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MONTHLY

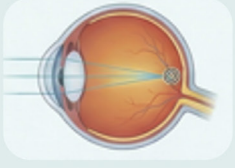
ORIGINAL ARTICLE REVIEW ARTICLE

Optical Interventions for Myopia Control

Modern optical management prioritizes progression control over simple refractive correction, because pediatric myopia's axial elongation raises the risk of severe vision complications.

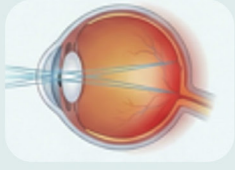
Principle of Optical Myopia Control

Emmetropia



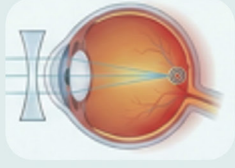
Images focusing perfectly on the fovea and peripheral retina

Uncorrected Myopia



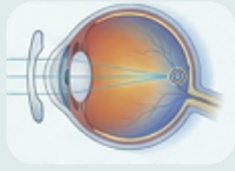
Images focusing in front of the fovea but behind peripheral retina

Standard Correction



Foveal focus is restored, but peripheral images remain behind peripheral retina **(Hyperopic Defocus)**

Myopia Control Lenses



Foveal focus is preserved, and peripheral images are shifted in front of the retina **(Myopic Defocus)**

Optical Interventions

Myopia Control Spectacles

32% – 62%

Reduction of axial growth

Soft Contact Lenses

29% – 52%

Reduction of axial growth

Orthokeratology

36% – 46%

Reduction of axial growth

SCAN FOR FULL TEXT

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Effectiveness of a Facilitator-Led Internet-Based Parent Management Training (Net PAMA Program) on Positive Parenting Skills Among Parents of Children Aged 7-12 Years: A Quasi-Experimental Study in Thailand

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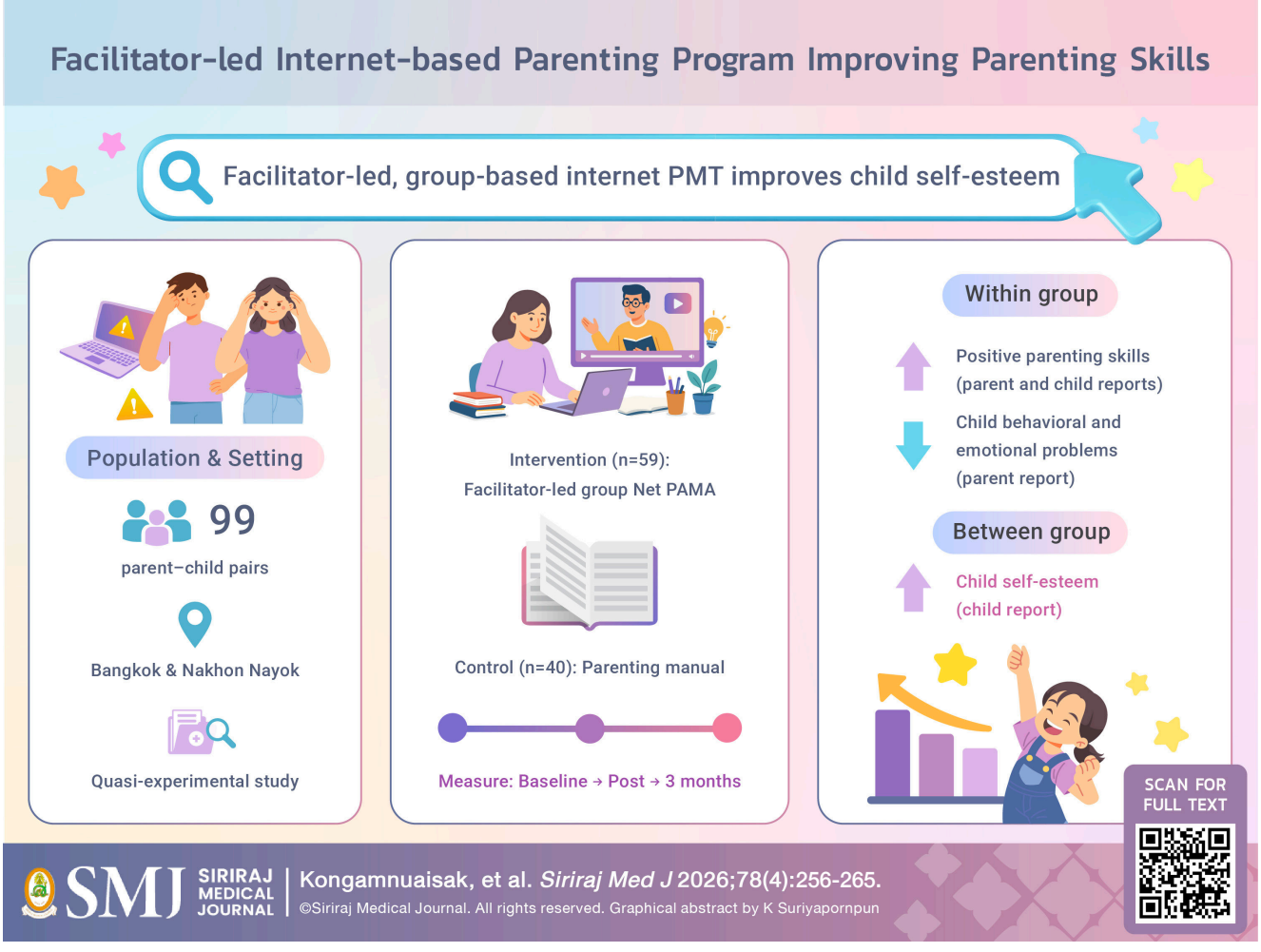

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ABSTRACT

Objective: This quasi-experimental study evaluated the effectiveness of a facilitator-led, internet-based parent training program (Net PAMA) in improving positive parenting skills among parents of children aged 7-12 years.

Materials and Methods: The study involved 99 parent-child pairs, divided into an intervention group of 59 pairs and a control group of 40 pairs. Data were collected at three time points: before training, immediately after, and at a 3-month follow-up. The effectiveness of the training was measured using the Positive Parenting Scale (POPS), the Thai version of the Pediatric Symptom Checklist (PSC-17), and a pictorial self-esteem scale for children. Statistical data were analyzed using a linear-mixed model.

Results: The study found no significant difference between the intervention and control groups in parent- or child-reported POPS scores at the 3-month follow-up. However, within the intervention group, both parent-reported ($p < 0.001$) and child-reported ($p = 0.017$) POPS scores significantly increased from baseline to the 3-month follow-up. Similarly, although between-group differences in PSC-17 scores were not significant, parent-reported PSC-17 scores in the intervention group decreased significantly from baseline ($p = 0.002$). Notably, children in the intervention group had significantly higher self-esteem scores than the control group at the 3-month follow-up ($p = 0.003$).

Conclusion: The facilitator-led Net PAMA program was effective in enhancing child self-esteem but ineffective in increasing positive parenting skills and reducing child behavioral problems. Nevertheless, the results are promising and support further investigation with a larger sample size and more rigorous study design.

Keywords: Children; internet-based intervention; parenting; problem behavior; self-esteem (Siriraj Med J 2026;78(4): 256-265)

INTRODUCTION

Behavioral problems in children, including externalizing problems such as aggression, defiance, and internalizing behaviors like withdrawal, anxiety, and depression, are considered one of the most severe mental health issues in childhood. These issues can negatively impact a child›s development and family relationships, and if left untreated, may increase the risk of future problems like peer rejection, academic failure, and criminal activity.[1-3] Parenting is a crucial factor influencing a child's mental and behavioral well-being.[4] Parent Management Training (PMT) is an evidence-based intervention grounded in social learning theory[5], with substantial empirical support for its effectiveness in treating children childhood behavioral problems. Numerous studies have demonstrated that PMT improves child behavior, with evidence showing a positive effect on reducing children's externalizing behavior problems, enhancing parenting skills, and reducing parenting stress.[6-8] Several well-established PMT models have been developed and validated internationally, including the Parent Management Training-Oregon Model (PMT-O)[9], The Incredible Years (IY)[10], the Positive Parenting Program (Triple P)[11], and Parent-Child Interaction Therapy (PCIT).[12] The primary goal of these programs is to reduce child behavioral problems through promotion of positive parenting skills.

To address challenges of accessibility, high costs, and the shortages of trained personnel, many PMT programs have transitioned to internet-based parent training. Emerging research supports the effectiveness of internet-based PMT in reducing childhood behavioral problems. Multiple randomized controlled trials have demonstrated that online PMT can effectively reduce conduct problems and improve parenting skills, with outcomes comparable to in-person interventions.[13-19] However, most existing internet-based PMT programs were designed in developed countries with different cultural and socioeconomic contexts from Thailand. Previous studies conducted in Thailand have emphasized the importance of caregivers' psychosocial factors in relation to children's psychosocial outcomes. For example, caregivers' parenting attitudes and mental health were found to be significantly associated with self-esteem among children and adolescents, highlighting the influential role of caregivers in child development.[20]

In Thailand, the first internet-based parenting program, Net PAMA, was developed in 2021. A previous randomized controlled trial confirmed its effectiveness, showing that parents who completed the self-paced program showed significant improvements in positive parenting skills and reductions in their children's behavioral problems ($p<0.001$).[21] Despite this success, a follow-up survey of Net PAMA users in August 2021 identified technology-related issues and low motivation as two main factors affecting

course completion. To overcome these challenges, a new facilitator-led model, known as Net PAMA Classroom, was developed. In this model, facilitators guide groups of 10–12 parents through the Net PAMA curriculum over six weekly three-hour sessions. This group-based approach fosters a supportive learning environment where parents can acquire knowledge, practice new skills, and share experiences, ultimately leading to improved parenting and better child outcomes.

This study aimed to examine the effectiveness of the facilitator-led Net PAMA program (Net PAMA Classroom) in increasing positive parenting, reducing child behavioral problems, and improving child self-esteem. This was a comparative study between a group of parents who received the six-session training and a control group who did not.

MATERIALS AND METHODS

Study design

This was a quasi-experimental study conducted from June 2023 to April 2024.

Participants

Participants were recruited via online platforms from Bangkok and Nakhon Nayok provinces. The study included parents aged 25-60 years who had been the primary caregiver of a child for at least six months and were able to read and write Thai. The children of these parents had to be between 7-12 years old and able to read and write Thai. Parents were excluded if they had previously completed the self-paced Net PAMA course or a similar parenting program. Additionally, children with a physical or mental health condition, such as severe autism or Down syndrome, as reported by parents, were excluded. Participants in the intervention group were withdrawn if they attended fewer than five classes. Participants in the control group were withdrawn if they participated in other child behavior modification programs during the study.

Sample size

The sample size was calculated based on a previous study reporting mean POPS scores of 42.1 (SD = 3.9) for the intervention group and 39.1 (SD = 6.5) for the control group after the program. With a 95% confidence level ($\alpha = 0.05$) and 80% power ($\beta = 0.20$), 51 participants per group were required. Allowing for potential errors and a 15% dropout rate, the final sample size was 60 participants per group.

Intervention

Net PAMA program

The Net PAMA program is an online parenting curriculum adapted from the Parent Management Training (PMT), accessible at www.netpama.com. The content is delivered through online video lessons in an interactive format to simulate a group training setting. The course consists of six main lessons covering behavior modification techniques, including knowledge about children's behavioral modification, communication skills, effective praise, rewarding techniques, effective punishment and token economy.

Facilitator-led Net PAMA program (Net PAMA classroom)

In this study, facilitators were carefully selected through a rigorous four-step training and evaluation program. This program included: (1) a half-day online training session; (2) completion of the full Net PAMA curriculum, culminating in a certification; (3) a three-day practical workshop at Siriraj Hospital; and (4) leading at least one six-week Net PAMA group. Candidates who successfully completed all four steps were then evaluated by experts and only those who passed were chosen to be facilitators for this study. For the intervention groups, two facilitators were assigned per class who remained with the same group throughout the entire three-hour session per week for the six-week training period. The facilitators guided parents through lessons, exercises, and group discussions to reinforce positive parenting skills and peer learning. However, a formal inter-rater reliability assessment was not conducted.

Measurements

Demographic questionnaire:

The study collected data on parent gender, age, education level, health conditions, and relationship with the child, as well as the child's gender, age, grade level, and health conditions.

Positive Parenting Scale (POPS)[22]:

This 16-item self-report scale was developed by *Pornnoppadol et al.* and measured positive parenting skills across three domains: Relationship, Respect, and Rules. It is rated on a 4-point scale (from "never" to "regularly"). The scale had a Cronbach's Alpha of 0.87 for the parent version and 0.86 for the child version.

Pediatric Symptom Checklist (PSC-17) - Thai version[23]:

This 17-item self-report scale for both parents and

children was adapted from Jellinek and Murphy's PSC-35. Its Thai version was developed by *Pornnoppadol et al.* It assesses three areas of child emotional and behavioral problems: depression/anxiety, attention-deficit, and conduct problems. The Cronbach's Alpha was 0.85 for the self-report version and 0.82 for the parent version. A score of 15 or higher indicates the presence of emotional and behavioral problems.

Pictorial Self-Esteem Scale for Elementary Students in Grades 2-6[24]

This scale was also developed by *Pornnoppadol et al.* and consists of 17 questions to assess self-esteem across three domains: self-satisfaction, ability and achievement, and self-worth. The Cronbach's Alpha was 0.91.

Study procedure

The research team advertised and recruited interested parents online. Those who met the inclusion criteria were invited to participate and were informed of the study's details, benefits, and risks. If parents agreed to the terms, they signed a consent form. Recruitment occurred in four separate rounds in Bangkok and Nakhon Nayok provinces. Participants were randomly assigned to either the intervention or control group using simple randomization. If a parent assigned to the intervention group could not attend the training, they were invited to join the control group. The intervention group participated in the six-week facilitator-led training, while the control group received written information on positive parenting. Data were collected from both groups at three time points: before the program (T0), immediately after (T1), and at three months post-intervention (T2). Parents completed their questionnaires independently, and for children's questionnaires, parents either supervised or read the questions aloud if the child was not a proficient reader or writer.

Data analysis

Data were analyzed using Linear Mixed Models (LMM) to assess changes in outcomes across three time points. The models included fixed effects for Time, Group, and the Time × Group interaction, with a random intercept for each participant. The primary effect of interest was the Time × Group interaction, indicating whether the rate of change differed between the groups.

RESULTS

A total of 99 parent-child pairs participated in the study — 59 pairs in the intervention group and 40 pairs in the control group. Nineteen pairs in the intervention group withdrew or were terminated for attending fewer than five sessions, being unreachable for follow-up, or a change in the parent completing the questionnaire. In the control group, 16 pairs withdrew due to loss to follow-up. At the 3-month follow-up, 64 pairs remained: 40 in the intervention group and 24 in the control group (Fig 1).

Participant characteristics

At baseline, there were no significant demographic differences between the intervention and control groups. The average age of parents in both groups was around 41 years, with the majority being mothers. Most families had sufficient income and lived in nuclear family settings, with children primarily raised by their parents. The average age of the children was nine years, with no significant difference in the proportion of males and females. Most children did not have pre-existing physical or mental health conditions (Tables 1&2). The baseline scores for POPS, PSC-17, and self-esteem (child versions) were not statistically different between the two groups (Table 3).

Primary outcome (Table 3)

Parent-Reported POPS:

At the 3-month follow-up, the mean parent-reported POPS score was 42.26 (0.56) in the intervention group and 40.57 (0.73) in the control group, with no statistically significant between-group difference (P=0.066). Within the intervention group, the parent-reported POPS scores significantly increased from a mean of 40.05 (0.47) at baseline to 42.26 (0.56) at the 3-month follow-up (p<0.001).

Child-Reported POPS:

At the 3-month follow-up, the mean child-reported POPS score was 39.56 (0.98) in the intervention group and 37.47 (1.24) in the control group, with no statistically significant between-group difference (P=0.188). Within the intervention group, the child-reported POPS scores significantly increased from a mean of 37.72 (0.83) at baseline to 39.56 (0.98) at the 3-month follow-up (p=0.017).

Secondary outcomes (Table 3)

Parent-Reported PSC-17:

At the 3-month follow-up, the mean parent-reported PSC-17 score was 9.31 (0.54) in the intervention group and 10.22 (0.70) in the control group, with no statistically significant between-group difference (P=0.306). Within the intervention group, the scores significantly decreased from a mean of 11.35 (0.45) at baseline to 9.31 (0.54) at the 3-month follow-up (p=0.002).

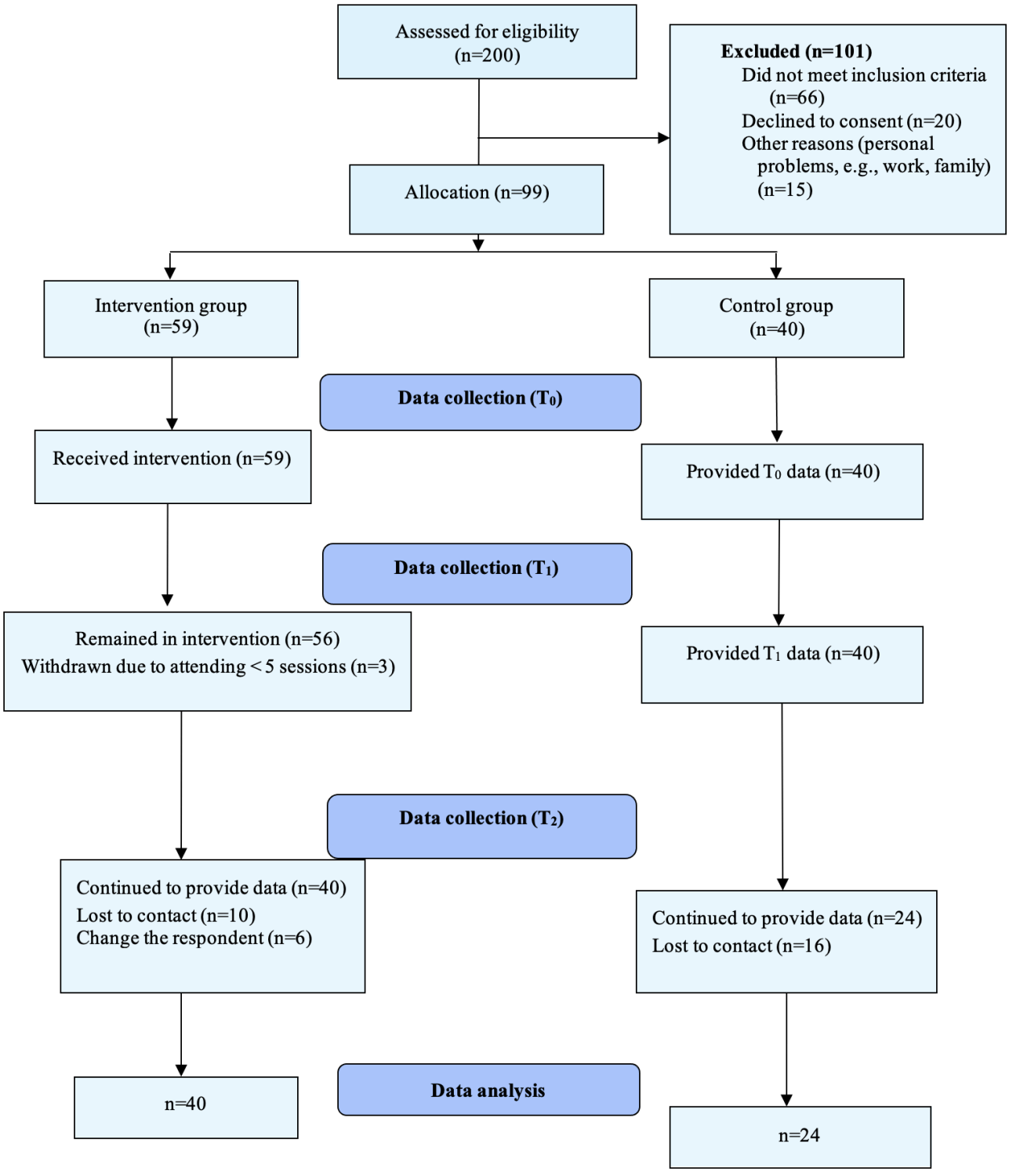

Fig 1. CONSORT flow diagram of the study.

Child-Reported PSC-17:

At the 3-month follow-up, the mean child-reported PSC-17 score was 10.65 (0.6) in the intervention group and 9.82 (0.76) in the control group, with no statistically significant between-group difference (p=0.393). There was also no significant change in scores within the intervention group from baseline (p=0.433).

Child Self-Esteem:

At the 3-month follow-up, the mean child self-esteem score was 57.57 (1.12) in the intervention group and 52.24 (1.36) in the control group. The child self-esteem scores in the intervention group were significantly higher than in the control group (P=0.003). Within the intervention group, the scores significantly increased from a mean of

TABLE 1. Baseline demographic and clinical features of parents in the intervention and control groups.

Baseline parents' characteristics	Total (n=99) n (%)	Intervention (n=59) n (%)	Control (n=40) n (%)	p-value
Gender				0.308
Male	10 (10.1)	4 (6.8)	6 (15.0)	
Female	89 (89.9)	55 (93.2)	34 (85.0)	
Age Mean±SD	41.52±7.17	41.58±7.61	41.43±6.53	0.440
Education level				0.709
Below bachelor degree	21 (21.2)	12 (20.3)	9 (22.5)	
Bachelor degree	37 (37.4)	24 (40.7)	13 (32.5)	
Master degree or more	41 (41.4)	23 (39)	18 (45.0)	
Employment				0.010
Employed	86 (86.9)	47 (79.7)	39 (97.5)	
Unemployed	13 (13.1)	12 (20.3)	1 (2.5)	
Perceived financial distress				0.731
No distress	53 (53.5)	32 (54.2)	21 (52.5)	
Some distress	34 (34.3)	19 (32.2)	15 (37.5)	
High level of distress	12 (12.1)	8 (13.6)	4 (10.0)	
Medical comorbidity				0.144
No	74 (74.7)	41 (69.5)	33 (82.5)	
Yes	25 (25.3)	18 (30.5)	7 (17.5)	
Underlying psychiatric condition				0.27
No	96 (97.0)	56 (94.9)	40 (100.0)	
Yes	3 (3.0)	3 (5.1)	9 (25.7)	
Marital status				0.241
Single	11 (11.1)	7 (11.9)	4 (10.0)	
Married and live together	73 (73.7)	41 (69.5)	32 (80.0)	
Married and live separate	6 (6.1)	6 (10.2)		
Widowed	1 (1.0)	1 (1.7)		
Divorced	8 (8.1)	4 (6.8)	4 (10.0)	
Number of children				0.802
1	38 (38.4)	23 (39.0)	15 (37.5)	
2	47 (47.5)	28 (47.5)	19 (47.5)	
3 and more	14 (14.1)	8 (13.6)	6 (15)	
Relationship with the child				0.403
Father	10 (10.1)	4 (6.8)	6 (15.0)	
Mother	75 (75.8)	46 (78.0)	29 (72.5)	
Others	14 (14.1)	9 (15.3)	5 (12.5)	

TABLE 2. Baseline demographic and clinical features of children in the intervention and control groups.

Baseline children's characteristics		Total (n=99) n (%)	Intervention (n=59) n (%)	Control (n=40) n (%)	p-value
Gender					0.367
	Male	50 (50.5)	32 (54.2)	18 (45.0)	
	Female	49 (49.5)	27 (45.8)	22 (55.0)	
Age	Mean±SD.	9.13±1.54	9.16±1.45	9.06±1.70	0.566
Underlying disease					0.739
	Medical comorbidity	24 (24.2)	15 (25.4)	9 (22.5)	
	Developmental problems	1 (1.0)	-	1 (2.5)	
	Emotional problems	3 (3.0)	2 (3.4)	1 (2.5)	
	Behavioral problems	13 (13.1)	10 (16.9)	3 (7.5)	

51.54 (0.91) at baseline to 57.57 (1.12) at the 3-month follow-up ($p<0.001$).

DISCUSSION

Although the within-group analysis showed that participants in the intervention group demonstrated improvements in POPS and reductions in PSC scores over time, indicating a positive impact, a statistically significant difference was not found in either the POPS or PSC scores when comparing the intervention and control groups. This suggests that while the intervention was effective, its effect size may not have been large enough to be clearly distinguished from the control group. This finding can be attributed to several plausible explanations, including the study's small sample size, the lack of true randomization and the potential influence of the Hawthorne effect in the control group, where participants may have sought out other positive parenting information. Furthermore, we did not track whether participants in the control group received other interventions during the study.

These findings are consistent with existing literature. A systematic review by *Martin et al.*[25] reported that the relationship between facilitator performance and program outcomes is often inconsistent, highlighting a limitation relevant to this study, which did not include a formal assessment of facilitator competence or inter-rater reliability, factors that could affect the results, especially with a small sample size. Similarly, *Rogers et al.*[26] found that perceived facilitator effectiveness can be influenced by participant characteristics and training context, which aligns with our finding of significant occupational differences between the groups. These demographic differences may have acted as a confounding variable, impacting participants' perceptions of the program. Given the lack of prior research with a similar study design, these findings provide a valuable foundation for future research. These findings are consistent with previous Thai studies demonstrating that caregivers' psychosocial characteristics and parenting-related factors are closely linked to children's psychosocial outcomes.[20] The present study extends this evidence by demonstrating that positive parenting skills can be enhanced through a structured, facilitator-led intervention.

The study's strengths include its focus on addressing parent needs in underserved areas and the use of diverse measurement tools incorporating both parent and child perspectives, thereby, enhancing the reliability of the findings by reducing subjective bias. Additionally, the 3-month follow-up allowed for a more comprehensive evaluation of the program's sustained impact.

