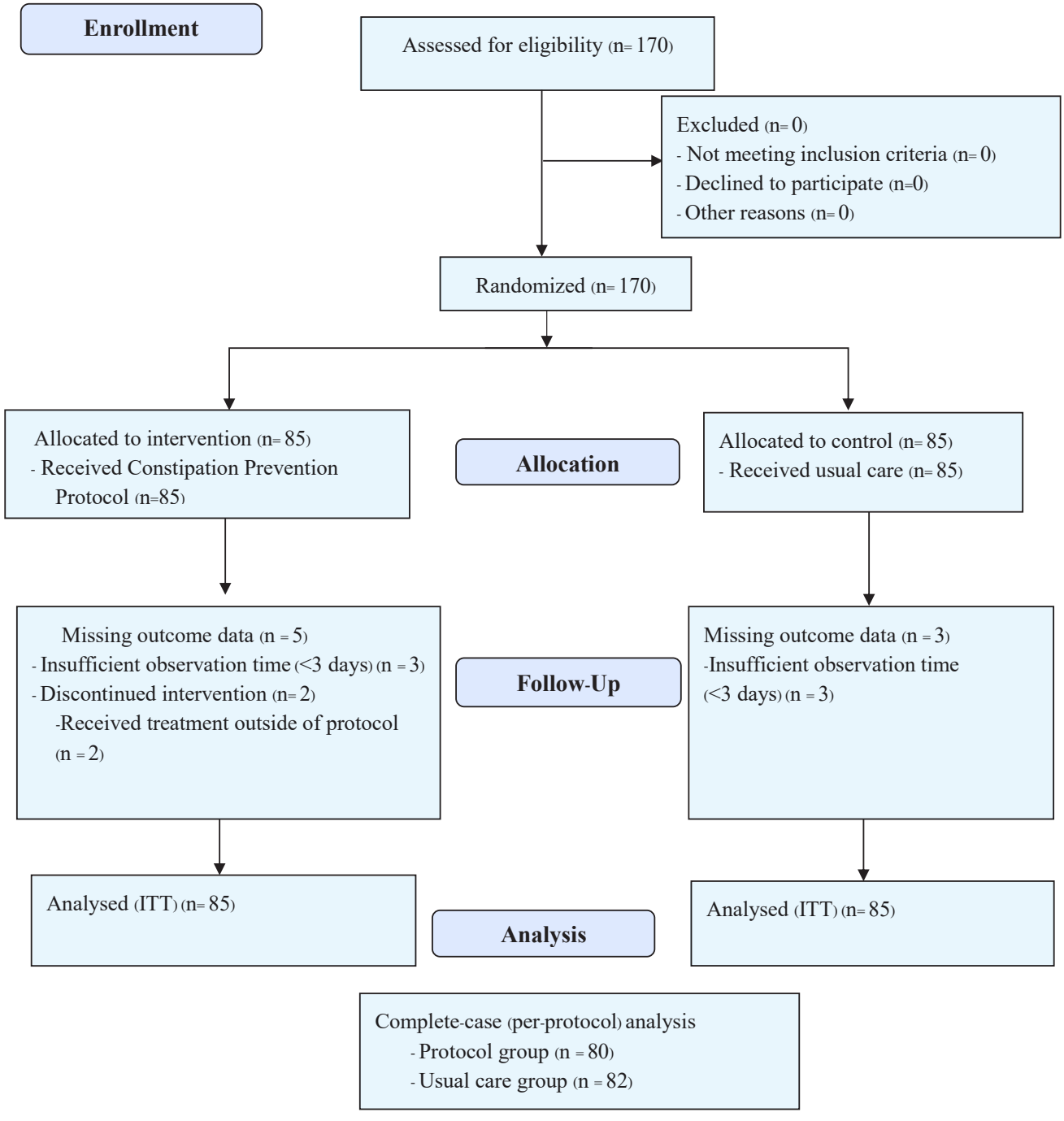


Fig 1. CONSORT flow diagram of participant recruitment, allocation, follow-up, and analysis.

implemented accordingly (Fig 2). In the intervention groups, constipation prevention and management were conducted according to a predefined stepwise protocol, with laxatives administered orally after breakfast at 8:00 AM.

Group 1 received lactulose syrup 20 mL on day 1. If no bowel movement occurred, the dose was increased to 40 mL on day 2. If defecation still did not occur, lactulose 40 mL combined with sennosides (7.5 mg) 2 tablets was administered on day 3. If no bowel movement occurred within 72 hours (day 4), evacuation and sodium phosphate enema were performed.

Group 2 received sennosides (7.5 mg) 2 tablets on day 1. If no bowel movement occurred, the dose was increased to 4 tablets on day 2. If defecation still did not occur, sennosides 4 tablets combined with lactulose 20 mL was administered on day 3. If no bowel movement occurred within 72 hours (day 4), evacuation and sodium phosphate enema were performed.

Group 3 did not receive prophylactic laxatives during

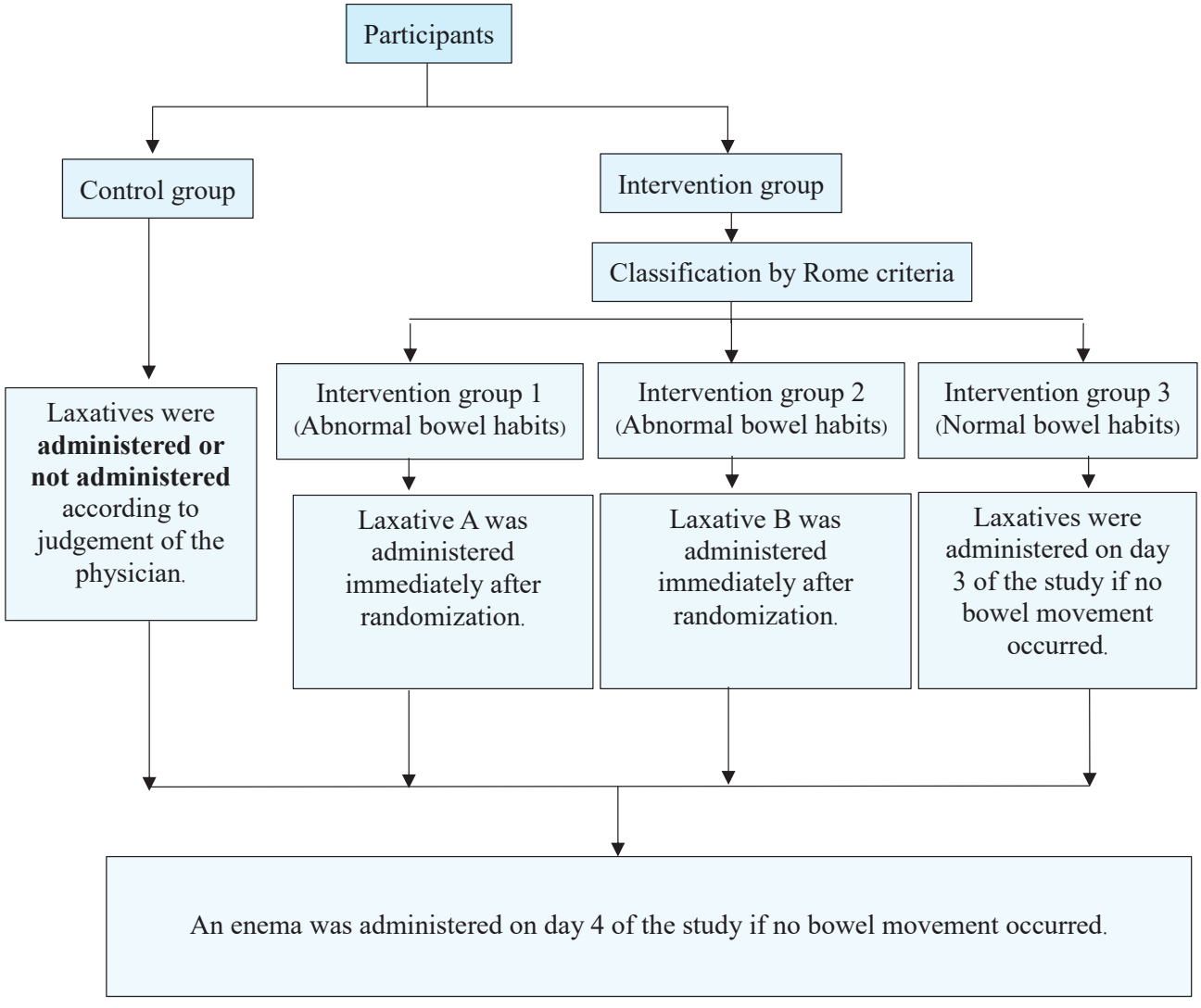


Fig 2. Flowchart of group assignment.

the first two days, and bowel movements were monitored. If no bowel movement occurred by day 3, sennosides (7.5 mg) 2 tablets were administered. If defecation still did not occur within 72 hours (day 4), evacuation and sodium phosphate enema were performed.

Study Outcomes were defined as follows:

Primary outcome

Enema administration rate: Defined as the proportion of patients who received an enema due to the absence of a bowel movement for ≥72 hours.

Secondary outcome

1. Constipation rate: Defined as the proportion of patients who had no bowel movement (stool passage) for ≥72 hours.

2. Diarrhea rate: Defined as the occurrence of three or more bowel movements per day, with stool characteristics classified as Type 6 or 7 according to the Bristol Stool Scale and a total stool volume exceeding 250 mL per day.[15]

3. Patient satisfaction: Satisfaction with bowel movements was assessed using a Likert-scale rating system, including bowel care and the use of laxatives. The questionnaire was administered using the same procedure for both groups. Participants were informed that their responses would remain confidential and would not affect their medical care.