However, the study also has several limitations. The quasi-experimental design may have introduced confounding factors. The outcome measures relied on self-report instruments, which are prone to bias. During the classroom session, there was no systematic monitoring to verify that the facilitators genuinely adhered to the teaching guidelines, which could affect the quality of training across different groups. The study also had a high attrition rate and the smaller-than-anticipated final sample size may have reduced the statistical power. Lastly,

TABLE 3. POPS, PSC-17, and self-esteem scores in the intervention and control groups across three time points.

Questionnaire	Intervention Group Mean (SE)	Control Group Mean (SE)	P-value (Between group)	group × time interaction
Parent's POPS				F(2, 201.32) = 2.03, p = 0.134
Pre	40.05 (0.47)	40.59 (0.57)	0.458	
Post	42.66 (0.48)	42.09 (0.57)	0.447	
Post 3m	42.26 (0.56)	40.57 (0.73)	0.066	
P-value (Within group)	<0.001	0.105		
Parent's PSC				F(2, 190.48) = 1.50, p = 0.226
Pre	11.35 (0.45)	10.54 (0.55)	0.255	
Post	9.36 (0.46)	8.86 (0.55)	0.487	
Post 3m	9.31 (0.54)	10.22 (0.70)	0.306	
P-value (Within group)	0.002	0.070		
Child's POPS				F(2, 164.44) = 1.76, p = 0.176
Pre	37.72 (0.83)	38.96 (1.09)	0.368	
Post	40.95 (0.83)	40.96 (1.09)	0.993	
Post 3m	39.56 (0.98)	37.47 (1.24)	0.188	
P-value (Within group)	0.017	0.051		
Child's PSC				F(2, 169.63) = 0.19, p = 0.830
Pre	11.24 (0.51)	10.95 (0.66)	0.724	
Post	10.35 (0.51)	9.39 (0.66)	0.249	
Post 3m	10.65 (0.6)	9.82 (0.76)	0.393	
P-value (Within group)	0.433	0.217		
Child self- esteem				F(2, 174.30) = 4.76, p = 0.010
Pre	51.54 (0.91)	52.77 (1.19)	0.415	
Post	57.38 (0.93)	54.67 (1.19)	0.076	
Post 3m	57.57 (1.12)	52.24 (1.36)	0.003	
P-value (Within group)	<0.001	0.308		

Abbreviations: SE, Standard error; POPS: Positive Parenting Scale; PSC: Pediatric Symptom Checklist.

the study did not track whether the control group sought out other parenting resources, which could have affected the comparison results. From a broader developmental perspective, positive parenting practices may function as protective environmental factors. Prior Thai research has highlighted the role of resilience in buffering the impact of adverse experiences on behavioral problems[27], suggesting that parenting interventions may contribute to strengthening such protective processes.

Future research should aim to replicate these findings using a larger sample size and a more rigorous research design to better control for confounding variables. Additional studies could also explore the program's impact on other variables, such as parent-child relationships, parental stress, or depression, to gain a more complete understanding of its overall effectiveness.

CONCLUSION

The facilitator-led Net PAMA program demonstrated effectiveness in enhancing child self-esteem, but it failed to significantly improve positive parenting skills or reduce child behavioral problems. These promising results warrant a future study with a larger sample size and more rigorous methodology to fully assess the program's potential.

Data Availability Statement

The data underlying the results of this study are not accessible to the public due to ethical and confidentiality constraints. However, de-identified data can be made available upon request to the corresponding author, subject to approval from the institutional ethics review board. Relevant secondary data sources are cited in the bibliography.

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DECLARATIONS

Grants and Funding Information

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Conflict of Interest

The research team declares no conflict of interest in this study.

Registration Number of Clinical Trial

The study was retrospectively registered with the Thai Clinical Trials Registry on February 22, 2026 (identification number TCTR20260222004). The trial registration record is publicly available at: https://www.thaiclinicaltrials.org/show/TCTR20260222004.

Author Contributions

Conceptualization and methodology, K.K., C.P., W.A. and S.C.; Investigation, K.K. and S.C.; Formal analysis, K.K. and W.A.; Visualization and writing – original draft, K.K.; Writing – review and editing, K.K., C.P., W.A. and S.C.; Funding acquisition, C.P. and S.C.; Supervision, W.A. and C.P. All authors have read and agreed to the final version of the manuscript.

Use of Artificial Intelligence

During the preparation of this manuscript, the authors used Google Gemini 2.5 Pro to improve language and readability. After using this tool/service, the authors reviewed and edited the content as needed and took full responsibility for the final content for publication.

Ethical Statement

This study was approved by the Siriraj Institutional Review Board at the Faculty of Medicine Siriraj Hospital, Mahidol University, on January 14, 2023. The Certificate of Approval (COA) number is Si 033/2023.

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Distribution and Pathological Findings of Intracranial Atherosclerosis in Thai Postmortem Cases

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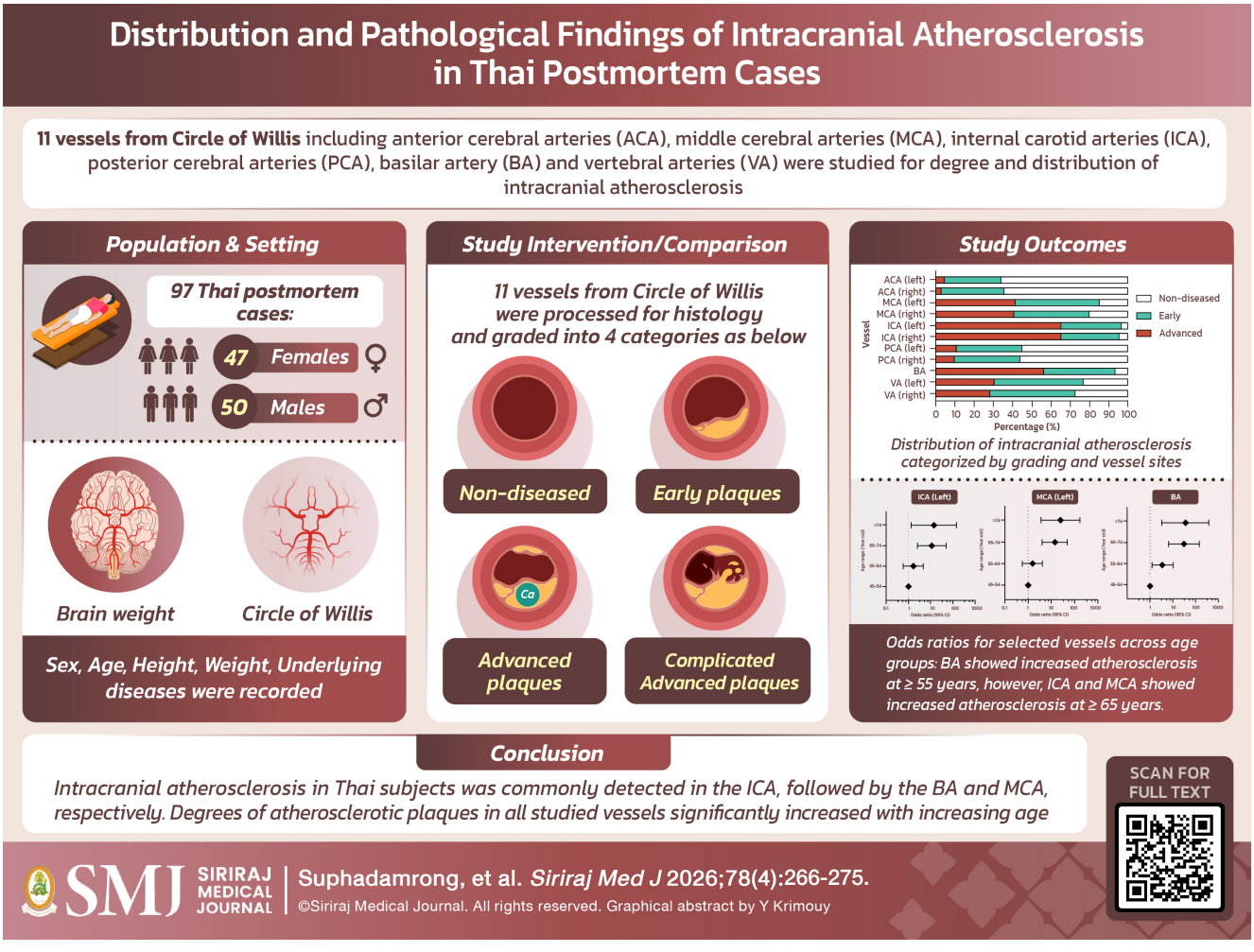

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ABSTRACT

Objective: To determine the distribution and pathological findings of intracranial atherosclerosis in Thai postmortem cases.

Materials and Methods: The prospective cross-sectional study was conducted on Thai postmortem cases aged 45 years or older. Sex, age, weight, height, and brain weight were recorded for each case. Intracranial atherosclerosis was assessed in 11 vessels of the Circle of Willis (CoW), including the anterior cerebral arteries (ACA), middle cerebral arteries (MCA), internal carotid arteries (ICA), posterior cerebral arteries (PCA), basilar artery (BA) and vertebral arteries (VA), using histological examination. Grading of atherosclerotic plaques in each vessel was recorded. Descriptive statistics, bivariate correlation, and ordinal logistic regression were performed where appropriate.

Results: A total of 97 Thai subjects were recruited, consisting of 47 female and 50 male subjects, with a mean age of 61.41 years. Brain weights in male subjects were significantly higher than those in female subjects ($p < 0.001$). Brain weights in both female and male subjects were negatively correlated with increasing age ($p < 0.001$). Early and advanced atherosclerotic plaques were most frequently detected in the ICA, followed by the BA and MCA, respectively. Using ordinal logistic regression, it was found that degrees of intracranial atherosclerosis in all vessels of the CoW significantly increased with increasing age ($p < 0.05$).

Conclusion: Intracranial atherosclerosis in Thai subjects was commonly detected in the ICA, followed by the BA and MCA, respectively. The degrees of atherosclerotic plaques in all studied vessels significantly increased with increasing age.

Keywords: Intracranial atherosclerosis; brain; Thai; autopsy (Siriraj Med J 2026;78(4):266-275)

INTRODUCTION

Stroke, or cerebrovascular disease (CVD), is one of the leading causes of death worldwide, including in Thailand.[1] Suwanwela NC reported that the prevalence of stroke in Thai people over 45 years old between 2004 and 2006 was 1.88%.[2] However, Chantkran W et al. indicated that the prevalence of stroke in 2018 was 3.9%, and the prevalence rates between 2014 and 2018 were relatively stable.[1] According to these two figures, it was suggested that the prevalence of stroke in Thai people was gradually increasing. In addition, both studies stated that the prevalence of stroke in Thai people was higher in males than in females and was more prevalent with increasing age.[1,2] Increased prevalence of stroke in Thai people also affects strategic plans to enhance quality of life in stroke patients. A previous study stated that high modified Barthel Index score at discharge time had an effect on good quality of life in Thai stroke patients.[3] Intracranial atherosclerosis is considered one of the main causes of ischemic stroke, and it is more prevalent in Asian populations than in Caucasian populations.[4,5] A previous study indicated that intracranial atherosclerosis was present in approximately 45–62% of patients with ischemic stroke[4], whereas the prevalence of intracranial atherosclerosis in asymptomatic Chinese and Japanese people was 20.6% and 15%, respectively.[5] In addition, the prevalence of the posterior circulation ischemic stroke in Korean people was 39.8% of all ischemic stroke[6] whereas overall prevalence of the posterior circulation stroke ranged from 5% to 19%.[7] These figures may indicate that Asian populations may have different patterns of intracranial atherosclerosis from Caucasian populations.

Data on the distribution of intracranial atherosclerosis are relatively limited. Denswil NP et al. stated that intracranial atherosclerosis was most commonly found in the basilar artery (BA), followed by the internal carotid arteries (ICA), vertebral arteries (VA), and middle cerebral arteries (MCA), respectively.[8] In addition, advanced stages of atherosclerosis were most commonly detected in the ICA followed by the BA and VA, respectively.[8] However, Llopis G et al. suggested that intracranial atherosclerosis was most commonly detected in the posterior cerebral arteries (PCA) and BA, followed by the MCA, ICA, and VA, respectively.[9] Moreover, people aged 40 years or older had a significantly higher prevalence of intracranial atherosclerosis than those aged 30–39 years or younger.[9] Furthermore, classification of intracranial atherosclerosis was potentially associated with ischemic stroke, because the degree of intracranial stenosis was not directly associated with occurrence of ischemic stroke, in contrast to coronary artery disease.[8,10] According to previous studies, plaque calcification and some types of complicated plaques, such as intraplaque hemorrhage, were potentially related to the occurrence of ischemic

stroke.[8,10] Therefore, the pathological characteristics and distribution of intracranial atherosclerosis are likely to be important data for further studies of stroke in the Thai population.

Currently, there is still scarce information about the distribution and characteristics of intracranial atherosclerosis in Thai people. Moreover, Thai people that are located in South East Asia may present with more prominent intracranial atherosclerosis in the posterior circulation. Thus, the authors aim to study its distribution and pathological findings in Thai postmortem cases. In addition, the authors will also consider the association between anthropological parameters and intracranial atherosclerosis in the Thai population. Age classification and severity of intracranial atherosclerosis in each vessel will be studied to demonstrate the difference patterns of vessels in the anterior and posterior circulation. This study will provide data on intracranial atherosclerosis in Thai people to expand regional analysis of intracranial atherosclerosis in Asian populations. Thai-specific age thresholds in developing intracranial atherosclerosis will be analyzed in this study to deliver fundamental findings in Thai population. This information will be important data for further studies of the occurrence of CVD and the relationship between sites of stroke and intracranial atherosclerosis in the Thai population.

MATERIALS AND METHODS

Study design and data collection

A prospective cross-sectional study was conducted on subjects sent for autopsy at the Department of Forensic Medicine, Siriraj Hospital, Mahidol University. The inclusion criteria were Thai individuals aged 45 years or older who were sent for autopsy at the Department of Forensic Medicine, Siriraj Hospital, Mahidol University between 16 December 2024 and 30 September 2025. The exclusion criteria included decomposed bodies, bodies with head injury, and bodies with any gross pathologies in the white matter of the brain. This study was approved by the Siriraj Institutional Review Board, Faculty of Medicine Siriraj Hospital, Mahidol University (COA No. Si 967/2024; SIRB protocol No. 888/2567 (IRB2)).

Sex, age, weight, height, brain weight, underlying diseases, and cause of death were recorded for each case. Body weights were quantified in kilograms (kg) on an Empire® digital balance. Body heights were measured in centimeters (cm) from the vertex to the heel using a stainless-steel tape measure. Brain weights were assessed by using a Sunford® digital balance, model FEH5000. Body mass index (BMI) was calculated by dividing weight (kg) by the square of height in meters. The Du Bois and Du Bois formula was employed for the calculation of body surface area (BSA), expressed in square meters, as described in Equation 1.[11,12]

$$BSA\ [m^2] = 0.007184 \times height\ [cm]^{0.725} \times weight\ [kg]^{0.425}$$

Equation 1

Evaluation of intracranial atherosclerosis

When the routine autopsy procedure was performed, the skull cap was removed and the brain was exposed. Then, the brain was removed from the base of the skull by severing the attachment sites of brain structures to the base of the skull, including the olfactory bulb, optic chiasma, both sides of the ICA, all cranial nerves, and both sides of the VA.[13] Next, each brain was placed for photography and was weighed on a digital balance to assess brain weight. Next, the collected brains were fixed in 10% formalin solution for one week. Then, the Circle of Willis (CoW) was carefully dissected from the base of the brain and preserved as completely as possible, as shown in Fig 1. After complete dissection, both ACA, both MCA, both ICA, both PCA, the BA, and both VA were identified. Thus, a total of 11 arteries were dissected from the CoW and prepared for the next step. Then, they

Fig 1. Dissection of the Circle of Willis.

were serially cut into multiple sections and prepared for histological study. The sampling strategy included all segments of both ICA, both VA and the BA whereas the other vessels were taken for 5 segments from the origins (around 2 cm from the origins of vessels) as the representative samples for histology. After histological slides of all vessels were prepared, the first author identified all slides and blinded them to send for the corresponding author and the consultant pathologist in the department for grading the atherosclerotic plaques. Pathological findings at each site of the Circle of Willis from both the left and right sides were identified according to the classification stated below.

Classification of atherosclerotic plaques

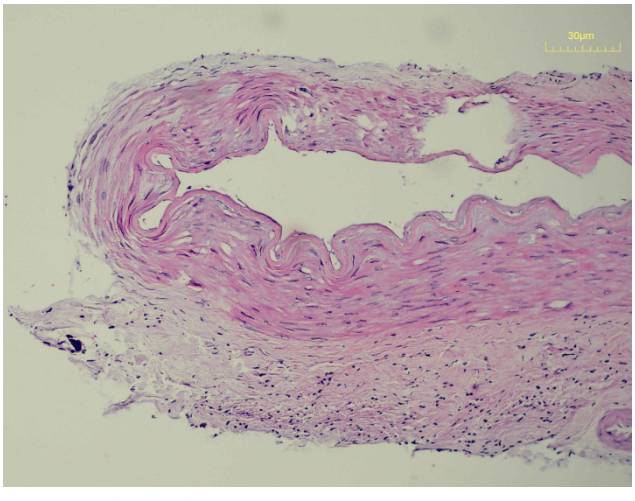
All CoW sections were stained with haematoxylin–eosin (H&E). Grading of intracranial atherosclerosis was categorized according to a revised American Heart Association classification[14] and the description from the study of Denswil NP et al.[8] Atherosclerotic plaques were classified into four groups, as described below and shown in Fig 2:

1. Non-diseased group: no intimal thickening or inflammatory infiltration
2. Early plaques: intimal thickening (accumulation of smooth muscle cells and/or proteoglycans) and fatty streaks (foamy macrophages)
3. Advanced plaques: fibrous, lipid-rich, and/or calcified tissue with a fibrous cap in which >40% of the area was lipid core or calcified tissue
4. Complicated advanced plaques: fibrous cap rupture, intraplaque hemorrhage (IPH), or chronic total occlusion of the lumen

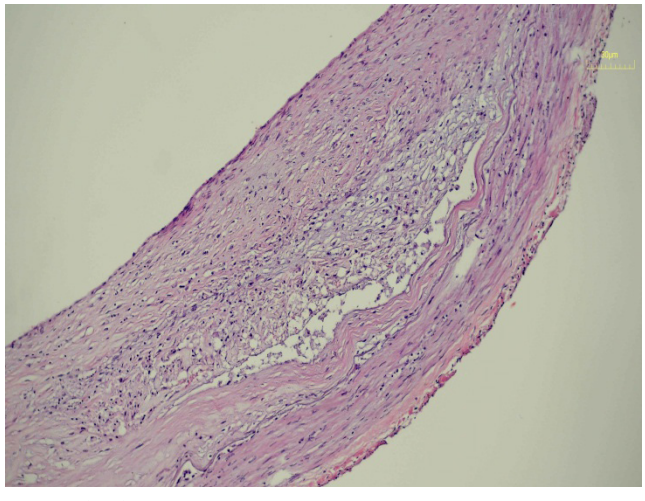
Histological findings were reviewed by two raters including the corresponding author and the consultant pathologist in the department. Raters were blinded and the information after review was collected by the first author to analyze for inter-rater reliability.

Statistical analysis

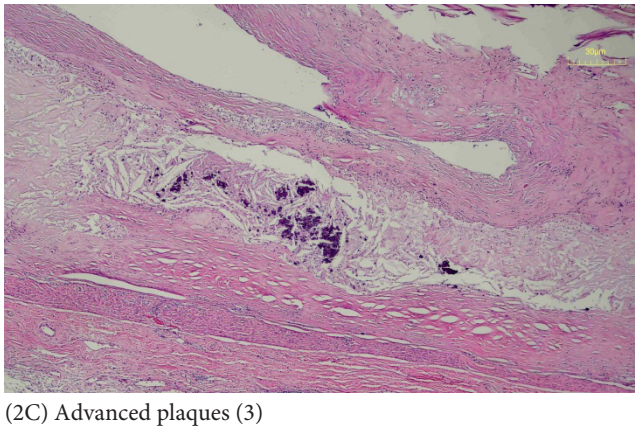
Statistical analysis was performed using IBM SPSS® Statistics for Windows, version 29. Descriptive statistics, including the mean, median, and standard deviation (SD), were analyzed. Comparisons of continuous data



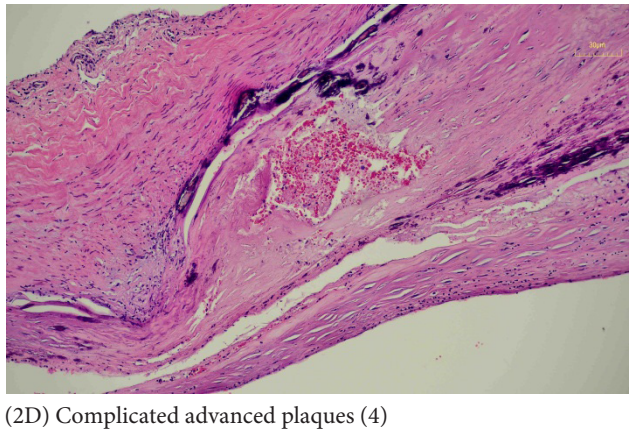
(2A) Non-diseased group (1)



(2B) Early plaques (2)



(2C) Advanced plaques (3)



(2D) Complicated advanced plaques (4)

Fig 2. Classification of pathological findings of intracranial atherosclerosis.

between female and male subjects were performed using the Mann–Whitney U test. Correlations between anthropometric parameters and brain weight were assessed using Spearman's correlation. Ordinal logistic regression with Bonferroni's correction was performed to evaluate associations between age and intracranial atherosclerosis. Cohen's Kappa coefficient score was analyzed for inter-rater reliability and a Kappa coefficient score in this study was 0.91 reflecting good agreement between the corresponding author and the consultant pathologist in the department.

RESULTS

There were 97 Thai subjects recruited in this study, consisting of 47 females (48.45%) and 50 males (51.55%). The mean age among the 97 subjects was 61.41 years. The mean BMI and BSA were 25.31 ± 4.83 kg/m^2 and 1.72 ± 0.17 m^2, respectively. A comparison of descriptive statistics between female and male subjects is shown in Table 1. BSA and brain weight in male subjects were significantly higher than those in female subjects ($p < 0.001$).

Table 2 shows correlations between brain weight and anthropometric parameters. The data showed significant negative correlations between brain weight and age in both female and male subjects ($p = 0.001$ and $p < 0.001$, respectively), whereas BMI and BSA did not show significant correlations with brain weight. Linear regression analysis between age and brain weight for both female and male subjects is shown in Fig 3. According to the linear regression curves, brain weight in male subjects decreased at a more rapid rate than in female subjects.

When subjects were divided into two groups based on underlying diseases related to metabolic syndrome, including diabetes mellitus, hypertension, dyslipidemia, coronary artery disease, gout, and chronic kidney disease, there were 42 subjects who did not have histories of these underlying diseases (35 subjects with no history of any underlying diseases and seven subjects with other underlying diseases, including asthma/chronic obstructive pulmonary disease and psychiatric disorders), whereas there were 55 subjects who had at least one of these underlying diseases. Comparison of brain weights between these two groups was performed using the Mann–Whitney U test.

TABLE 1. Comparison of descriptive statistics between female and male subjects.

Parameters	Female (mean ± SD, range)	Male (mean ± SD, range)	p-value
Age (years)	61.15 ± 10.62 (45–85)	61.66 ± 10.32 (45–85)	0.795
BMI (kg/m^2)	26.33 ± 5.78 (16.81–41.20)	24.34 ± 3.54 (17.64–35.45)	0.161
BSA (m^2)	1.66 ± 0.20 (1.35–2.12)	1.78 ± 0.13 (1.54–2.27)	<0.001
Brain weight (g)	1,163.66 ± 83.31 (1,032–1,317)	1,295.64 ± 102.59 (1,060–1,454)	<0.001

TABLE 2. Correlation between brain weight and anthropometric parameters.

Subjects	Correlation between brain weight and anthropometric parameters		Spearman's correlation	p-value
Female (N = 47)	Brain weight vs	Age (years)	−0.457	0.001
		BMI (kg/m^2)	0.238	0.108
		BSA(m^2)	0.201	0.175
Male (N = 50)	Brain weight vs	Age (years)	−0.747	<0.001
		BMI (kg/m^2)	0.118	0.414
		BSA(m^2)	0.120	0.408

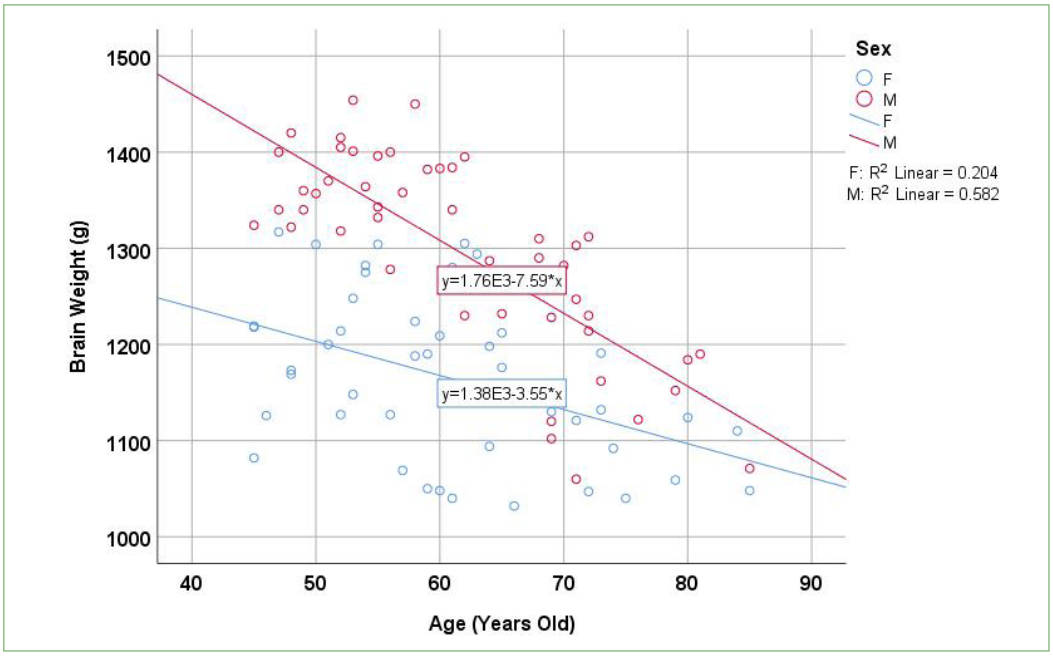


Fig 3. Relationship between age and brain weight (g) in both female (blue dots and line) and male (red dots and line) subjects.

Median (mean ± SD) brain weights in subjects without underlying diseases and in subjects with underlying diseases related to metabolic syndrome were 1,247.50 g (1,238.33 ± 112.87 g) and 1,212.00 g (1226.62 ± 116.38 g), respectively. Although brain weights in subjects without underlying diseases were relatively higher than those in subjects with underlying diseases related to metabolic syndrome, statistical analysis did not show a significant difference between these two groups (p = 0.526).

The distribution of intracranial atherosclerosis across six vessel types of the Circle of Willis is shown in Fig 4. It was found that advanced stages of atherosclerosis were more common in the ICA, followed by the BA and MCA, respectively, whereas the ACA was least likely to have advanced stages of atherosclerosis.

The subjects were divided into four groups according to age: 45–54, 55–64, 65–74 and ≥75 years. As the number of cases in group 4 (degree of intracranial atherosclerosis) was small, further statistical analysis was performed by combining groups 3 and 4. Thus, the degree of intracranial atherosclerosis was classified into three groups for statistical analysis in this study. Ordinal logistic regression with Bonferroni's correction was performed on the three severity groups of intracranial atherosclerosis in each vessel and the four age groups to demonstrate the degree of risk associated with age. The results are shown with forest plots in Fig 5A and 5B. These findings showed that the degrees of intracranial atherosclerosis in all vessels increased with increasing age, with the highest odds ratio (OR) observed in the BA. In addition, the BA and left VA (posterior circulation) showed a significantly increased degree of intracranial atherosclerosis from age ≥55 years, whereas the other vessels showed this increase from age ≥65 years.

DISCUSSION

This study showed that brain weights in Thai male subjects were significantly higher than those in Thai

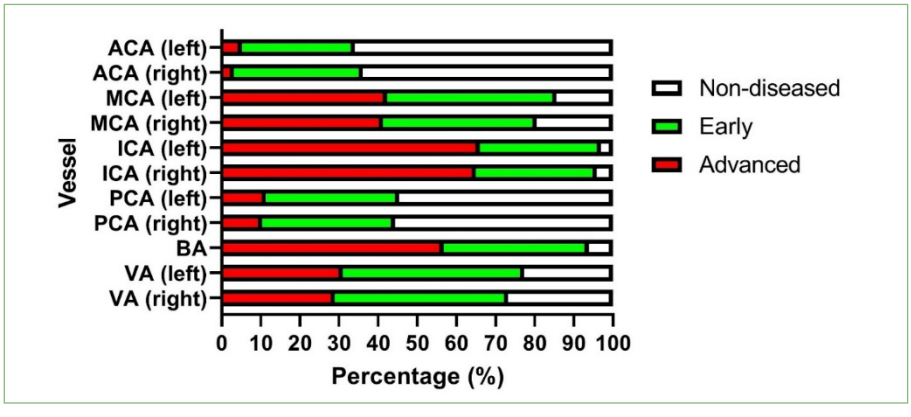


Fig 4. Distribution of intracranial atherosclerosis across six vessel types of the CoW (11 vessels).

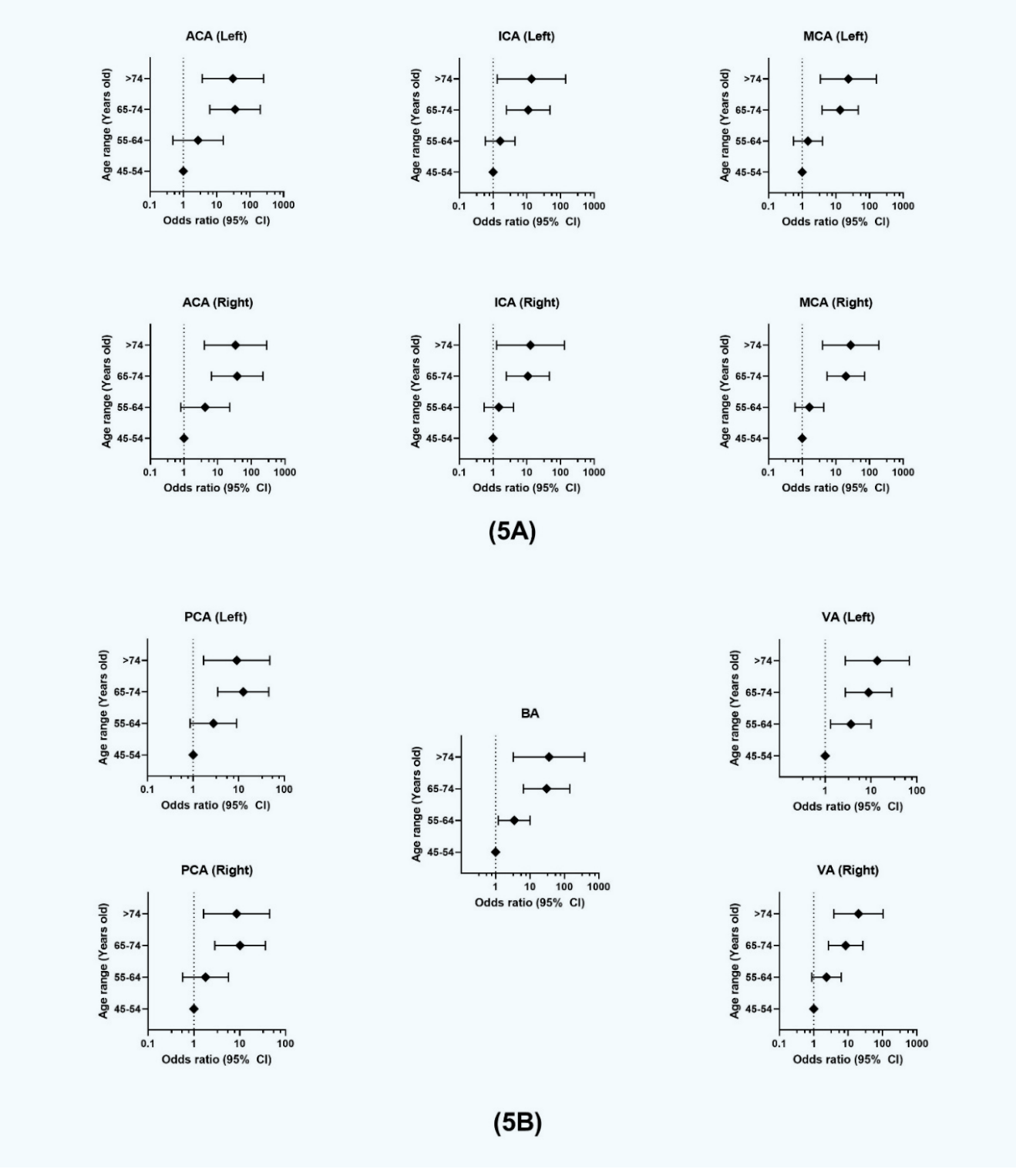


Fig 5. Odds ratios and 95% confidence interval (95% CI) for six vessel types of the CoW (11 vessels) across four age groups: (5A): ACA (left and right), ICA (left and right) and MCA (left and right) and (5B): PCA (left and right), BA and VA (left and right).

female subjects. In addition, brain weights in both Thai male and female subjects significantly decreased with increasing age. These findings were consistent with previous studies.[15,16] When focusing on brain weight after 45 years of age, it was suggested that brain weights in Thai male and female subjects were smaller than those reported in a previous study.[16] That study indicated that rate of brain weight reduction in both male and female subjects occurred to a similar degree, resulting in brain weights that were 10-15% higher in males than in females.[16] However, this study showed that the rate of brain weight reduction in Thai male subjects was

more rapid than that in Thai female subjects, as shown in Fig 3. This study also showed that brain weights in subjects who had underlying diseases related to metabolic syndrome were not significantly different from those in subjects who had no underlying diseases. However, this finding was in contrast to a previous study that showed a significant difference in brain weights between subjects who had underlying diseases and those who had no underlying diseases.[15] Brain weights in subjects who had hypertension, coronary artery disease, dyslipidemia, and a history of smoking were significantly lower than those in subjects who had no underlying diseases.[15] As this study consisted of a relatively small number of subjects, a larger sample size should be recruited in further studies to elucidate this finding.

This study showed that intracranial atherosclerosis was most commonly detected in the ICA, followed by the BA, MCA, and VA, respectively (as shown in Fig 4). In addition, early and advanced atherosclerotic plaques were present in a similar sequence (Fig 4). Our results were comparable to a previous study that showed the most common areas of intracranial atherosclerosis occurring in the BA, followed by the ICA, VA, and MCA, respectively.[8] However, the previous study also reported that advanced stages of intracranial atherosclerosis were most commonly found in the ICA, followed by the BA, VA, and MCA, respectively.[8] When considering the ACA and PCA, it was found that atherosclerosis in the ACA and PCA was present in approximately 30–40%, whereas advanced atherosclerotic plaques were present in <10% for the ACA and around 10% for the PCA, respectively. This finding contrasts with the previous study, which reported atherosclerosis in the ACA and PCA at 75–80%[8], while advanced atherosclerotic plaques were present in 10–20%. This may result from the difference in age range between these two studies, because our study had an overall mean age of 61.41 years, with a similar mean age between male and female subjects. However, the previous study had an overall median age of 68 years, with the mean ages for male and female subjects being 62.4 and 72.9 years, respectively.[8] The higher age group in the previous study may have resulted in a higher prevalence of intracranial atherosclerosis in the ACA and PCA.

After atherosclerotic involvement of each vessel in CoW was examined, age group and all six vessel types in CoW were analyzed for potential difference between the anterior and posterior circulation. When ordinal logistic regression was performed, it was found that the degree of intracranial atherosclerosis in all of vessels of the CoW significantly increased with increasing age groups both in the anterior and posterior circulation. For the anterior circulation, including the ICA, MCA, and ACA, the risk of intracranial atherosclerosis increased significantly at the age group ≥65 years. Interestingly, for the posterior circulation, including the BA and left VA, the risk of intracranial atherosclerosis increased significantly at the age group ≥55 years, with the BA showing a higher OR than the other common vessels, including the ICA and MCA. This finding suggests that the BA (posterior circulation) in Thai subjects in this study presents an earlier and higher risk of atherosclerosis than the ICA and MCA. Because intracranial atherosclerotic stenosis is more prevalent in Asian and African-American populations compared to Caucasian populations[4,5,10], this finding may serve as a foundational basis for future research, particularly in Thai patients ≥55 years old, who are more prone to have intracranial atherosclerosis. Moreover, this result was consistent with the finding in the previous research that showed the higher rate of infarction location at the middle territory supplied by the BA than other territories in the posterior circulation and this study suggested that developed atheromatous plaque in the BA may play an important role in the posterior circulation stroke.[6] The study in Spanish people in Madrid showed that the BA as well as MCA and PCA presented with the highest frequency in atheromatous plaques among overall vessels in CoW.[9] This previous study hypothesized that this may be related to high turbulent flow in these vessels and this may explain earlier atherosclerotic development of the BA in this study.[9] In addition, a previous study suggested that subjects with posterior circulation strokes had higher plaque thickness and luminal area at the plaque than subjects with anterior circulation strokes, even though they had similar degrees of atherosclerosis.[17] Because plaque characterization in this study was limited to histological grading without further identification of plaque composition and the supporting study in molecular staining and hemodynamic findings, the association between plaque development and other biological characteristics could not be performed. Thus, further research should concentrate on comparing the characteristics of atherosclerotic plaques between anterior and posterior circulation.

This study had several limitations. First, the validity of the histories of underlying diseases in autopsy cases may be questionable, because subjects might not have informed their relatives about their underlying conditions. In addition, some subjects might have experienced symptoms related to underlying diseases but did not seek medical attention or treatment for these symptoms. This may lead to categorical bias for negative information in underlying diseases related to metabolic syndromes.

Second, the number of subjects who were ≥75 years old was relatively small compared with other age groups. This may have affected the prevalence of intracranial atherosclerosis, especially in the ACA and PCA, where the incidence of advanced atherosclerotic plaques was low. Third, this study did not include brains that had any gross pathological findings such as infarction or hemorrhage. Thus, this study did not provide the correlation between pathological findings and gross stroke patterns. Functional implication of atheromatous plaque characteristics for gross stroke patterns should be carefully interpreted. Lastly, our study had a relatively small sample size. Therefore, the ordinal logistic regression analysis could not be performed separately between male and female subjects to assess the effect of sex in the Thai population, although a previous study showed no significant difference in the degree of atherosclerosis between male and female subjects.[8] Thus, further research with a larger sample size should be conducted to elucidate this finding in the Thai population.

CONCLUSIONS

Brain weight was significantly negatively associated with increasing age. In addition, brain weight in Thai male subjects was significantly higher than in female subjects. Intracranial atherosclerosis in Thai subjects was most prevalent in the ICA, followed by the BA, MCA, and VA, respectively. The degree of atherosclerotic plaques in all 11 vessels of the CoW significantly increased with age, particularly in the BA.

Data Availability Statement

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

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DECLARATIONS

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The authors did not receive grants or funding for this research.

Conflict of Interest

The authors declare no potential conflict of interest.

Registration Number of Clinical Trial

Not applicable.

Authors' Contributions

Conceptualization and Methodology, P.S., P.P.; Investigation, P.S.; Formal analysis, P.S.; Data Curation, P.S., P.P.; Visualization and Writing – Original Draft, P.S.; Writing – Review & Editing, P.S., P.P.; Supervision, P.P. All authors read and approved the final version of this manuscript submitted for publication.

Use of Artificial Intelligence

The authors did not employ any artificial intelligence tools in the analysis, writing or any steps of development of this research.

Ethical Approval

This study was approved by the Siriraj Institutional Review Board, Faculty of Medicine Siriraj Hospital, Mahidol University (COA No. Si 967/2024; SIRB protocol No. 888/2567 (IRB2)).

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Preoperative Antihypertensive Use and Risk of Post-Spinal Hypotension in Elderly Patients Undergoing Hip Fracture Surgery: A Retrospective Secondary Analysis

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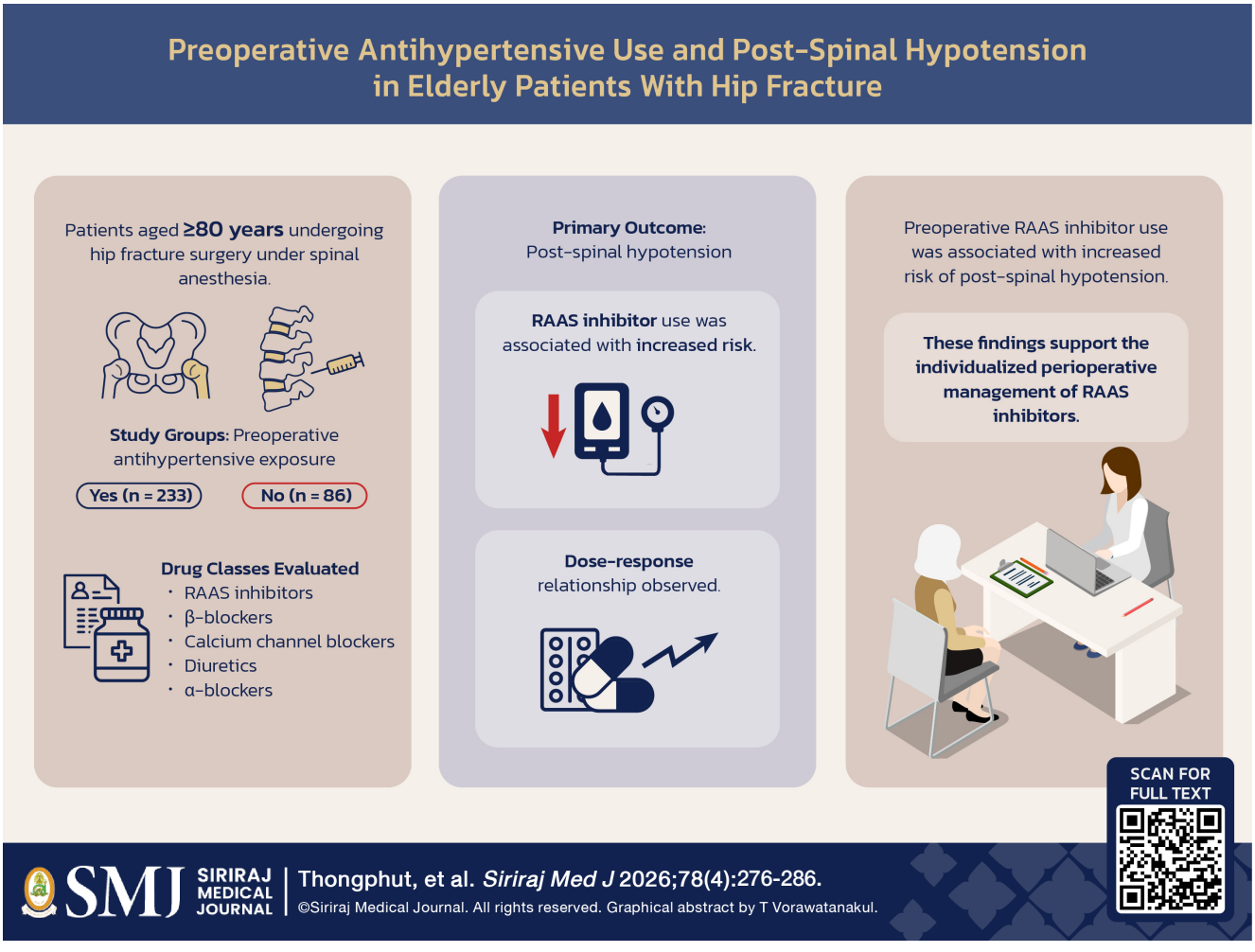

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ABSTRACT

Objective: To examine the association between preoperative antihypertensive medication use and the risk of post-spinal hypotension in patients aged ≥80 years undergoing hip fracture surgery.

Materials and Methods: This retrospective cohort study was a secondary analysis of patients aged ≥80 years who underwent hip fracture surgery under spinal anesthesia at a tertiary-care hospital between October 2016 and September 2023. Patients were categorized according to whether antihypertensive medications were taken on the day of surgery. The primary outcome was post-spinal hypotension. Univariable and multivariable risk ratio regression analyses were performed.

Results: Overall, 63% of patients developed post-spinal hypotension. Preoperative antihypertensive use was not significantly associated with hypotension in the multivariable analysis. However, use of renin–angiotensin–aldosterone system (RAAS) antagonists was independently associated with an increased risk (RR 1.38; 95% CI 1.13–1.68; p = 0.002). A significant dose–response relationship was observed between the number of antihypertensive agents and the incidence of hypotension (p for trend = 0.036). Patients receiving ≥3 antihypertensive agents had the highest adjusted risk ratio, although this was not statistically significant.

Conclusion: Preoperative antihypertensive use was not associated with an increased risk of post-spinal hypotension in patients aged 80 years and older with hip fractures. However, RAAS antagonists and multiple-antihypertensive regimens may increase susceptibility to hemodynamic instability. Careful preoperative assessment of antihypertensive therapy is recommended.

Keywords: Antihypertensive agents; elderly; hip fractures; spinal anesthesia; intraoperative hypotension; surgical procedures (Siriraj Med J 2026;78(4):276-286)

INTRODUCTION

Spinal anesthesia is widely used in elderly patients undergoing hip fracture surgery because of its favorable safety profile and lower risk of postoperative complications compared with general anesthesia.[1,2] However, hypotension following spinal anesthesia remains a common and clinically significant complication,[3–5] particularly in elderly individuals, who often have reduced physiological reserves, multiple comorbidities, and polypharmacy.[6]

Hypotension after spinal anesthesia is mainly caused by sympathetic blockade, which produces arterial and venous vasodilation, reduced systemic vascular resistance, and decreased venous return. Maintenance of arterial pressure under these conditions relies on compensatory vasoconstrictive mechanisms, including activation of the renin–angiotensin–aldosterone system (RAAS). Consequently, patients receiving RAAS inhibitors, such as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, may be more susceptible to hypotension, as these agents blunt angiotensin II–mediated vasoconstriction and limit hemodynamic compensation during sympathetic blockade.

Several factors have been associated with post-spinal hypotension in older adults, including advanced age, higher American Society of Anesthesiologists physical status, baseline blood pressure, preoperative antihypertensive therapy, and intrathecal local anesthetic dose.[5,7-8] Among these factors, preoperative antihypertensive medication use is potentially modifiable. Although these medications are commonly prescribed for elderly patients with hypertension or cardiovascular comorbidities, their independent effect on hypotension following spinal anesthesia remains unclear. Previous studies have reported inconsistent results, and evidence specifically addressing patients aged ≥80 years—who are particularly vulnerable to hypotension-related complications—remains limited.[9–11]

Therefore, this study aimed to evaluate the association between preoperative antihypertensive use and the occurrence of hypotension after spinal anesthesia in patients aged ≥ 80 years undergoing hip fracture surgery, based on secondary analysis of retrospective cohort data.

MATERIALS AND METHODS

Study design and setting

This study was a retrospective secondary analysis of data derived from a previous investigation of post-spinal hypotension in elderly patients. Patients aged 80 years or older who underwent hip fracture surgery under spinal anesthesia at a tertiary referral center in Southern Thailand between October 1, 2016, and September 30, 2023, were included. The study protocol was approved by the Institutional Ethics Committee.

Study population

All patients aged ≥80 years who underwent hip fracture surgery under spinal anesthesia during the study period were screened. Patients were excluded if they had incomplete medical records, failed or inadequate spinal anesthesia, required deep sedation, had pre-existing hypotension, or received vasoactive agents prior to induction of anesthesia.

Exposure and outcome definitions

Patients were categorized according to whether antihypertensive medications were taken on the day of surgery prior to spinal anesthesia. Antihypertensive agents were classified into the following groups: renin–angiotensin–aldosterone system (RAAS) antagonists, beta-blockers, calcium channel blockers, diuretics, and alpha-blockers. The total number of antihypertensive agents used by each patient was also recorded. Preoperative antihypertensive exposure was defined as medications actually administered on the morning of surgery by ward nurses, based on medication administration records documented in the medical charts.

The primary outcome was post-spinal hypotension, defined as systolic blood pressure <90 mmHg or a >20% reduction from baseline within one hour after spinal anesthesia. Blood pressure was measured at 1-minute intervals during the first 10 minutes and every 5 minutes thereafter according to institutional monitoring protocols. A single measurement meeting either criterion was considered hypotension. Patients receiving prophylactic vasopressors were excluded to avoid masking hypotension incidence.

Data collection

Data were extracted from electronic medical records and included demographic characteristics (age, sex, and body mass index), comorbidities, American Society of Anesthesiologists (ASA) physical status classification, fracture type, surgical procedure, baseline blood pressure measured in the ward prior to transfer to the operating room, and preoperative laboratory values. Intraoperative variables included anesthetic technique, intrathecal drug administration, hemodynamic parameters, fluid administration, vasopressor use, and operative duration.

Spinal anesthesia was performed according to institutional routine practice. After standard monitoring was established, intravenous crystalloid or colloid loading (preload or co-load) was administered at the attending anesthesiologist's discretion. Patients were placed in the lateral decubitus position, and spinal anesthesia was performed using standard aseptic technique.

A midline or paramedian approach at the L2–3, L3–4, or L4–5 interspace was used with a 25–27G spinal needle. Hyperbaric or isobaric bupivacaine was administered intrathecally, with the dose determined by the attending anesthesiologist. Intrathecal opioids (fentanyl or morphine) were added at discretion.

After injection, patients were generally maintained in the lateral position for approximately 5 minutes. Sensory block level was assessed using cold or pinprick testing until approximately 10 minutes post-block according to institutional protocol. The highest sensory level, when available, was included in the analysis. No fixed institutional protocol for fluid loading or prophylactic vasopressor administration was used during the study period.

Sample size and power estimation

As this study was a secondary analysis of existing retrospective data, no prospective sample size calculation was performed. All eligible patients from the original dataset who met the inclusion criteria were included. A post hoc power estimation based on the adjusted risk ratio for RAAS antagonist use (RR 1.38; 95% CI 1.13–1.68) and its corresponding standard error indicated an approximate statistical power of 89% at a two-sided alpha level of 0.05 for detecting this association.

Statistical analysis

The distribution of continuous variables was assessed for normality using graphical methods and the Shapiro–Wilk test. Normally distributed variables were presented as mean ± standard deviation and compared using Student's t-test, whereas non-normally distributed variables were summarized as median (interquartile range) and compared using the Mann–Whitney U test. Categorical variables were expressed as frequencies and percentages and compared using Fisher's exact test because of small expected cell counts.