Statistical analyses

All randomized participants were included in the analysis according to the intention-to-treat principle. Missing outcome data were handled using multiple imputation based on clinically relevant variables, including treatment group, baseline characteristics, and variables associated with the outcomes. Five imputed datasets were generated,

and the results were pooled for analysis. A complete-case (per-protocol) analysis including only participants with complete outcome data was performed as a sensitivity analysis. Categorical variables are presented as numbers or percentages and continuous variables with a normal distribution are reported as mean ± standard deviation (SD), whereas those with a non-normal distribution are presented as median (interquartile range [IQR]). Group comparisons were performed using the chi-square test or Fisher's exact test for categorical variables, and the independent t-test or Mann–Whitney U test for continuous variables, depending on the distribution. All statistical analyses were performed using IBM SPSS Statistics, version 22 (IBM Corp, Armonk, NY, USA). A *p*-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 170 patients were randomized and included in the intention-to-treat analysis (Fig 1). Eight participants had missing outcome data due to insufficient observation time or protocol discontinuation. Missing outcome data were handled using multiple imputation. Baseline demographics (Table 1) and laboratory data (Table 2) were similar between the two groups. The primary diagnoses leading to CCU admission included acute myocardial infarction, heart failure, valvular heart disease and arrhythmia, with no significant differences between the two groups. However, the protocol group had a higher proportion of males than the usual care group (78.8% vs 64.7%, $p = 0.041$). Additionally, a history of stroke was more common in the usual care group than in the protocol group (9.4% vs 1.2%, $p = 0.034$).