Univariable and multivariable risk ratio regression analyses were performed using a generalized linear model with a Poisson distribution and robust variance estimation to identify factors associated with post-spinal hypotension. Variables deemed clinically relevant or with a p-value <0.05 in univariable analysis were entered into the multivariable model. Results were reported as risk ratios (RRs) with 95% confidence intervals (CIs). Missing data were handled using complete-case analysis. All statistical tests were two-sided, and a p-value <0.05 was considered statistically significant. Statistical analyses were conducted using Stata version 16.0 (StataCorp, College Station, TX, USA).

RESULTS

A total of 319 patients aged ≥80 years who underwent hip fracture surgery under spinal anesthesia were included. Of these, 233 patients (73.0%) received preoperative antihypertensive medication. Baseline characteristics of the study population are summarized in Table 1. Patients in the antihypertensive group were more frequently female and had higher American Society of Anesthesiologists (ASA) physical status classifications. Comorbidities were more prevalent in this group, including hypertension, prior cerebrovascular accident, and chronic kidney disease stage 3–5. No significant differences were observed in age, body mass index, baseline blood pressure, or most preoperative laboratory parameters between groups.

Intraoperative characteristics are shown in Table 2. The distribution of fracture types and surgical procedures differed significantly between groups. Intertrochanteric fractures were more common in patients not receiving antihypertensive medication, whereas arthroplasty procedures were more frequent in those receiving antihypertensive therapy. The mean dose of hyperbaric bupivacaine was lower in the antihypertensive group, and intrathecal morphine was used more frequently. There were no significant differences between groups in operative time, estimated blood loss, anesthetic level, vasopressor use, or type and volume of fluid preload.

Spinal anesthesia characteristics according to RAAS antagonist exposure are summarized in Table 3. No significant between-group difference in sensory block level was observed. Similarly, intrathecal local anesthetic type and dose, as well as intrathecal opioid use, were comparable between groups.

The overall incidence of post-spinal hypotension was 63.0%. The incidence was 64.8% in patients who received preoperative antihypertensive medication and 58.1% in those who did not, with no statistically significant difference between groups (Table 4). When stratified by antihypertensive drug class, higher incidences of hypotension were observed among patients receiving renin–angiotensin–aldosterone system (RAAS) antagonists and beta-blockers. A significant dose–response trend was observed between the number of concurrent antihypertensive agents and the incidence of hypotension, with the highest incidence observed among patients receiving four agents (Fig 2).

Multivariable risk ratio regression analysis adjusted for age, sex, body mass index, ASA classification, comorbidities, fracture type, baseline blood pressure, hemoglobin level, intrathecal local anesthetic type and dose, intrathecal opioid, fluid administration, anesthetic level, and time to surgery demonstrated that overall preoperative antihypertensive use was not independently associated with post-spinal hypotension (adjusted RR = 1.00; 95% CI, 0.72–1.40; p = 0.981). The use of RAAS

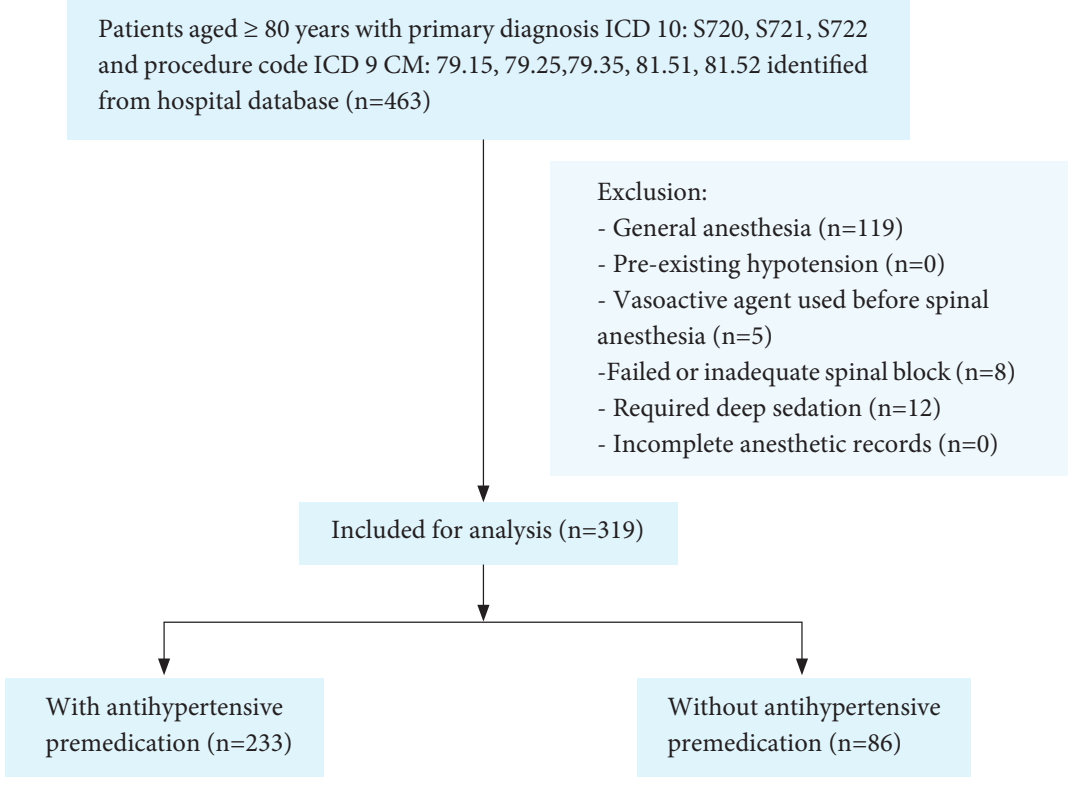

Fig 1. Study flow diagram

TABLE 1. Patients' characteristics.

Characteristics	With antihypertensive medication n=233 (73%)	Without antihypertensive medication n=86 (27%)	p value
Female	201 (86.3)	62 (72.1)	0.005*
Age (years)	85.2 ± 4.0	85.8 ± 4.2	0.288
Height (cm)	153.8 ± 7.8	152.8 ± 6.1	0.314
Body mass index (kg/m^2)	21.9 ± 4.1	21.1 ± 4.0	0.099
ASA classification			<0.001*
II	25 (10.7)	27 (31.4)	
III-IV	208 (89.3)	59 (68.6)	
Comorbidity	232 (99.6)	49 (57.0)	<0.001*
Hypertension	229 (98.3)	25 (29.1)	<0.001*
Previous/History of myocardial infarction	8 (3.4)	1 (1.2)	0.453
Previous/History of cerebrovascular disease	35 (15.0)	4 (4.7)	0.012*
Chronic kidney disease stage 3-5	36 (15.5)	2 (2.3)	0.001*
COPD	17 (7.3)	11 (12.8)	0.179
Dementia	11 (4.7)	3 (3.5)	0.766
Laboratory value			
Admission hemoglobin (gm/dl)	10.8 ± 1.9	10.6 ± 1.9	0.305
Preoperative hematocrit (%)	34 ± 3.4	33.7 ± 3.3	0.537
Blood urea nitrogen (mg/dl)	16 (13, 22)	16 (12, 23)	0.892
Creatinine (mg/dl)	0.79 (0.64, 1.08)	0.75 (0.62, 1.03)	0.359
eGFR (ml/min/1.73 m^2)	71.0 ± 26.1	76.0 ± 26.0	0.125
Albumin (g/dl)	3.6 ± 0.5	3.5 ± 0.4	0.678
Baseline SBP (mmHg)	135.6 ± 17.0	134.1 ± 17.7	0.480
Baseline DBP (mmHg)	71.6 ± 10.8	72.5 ± 11.2	0.510
Preoperative transfusion (unit)	0 (0, 1)	0 (0, 1)	0.931

Values are presented as mean ± SD, number (%), and median (Q1, Q3)

Abbreviations: ASA: American Society of Anesthesiologists, COPD: Chronic Obstructive Pulmonary Disease, eGFR: Estimated Glomerular Filtration Rate, SBP: systolic blood pressure, DBP: diastolic blood pressure

antagonists remained significantly associated with post-spinal hypotension (adjusted RR = 1.38; 95% CI, 1.13–1.68; p = 0.002). When the combined effect of multiple antihypertensive agents was evaluated, a significant dose–response trend was observed between the number of concurrent medications and the risk of hypotension. Patients receiving three or more antihypertensive agents exhibited the highest adjusted risk, although this was not statistically significant (adjusted RR = 1.45; 95% CI, 0.96–2.17; p = 0.074) (Table 5 and Fig 3).

TABLE 2. Intraoperative prognostic factors.

Prognostic factor	With antihypertensive n=233 (73%)	Without antihypertensive n=86 (27%)	p value
Injury to surgery (days)	5 (3, 8)	4 (2, 7)	0.014*
Type of fracture			0.015*
Neck	94 (40.3)	21 (24.4)	
Intertrochanteric	136 (58.4)	62 (72.1)	
Subtrochanteric	3 (1.3)	3 (3.5)	
Operation			0.045*
Arthroplasty	86 (36.9)	21 (24.4)	
Fixation	147 (63.1)	65 (75.6)	
Intrathecal bupivacaine			0.838
Hyperbaric	26 (11.2)	8 (9.3)	
Isobaric	207 (88.8)	78 (90.7)	
0.5% Hyperbaric bupivacaine dose (ml)	2.5 ± 0.4	2.9 ± 0.4	0.022*
0.5% Isobaric bupivacaine dose (ml)	2.7 ± 0.3	2.6 ± 0.4	0.458
Intrathecal opioid			0.043*
Morphine	30 (12.9)	5 (5.8)	
Fentanyl	3 (1.3)	4 (4.7)	
Anesthetic level			0.556
≥ T6	41 (17.6)	12 (14.0)	
Below T6	144 (61.8)	52 (60.4)	
Undetermined	48 (20.6)	22 (25.6)	
Operative time (min)	59.2 ± 26.7	61.4 ± 24.3	0.498
Estimated blood loss (ml)	100 (50, 200)	100 (50, 250)	0.838
Intravenous sedation	171 (73.4)	54 (62.8)	0.073
Fluid preload/ co-load			0.614
Crystalloid	132 (56.7)	46 (53.5)	
Colloid	101 (43.4)	40 (46.5)	
Crystalloid volume (ml)	454.9 ± 179.9	437.0 ± 191.6	0.567
Colloid volume (ml)	353.5 ± 124.3	395.0 ± 102.4	0.063

Values are presented as mean ± SD, number (%), and median (Q1, Q3)

TABLE 3. Spinal anesthesia characteristics by RAAS antagonist exposure.

Anesthetic characteristics	RAAS antagonist n=70 (21.9%)	Non-RAAS antagonist n=249 (78.1%)	p-value
Intrathecal bupivacaine			1.000
Hyperbaric	7 (10.0)	27 (10.8)	
Isobaric	63 (90.0)	222 (89.2)	
0.5% Hyperbaric bupivacaine dose (ml)	2.5 ± 0.3	2.6 ± 0.4	0.509
0.5% Isobaric bupivacaine dose (ml)	2.7 ± 0.3	2.7 ± 0.4	0.091
Intrathecal opioid			0.156
Morphine	11 (15.7)	24 (9.6)	
Fentanyl	0 (0.0)	7 (2.8)	
Anesthetic level†			1.000
≥ T6	13 (21.0)	40 (21.4)	
Below T6	49 (79.0)	147 (78.6)	

Values are presented as mean ± SD, and number (%)
†Analysis of anesthetic level was performed after excluding cases with an undocumented sensory level.

TABLE 4. Antihypertensive premedication and risk of post-spinal hypotension.

Type and combination of antihypertensive premedication	Total (n=319)	Risk of hypotension	p value
Premedication			0.297
No	86 (27.0)	50 (58.1)	
Yes	233 (73.0)	151 (64.8)	
Type			
Calcium blocker	210 (65.8)	135 (64.3)	0.542
RAAS antagonist	70 (21.9)	52 (74.3)	0.035*
Beta blocker	35 (11.0)	28 (80.0)	0.027*
Diuretic	25 (7.8)	20 (80.0)	0.084
Alpha blocker	7 (2.2)	5 (71.4)	1.000
Combination			0.004**
0	86 (27.0)	50 (58.1)	
1	143 (44.8)	84 (58.7)	
2	72 (22.6)	50 (69.4)	
3	13 (4.1)	12 (92.3)	
4	5 (1.6)	5 (100)	

Values are presented as number (%), **p value for trend
Abbreviation: RAAS antagonist: renin–angiotensin–aldosterone system antagonist.

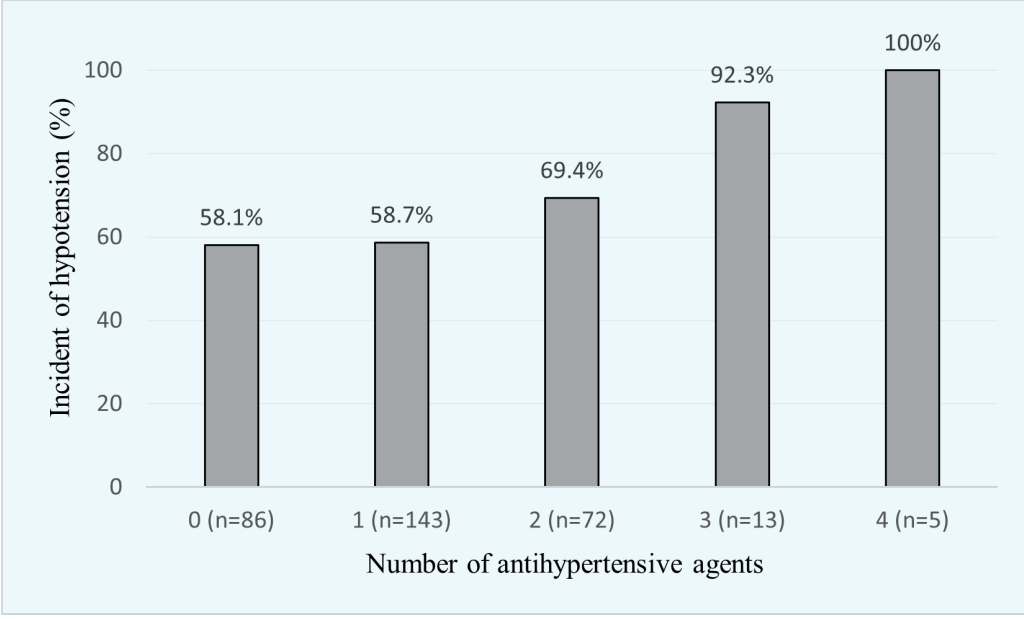

Fig 2. Incidence of post-spinal hypotension according to the number of antihypertensive agents. The incidence increased progressively with the number of agents, suggesting a dose–response relationship (P for trend = 0.004).

TABLE 5. Risk of post-spinal hypotension.

Antihypertensive	Univariable RR	Multivariable RR†	95% CI	p value
Premedication				
No	ref	ref	ref	
Yes	1.11	1.00	0.72 – 1.40	0.981
Type				
Calcium channel blocker	1.06	0.98	0.76 – 1.27	0.891
RAAS antagonist	1.24	1.38	1.13 – 1.68	0.002*
Beta blocker	1.31	1.10	0.84 – 1.45	0.476
Diuretic	1.30	1.07	0.80 – 1.43	0.656
Alpha blocker	1.14	1.05	0.53 – 2.06	0.898
Combination				0.036**
0	ref	ref	ref	
1	1.01	0.93	0.66 – 1.31	0.679
2	1.19	1.06	0.74 – 1.52	0.755
≥ 3	1.62	1.45	0.96 – 2.17	0.074

†adjusted for age, sex, height, BMI, co-morbidities, ASA, hemoglobin level, baseline blood pressure, time to surgery after injury, fracture type and surgery, local anesthetic type and dose, intrathecal opioid, intravenous fluid pre-load type and volume, and anesthetic level.
**p value for trend, RAAS antagonist: renin–angiotensin–aldosterone system antagonist.

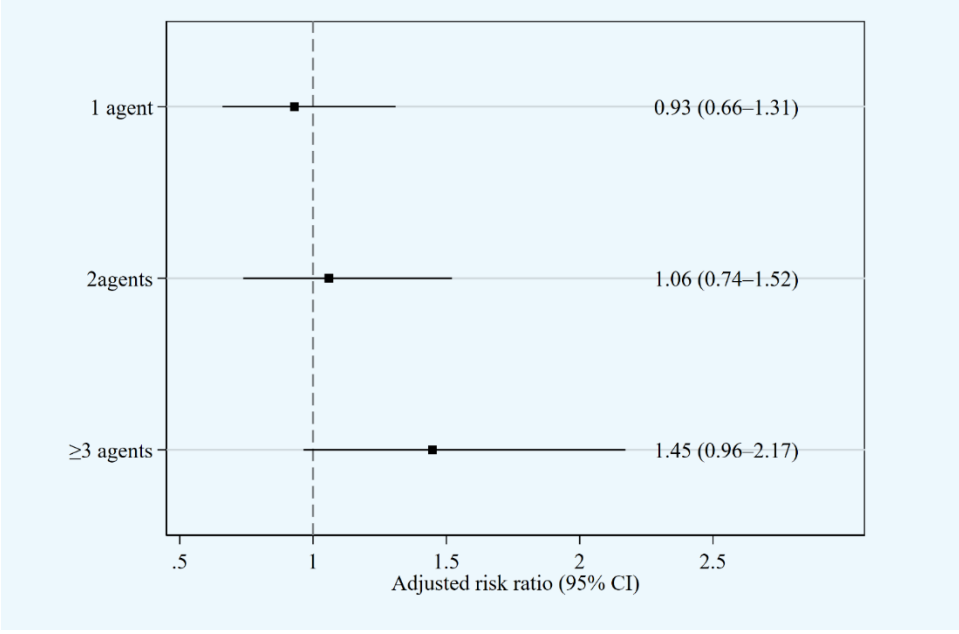

Fig 3. Adjusted risk ratios for post-spinal hypotension according to the number of antihypertensive agents. Squares represent adjusted risk ratios and horizontal lines indicate 95% confidence intervals. The dashed vertical line indicates a risk ratio of 1. A dose–response trend was observed (P for trend = 0.036).

DISCUSSION

This secondary analysis demonstrated that overall preoperative antihypertensive medication use was not independently associated with post-spinal hypotension in patients aged 80 years and older undergoing hip fracture surgery. However, the use of renin–angiotensin–aldosterone system (RAAS) antagonists was associated with an increased risk of hypotension. In addition, a dose–response relationship was observed between the number of concurrent antihypertensive agents and the incidence of post-spinal hypotension.

These findings suggest that not all antihypertensive medications pose the same hemodynamic risk in the setting of spinal anesthesia. RAAS antagonists may impair compensatory vasoconstrictive responses following sympathetic blockade, thereby predisposing elderly patients to hypotension. Similar sensory block levels and comparable intrathecal opioid use between RAAS antagonist and non-RAAS antagonist groups suggest that differences in anesthetic technique were unlikely to explain the findings. These findings are consistent with a previous report identifying RAAS antagonists, including ACE inhibitors and angiotensin receptor blockers, as contributors to perioperative hypotension.[12] However, another study found that long-term ACEI therapy, even when continued until the morning of surgery, did not significantly influence early post-spinal blood pressure changes.[13]

These observations should be interpreted in the context of contemporary perioperative cardiovascular recommendations. The 2024 AHA/ACC/ACS guideline suggests that temporary omission of RAAS inhibitors before elevated-risk noncardiac surgery may reduce intraoperative hypotension in selected patients treated for hypertension (Class IIb recommendation).[14] The present findings are broadly aligned with this perspective. However, the same guideline supports continuation of RAAS inhibitors in patients with heart failure with reduced ejection fraction (Class IIa), emphasizing individualized perioperative management based on underlying indication. In this frail elderly cohort, temporary withholding may be considered when hypertension is the primary indication.

In this study, no significant association was observed between beta-blocker or calcium channel blocker use and post-spinal hypotension, although the relatively small subgroup sizes may have limited statistical power. Previous studies have reported conflicting results. Kaimar et al. and Parasuram et al. found no increased incidence of hypotension among patients receiving calcium channel blockers or beta-blockers, although the former required greater vasopressor use.[11,15] In contrast, Dohare et al. and Prasad et al. reported higher rates of post-spinal hypotension in hypertensive patients on calcium channel blockers compared with those on beta-blockers or normotensive controls.[10,16]

Although diuretics are widely used for the management of hypertension and heart failure, alpha-blockers are commonly prescribed for hypertension or benign prostatic

hypertrophy in elderly patients. In this study, no significant association between their use and post-spinal hypotension was found. Evidence directly addressing the relationship between these drug classes and spinal anesthesia–induced hypotension remains limited. Diuretics may predispose patients to hypovolemia or electrolyte disturbances, while alpha-blockers reduce systemic vascular resistance through alpha-1 antagonism, thereby increasing the risk of perioperative hypotension, particularly with nonselective or alpha-1 selective agents.[17] However, the current evidence is insufficient to establish a definitive causal link, underscoring the need for well-designed prospective studies to further clarify the hemodynamic effects of these agents in patients undergoing neuraxial anesthesia.

Resistant hypertension, defined as uncontrolled blood pressure despite the use of three or more antihypertensive agents or controlled blood pressure requiring four or more drugs, is more prevalent among older adults and those with diabetes or chronic kidney disease.[18] In this study, a significant dose–response relationship was observed between the number of concurrent antihypertensive agents and the incidence of post-spinal hypotension (p for trend = 0.036). Although patients receiving three or more agents demonstrated the highest adjusted risk, the association was not statistically significant. The concurrent use of multiple antihypertensive drugs may induce complex alterations in sympathetic tone, vascular compliance, and baroreceptor responsiveness,[19] thereby modifying the normal cardiovascular adaptation to spinal anesthesia. Clinicians should therefore consider both the number and pharmacologic mechanisms of antihypertensive agents when evaluating perioperative hemodynamic risk in elderly patients.

This study has limitations. First, as a retrospective analysis, causal relationships cannot be established, and unmeasured confounding may exist. Second, although antihypertensive use was defined based on medications administered on the morning of surgery according to medication administration records, the exact timing relative to spinal anesthesia was not available in the original dataset. Third, the definition of hypotension relied on intraoperative records, which may vary in accuracy. Finally, the study focused on the occurrence of hypotension without evaluating its duration, severity, or related clinical outcomes, which may have underestimated its clinical impact. Future prospective studies incorporating precise medication timing, standardized definitions of hypotension, and clinically relevant outcomes are needed to better define the impact of preoperative antihypertensive therapy on perioperative hemodynamics in elderly patients. Randomized or carefully controlled observational studies focusing on RAAS antagonists and combination therapy may better guide perioperative medication management in very elderly patients undergoing spinal anesthesia.

CONCLUSIONS

Preoperative antihypertensive use was not independently associated with post-spinal hypotension in patients aged ≥80 years undergoing hip fracture surgery. However, risk differed by drug class, with RAAS antagonists independently associated with increased hypotension. These findings suggest that hemodynamic vulnerability may relate more to medication class than overall antihypertensive use. Individualized preoperative management, particularly in patients receiving RAAS antagonists or combination therapy, may improve perioperative hemodynamic stability.

Data Availability Statement

The datasets generated and/or analyzed during the current study are not publicly available due to institutional restrictions and the presence of sensitive patient information but are available from the corresponding author on reasonable request and with permission from the Institutional Ethics Committee.

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DECLARATIONS

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Conflict of Interest

The author declares no conflict of interest.

Registration Number of Clinical Trial

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Author Contributions

The author contributed to conceptualization, methodology, investigation, formal analysis, visualization, and manuscript preparation, including writing the original draft as well as review and editing. The author has read and approved the final version of the manuscript.

Use of Artificial Intelligence

The author used ChatGPT (OpenAI, San Francisco,

CA, USA) for assistance with language editing and grammatical revision of the manuscript. All content was reviewed and approved by the author.

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The Upregulation of Anti-apoptotic BIRC3 Expression Facilitates Zika Virus Infection

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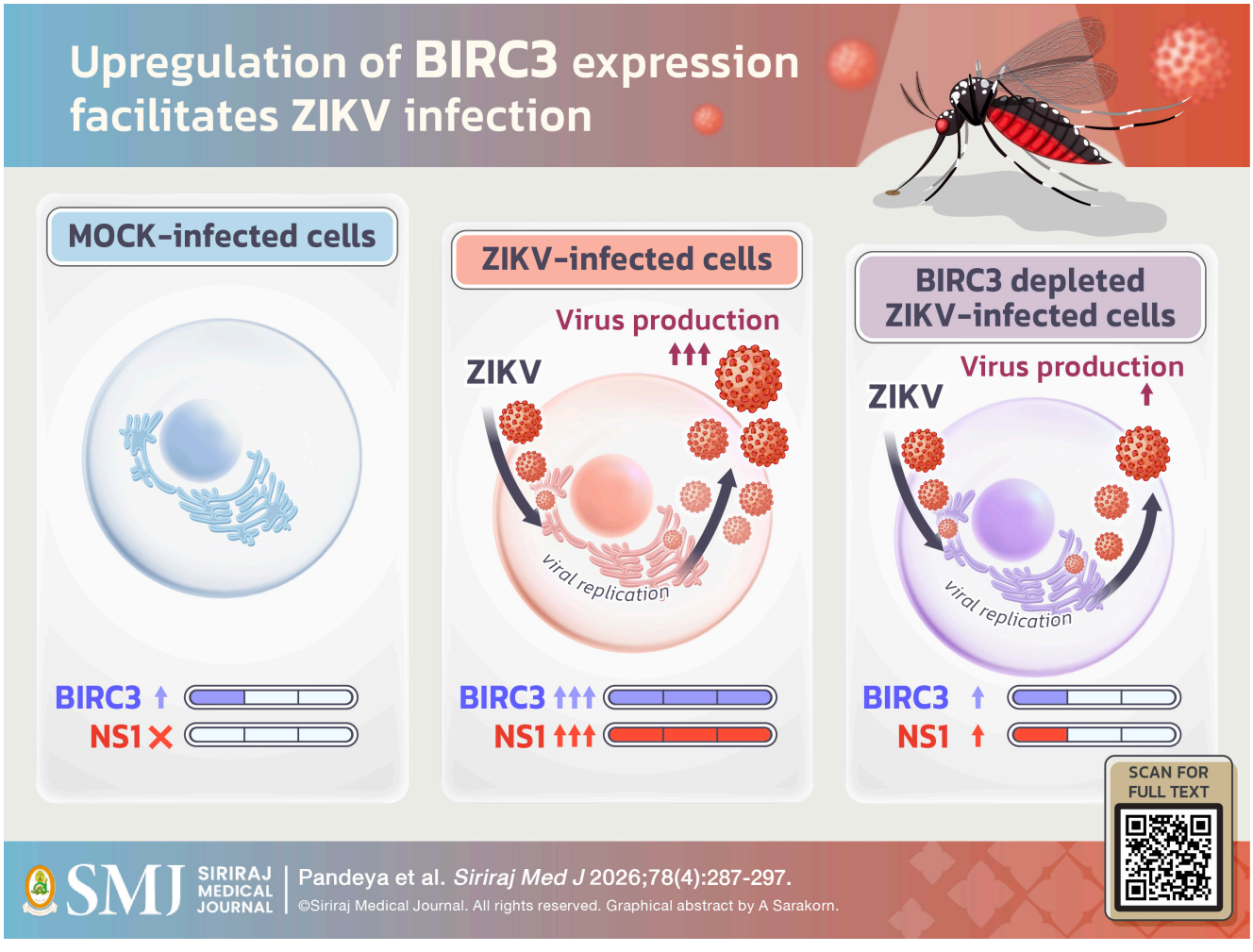

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ABSTRACT

Objective: The aim of this study was to investigate the apoptotic gene expression profile and to identify the genes involved in apoptosis and ZIKV infection.

Materials and Methods: SH-SY5Y cell line was infected with ZIKV at an MOI of 5. The cells were stained with Annexin V and propidium iodide to determine apoptosis. A real-time polymerase chain reaction array was employed to determine the apoptotic gene expression profile in a ZIKV-infected SH-SY5Y cell line. Western blot analysis was performed to confirm the expression of BIRC3 in both SH-SY5Y and A549 cell lines. Knockdown of the *BIRC3* was done in ZIKV-infected A549 cell line using *BIRC3* -specific siRNA. The ZIKV production was measured by focus-forming unit assay.

Results: Apoptotic genes in both extrinsic and intrinsic pathways, such as *TNF-α, TRAIL, FAS, CASP8, CASP9,* and *BIRC3*, were found to be upregulated. The anti-apoptotic gene *BIRC3* was selected and found to be upregulated at the protein level in both ZIKV-infected SH-SY5Y and ZIKV-infected A549 cell lines. Knockdown of the *BIRC3* gene in ZIKV-infected A549 cell line decreased Zika virus NS1 protein expression and Zika virion production.

Conclusion: The upregulation of anti-apoptotic *BIRC3* expression facilitates Zika virus infection.

Keywords: Apoptosis; *BIRC3* gene; Zika virus infection (Siriraj Med J 2026;78(4):287-297)

INTRODUCTION

Zika virus (ZIKV) is a member of the *Flavivirus* genus within the *Flaviviridae* family. ZIKV was first isolated from a blood sample taken from a sentinel rhesus monkey living in the Zika forest of Uganda.[1] The primary mode of ZIKV transmission is via the bite of infected *Aedes* species mosquitoes.[2] Notably, the transmission of ZIKV differs from that of other arboviral infections in that it can be transmitted sexually and via vertical transmission from mother to fetus.[3-5] The most severe consequence of ZIKV infection manifests in the developing fetus, with serious neurological complications, such as microcephaly, often observed in newborns.[6,7] ZIKV infection is also associated with other developmental defects, including cutaneous manifestations[8], sensorineural loss, vision impairment, and fetal death.[9,10] ZIKV was reported to induce immune-mediated neurological manifestations in adults, which is known as Guillain-Barré syndrome.[11] Given the seriousness of this infection, the World Health Organization (WHO) declared ZIKV a public health emergency of international concern in 2016.[12]

In vitro and *in vivo* studies demonstrated a connection among ZIKV-induced cell death, brain atrophy, and microcephaly in newborns.[13,14] The involvement of apoptosis in the pathogenesis of ZIKV infection was previously investigated using various cell lines and ZIKV strains.[15-18] ZIKV was shown to induce apoptotic cell death *in vitro*[18-21], and *in vivo* by impairing the development of the central nervous system in non-human primates.[22,23] The apoptosis process in ZIKV infection involves both cell death receptor and mitochondrial pathways.[24,25] Notably, ZIKV promotes apoptosis in neural progenitor cells partially via the induction of the tumor necrosis factor-related apoptosis-inducing ligand *(TRAIL)*.[26] Moreover, ZIKV was reported to induce neuronal apoptosis via increased mitochondrial fragmentation.[27]

The balance between pro- and anti-apoptotic proteins is essential for maintaining cellular homeostasis in virus-infected cells. By way of example, inhibition of apoptosis may facilitate viral replication. Anti-apoptotic proteins, such as heat shock proteins in host cells, were previously shown to facilitate and promote viral replication.[28-30] Clonal expansion of cloned cluster of differentiation 8^+ ($CD8^+$) T cells in human T-lymphotropic virus type 1 (HTLV1)-infected cells becomes resistant to tumor necrosis factor receptor superfamily member 6 (FAS)-mediated cell death, and requires overexpression of baculoviral IAP repeat-containing 3 (BIRC3).[31] However, and in this context, inhibition of apoptosis may limit viral replication. BIRC3 inhibits hepatitis B infection by accelerating the ubiquitin-proteasome-mediated destruction of viral polymerase.[32] BIRC3 protects the host by maintaining pulmonary tissue homeostasis in influenza infection, and an insufficient level of BIRC3 was reported to increase susceptibility to and mortality in influenza A virus infection.[33]

MATERIALS AND METHODS

The protocols for this study were approved by the Siriraj Institutional Review Board (SIRB) of the Faculty of Medicine Siriraj Hospital, Mahidol University (COA No. Si 919/2020), and by the Siriraj Biosafety Risk Management Taskforce (COA No. Si 2020-027).

Cell lines and virus

The human neuroblastoma SH-SY5Y cell line (American Type Culture Collection (ATCC) CRL-2266, CVCL_0019) and the human lung epithelial cell line A549 (ATCC CCL-185, CVCL_0023) were cultured in Dulbecco's Modified Eagle Medium (DMEM) (Gibco; Thermo Fisher Scientific, Waltham, MA, USA) supplemented with 10% heat-inactivated fetal bovine serum (FBS) (Gibco), 1% non-essential amino acid (NEAA) (Gibco), and 1.2% penicillin G-streptomycin antibiotic solution in a 37-degree Celsius (°C), 5% carbon dioxide (CO2), and humidified atmosphere. *The Aedes albopictus* clone C6/36 cell line (ATCC CRL-1660, CVCL_Z230) was cultured in L-15 media supplemented with 10% FBS, 100 U/ml penicillin, 100 µg/ml streptomycin, and 10% tryptose phosphate broth. ZIKV was propagated in C6/36 cell line and these cells were maintained in a 28°C incubator. The Vero cell line (ATCC CCL-81, CVCL_0059) was cultured in Eagle's minimal essential medium (MEM) supplemented with 10% FBS, 100 U/ml penicillin, and 100 mg/ml streptomycin. Those cells were subsequently maintained in a 5% CO_2 humidified incubator at 37°C. ZIKV strain MU1-2017 was previously isolated at the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.[34]

ZIKV infection

SH-SY5Y and A549 cells were seeded into 12-well plates and infected with ZIKV at multiplicity of infections (MOIs) of 1 and 5. The cells were incubated at 37°C for 2 hours. The cells were then washed with PBS for 2 hours after incubation, after which the PBS was replaced with complete growth media for continued incubation. The cells and supernatants were collected at 24- and 48-hours post-infection (hpi). The percentage of ZIKV infection was then analyzed by flow cytometry. Briefly, SH-SY5Y and A549 cells were detached using 0.1% trypsin and washed with PBS. The cells were fixed with 4% paraformaldehyde in PBS for 20 minutes, followed by permeabilization with 0.2% Triton X-100 in PBS for 10 minutes. The cells were washed with PBS and stained with 4G2 at room temperature for 1 hour. After washing with PBS, the cells were stained with Alexa 488-conjugated goat anti-mouse IgG (Invitrogen Corporation, Carlsbad, CA, USA) at room temperature for 1 hour. The ZIKV-positive cells were evaluated using a BD Accuri C6 Plus flow cytometer (BD Biosciences, San Jose, CA, USA) and FlowJo software (FlowJo LLC, Ashland, OR, USA). The viral titer was determined by Focus-Forming Unit (FFU) assay in Vero cells and calculated based on foci staining of the E protein and reported as focus-forming units per milliliter (FFU/ml).[35] Cell viability was analyzed using the trypan blue exclusion assay.[36]

Immunofluorescence analysis

SH-SY5Y cells were grown on coverslips for 24 hours and infected with ZIKV at MOIs of 1 and 5. At 24 and 48 hpi, Cells were fixed and permeabilized with 4% paraformaldehyde in PBS for 20 minutes and 0.2% Triton X-100 in PBS for 10 minutes, respectively. The cells were then incubated with 4G2 for 1 hour, followed by the addition of a mixture of Cy3-conjugated goat anti-mouse IgG (Invitrogen) and Hoechst 33342 (Invitrogen) for nuclear staining at room temperature for 1 hour. Images were visualized using a laser-scanning confocal microscope (LSM800; ZEISS Microscopy, Jena, Germany).

Apoptosis assay

A total of 1×10^6 SH-SY5Y cells per well was seeded in a 6-well plate and cultured for 24 hours. The SH-SY5Y cells were infected with ZIKV at an MOI of 5 and incubated for 48 hours. Thereafter, the cells were stained with Annexin V and propidium iodide (PI) (ImmunoTools, Friesoythe, Germany) (37), followed by data acquisition using a BD Accuri C6 Plus flow cytometer (BD Biosciences). Post-acquisition data analysis was performed using FlowJo software (FlowJo, LLC). The apoptotic gene expression profile was identified using a real-time polymerase chain reaction array. Specifically, a human apoptosis RT2 profiler Real-time PCR array (Qiagen, Hilden, Germany), precoated with primers specific to 84 apoptosis-relevant genes, was used for the profiling. Ribonucleic acid (RNA) was extracted from both mock- and ZIKV-infected cells using the RNeasy Mini Kit (Qiagen). Five hundred (500) nanograms (ng) of purified RNA (optical density [OD] 260 nm/OD 280 nm ≥2.0) was transcribed into complementary deoxyribonucleic acid (cDNA) using an RT^2 First Strand Kit (Qiagen). Real-time PCR was performed using a Light-Cycler 480 instrument (Roche Life Science, Basel, Switzerland). For the real-time PCR, 640 ng of cDNA was mixed with RT^2 qPCR Master Mix (Qiagen). The mixture was carefully aliquoted into each well of the array. The temperature profile was set at 95°C for 10 minutes, followed by 45 cycles of 95°C for 15 seconds, followed by 60°C for 1 minute. The threshold cycle (Ct) was calculated for each sample. Using the $2^{-\Delta\Delta Ct}$ method[38], the expression of apoptotic genes was expressed as the fold change between ZIKV-infected and mock samples. Beta-actin (β-actin) was used as a housekeeping gene in the comparison. Analysis was performed using a web-based program created and published by Qiagen (https://dataanalysis2.qiagen.com/pcr).

siRNA transfection

A549 cells were transfected with either BIRC3-specific siGENOME SMARTPool siRNAs for BIRC3 (M-004099-02-0010, Dharmacon, Inc., Lafayette, CO, USA) that targeted the position of reference BIRC3 gene sequence NM_001165.5, or control siGENOME non-targeting siRNA Pool #2 (D-001206-14-05, Dharmacon) using Lipofectamine RNAiMax (Invitrogen). The siRNA and Lipofectamine RNAiMAX complex were added to and incubated with A549 cells for 6 hours, followed by a switch to complete growth media. After knockdown for 24 hours, cells were infected with ZIKV at an MOI of 1 and incubated for 2 hours. After virus removal, the cells were washed and replaced with complete growth media. Mock- or ZIKV-infected and siRNA-transfected cells as well as culture supernatants were harvested at 48 hpi. To determine the efficiency of siRNA transfection, BIRC3 messenger ribonucleic acid (mRNA) and protein expression in the cells were measured using real-time PCR and Western blot analysis. ZIKV NS1 protein expression in the cells was determined by Western blot analysis. ZIKV production was assessed by FFU assay using culture supernatant.[35]

Real-time PCR

Total RNA was isolated from mock- and ZIKV-infected A549 cells that were transfected with control siRNA or BIRC3 siRNA. The SuperScript III First-Strand Synthesis System (Invitrogen) was used to synthesize cDNA from the isolated total RNA. The cDNA was amplified using a LightCycler 480 SYBR Green I Master Kit (Roche Life Science). The mixture for each reaction consisted of 3 µl of PCR grade water, 5 µl of 2× SYBR Green I Master Mix, 0.5 µl of forward primer, 0.5 µl of reverse primer, and 1 µl of cDNA. The nucleotide primers used were specific to BIRC3 (BIRC3_Forward 5'-AAGCTACCTCTCAGCCTACTT T-3' and BIRC3_Reverse 5'-CCACTGTTTTCTGTACCCGGA-3') and β-actin (β-actin_Forward 5'-AGAAAATCTGGCACCACACC-3' and β-actin_Reverse 5'-CTCCTTAATGTCACGCACGA-3'). The temperature profile included pre-incubation at 95°C for 5 minutes, followed by 50 cycles of denaturation at 95°C for 10 seconds, annealing at 60°C for 10 seconds, and extension at 72°C for 20 seconds. The Ct value of each selected gene was normalized to the Ct value of the β-actin housekeeping gene. The relative expression of genes ($2^{-\Delta\Delta Ct}$) was analyzed by comparing the siRNA control group to siRNA specific to BIRC3.

Western blot analysis

SH-SY5Y and A549 cells were harvested at 48 hours after ZIKV infection in the presence or absence of control or specific siRNA transfection. Cell pellets were lysed on ice for 30 minutes using radioimmunoprecipitation assay (RIPA) buffer, followed by centrifugation at 13,000 revolutions per minute (rpm) for 5 minutes at 4°C. After collection of the lysate, the protein concentration was measured using a Bradford protein assay (Bio-Rad Laboratories, Hercules, CA, USA). A total of 20-60 µg of protein was loaded, followed by separation via sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and blotting onto a nitrocellulose membrane. The membrane was blocked with 5% skim milk in PBS for 1 hour and washed three times. The membrane was then incubated with rabbit monoclonal antibody against BIRC3 or c-IAP2 (1:1000) (Cell Signaling Technology, Danvers, MA, USA), mouse anti-human ZIKV NS1 monoclonal antibody (1:1000) (Arigo Biolaboratories, Hsinchu City, Taiwan), or mouse anti- human GAPDH (1:1000) (Santa Cruz Biotechnology, Dallas, TX, USA) at 4°C overnight. After washing the membrane one time with PBS, HRP-conjugated goat anti-rabbit (Jackson ImmunoResearch, West Grove, PA, USA) or rabbit anti-mouse secondary antibody (Dako Denmark A/S, Glostrup, Denmark) was added onto the membrane and incubated at RT for 1 hour. Enhanced chemiluminescence (ECL) substrate was then added and the signal was visualized using plain radiographic film (X-ray). The quantity of protein was analyzed using ImageJ software (https://imagej.nih.gov/ij; United States National Institutes of Health, Bethesda, MD, USA).

Statistical analyses

All statistical analyses were performed using GraphPad Prism 5 software (GraphPad Software, Inc., La Jolla, CA, USA). Data from three independent experiments are presented as the mean plus/minus (±) the standard error of the mean (SEM). The data were analyzed using either Student's *t*-test or one-way analysis of variance (ANOVA) followed by Bonferroni's multiple comparison test. A probability (*p*) value less than 0.05 was regarded as being statistically significant.

RESULTS

ZIKV infection and ZIKV-induced apoptosis in SH-SY5Y cell line

SH-SY5Y cells were infected with ZIKV at MOIs of 1 and 5 or left uninfected (mock control) and then collected at 24 and 48 hpi. The percentage of ZIKV infection was analyzed by flow cytometry. Results showed that the infection rates of ZIKV at 24 and 48 hpi were approximately 26.86% and 56.47% for the MOI of 1 vs.

40.07% and 72.37% for the MOI of 5, respectively (Figs 1a and 1b). This was consistent with the proportion of ZIKV E-positive SH-SY5Y cells observed by a laser-scanning confocal microscopy (Fig 1c). While infection with the MOI of 1 did not affect cell viability at 24 and 48 hpi, infection with the MOI of 5 significantly reduced the viability of ZIKV-infected SH-SY5Y cells at 48 hpi ($p<0.05$) (Fig 1d).

Further analysis of apoptotic cells by Annexin V/propidium iodide (PI) staining and flow cytometry demonstrated significantly higher prevalence of apoptosis in ZIKV-infected cells compared to the proportion observed in the mock-infected cells (32.7 % *vs.* 1.0 %, respectively; $p<0.0001$) (Fig 2b). A representative flow cytometric scatter plot of Annexin V/PI-stained cells is shown in Fig 2a.

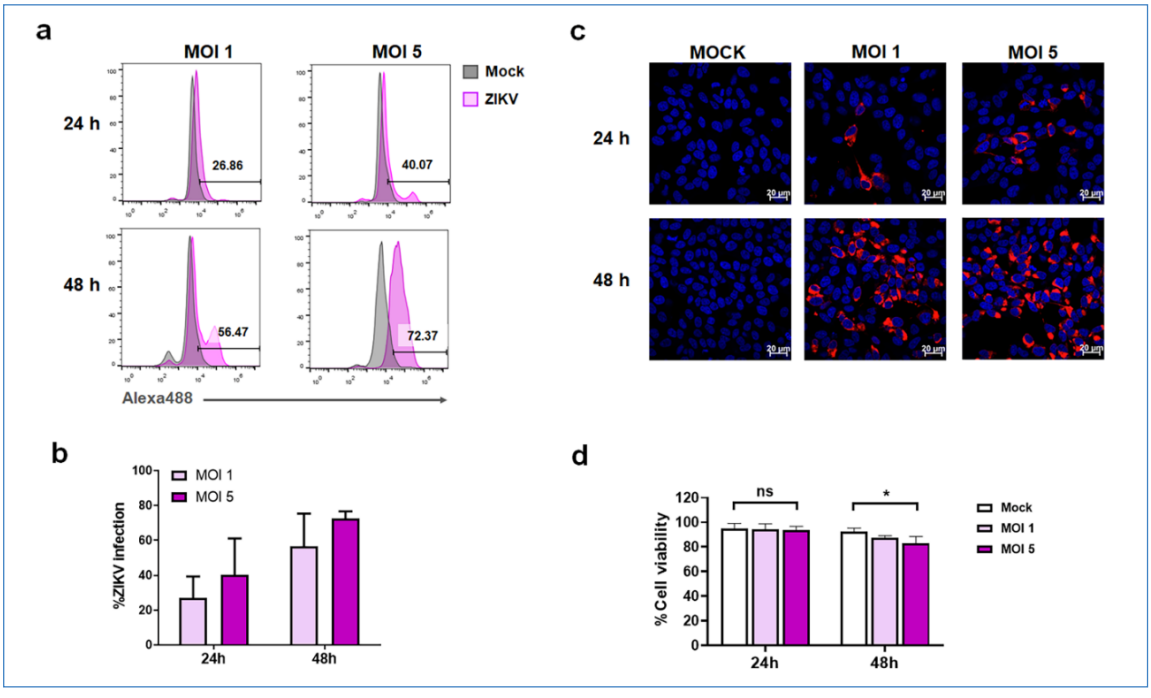

Fig 1. ZIKA virus (ZIKV) infection in human neuroblastoma SH-SY5Y cells.
(a) Representative of histogram plots from three independent experiments illustrating ZIKV E protein expression in ZIKV-infected cells with MOIs of 1 and 5 (purple) compared to mock-infected cells (control, gray) at 24 and 48 hpi. **(b)** Kinetics of ZIKV infection in SH-SY5Y cells at 24 and 48 hpi (mean ± SEM). **(c)** Analysis of ZIKV E protein expression and localization by a laser-scanning confocal microscopy compared between mock and ZIKV-infected cells at 24 and 48 hpi. ZIKV E in red, nucleus in blue. **(d)** Percentage of cell viability compared between mock and ZIKV-infected cells at 24 and 48 hpi (mean ± SEM ; *p<0.05).

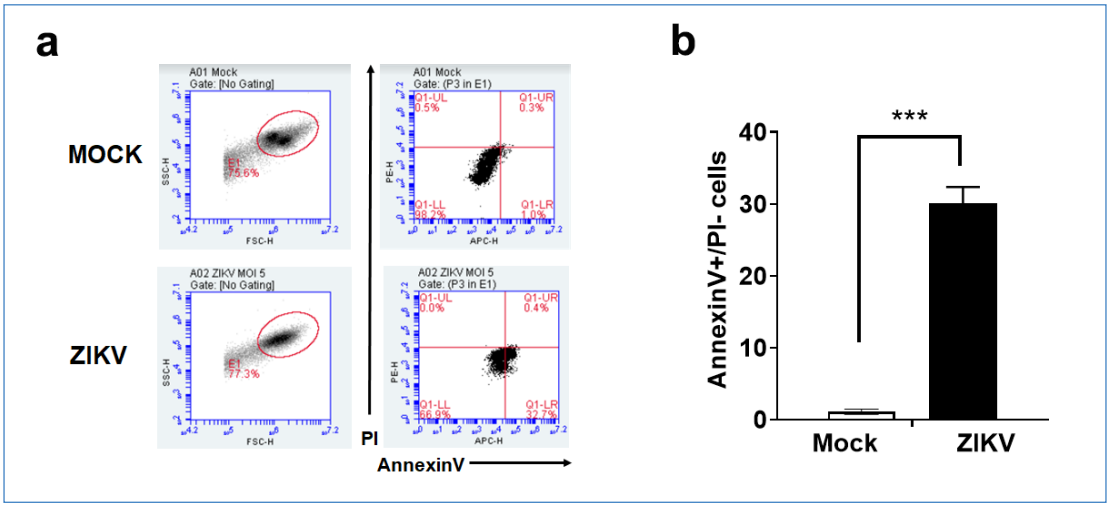

Fig 2. Annexin V/PI staining in the human neuroblastoma SH-SY5Y cells.
(a) Representative of scatter plots of the flow cytometric analysis demonstrates the profile of Annexin V/PI staining for mock and ZIKV-infected SH-SY5Y cells. **(b)** Percentage of early apoptotic cells (Annexin V+/PI-) compared between mock and ZIKA virus (ZIKV)-infected SH-SY5Y cells from three independent experiments (***p<0.0001).

Apoptotic gene expression profiling in ZIKV-infected SH-SY5Y cell line

A human apoptosis RT2 profiler polymerase chain reaction array was used to profile gene expression in ZIKV-infected cells. The β-actin gene served as a housekeeping gene for normalizing the data. Of the 84 apoptosis-related genes, 61 were upregulated and 17 were downregulated in the ZIKV-infected SH-SY5Y cells. The mRNA expression of the top 20 upregulated genes is presented in Table 1. The expression levels of the *BIRC3* and interleukin 10 (*IL-10*) genes were significantly upregulated in the ZIKV-infected SH-SY5Y cells, with 22.01-fold and 19.70-fold changes in expression, respectively – both compared to the mock-infected cells. Three crucial genes in the extrinsic pathway (*TNF-α, TRAIL,* and *FAS*) were upregulated with 13.55-fold, 12.82-fold, and 10.93-fold increases, respectively. Three key regulator genes of apoptosis (*CASP8, CASP9,* and *CASP3*) were upregulated with 2.06-fold, 4.44-fold, and 1.33-fold increases, respectively.

BIRC3 was upregulated in both ZIKV-infected SH-SY5Y and A549 cell lines

The *BIRC3* gene was selected for further analysis due to its highest upregulated mRNA expression in apoptotic gene expression profiling in ZIKV-infected SH-SY5Y cells. Verification of BIRC3 protein expression in SH-SY5Y cells was performed in parallel with that in human lung epithelial A549 cells, which is highly permissive to ZIKV infection. When the SH-SY5Y and A549 cells were infected with ZIKV at MOIs of 1 and 5 for 48 hours followed by Western blot analysis, BIRC3 protein was found to be upregulated in both ZIKV-infected A549 (Figs 3 a, b) and ZIKV-infected SH-SY5Y cells (Figs 3 a, c).

TABLE 1. Fold change of apoptotic gene expression in ZIKA virus-infected SH-SY5Y cells.