Enema use was observed in 17.41% of patients in the protocol group and 16.45% in the usual care group. Constipation occurred in 25.41% and 36.94% of patients, respectively. The incidence of diarrhea was low in both groups (1.0% vs 1.2%). Patient satisfaction with bowel movements did not differ significantly between the groups ($p > 0.05$). A complete-case (per-protocol) analysis, performed as a sensitivity analysis, including 162 participants (80 in the protocol group and 82 in the usual care group) yielded similar results to the primary analysis (Table 3).

Further exploratory per-protocol analysis of bowel movement within 24 hours among the protocol subgroups showed that Group 2 had the highest rate (40.0%), followed by Group 1 (33.3%), while Group 3 had the lowest rate (2.2%). This difference was statistically significant ($p = 0.002$).

DISCUSSION

This study compared the effects of a constipation prevention and management protocol with usual care procedures on enema use, constipation, diarrhea, and patient satisfaction with defecation in critically ill cardiac patients. The results showed that enema administration and constipation rates tended to be lower in the protocol group than in the usual care group. These findings are consistent with previous studies evaluating constipation prevention and management protocols in critically ill patients.[12,13] However, this study differs from others in its use of the ROME criteria to assess bowel habits. Despite the use of the ROME criteria, the results are largely similar, likely due to common factors among cardiac patients, such as fluid restriction and the use of diuretic or calcium channel blockers, both of which are known to increase the risk of constipation.[8,16] Furthermore, the heterogeneity of underlying diseases among participants may have influenced the findings, as this study included eligible participants with various cardiac conditions, although no significant differences were observed between the groups.

A per-protocol analysis was conducted to compare three subgroups within the protocol group, further classified according to individual defecation behavior. As described previously, patients in Groups 1 and 2 had difficulty with defecation based on the ROME criteria and therefore received laxatives on the first day of admission. In contrast, patients in Group 3 had normal defecation patterns and received laxatives only if no bowel movement occurred within 48 hours after randomization. The results showed that patients in Group 3 had the lowest rate of bowel movements within 24 hours. However, this subgroup analysis was exploratory, and the study was not powered to detect differences among these subgroups. Therefore, these findings should be interpreted with caution and considered hypothesis-generating. Likewise, *Guardiola et al.* demonstrated that prophylactic laxative administration effectively reduced constipation in intensive care unit patients.[14] These findings support the idea that early constipation prevention and management protocols should include laxatives for all critically ill patients on the first day of admission. Furthermore, non-pharmacological strategies may also contribute to improving gastrointestinal motility. Chewing gum, considered a form of sham feeding, has been reported to stimulate vagal activity and facilitate earlier recovery of bowel function. Previous studies have shown that chewing gum combined with standard nursing care can reduce postoperative ileus and promote an earlier return of bowel

TABLE 1. Demographic and baseline characteristics of patients in the protocol and usual care groups.

Characteristics	Protocol group N = 85 (%)	Usual care group N = 85 (%)	*p* value
Age (mean ± SD)	65.2 ± 12.3	66.4 ± 13.7	0.540
Sex (male)	67 (78.8%)	55 (64.7%)	0.041*
Primary diagnosis			
MI		0.121	
STEMI	50 (58.8%)	49 (57.6%)	
NSTEMI	24 (28.2%)	16 (18.8%)	
Heart failure	13 (15.3%)	11 (12.9%)	0.660
Valvular heart disease	3 (3.5%)	5 (5.9%)	0.720
Arrhythmia	3 (3.5%)	9 (10.6%)	0.072
Underlying disease			
Diabetes mellitus	26 (31.0%)	30 (35.3%)	0.550
Hypertension	21 (25.0%)	13 (15.3%)	0.120
Dyslipidemia	19 (22.6%)	12 (14.1%)	0.150
Stroke	1 (1.2%)	8 (9.4%)	0.034*
Hypothyroid	1 (1.2%)	1 (1.2%)	1.000
Parkinson	2 (2.4%)	1 (1.2%)	0.620
Medications prior to admission			
Calcium channel blockers	7 (8.3%)	8 (9.5%)	0.790
Diuretic	4 (4.8%)	11 (13.1%)	0.058
Metformin	2 (2.4%)	0 (0.0%)	0.500
Iron supplements	6 (7.1%)	1 (1.2%)	0.12
Medications on admission			
Potassium Chloride Elixir	67 (81.7%)	59 (71.1%)	0.110
5% MgCl2 solution	2 (2.4%)	5 (6.0%)	0.440
Colchicine	1 (1.2%)	1 (1.2%)	1.000
Piperacillin/tazobactam inj.	3 (3.7%)	4 (4.8%)	1.000
Midazolam inj.	1 (1.2%)	1 (1.2%)	1.000
Fentanyl inj.	3 (3.7%)	4 (4.8%)	1.000
Morphine inj.	0	1 (1.2%)	1.000
Calcium polystyrene sulfonate	1 (1.2%)	2 (2.4%)	1.000
LOS (Day), median (IQR)	3 (2.0 - 4.0)	3 (2.0 - 4.0)	0.460