Gene no.	Fold change	Gene name	Gene description
1	22.01	*BIRC3*	Baculoviral IAP repeat-containing 3
2	19.70	*IL10*	Interleukin 10
3	13.55	*TNF*	Tumor necrosis factor
4	12.82	*TNFSF10*	Tumor necrosis factor (ligand) superfamily, member 10
5	10.93	*FAS*	Fas (TNF receptor superfamily, member 6)
6	9.51	*CASP 10*	Caspase 10, apoptosis-related cysteine peptidase
7	8.51	*CD27*	CD27 molecule
8	8.11	*TNFRSF9*	Tumor necrosis factor receptor superfamily, member 9
9	5.86	*BAK1*	BCL2-antagonist/killer 1
10	5.82	*CASP 5*	Caspase 5, apoptosis-related cysteine peptidase
11	5.28	*CASP 1*	Caspase 1, apoptosis-related cysteine peptidase (interleukin 1, beta, convertase)
12	5.28	*CASP 14*	Caspase 14, apoptosis-related cysteine peptidase
13	5.28	*CD40*	CD40 molecule, TNF receptor superfamily member 5
14	5.28	*FASLG*	Fas ligand (TNF superfamily, member 6)
15	4.79	*BAD*	BCL2-associated agonist of cell death
16	4.44	*CASP 9*	Caspase 9, apoptosis-related cysteine peptidase
17	4.23	*RIPK2*	Receptor-interacting serine-threonine kinase 2
18	2.06	*CASP 8*	Caspase 8, apoptosis-related cysteine peptidase
19	1.33	*CASP 3*	Caspase 3, apoptosis-related cysteine peptidase
20	1.12	*BAX*	BCL2-associated X protein

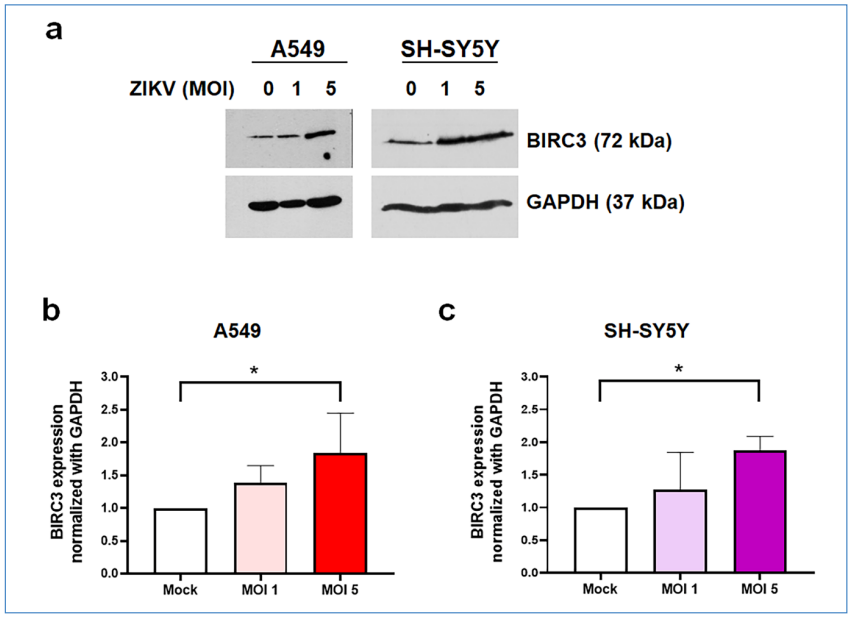

Fig 3. Baculoviral IAP repeat-containing 3 (BIRC3) protein expression in ZIKA virus (ZIKV)-infected human neuroblastoma SH-SY5Y and human lung epithelial A549 cells.
(a) Western blot analysis for BIRC3 expression in SH-SY5Y and A549 cell lines infected with ZIKV at MOIs of 1 and 5. **(b)** Densitometric analysis of Western blot results compared between ZIKV-infected A549 and mock control. **(c)** Densitometric analysis of Western blot results compared between ZIKV-infected SH-SY5Y and mock control (*p<0.05).

Small interfering ribonucleic acid (siRNA)-mediated knockdown of the BIRC3 gene in mock- and ZIKV-infected human lung epithelial A549 cells

After several attempts failed to knock down BIRC3 in ZIKV-infected SH-SY5Y cells, we decided to conduct further experiments in ZIKV-infected A549 cells. Human A549 cells were transfected with control siRNA or BIRC3-specific siRNA for 24 hours and then infected with ZIKV at an MOI of 1 or left uninfected (mock). Knockdown efficiency was examined by investigating both mRNA and protein expressions of BIRC3 at 48 hpi. We observed no adverse effect of siRNA transfection and ZIKV infection on cell viability of human A549 cells (Fig 4a). The siRNA knockdown of BIRC3 was successful under the tested conditions as evidenced by the significant reduction of BIRC3 at both mRNA level (Fig 4b) and protein level (Fig 4c).

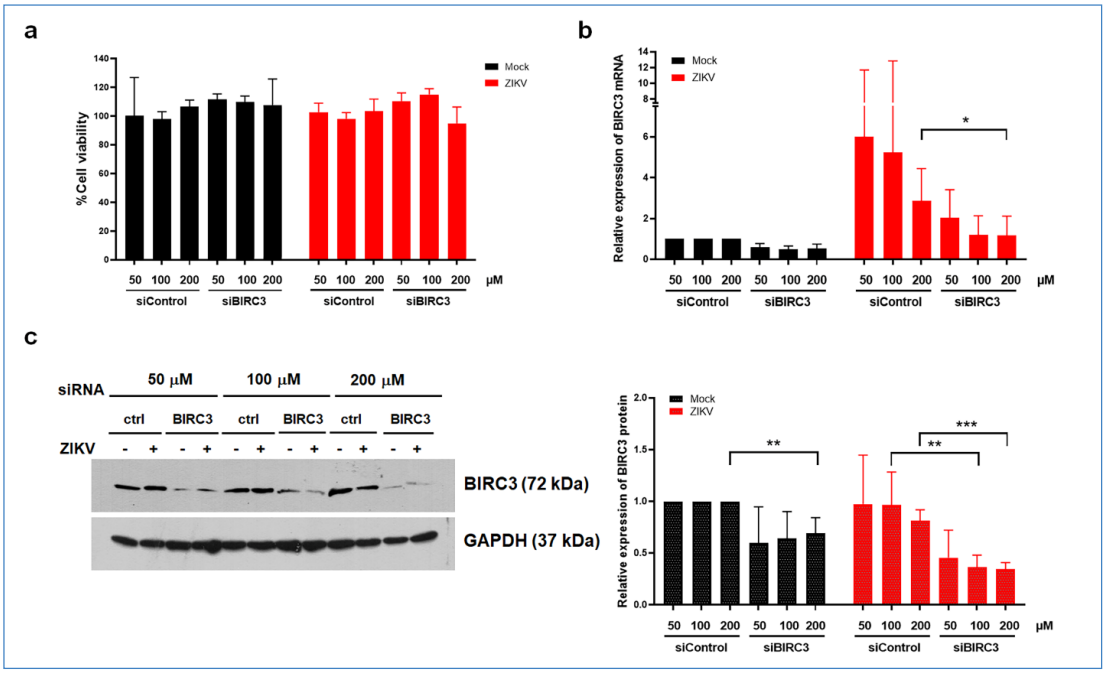

Fig 4. Small interfering ribonucleic acid (siRNA)-mediated knockdown of the BIRC3 gene in mock- and ZIKV-infected human lung epithelial A549 cells.
Three independent experiments were performed. **(a)** Percentage of cell viability compared between control siRNA- and BIRC3 siRNA-transfected A549 cells in the presence or absence of ZIKV infection. **(b)** Relative expression of the mRNA expression of BIRC3 mRNA in mock- and ZIKV-infected A549 cells following siRNA knockdown (*p<0.05). **(c)** Western blot analysis of BIRC3 protein expression in mock- and ZIKV-infected A549 cells following siRNA knockdown. A representative of three independent experiments is shown (left panel). Relative expression of the BIRC3 protein expression in mock- and ZIKV-infected A549 cells following siRNA knockdown (**p<0.001, ***p<0.0001).

Knockdown of BIRC3 reduced ZIKV NS1 protein expression and ZIKV production in ZIKV-infected A549 cell line

The effect on virion production and NS1 protein expression was examined at 48 hpi by focus forming unit (FFU) assay and Western blot analysis, respectively. We found a significant reduction in ZIKV production by approximately 70-80% in the BIRC3 knockdown cell cultures compared to that of control cell cultures (Fig 5a). In agreement with this finding, ZIKV NS1 protein expression was significantly decreased in ZIKV-infected cells following BIRC3 knockdown in a dose-dependent manner. These results suggest the role of BIRC3 in supporting ZIKV replication in human A549 cells (Fig 5b).

DISCUSSION

Importantly, the results of this study indicate that ZIKV infection induces apoptotic cell death.[18-21] Previous studies demonstrated that ZIKV triggers neuronal cell death by activating extrinsic, intrinsic, or both apoptotic pathways.[21,26,27] In this study, pro-apoptotic genes associated with the extrinsic apoptotic pathway, including *TNF-α, TRAIL, FAS, FASL,* and *CASP8*, were upregulated in ZIKV-infected SH-SY5Y cell line. Moreover, apoptotic genes related to the intrinsic apoptotic pathway, including *BAK, BID,* and *CASP9*, were upregulated in the ZIKV-infected *SH-SY5Y* cell line. ZIKV infection was previously reported to induce apoptosis by modulating the recruitment and activation of the pro-apoptotic protein *BAX*.[39] Both *BAX* and *BAK* are considered to be key members of B cell lymphoma-2 (BCL2) protein family, which plays a critical role in modulating apoptosis.[40] Cellular inhibitors of apoptosis proteins (cIAPs), including *BIRC2* and *BIRC3*, were found to be upregulated in ZIKV-infected *SH-SY5Y* cells in our study.

BIRC3 is a member of the inhibitor of apoptosis (IAP) family, and it was the first in that family shown and reported to inhibit cell death.[41] BIRC3 is characterized by the presence of the baculoviral IAP repeat (BIR) domain, the ubiquitin-conjugating (UBC) domain, the caspase recruitment (CARD) domain, and the ring zinc finger (RING) domain.[42] The *BIRC3* gene was selected for further analysis in our study since it had the highest upregulated expression among any evaluated gene in apoptotic gene expression profiling. In addition, the

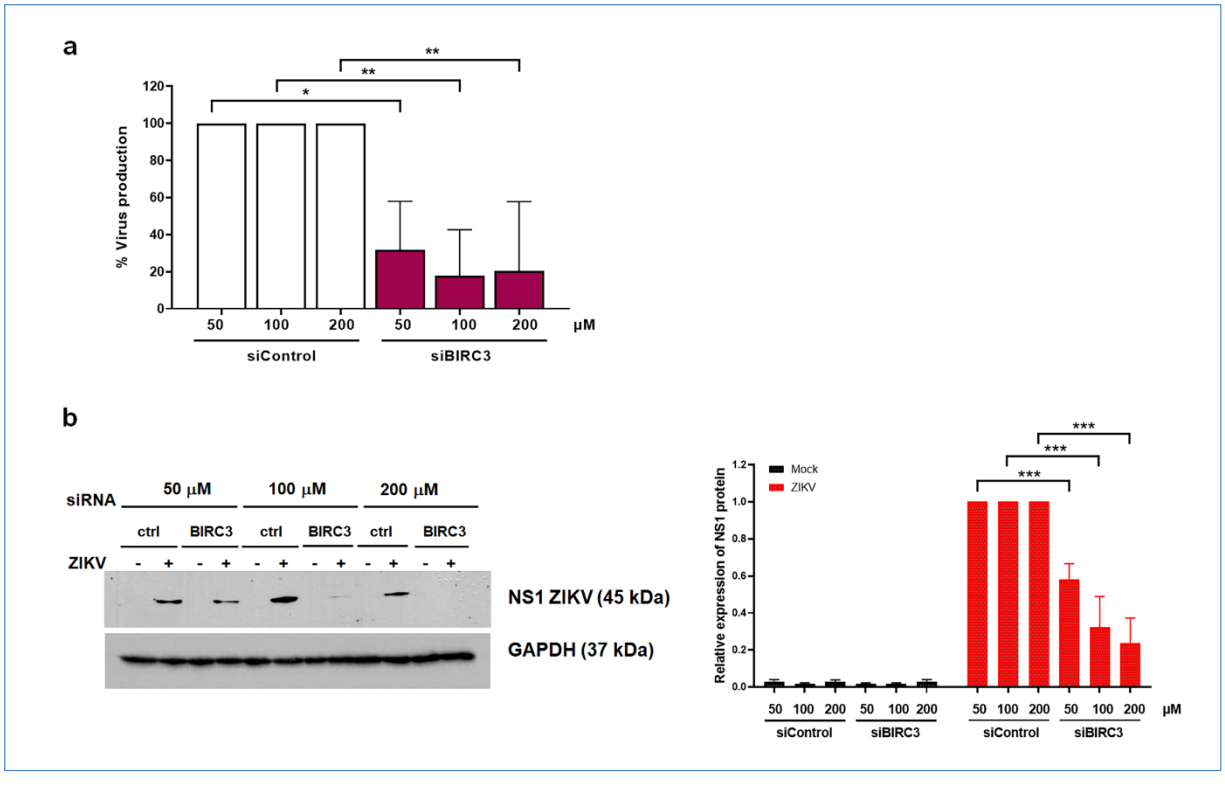

Fig 5. ZIKV NS1 protein expression and infectious ZIKV production in human lung epithelial A549 cells following ZIKV infection and siRNA knockdown.

(a) Percentage of infectious virions in culture supernatants following ZIKV infection and siRNA knockdown as determined by FFU assay (*p<0.05, **p<0.001). Analysis of ZIKV NS1 protein expression via Western blot analysis. **(b)** Western blot analysis of ZIKV NS1 protein expression in mock- and ZIKV-infected A549 cells following siRNA knockdown. A representative of three independent experiments is shown (left panel). Relative expression of ZIKV NS1 protein expression in mock- and ZIKV-infected A549 cells following siRNA knockdown (***p<0.0001).

protein expression of BIRC3 was found to be upregulated in both ZIKV-infected A549 and ZIKV-infected SH-SY5Y cell lines. After several attempts failed to knock down BIRC3 in ZIKV-infected SH-SY5Y cells, we decided to conduct further experiments in ZIKV-infected A549 cells. Interestingly, knockdown of BIRC3 in ZIKV-infected A549 cells impaired ZIKV production at 48 hpi without affecting cell viability. In addition, siRNA against BIRC3 reduced ZIKV NS1 protein expression. These results suggest an important role of BIRC3 to facilitate ZIKV replication. The mechanisms by which ZIKV uses host cell machinery via the upregulation of NF-kB-dependent anti-apoptotic proteins, such as BIRC3, for its own replication warrant further investigation. Human immunodeficiency virus 1 (HIV-1) also developed strategies to favor the persistent replication of HIV-1 in infected T cells. This developed protection was characterized by deregulation of proteins that stabilize mitochondrial membrane integrity, and by upregulation of nuclear factor kappa-light-chain-enhancer of activated B cells or nuclear factor-kB (NF-kB)-dependent anti-apoptotic proteins, such as BIRC3.[43] Activated NF-kB is also a mechanism by which lymphoma cells infected by the Epstein-Barr virus or Kaposi's sarcoma herpesvirus are protected from apoptotic stress.[44] ZIKV NS2A and NS4A were previously shown to suppress NF-kB promoter activity by inhibiting signaling factors involved in the melanoma differentiation-associated protein 5 (MDA5)/retinoic acid-inducible gene I (RIG-I) signaling pathway.[45] ZIKV delays cell death through the anti-apoptotic Bcl-2 family proteins.[46] If this host cell protection is the mechanism by which BIRC3 promotes viral replication, whether downregulation of BIRC3 leads to alterations in the apoptotic process merits further investigation.

CONCLUSION

Significant upregulation of BIRC3 protein was detected in both human neuroblastoma SH-SY5Y and human lung epithelial A549 cells following ZIKV infection. Knockdown of the *BIRC3* gene significantly decreased ZIKV NS1 protein expression and virion production in ZIKV-infected A549 cells without any adverse effect on cell viability. These findings suggest the involvement of BIRC3 in ZIKV replication and pathogenesis.

Data Availability Statement

The data are available from the corresponding author upon request.

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DECLARATIONS

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Conflict of Interest

All authors declare no personal or professional conflicts of interest, and no financial support from the companies that produce and/or distribute the drugs, devices, or materials described in this report.

Registration number of clinical trial

None.

Author Contributions

Conceptualization and methodology, A.P., P.S., S.M., S.N., P.Y., and T.L. ; Investigation, A.P., P.S., P.R., S.M., and A.M. ; Formal analysis, A.P., P.S., P.R., S.M., and A.M. ; Writing – review and editing, A.P., P.S., S.M., S.N., and T.L. ; Resources, P.A., M.U., and C.P. ; Funding acquisition, T.L. All authors have read and agreed to the final version of the manuscript.

Use of Artificial Intelligence

No form of artificial intelligence (AI) was used in this study.

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Comparison of Local Versus General Anesthesia in Open Inguinal Hernioplasty: A Prospective Study on Postoperative Outcomes and Cost-Effectiveness

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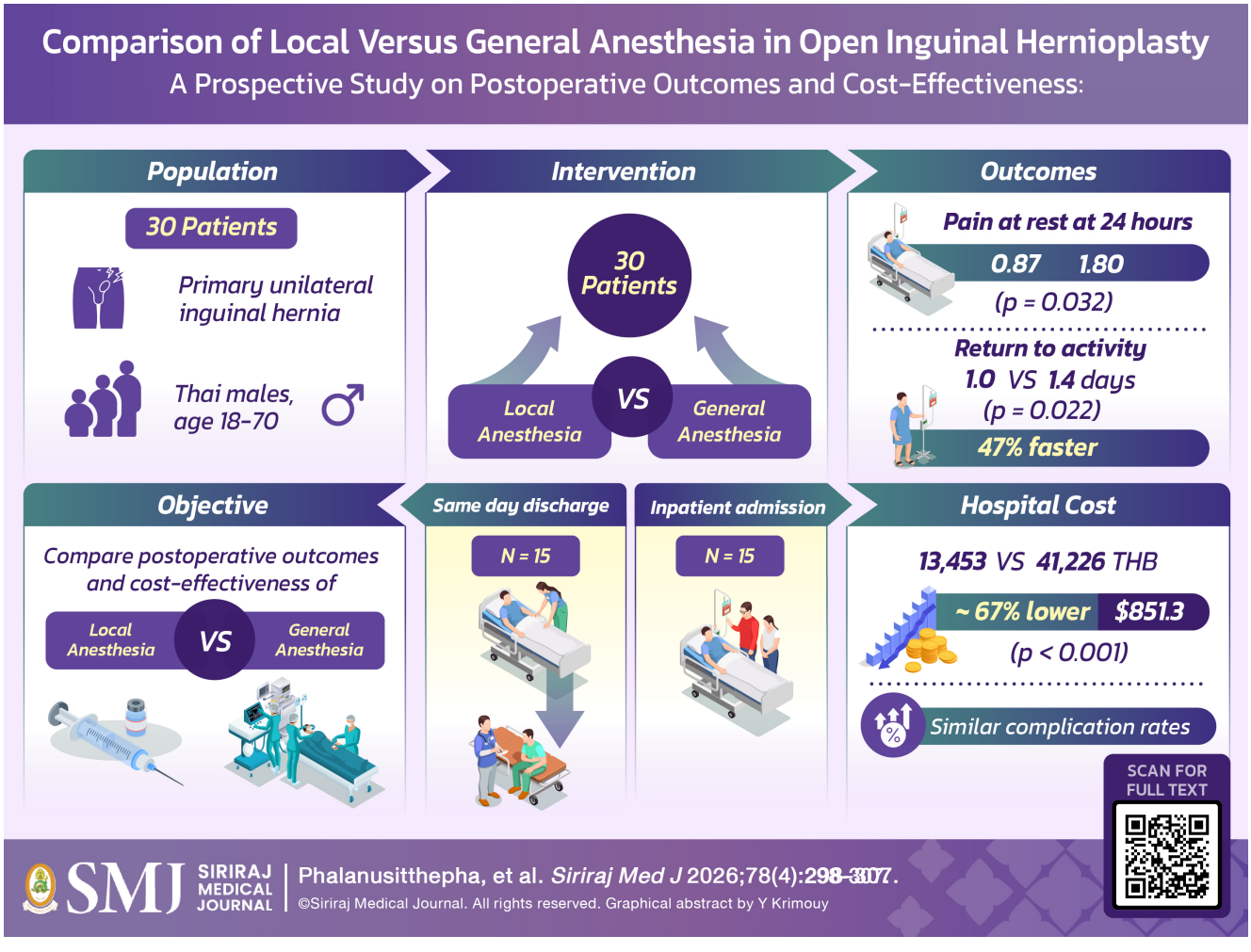

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ABSTRACT

Objective: This study evaluates whether performing open inguinal hernia repair under local anesthesia with same-day discharge is comparable to general anesthesia with inpatient admission, with respect to postoperative outcomes, recovery time, and healthcare costs.

Materials and Methods: This prospective cohort study was conducted at Siriraj Hospital and included 30 adults undergoing unilateral open inguinal hernioplasty. Patients were allocated to either local anesthesia with same-day discharge (n=15) or general anesthesia with inpatient admission (n=15). Postoperative pain, recovery time, operative efficiency, complications, and total hospital costs were assessed.

Results: Postoperative pain at rest at 8 and 24 hours was lower in the LA group compared with the GA group (1.93±1.10 vs 2.53±1.55 p=0.233, 0.87±0.83 vs 1.80±1.65 p=0.032). Patients in the LA group resumed normal activities significantly earlier, and total hospital costs were significantly lower (1.00+0.54 vs 1.40+0.51 p = 0.022, 13,453 THB vs. 41,226 THB; p<0.001). Operative time, theater time, complications, and patient demographics (age, BMI, ASA classification) were comparable between groups.

Conclusions: Open inguinal hernioplasty under local anesthesia in a day-surgery setting demonstrated clinical outcomes comparable to those of general anesthesia with inpatient admission. Additionally, this approach was associated with faster functional recovery and significantly reduced hospital costs. Local anesthesia represents a safe, efficient, and cost-effective alternative for appropriately selected patients.

Keywords: Hernioplasty; inguinal hernia; local anesthesia; day surgery; cost-effectiveness (Siriraj Med J 2026;78(4): 298-307)

INTRODUCTION

Inguinal hernia repair is one of the most performed procedures in general surgery worldwide, including in Thailand. The lifetime incidence of inguinal hernia is approximately 27% in males and 3% in females.[1,2] Open Lichtenstein mesh-based inguinal hernia repair performed under local anesthesia is currently a widely accepted and recommended treatment. This approach is endorsed by both the European Hernia Society (EHS) and the Asian Pacific Hernia Society guidelines.[3-5] Open inguinal hernia repair can be performed using various anesthetic techniques, including general anesthesia, spinal anesthesia, and local anesthesia.[6-11] Although both the EHS and Asia-Pacific Hernia Society guidelines recommend local anesthesia with same-day discharge, anesthetic techniques administered by anesthesiologists — particularly general and spinal anesthesia — remain widely practiced.[12] At Siriraj Hospital, anesthesiologist-administered anesthesia is still predominantly used. This preference may be attributed to patient anxiety, surgeons' concerns regarding intraoperative pain control, and the limited availability of structured training in local anesthesia techniques. Local anesthesia requires specific technical expertise and patient cooperation, as patients remain conscious during the procedure. In contrast, general and spinal anesthesia provide complete patient unawareness but are associated with potential. Systemic complications, including respiratory, cardiovascular, and gastrointestinal adverse effects related to anesthetic agents.[13-15] Therefore, selecting the most appropriate anesthetic technique is crucial and should involve a balanced consideration of potential benefits and risks. Factors such as postoperative outcomes, recurrence rates, operative time, and healthcare costs remain subjects of ongoing debate.[16,17] With the increasing demand for healthcare services in Thailand, the One Day Surgery (ODS) initiative was launched in 2017 to enhance surgical capacity, improve patient access, and optimize hospital bed utilization for patients requiring inpatient care. Inguinal hernia repair represents an ideal model for comparing local anesthesia with anesthesiologist-administered anesthesia, as well as evaluating same-day discharge versus conventional inpatient admission.

This study aims to assess treatment efficacy, postoperative pain control, surgical and anesthetic complications, patient and caregiver satisfaction, and total healthcare costs. The findings are expected to support the development of evidence-based clinical practice guidelines for inguinal hernia management at Siriraj Hospital and within the Thai healthcare system.

MATERIALS AND METHODS

Patient selection

This prospective cohort study was conducted at the

Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand. The research protocol was reviewed and approved by the Institutional Review Board of the Faculty of Medicine Siriraj Hospital (Certificate of Approval No. Si 812/2023). Eligible participants were Thai male patients aged 18 to 70 years who provided written informed consent for participation in the study. All included patients were diagnosed with primary unilateral inguinal hernia and had no history of previous inguinal hernia repair. Patients underwent elective open tension-free mesh-based inguinal hernioplasty and were classified as American Society of Anesthesiologists physical status I to III. In addition, all participants demonstrated good functional capacity, defined as a metabolic equivalent level of at least 4 METs. Patients were excluded if they presented with incarcerated inguinal hernia requiring emergency surgery or had a prior history of inguinal hernia repair. Additional exclusion criteria included contraindications to local or general anesthesia, a family history of malignant hyperthermia in first-degree relatives, and known allergies to paracetamol or tramadol. Patients were also excluded if they were unable to independently decide on the type of anesthesia or had cognitive, communication, or other limitations that prevented reliable completion of questionnaires or accurate assessment of pain scores. Participants were withdrawn from the study if they refused to provide study-related information or complete research questionnaires, or if they were unable to attend postoperative follow-up visits.

Sample size calculation

The primary outcome was postoperative wound pain at 8 hours after inguinal hernia repair, assessed using a pain score. The sample size was calculated to compare mean pain scores between two independent groups. The type I error (α) was set at 0.05 with a two-sided test ($Z_{\alpha/2}$ = 1.96), and the type II error (β) was set at 0.20 (Z_{β} = 0.84). Group 1 consisted of patients undergoing outpatient inguinal hernia repair under local anesthesia, while Group 2 consisted of patients undergoing inpatient inguinal hernia repair under anesthesiologist-administered anesthesia. Based on a literature review of postoperative pain following inguinal hernia repair[19], the mean pain score was reported as 2.12 in the local anesthesia group and 3.58 in the anesthesiologist-administered anesthesia group, with standard deviations of 1.0 and 1.5, respectively. These values were used as reference parameters for sample size estimation. The required sample size per group was calculated using the following formula:

$$n = \frac{(Z_{\alpha/2}+Z_{\beta})^2(\sigma_1^2+\sigma_2^2)}{(\mu_1-\mu_2)^2}$$

The calculated minimum sample size was 12 patients per group. To account for an anticipated dropout rate of 20%, the final sample size was increased to 15 patients per group.

Data Collection

Baseline patient characteristics were collected, including age, body weight, height, body mass index, underlying comorbidities, and history of drug allergies. Preoperative health status was assessed using the American Society of Anesthesiologists (ASA) physical status classification and functional capacity (functional class).

Patients who met the eligibility criteria were invited to participate in the study by surgical residents or study investigators at the outpatient surgical clinic. All eligible patients were provided with detailed written information regarding study participation and were given sufficient time to read the document thoroughly. Investigators explained the study protocol and answered any questions raised by the patients.

Patients independently selected their preferred method of anesthesia after undergoing standard pre-anesthetic risk assessment rather than randomization. Both local anesthesia and anesthesiologist-administered anesthesia were explained in detail, including the potential benefits and risks of each approach, to ensure informed decision-making. Patients were informed of their right to decline participation in the study without any impact on their standard medical care. Written informed consent was obtained from all patients prior to enrollment.

Procedural Care and Operative Technique

In the local anesthesia group, patients were scheduled for surgery in a minor operating room on the day of the procedure. They were performed under pure local infiltration without sedation or airway manipulation. Therefore, routine preoperative fasting was not required. In contrast, patients in the regional or general anesthesia group were admitted one day prior to surgery, underwent preoperative evaluation by an anesthesiologist, and were instructed to fast according to standard anesthesia guidelines and discontinue medications as advised. All patients in both groups received prophylactic antibiotics 30 minutes prior to skin incision. In the local anesthesia group, local infiltration was performed using a mixture of 1% lidocaine with adrenaline (30 mL) and 0.5% bupivacaine (20 mL). Local anesthetic was administered at four anatomical sites: the iliohypogastric nerve, superficial inguinal ring, incision site, and deep inguinal ring. Patients then underwent open inguinal hernioplasty using the Lichtenstein mesh-based tension-free technique. After surgery, patients in

the local anesthesia group were observed in the recovery room for 2 hours and were discharged on the same day if no complications occurred. In the regional or general anesthesia group, anesthesia was administered by an anesthesiologist, and patients underwent open inguinal hernioplasty using the same Lichtenstein mesh-based technique. Postoperatively, patients were monitored in the recovery room for 2 hours before being transferred to the inpatient ward and discharged on the following day if no complications were observed.

Postoperative Care and Follow-up

Both groups received the same postoperative oral analgesic regimen, consisting of paracetamol 500 mg every 6 hours for 3 days, with tramadol 50 mg every 6 hours as needed for breakthrough pain. Postoperative wound pain was assessed at 8 and 24 hours after surgery using the visual analog scale (VAS). Pain assessment was conducted via telephone interview for patients in the local anesthesia group and by direct assessment in the inpatient ward for patients in the anesthesiologist-administered anesthesia group. Discharge in the local anesthesia group was based on standardized clinical stability criteria, including stable vital signs, adequate pain control, and ability to ambulate. Although no formal geographic or caregiver-based exclusion criteria were applied, all patients received a 24-hour contact number for postoperative consultation in the event of complications after discharge. If patients presented to the emergency department, appropriate medical care was provided immediately. Patients were scheduled for follow-up visits at 2 weeks and 4 weeks postoperatively to assess surgical and anesthetic complications, healthcare costs (categorized as fixed operative costs and variable costs), and patient satisfaction. Return to normal activity was defined as the number of days until the patient self-reported resumption of routine daily activities without limitation and was assessed via direct questioning during follow-up. Surgical satisfaction was evaluated using a modified version of the Surgical Satisfaction Questionnaire (SSQ-8)(18). An additional follow-up at 1 year was conducted to assess the recurrence rate of inguinal hernia, and chronic groin pain. All treatment costs were covered under standard healthcare entitlements, as inguinal hernia is considered a basic disease covered by all healthcare schemes in Thailand, regardless of the anesthesia method used.

Endpoints

The primary objective of this study was to compare the effectiveness of unilateral inguinal hernia repair between day-case surgery (same-day discharge) surgery and conventional inpatient surgery. The secondary objectives included comparisons of postoperative complications, patient satisfaction, and healthcare costs between the day-case surgery and conventional inpatient surgery.

Statistical analysis

Baseline patient characteristics, including age, body weight, height, body mass index (BMI), postoperative length of stay, American Society of Anesthesiologists (ASA) physical status classification, and operative time, were summarized using descriptive statistics. Continuous variables were presented as mean and standard deviation (SD) or median with interquartile range (IQR), depending on data distribution, while categorical variables were reported as frequencies and percentages. Comparisons of postoperative pain scores and surgical satisfaction between patients undergoing inguinal hernia repair under local anesthesia and those receiving anesthesiologist-administered anesthesia were performed using the independent samples t-test. Categorical outcomes, including postoperative complications, were compared between groups using the chi-square test. This study was designed as a comparative prospective cohort study. Statistical analyses were performed using two-sided superiority testing with a significance threshold of $p < 0.05$.

RESULTS

Baseline Characteristics

A total of 30 patients were included in this study, with 15 patients in the local anesthesia group and 15 in the general anesthesia group. All patients were male. Baseline demographic characteristics, including age and body mass index (BMI), were comparable between the two groups. The prevalence of most underlying comorbidities did not differ significantly between groups; however, dyslipidemia was more frequently observed in the general anesthesia group compared to the local anesthesia group (73.3% vs. 33.3%, $p = 0.028$). There was no statistically significant difference in ASA physical status distribution, although a higher proportion of patients in the local anesthesia group were classified as ASA more than III compared with the general anesthesia group (6.7% vs. 33.3%, $p = 0.084$). Hernia laterality and hernia type (direct, indirect, or pantaloon) were similar between groups.

Operative details and postoperative recovery

Operative time and total operating room time were comparable between the two groups. The mean operative time was 79.00 ± 11.05 minutes in the local anesthesia group and 78.00 ± 25.55 minutes in the general anesthesia

TABLE 1. Demographic data.

	Local anesthesia (n = 15)	General anesthesia (n = 15)	*p-value*
Sex (male)	15 (100%)	15 (100%)	N/A
Age (year)	72.53±6.87	71.07±3.90	0.478
BMI (kg/m^2)	21.76±2.80	21.69±3.16	0.947
Underlying disease			
Hypertension	9 (60%)	10 (66.7%)	0.705
Dyslipidemia	5 (33.3%)	11 (73.3%)	**0.028**
Diabetes mellitus	4 (26.7%)	4 (26.7%)	1.000
Benign prostatic hypertrophy	5 (33.3%)	6 (40%)	0.705
Valvular heart disease	1 (6.7%)	2 (13.3%)	0.543
Arrhythmia	0 (0%)	3 (20%)	0.068
Chronic kidney disease	0 (0%)	2 (13.3%)	0.143
COPD	2 (13.3%)	2 (13.3%)	1.000
ASA classification			0.084
1-2	14 (93.3%)	10 (66.7%)	
≥ 3	1 (6.7%)	5 (33.3%)	
Laterality (Right side)	7 (46.7%)	8 (53.3%)	0.500
Hernia Type			0.550
Direct	3 (20.0%)	4 (26.7%)	
Indirect	9 (60.0%)	10 (66.7%)	
Pantaloon	3 (20.0%)	1 (6.7%)	

Data presented in n (%) for categorical variables, mean±standard deviation for normally distributed data, and median (P25, P75) for non-normally distributed data.
Abbreviations: BMI = Body mass index; COPD = Chronic Obstructive Pulmonary Disease; ASA = American Society of Anesthesiologists

TABLE 2. Operative details, postoperative pain scores, and recovery outcomes.

	Local anesthesia[15]	General anesthesia[15]	*p-value*
Operative time (minute)	79.00±11.05	78.00±25.55	0.891
Theater time (minute)*	101.67±12.91	107.67±25.77	0.429
Postoperative pain**			
Resting pain 8 hours	1.93±1.10	2.53±1.55	0.233
Resting pain 24 hours	0.87±0.83	1.80±1.65	**0.032**
Pain on movement 8 hours	4.67±1.17	4.67±1.17	0.310
Pain on movement 24 hours	2.33±0.82	2.47±1.55	0.386
Return to normal activity***	1.00±0.54	1.40±0.51	**0.022**

*Theater time includes the period from patient room-in, anesthesia induction, surgical procedure, and recovery of consciousness before room-out.
**Hour after surgery.
***Day after surgery.

group (p = 0.891). Similarly, total theater time did not differ significantly (101.67 ± 12.91 minutes vs. 107.67 ± 25.77 minutes, p = 0.429).

Postoperative pain scores at 8 hours, both at rest and during movement, were not significantly different between groups. At 24 hours postoperatively, pain at rest was significantly lower in the local anesthesia group compared to the general anesthesia group (0.87 ± 0.83 vs. 1.80 ± 1.65, p = 0.032), whereas pain during movement remained comparable between groups (p = 0.386). Although rescue analgesia was available under a standardized protocol, the exact number of rescue doses was not formally recorded, which may influence interpretation of VAS differences.

Patients in the local anesthesia group returned to normal activity significantly earlier than those in the general anesthesia group (1.00 ± 0.54 days vs. 1.40 ± 0.51 days, p = 0.022).

Postoperative complications

Early postoperative complications were infrequent and did not differ significantly between groups. Acute urinary retention (AUR), seroma, neurapraxia, and early postoperative groin pain occurred at low and comparable rates, and all postoperative complications were minor complications (Clavien–Dindo grade I–II), with no major complications observed. In the local anesthesia group, one patient with a pantaloon hernia developed a postoperative seroma at 2 weeks, which resolved spontaneously. One high-risk patient with multiple comorbidities — including dilated cardiomyopathy, triple-vessel disease requiring percutaneous coronary intervention while on aspirin therapy, and chronic obstructive pulmonary disease — experienced transient neurapraxia, likely due to inadvertent femoral nerve block. The patient was admitted for observation, and symptoms resolved within 24 hours without sequelae. He was discharged without residual weakness. Early postoperative groin pain occurred in one patient and resolved during follow-up, with no cases of chronic groin pain observed. In the general anesthesia group, one patient experienced postoperative AUR requiring temporary Foley catheterization, which was successfully discontinued during outpatient follow-up. Two patients developed postoperative seroma following repair of indirect inguinal hernias with defect sizes of 3 cm and 4 cm, respectively, both resolving spontaneously within 3 months.

Late postoperative outcomes were comparable between groups. One patient in the general anesthesia group with an indirect inguinal hernia defect of 4 cm reported early postoperative groin numbness and subsequently developed chronic groin pain persisting at 1 year. One-year hernia recurrence occurred in one patient in each group (6.7%), with no statistically significant difference (p = 0.759). In the local anesthesia group, one patient with a left direct inguinal hernia developed a recurrent defect measuring approximately 3 cm at 1-year follow-up and subsequently underwent laparoscopic totally extraperitoneal (TEP) repair. In the general anesthesia group, one patient who initially underwent right direct inguinal hernia repair developed a recurrent right indirect inguinal hernia at 1 year and proceeded to laparoscopic TEP repair. There were no 28-day readmissions in either group.

Patient satisfaction and healthcare costs

Patient satisfaction scores were high in both groups, with no statistically significant difference between the local anesthesia and general anesthesia groups (8.60 ± 1.24 vs. 8.87 ± 1.13, p = 0.653).

In contrast, total hospital cost was significantly lower in the local anesthesia group (median 13,453 THB [IQR 12,983, 14,225]) compared with the general anesthesia group (41,226 THB [40,092, 43,184]; p < 0.001). Fixed operative cost was also lower with local anesthesia (13,332 THB [12,980, 14,004] vs 30,656 THB [29,394, 32,108]; p < 0.001). Regarding variable costs, anesthesia service fees and inpatient stay costs were absent in the local anesthesia group for both, whereas these costs were substantial in the general anesthesia group (7,725 THB [6,882, 8,368] and 3,400 THB [3,198, 5,350], respectively; both p < 0.001).

Overall, open hernia repair with local anesthesia was associated with comparable patient satisfaction but significantly reduced hospital expenditures.

DISCUSSION

This prospective cohort study demonstrates that open inguinal hernioplasty performed under local anesthesia with same-day discharge yields clinical outcomes comparable to those of general anesthesia with inpatient admission, while offering significant advantages in postoperative recovery and healthcare cost reduction.

Postoperative outcomes and safety

Postoperative pain control was at least equivalent — and in some respect superior — in the local anesthesia group. Although pain scores at 8 hours postoperatively did not differ significantly between groups, pain at rest at 24 hours was significantly lower in patients receiving local anesthesia. This finding reflects a sustained analgesic

TABLE 3. Overall postoperative complications.

	Local anesthesia[15]	General anesthesia[15]	*p-value*
Early postoperative complication			0.357
Acute urinary retention	0 (0%)	1 (6.7%)	
Seroma	1 (6.7%)	2 (13.3%)	
Neurapraxia	1 (6.7%)	0 (0%)	
Groin pain	2 (13.3%)	0 (0%)	
Clavien-dindo classification			N/A
Minor complication (I-II)	4 (%)	3 (100%)	
Major complication (III-IV)	0 (0%)	0 (0%)	
Late postoperative complication			
Chronic groin pain	0 (0%)	1 (6.7%)	0.500
1-year recurrence	1 (6.7%)	1 (6.7%)	0.759
28-day readmission	0 (0%)	0 (0%)	N/A

TABLE 4. Satisfaction and hospital cost.

	Local anesthesia[15]	General anesthesia[15]	*p-value*
Patient satisfaction score	8.6±1.24	8.87±1.13	0.653
Total hospital cost* (THB) (Median, IQR)	13,453 (12,983, 14,225)	41,226 (40,092, 43,184)	< 0.001
Fixed Operative cost** (THB) (Median, IQR)	13,332 (12,980, 14,004)	30,656 (29,394, 32,108)	< 0.001
Variable cost (THB) (Median, IQR)			
Anesthesia services***	0 (0, 0)	7,725 (6,882, 8,368)	< 0.001
Inpatient stay ****	0 (0, 0)	3,400 (3,198, 5,350)	< 0.001

*Total hospital cost included the surgery cost in addition to inpatient care and medications administered during the hospital stay.
**Fixed operative cost included operative-related expenses, such as sterile surgical instruments, prostheses, operating room services, surgeon/scrub nurse fee and intraoperative medications used during surgery.
***Anesthesia service cost included anesthetic equipment, intraoperative anesthetic medications, anesthetic doctor/nurse fee, and monitoring equipment used during anesthetic process.
****Inpatient stay cost included ward care service, private room charges varied by room type and medical care fee during admission.

benefit beyond the immediate postoperative period and may facilitate earlier mobilization and functional recovery. Similar observations have been reported in both randomized controlled trials and meta-analyses, in which local anesthesia was associated with comparable or reduced postoperative pain compared with general or regional anesthesia.[19-21]

Importantly, postoperative complications were infrequent and mild in both groups, with no major complications observed. All early adverse events were classified as Clavien–Dindo grade I–II, and no 28-day readmissions occurred. The low complication rate in the local anesthesia group suggests comparable short-term safety within this cohort. However, the sample size was insufficient to exclude rare complications. This finding is consistent with recent evidence demonstrating favorable short-term outcomes of local anesthesia-based inguinal hernia repair, including in elderly and frail patients, without increased risks of bleeding, surgical site infection, or mortality.[22]

Acute urinary retention, a well-recognized complication associated with general and regional anesthesia, occurred only in the general anesthesia group in our study. This finding mirrors results from prior randomized trials and meta-analyses showing a lower incidence of urinary retention following local anesthesia–based hernia repair.[20,22] Avoidance of neuraxial or systemic anesthetic agents may therefore represent an additional advantage of local anesthesia, particularly in older patients or those with underlying urological risk factors.

Operative efficiency and recovery

Operative time and total theater time were comparable between groups, indicating that local anesthesia does not compromise procedural efficiency. Although an earlier multicenter randomized trial reported longer theater times in the local anesthesia group[20], subsequent studies and meta-analyses have shown equivalent or even shorter theater times when local anesthesia is performed by experienced surgical teams.[3,22] The slight numerical reduction in theater time observed in our study, although not statistically significant, likely reflects standardized local infiltration techniques and streamlined perioperative workflows within the day-surgery pathway.

Patients undergoing surgery under local anesthesia returned to normal daily activities significantly earlier than those receiving general anesthesia. This finding is clinically relevant and aligns with prior reports demonstrating shorter length of stay and faster functional recovery following local anesthesia–based inguinal hernia repair.[19-21] Early ambulation and reduced postoperative fatigue may be attributed to the avoidance of systemic anesthetic effects and inpatient admission.

Patient satisfaction

Despite differences in anesthetic technique and discharge timing, patient satisfaction scores were high and comparable between groups. Even patients who remained awake during surgery under local anesthesia reported high levels of satisfaction. This may be attributable to several factors, including earlier discharge, shorter preoperative and postoperative fasting periods, short work leave, faster return to normal activities, reduced postoperative pain at 24 hours, and reduced anxiety regarding anesthesia-related complications. This suggests that concerns regarding patient discomfort or dissatisfaction with awake surgery may be overstated when appropriate patient counseling and intraoperative pain control are provided. Similar levels of satisfaction between local and general anesthesia have been reported in randomized trials and systematic reviews.[18,20,22] These findings support the acceptability of local anesthesia from the patient perspective.

Cost implications and healthcare system impact

One of the most striking findings of this study is the substantial reduction in both surgical and total hospital costs associated with local anesthesia and same-day discharge. Total hospital costs in the local anesthesia group were approximately one-third of those in the general anesthesia group. This cost difference was primarily driven by the avoidance of inpatient admission and anesthesiologist-administered anesthesia, rather than differences in operative time or complication-related costs.

Previous studies have demonstrated similar cost advantages of local anesthesia for inguinal hernia repair at both institutional and national levels. *Balentine et al.* reported potential national cost savings ranging from 9 to 45 million USD with broader adoption of local anesthesia in older patients.[21] Although our study did not assess national-level economic impact, the marked cost reduction suggests that wider implementation of local anesthesia–based day surgery could significantly improve resource utilization and surgical capacity within the Thai healthcare system, particularly in the context of the One Day Surgery policy initiative.

Clinical implications

Taken together, these findings support the routine consideration of local anesthesia with same-day discharge for primary unilateral inguinal hernia repair in appropriately selected patients. Beyond cost savings, this approach

offers equivalent safety, comparable patient satisfaction, and faster functional recovery. From a health system perspective, increased adoption of this strategy may help alleviate inpatient bed shortages and improve access to elective surgical care.

Successful implementation, however, requires surgeon preference with local anesthesia techniques, appropriate patient selection, and structured perioperative pathways. Patient education and expectation management remain critical, particularly in settings where general anesthesia has traditionally been preferred.

Limitations

This study has several limitations. First, the non-randomized design and patient self-selection of anesthesia may introduce selection bias. Patients choosing local anesthesia may have differed in motivation, expectations, or perceived recovery priorities compared with those choosing general anesthesia. Second, although the study was adequately powered for the primary endpoint of postoperative pain at 8 hours, the sample size was insufficient to detect rare complications. Third, the cost analysis was performed at the institutional level and may not fully capture indirect or societal costs. Despite these limitations, the prospective design, standardized surgical technique, and comprehensive outcome assessment strengthen the validity of the findings.

CONCLUSIONS

Open inguinal hernioplasty performed under local anesthesia with same-day discharge provides clinical outcomes comparable to those of general anesthesia with inpatient admission. This approach is associated with equivalent operative efficiency, low complication rates, and high patient satisfaction, while offering advantages in postoperative pain control, faster return to normal activities, and a substantial reduction in healthcare costs. These findings support the use of local anesthesia–based day surgery as a safe, effective, and cost-efficient strategy for appropriately selected patients with primary unilateral inguinal hernia. Wider adoption of this approach may contribute to improved resource utilization and surgical capacity within the healthcare system.

Data Availability Statement

The data supporting the findings of our study are available from the corresponding author upon request at the following contact information.

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DECLARATIONS

The study was conducted in accordance with the Declaration of Helsinki and relevant ethical guidelines. The patient confidentiality was strictly maintained, and no identifying information was disclosed.

Grants and Funding Information

This was an unfunded study.

Conflict of Interest

The authors declare that there are no conflicts of interest or financial ties.

Author Contributions

Conceptualization and methodology, C.P., B.D., C.T., T.S., T.A., and S.J. ; Investigation, C.P., B.D., C.T., T.S., T.A., and S.J. ; Formal analysis, C.P., B.D., C.T., T.S., T.A., and S.J. ; Visualization and writing – original draft, C.P., B.D., C.T., T.S., T.A., and S.J. ; Writing – review and editing, C.P., B.D., C.T., T.S., T.A., and S.J. ; Funding acquisition, none; Supervision, C.P., T.S., T.A., and S.J. All authors have read and agreed to the final version of the manuscript.

Use of Artificial Intelligence

Artificial intelligence tools were used to assist with language editing and the improvement of grammar in the manuscript. The authors critically reviewed and revised all content, took full responsibility for the accuracy, integrity, and originality of the work, and confirmed that the use of artificial intelligence did not influence the study design, data analysis, interpretation of results, or conclusions.

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Incidence and Associated Factors for Inappropriate Blood Cross Matching in Cardiovascular Thoracic Surgeries at a Tertiary Care Center: A Retrospective Study Using Binary Logistic Regression

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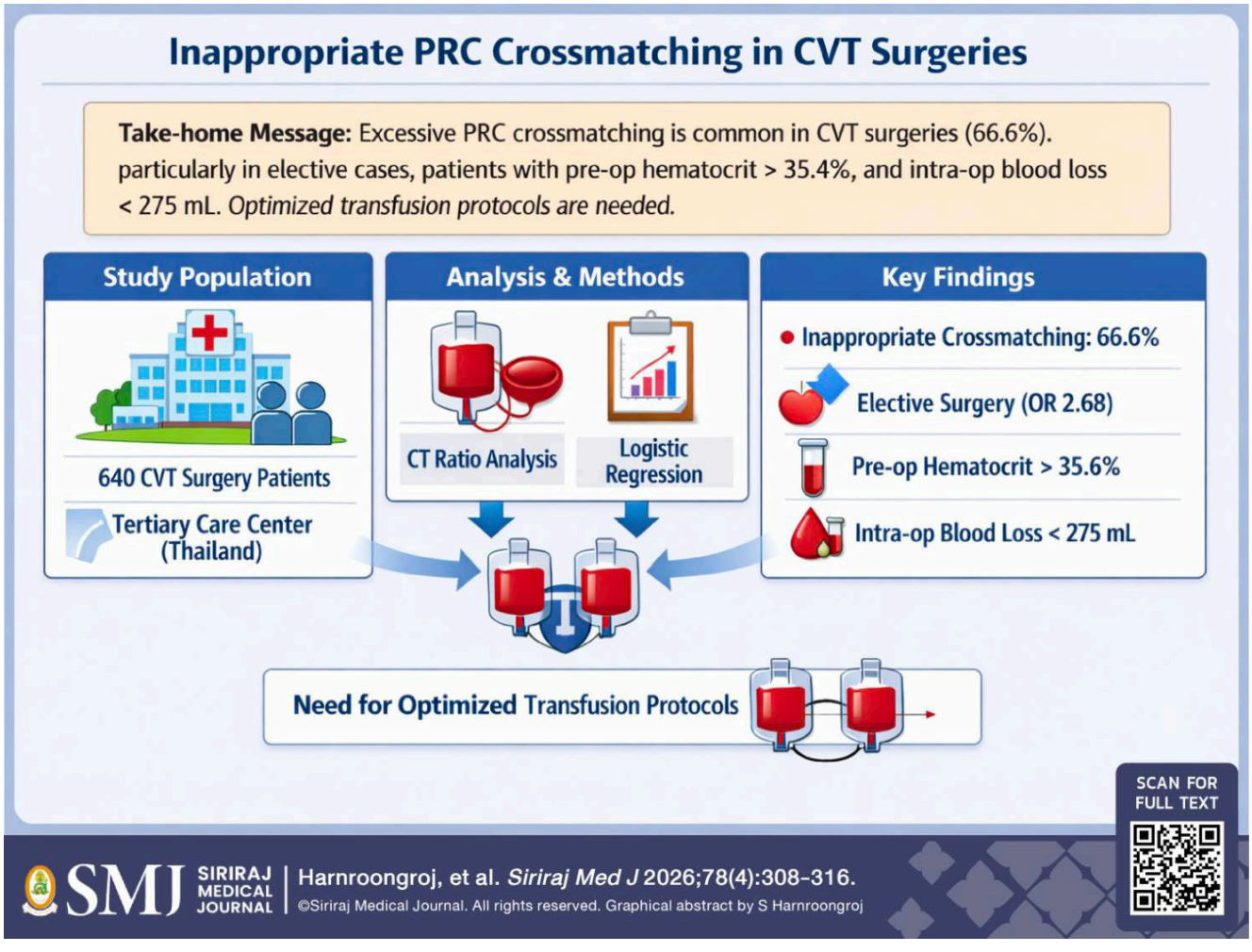

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ABSTRACT

Objective: To determine the incidence of inappropriate packed red cell (PRC) crossmatching in Cardiovascular Thoracic (CVT) surgeries at a service-focused tertiary care center, and to identify the associated factors for the inappropriate PRC cross-matching.