*$p < 0.05$

Abbreviations: Inj, injection; IQR, Interquartile Range; LOS, Length of stay; NSTEMI, non-ST-elevation myocardial infarction; SD, Standard Deviation; STEMI, ST-elevation myocardial infarction.

TABLE 2. Baseline laboratory results in the protocol and usual care groups.

Laboratory	Protocol group N = 85	Usual care group N = 85	*p* value
BUN (mg/dL)	15.2 (12.0 - 26.0)	17.5 (13.6 - 26.6)	0.130
Creatinine (mg/dL)	1.0 (0.8 - 1.6)	1.1 (0.8 - 1.4)	0.550
Sodium (mmol/L)	137.2 ± 3.4	137.3 ± 3.9	0.880
Potassium (mmol/L)	4.0 ± 0.5	3.9 ± 0.5	0.360
Chloride (mmol/L)	101.3 ± 4.0	101.8 ± 4.8	0.440
Bicarbonate (mmol/L)	21.7 ± 2.7	21.9 ± 3.6	0.750
Magnesium (mg/dL)	2.1 ± 0.3	2.1 ± 0.3	0.630
Phosphorus (mg/dL)	3.3 (2.9 - 3.9)	3.5 (3.2 - 3.9)	0.390
Ionized calcium (mg/dL)	6.4 ± 2.4	5.4 ± 1.9	0.110
Hematocrit (%)	39.7 ± 7.1	38.8 ± 6.0	0.380
Hemoglobin (g/dL)	13.0 ± 2.5	12.8 ± 2.1	0.520
White blood cells (x 10^3/μL)	10.065 (8.130 - 12.300)	10.720 (8.140 - 13.305)	0.510
Platelets (x 10^3/μL)	246.000 (194.000 -280.000)	226.000 (192.000 - 286.000)	0.640

Abbreviations: mg/dL, milligrams per deciliter; mmol/L, millimoles per liter; μL, microliter.

TABLE 3. Clinical outcomes according to ITT and per-protocol analyses.

Outcomes	Protocol group (ITT, N=85), %	Usual care group (ITT, N=85), %	*p* value	Protocol group (PP, N=80), %	Usual care group (PP, N=82), %	*p* value
Enema	17.41	16.45	-	15.00	17.10	0.719
Constipation	25.41	36.94	-	25.00	35.40	0.151
Diarrhea	1.00	1.20	-	0	1.20	1.000
Satisfaction with defecation (mean ± SD)	4.43± 0.09	4.27± 0.09	0.221	4.38± 0.64	4.27± 0.66	0.210

ITT results are presented as pooled percentages from multiple imputed datasets. P-values for some ITT outcomes were not reported because of instability of the pooled estimates across imputed datasets. PP analysis was conducted using complete-case data.
Abbreviations: ITT, intention-to-treat; PP, per-protocol; SD, Standard Deviation.

function.[17] Additionally, physical stimulation techniques such as abdominal massage have also been reported to enhance bowel movement and promote defecation in hospitalized patients. A study published in *Siriraj Medical Journal* demonstrated that Thai traditional abdominal massage improved defecation outcomes in patients following lumbar laminectomy.[18] In the present study, only one case of diarrhea occurred in the usual care group, with none in the protocol group. This lower incidence, compared to previous studies,[12,13] may be explained by shared clinical factors among cardiac patients, as previously discussed. Moreover, nearly half of the patients with constipation refused enema administration. This could be due to previous experiences of dissatisfaction, including embarrassment, anal pain, and abdominal cramps, among other factors.[19]

Patient satisfaction is a subjective measure and may be influenced by individual perceptions of the care received. To mitigate potential response bias, we standardized the administration procedure for both groups and assured participants that their responses would remain confidential and would not affect their medical care. In the present study, patient satisfaction with defecation was similar between the two groups. This finding may be related to the stigma and embarrassment associated with discussing defecation, leading to reluctance among patients to express their true feelings. Furthermore, with the division of the protocol group into three subgroups based on individual defecation behavior assessed via a questionnaire, some patients may have felt embarrassed about providing information openly,[20] leading to most patients being categorized into Group 3 (normal defecation). This possible misclassification may have resulted in Group 3 being contaminated with patients who should have been assigned to other groups.

The primary strength of this study is the application of the ROME criteria to evaluate constipation in acute cardiac patients, a population at high risk for bowel dysfunction. This standardized approach offers a foundation for future investigations on early bowel assessment and supports its integration into routine clinical practice. In addition, the study employed a randomized controlled design, with outcomes analyzed according to the intention-to-treat principle and missing data addressed using multiple imputation, which strengthens the validity of the findings. The protocol also highlights the important role of critical care nurses and physicians in delivering individualized bowel management.

Limitations

This study has several limitations. First, some participants had missing outcome data due to insufficient observation time or protocol discontinuation. Although multiple imputation was used to address missing data, residual bias cannot be completely excluded. However, consistent findings in sensitivity analyses support the robustness of the results. Second, the use of a Glasgow Coma Scale (GCS) score >8 as an inclusion criterion may not accurately capture the cognitive status of critically ill patients, who are often affected by sedation, delirium, or altered levels of consciousness. Incorporating validated assessment tools such as the Confusion Assessment Method for the ICU (CAM-ICU) and the Richmond Agitation-Sedation Scale (RASS) is recommended to improve cognitive evaluation and the reliability of outcomes. Third, the short median length of stay (three days) may have limited the ability to fully observe the development and progression of constipation, which frequently requires longer monitoring. Therefore, extended follow-up beyond ICU discharge is necessary to assess long-term outcomes. Future studies should also include post-transfer follow-up to evaluate delayed complications and the sustained effectiveness of the protocol.

CONCLUSIONS

This study found no significant differences between the protocol and usual care groups. Nevertheless, the use of the ROME criteria may assist physicians and nurses in assessing defecation patterns and guiding bowel management in critically ill cardiac patients.

Data Availability Statement

The datasets generated and analyzed during the current study are not publicly available due to ethical and privacy restrictions but are available from the corresponding author upon reasonable request.

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Conflict of Interest

The authors declare no conflict of interest regarding the publication of this paper.

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Author Contributions

Conceptualization, Validation, Visualization and Resources, P.S., C.D., S.K., P.W., and T.B.; Methodology, Formal analysis, Supervision, Writing – original draft, Writing – review & editing P.S., and T.B; Investigation, P.S., C.D., S.K., and P.W.; Data curation, P.S., C.D., and S.K.; Project administration, P.S. All authors have read and agreed to the final version of the manuscript.

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Ethics Approval

This study was reviewed and approved by the Institutional Review Board (COA No. Si539/2021). All patients provided written informed consent prior to participation.

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