Materials and Methods: A retrospective cross-sectional study was conducted involving 640 patients who underwent CVT surgery between 2022 and 2025. The data reviewed included the patients' demographics, operative details, and PRC utilization (specifically, crossmatching and transfusion within 24 hours postoperatively). The crossmatch to transfusion (CT) ratio, transfusion probability (%T), and transfusion index (Ti) were calculated. An individual CT ratio > 2.0 was defined as inappropriate crossmatching. Binary logistic regression was used to identify the associated factors for inappropriate PRC crossmatching, and the Youden index to determine the optimal cutoff values.

Results: Inappropriate PRC crossmatching occurred in 426 of the 640 cases (66.6%). The overall CT ratio was 2.36, exceeding the recommended threshold limit of 2.0 and suggesting excessive blood ordering. Closed heart surgeries had the highest CT ratio (13.8), followed by thoracic surgeries (4.21). Significant factors associated with inappropriate crossmatching included elective surgery, a pre-operative hematocrit level > 35.4%, and intraoperative blood loss < 275 mL.

Conclusion: Inappropriate PRC crossmatching is common in CVT surgeries, with an incidence of 66.6% in this study cohort. Elective procedures, a higher pre-operative hematocrit level, and lower intraoperative blood loss were found to be key predictors for inappropriate PRC crossmatching. These findings highlight the need for more evidence-based transfusion protocols to minimize excessive crossmatching in CVT surgeries, and optimize the utilization of blood resources.

Keywords: Inappropriate PRC cross-matching; cardiovascular thoracic surgeries; cross-match to transfusion ratio; elective surgery; pre-operative hematocrit; intraoperative blood loss (Siriraj Med J 2026;78(4):308-316)

INTRODUCTION

Most Cardiovascular Thoracic (CVT) surgeries are inherently associated with substantial blood loss and require the availability of appropriate blood resources and therefore effective packed red cell (PRC) crossmatching.[1] An appropriate crossmatching protocol is thus essential to ensure the availability of adequate intraoperative PRC resources while avoiding excessive and inappropriate crossmatching, which could lead to unnecessary resource utilization and an increased financial burden to the healthcare center.

Intrathoracic procedures, closed-heart surgeries, and aortic operations performed using endovascular techniques have been identified as being associated with excessive PRC cross-matching, reflected by having cross-match to transfusion (CT) ratios greater than 2.5.[1] Other studies have reported CT ratios for CVT surgeries ranging from 2.12 to 13.5, all exceeding the recommended upper limit of 2.0.[2-4] Among cardiac surgeries, coronary artery bypass grafting (CABG) demonstrated the highest CT ratio at 11.70.[2] However, it is notable that the aforementioned studies were conducted in academic tertiary care centers, which may differ substantially from servicefocused tertiary care settings in terms of the patients' characteristics, surgical practices, and transfusion protocols. Therefore, despite the valuable insights provided in these studies, the true incidence and descriptive factors of inappropriate PRC cross-matching in CVT surgeries in other settings have not been clearly established, leaving an important knowledge gap.

Therefore, the primary objective of the present study was to determine the incidence of inappropriate PRC cross-matching in CVT surgeries within a servicefocused tertiary care center. A secondary objective was to identify the factors associated with inappropriate crossmatching in this context. It is expected that the findings from this study will serve as foundational evidence of the development of an optimized PRC crossmatching protocol.

MATERIALS AND METHODS

The present study was conducted following approval from the institutional review board. This was a single-center, retrospective cross-sectional study. Patients aged over 18 years old who underwent CVT surgery between January 2022 and August 2025 were included in the study. The exclusion criterion was incomplete medical record data, which led to the exclusion of 5 patients, leaving a total of 640 patients enrolled in the study.

The demographic characteristics of the patients were reviewed, including sex, body mass index (BMI), diagnosis,

preoperative American Society of Anesthesiologists (ASA) physical status, and preoperative hemoglobin and hematocrit levels. surgical-related information was also examined, such as the urgency of the procedure (emergency vs. elective), type of operation (closed heart, open heart, thoracic, or vascular), operative time, intraoperative blood loss, use and duration of cardiopulmonary bypass (CPB), and use and duration of aortic crossclamping.

For the PRC-related analysis, data on PRC crossmatching and intraoperative and 24-hour postoperative PRC usage were collected. Three parameters were calculated to evaluate the appropriateness of the PRC preparation: the crossmatch to transfusion ratio (CT ratio), transfusion probability (%T), and transfusion index (Ti). Herein, the CT ratio was defined as the number of PRC units crossmatched divided by the number of PRC units transfused, with an acceptable value being less than or equal to 2.0.[5-8] The %T represented the proportion of patients who actually received PRC among those for whom PRC was crossmatched, multiplied by 100; wherein a value greater than 30% was considered appropriate.[5,6,8] The Ti was calculated as the number of PRC units transfused divided by the number of patients for whom PRC was crossmatched, with an acceptable value being >0.5.[5,6]

After reviewing the data, the included patients were categorized into two groups based on their individual CT ratio: the *appropriate CT ratio* group (n=214), and the inappropriate *CT ratio group* (n=426). An *appropriate CT ratio* was defined as a value ≤ 2.0, while the *inappropriate CT ratio* was defined as a value > 2.0. Binary logistic regression analysis was then performed to identify factors associated with an inappropriate CT ratio in CVT surgeries.

All the patients' medical records were collected and independently reviewed by two authors who were not directly involved in the PRC crossmatching protocol or the surgical procedures. Both reviewers underwent training prior to initiating the data collection.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 21.0 (IBM, Armonk, NY). Categorical data were presented as numbers, percentages, and ratios. Normality was assessed using the Kolmogorov–Smirnov test. Numerical data were reported as the mean with the standard deviation (SD) or median with the interquartile range (IQR), depending on the distribution.

Comparisons of the categorical variables between groups were made using the chi-square test. For the numerical variables, comparisons between the two groups were performed using either the unpaired t-test or the Mann–Whitney U test, according to the data distribution. Comparisons across more than two groups were conducted using one-way ANOVA. A p-value < 0.05 was considered statistically significant.

Binary logistic regression analysis was used to identify factors associated with an inappropriate CT ratio in CVT surgeries. The patients' demographic characteristics and operative details were first examined using univariate analysis. Variables with $p<0.2$ were then included in a multivariate model to determine the odds ratios (ORs) and 95% confidence intervals (CIs). Variables with $p<0.05$ in the multivariate analysis were considered significant predictors of an inappropriate CT ratio. Cutoff values for the significant descriptive factors were determined using Receiver Operating Characteristic (ROC) curve analysis and the Youden index.

The minimum required sample size was determined in relation to the primary research objective: reporting the incidence of inappropriate PRC cross-matching in CVT surgeries within a service-focused tertiary care center. Based on pilot data from 40 patients, the incidence of inappropriate CT ratio in this setting was 0.4. With a 95% confidence interval and a margin of error of 5%, the calculated minimum sample size was 369.

To further evaluate the risk of statistical underpower in the binary logistic regression analysis, an additional sample size estimation was performed using the logistic regression formula. Based on pilot data from 40 patients, the incidence of inappropriate CT ratio was 0.4. The significance level (α) and power (1–β) were set at 0.05 and 0.8, respectively. As no previous studies had reported odds ratios related to inappropriate CT ratio in this context, an expected odds ratio of 1.5 was chosen to reflect a moderate effect size appropriate for an exploratory study. This calculation indicated that the minimum required sample size was 202 patients, comprising 81 with inappropriate CT ratio and 121 with appropriate CT ratio.

In this study, the actual sample size was 640 (426 with inappropriate CT ratio and 214 with appropriate CT ratio), which was considered sufficient to address both the primary research question and the requirements for logistic regression analysis.

RESULTS

From the 640 patients included in the analysis, an inappropriate CT ratio was found in 426 cases, indicating that the incidence of an inappropriate CT ratio in CVT surgeries in this patient cohort was 66.6%. Comparisons between the groups revealed that the inappropriate CT ratio group had statistically significantly lower numbers

of patients with an ASA physical status less than grade 3 (p<0.001), less intra-operative blood loss (p<0.001), less CPB and aortic crossclamping use (p<0.001), and also less multiple CPBs (p=0.005) and aortic crossclamping (p=0.009). The CPB time and aortic cross-clamping time were also statistically significantly shorter in the inappropriate CT ratio group (p<0.001), while the pre-operative Hb and Hct levels were statistically significantly higher in this group (p<0.001) (Table 1).

In terms of the PRC-related analysis, the overall CT ratio, %T, and Ti for the total patient cohort were 2.36, 57, and 2.22, respectively. Regarding the urgency of the procedures, both elective and emergency types of surgery had CT ratios at inappropriate levels, namely as 2.39 and 2.18, respectively. In terms of the types of surgery, closed heart surgery and thoracic surgery had CT ratios at inappropriate levels, namely as 13.8 and 4.21, sequentially (Table 2).

TABLE 1. Univariate analysis comparing variables between the inappropriate CT ratio group and the appropriate CT ratio group

Variables	Total sample (n=640)	Inappropriate CT ratio (n=426)	Appropriate CT ratio (n=214)	*p*-value
Patient factors				
Female sex n (%)	236 (36.9 %)	151 (35.4 %)	85 (39.7 %)	0.290[a]
Age (years)				
Mean (SD)	56.1 (15.9)	55.2 (16.4)	57.9 (15.1)	0.040[b]
ASA 3 and above n (%)	559 (87.3%)	352 (82.6%)	207 (96.7%)	<0.001[a]
BMI (kg/m^2)				
Mean (SD)	27.2 (53.9)	28.3 (64.2)	25.0 (22.1)	0.641[b]
Pre-operative hemoglobin level (g/dl)				
Mean (SD)	11.7 (2.23)	12.2 (2.00)	10.8 (2.42)	<0.001[b]
Pre-operative hematocrit level (%)				
Mean (SD)	35.5 (6.34)	37.0 (5.91)	32.6 (6.2)	<0.001[b]
Pre-operative PRC transfusion n (%)	77 (12.0%)	37 (8.7%)	40 (18.7%)	<0.001[a]
Surgical-related factors				
Elective surgery n (%)	528 (82.5%)	359 (84.0%)	169 (79.0%)	0.096[a]
Intraoperative blood loss (milliliters)				
Mean (SD)	419.2 (441.8)	268.0 (279.4)	720.2 (541.4)	<0.001[b]
CPB usage n (%)	218 (34.1%)	94 (22.1%)	124 (57.9%)	<0.001[a]
Multiple CPBs n (%)	9 (1.41%)	2 (0.5%)	7 (3.3%)	0.005[a]
CPB time (minutes) *				
Mean (SD)	139.0 (55.4)	121.7 (42.7)	152.1 (60.2)	<0.001[b]
Aortic X-clamp usage n (%)	214 (33.4%)	90 (21.1%)	124 (57.9%)	<0.001[a]
Multiple aortic X-clamps n (%)	6 (1.0%)	1 (0.2%)	5 (2.3%)	0.009[a]
Aortic X-clamp time (minutes) **				
Mean (SD)	98.8 (36.7)	89.2 (30.7)	105.8 (39.4)	0.001[b]

[a] Chi-square test, [b] Unpaired t-test.
* CPB time was analyzed in 218 patients (94 with inappropriate CT ratios vs. 124 with appropriate CT ratios) in whom CPB was utilized.
** Aortic X-clamp (cross-clamp) time was analyzed in 214 patients (90 with inappropriate CT ratios vs. 124 with appropriate CT ratios) in whom an aortic cross-clamp was applied.

TABLE 2. CT ratio, %T, and Ti of the patient cohort.

Variables	CT ratio	%T	Ti
Total patient cohort (n=640)	2.36	57	2.22
Urgency of the procedures			
Elective (n=528)	2.39	57.4	2.34
Emergency (n=112)	2.18	54.5	1.58
Open heart surgery (n=218)	1.92	97.7	5.20
Single valve repair/replacement (n=68)	1.65	100	6.06
CABG (n=89)	2.05	96.6	4.89
Complex valve surgery (n=17)	2.24	100	4.47
CABG + valve repair/replacement (n=29)	2.12	96.6	5.07
ASD/VSD closure (n=6)	2.14	83.3	4.67
Ascending aorta surgery (n=4)	2.11	100	4.75
Other (n=5)	1.85	100	5.40
Closed heart surgery (n=36)	13.8	13.9	0.17
Pericardial window/biopsy (n=34)	14.6	12.1	0.15
Others (n=2)	10.0	33.3	0.33
Thoracic surgery(n=379)	4.21	23.7	0.65
Mediastinal surgery (n=31)	Infinity	0.0	0.0
Lung lobectomy/wedge resection (n=44)	Infinity	0.0	0.0
VATS (n=109)	Infinity	0.0	0.0
Lung decortication (n=131)	2.94	58.8	0.95
Other (n=64)	1.76	100	1.92
Vascular surgery (n=7)	1.08	100	3.70
TEVAR (n=4)	1.08	100	3.00
ECMO related procedure (n=3)	1.08	100	4.67

Regarding the univariate analysis, the variables that had *p*-values less than 0.2 were an ASA physical status less than grade 3, elective surgeries, pre-operative Hb–Hct, pre-operative PRC transfusion, CPB use, multiple CPBs, CPB time, aortic cross-clamping, multiple aortic cross-clampings, and aortic cross-clamping time (Table 1). All these factors were included in the multivariate analysis, and the analysis results demonstrated that the pre-operative Hct level, intraoperative blood loss, and elective surgery were significant descriptive factors related to an inappropriate CT ratio in CVT surgeries, with $p<0.001$, <0.001, and =0.004, respectively (Table 3).

TABLE 3. Multivariate analysis of the descriptive factors related to an inappropriate CT ratio in CVT surgeries.

Variables	p-value	Exp (B)	95% confidence interval
Pre-operative hematocrit level	<0.001	1.20	1.13–1.28
Intraoperative blood loss	<0.001	0.997	0.996–0.998
Elective surgery	0.004	2.68	1.37–5.25

According to ROC curve analyses, the cut-off point for the pre-operative Hct level related to an inappropriate CT ratio in CVT surgeries was 35.4%, with an AUC of 0.701, sensitivity of 64.2%, and specificity of 65.0% (Fig 1). Also, the cut-off point for intraoperative blood loss related to an inappropriate CT ratio in the CVT surgeries was 275 mL, with an AUC of 0.806, sensitivity of 87.0%, and specificity of 62.0% (Fig 2).

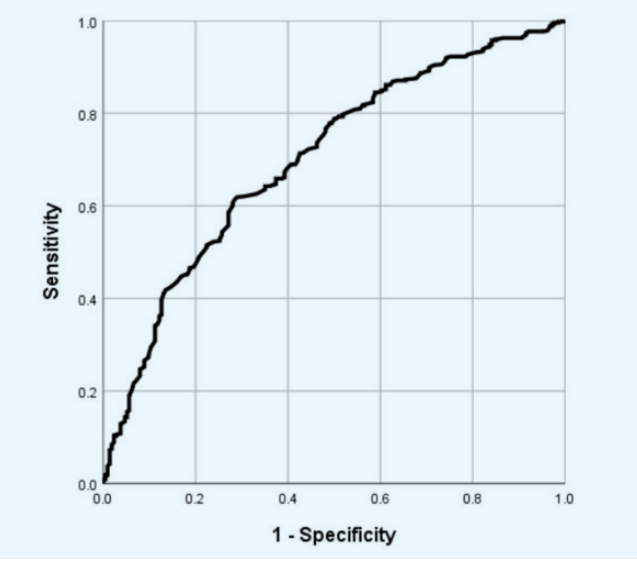

Fig 1. The ROC curve of the pre-operative Hct to determine the inappropriate CT ratio for CVT surgeries demonstrated the AUC of 0.701. The pre-operative Hct of 35.4% was considered as an appropriate cut-off point relating to inappropriate CT ratio for CVT surgeries with the sensitivity of 64.2% and specificity of 65.0%.

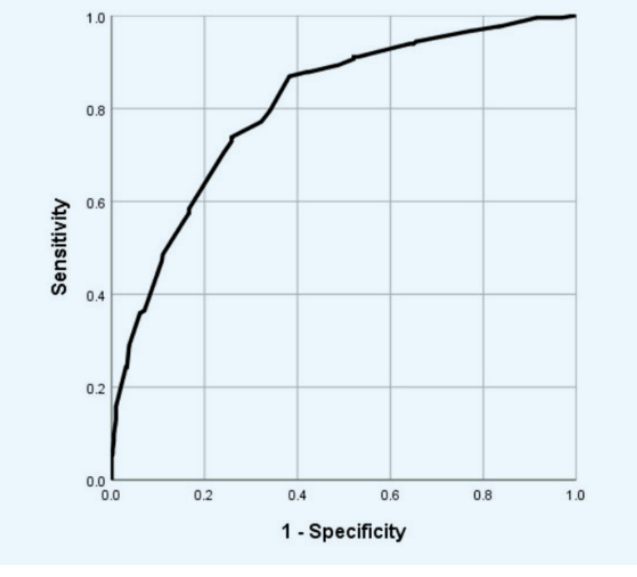

Fig 2. The ROC curve of the intra-operative blood loss to determine the inappropriate CT ratio for CVT surgeries demonstrated the AUC of 0.806. The intra-operative blood loss of 275 millimeters was considered as an appropriate cut-off point relating to inappropriate CT ratio for CVT surgeries with the sensitivity of 87.0% and specificity of 62.0%.

DISCUSSION

The incidence of an inappropriate CT ratio in CVT surgeries in the study cohort was 66.6%, a notably high value. The overall CT ratio of 2.36 further confirmed that the crossmatching protocol in our tertiary care center exceeded the acceptable threshold. Compared with previous reports, the CT ratio in our servicebased tertiary hospital was comparable to other values reported in both academic and servicebased tertiary care centers, which range from 2.12 to 13.5.[2-4] These findings indicate that inappropriate and excessive PRC crossmatching in CVT surgeries is a consistent issue across different institutional contexts. Notably, the study most similar to ours, conducted in a servicebased tertiary care center, reported a CT ratio of 2.12, which closely aligned with our results.[3] However, we believe our study adds further value by providing more detailed PRCrelated data and subcategory analyses, including for closedheart surgeries, thereby offering a more comprehensive understanding of crossmatching practices in CVT procedures.

In terms of the in-depth comparisons with previous studies conducted primarily in academic tertiary care centers[2-7], our findings in a servicebased tertiary care setting were similar in several respects. For instance, thoracic and closedheart surgeries were the two categories most frequently associated with excessive CT ratios.[1,3,4] This likely reflects institutional practice, wherein at least one unit of PRC is routinely crossmatched for these procedures without consideration of the transfusion-related factors, resulting in unnecessary pre-operative crossmatching. In our study, three thoracic operations demonstrated infinite CT ratios—mediastinal surgery (mass removal, biopsy, or abscess drainage), lung lobectomy/wedge resection, and video-assisted thoracoscopic surgery (VATS)—indicating that the crossmatched PRC was never transfused (Table 2). These results are consistent with those of Chantawong et al., who also reported infinite CT ratios in lung lobectomy and VATS procedures.[1] Similarly, Galata et al. reported a CT ratio of 13.5 in noncardiac thoracic surgeries[4], which aligns with our finding of an inappropriate CT ratio of 4.21 for thoracic surgery overall. However, Galata et al. did not provide CT ratios for specific surgical subtypes. By contrast, our analysis calculated CT ratios by procedure and identified infinite values in mediastinal surgery, lung lobectomy/wedge resection, and VATS. Collectively, these findings suggest that crossmatching protocols for thoracic procedures should be less aggressive to avoid excessive and unnecessary PRC preparation.

For closedheart surgery, the procedure most strongly associated with an excessively high CT ratio in the present study was pericardial window/biopsy (Table 2). This finding

is comparable to that found by Chantawong et al., who reported an infinite CT ratio for the same procedure.[1] However, a limitation of the Chantawong study was their small sample size (n=2), whereas our study included 34 patients undergoing pericardial window/biopsy, providing more additional conclusive evidence. In contrast, the CT ratio for open-heart surgery in our cohort was within acceptable ranges, consistent with earlier reports.[1,9,11,12] As openheart procedures represent the most common operations performed by CVT surgeons in most centers, greater familiarity with these surgeries may contribute to more appropriate confidence in PRC crossmatching.

Regarding vascular surgery, our study found appropriate CT ratios in this category. This finding is in contrast with the earlier studies of Chanthawong et al., Mangwana et al. and DavoudiKiakalayeh et al., which reported excessive CT ratios in similar operations.[1,3,10] However, the number of vascular surgeries in our cohort was very small (n=7), raising a concern about potential statistical underpower and limiting our ability to draw definitive conclusions for this subgroup.

The inappropriate crossmatching of PRC has previously been identified as a leading cause of unnecessary resource utilization and increased financial burden for hospitals.[6,7] This issue therefore warrants specific attention to reduce its incidence in CVT surgeries. In this study, we thoroughly reviewed the PRC crossmatching parameters, and performed binary logistic regression analysis to explore the root causes of inappropriate crossmatching. The results from the total cohort revealed an inappropriate CT ratio of 2.36 (Table 2); whereas both the %T and Ti values were within acceptable ranges. This suggests that the problem was primarily related to excessive preoperative PRC crossmatching rather than deficiencies in the criteria for patients requiring intraoperative transfusion. Subgroup analysis further demonstrated that inappropriate CT ratios were most pronounced in thoracic surgery and closedheart surgery, highlighting the need for more focused attention on these procedures. Our logistic regression analysis identified elective surgery, a preoperative hematocrit level above 35.4%, and intraoperative blood loss less than 275 mL as significant descriptive factors associated with inappropriate CT ratios in CVT surgeries.

Taken together, these factors suggest that the crossmatching protocol should be less aggressive in thoracic and closedheart surgeries, particularly in elective cases, in patients with a preoperative hematocrit level above 35.4%, and in procedures with an estimated blood loss of less than 275 mL. These significant findings provide a foundation for developing more appropriate and feasible crossmatching protocols for CVT surgeries, with the aim of reducing the incidence of inappropriate and excessive PRC crossmatching.

Potential methods to reduce inappropriate and excessive PRC crossmatching in this context include establishing a standardized PRC preparation protocol—such as implementing "type and screen" protocol for appropriate patients and surgeries—and conducting collaborative reviews of PRC preparation for individual cases.[12,13] Ural et al. reported significant improvements in costeffectiveness and blood product utilization after introducing a structured PRC ordering algorithm for cardiac surgeries, with the CT ratio decreasing markedly from 7.97 to 2.14.[13] Similarly, Singh et al. demonstrated the effectiveness of collaborative reviews, in which surgeons and blood bank physicians jointly determined the appropriate number of PRC units to crossmatch. Their study showed a reduction in CT ratio from 2.13 to 1.66.[12] These findings support our plan to develop an optimized PRC preparation protocol for CVT surgeries, incorporating consideration of the significant associated factors identified in our study and introducing type and screen protocol for selected surgeries, particularly thoracic and closedheart surgeries.

Based on current knowledge, this study addressed the current knowledge gap regarding inappropriate PRC crossmatching in CVT surgeries within the context of a servicebased tertiary care center, which has scarcely been reported to date. Our findings demonstrated that the primary characteristics of inappropriate PRC crossmatching were comparable to those reported in academic and serviced-based tertiary care centers.[2-7] The incidence of inappropriate crossmatching was objectively measured at 66.6% in our cohort, which is considered high. Furthermore, binary logistic regression analysis identified meaningful descriptive factors associated with inappropriate PRC crossmatching. Importantly, all of these factors are correctable, providing valuable insights for healthcare providers to enable them to develop more effective PRC crossmatching protocols aimed at reducing the incidence of inappropriate practices in CVT surgeries. The implementation of an effective protocol has previously been reported to reduce PRC transfusion in a surgical intensive care unit setting at an academic tertiary care center.[14]

Despite the meaningful findings from our study, certain limitations should be acknowledged. First, the data were collected from a single tertiary care center, which may limit the generalizability of the results. Nevertheless, the background characteristics for inappropriate PRC crossmatching observed in this study were consistent with those reported in previous research.[2-7] As such, the

additional descriptive factors identified here may have applicability across other centers, thereby extending the relevance of the findings beyond this setting. Second, the retrospective design of this study restricted the identified factors to being considered as "descriptive" rather than "prognostic". Third, certain factors that might have influenced the CT ratio were not included in the analysis. These factors included the protocol for PRC cross-matching, which was determined solely by a single CVT surgeon, as well as variations in transfusion thresholds during the perioperative period that depended on the individual judgment of each anesthesiologist and CVT surgeon. Finally, the relatively small sample size in our vascular procedure subgroup may have resulted in a limited statistical power for a fuller analysis in this category. A prospective, multicenter study with larger subgroup samples is recommended to strengthen future investigations.

CONCLUSION

In our servicebased tertiary care center, the incidence of an inappropriate CT ratio in CVT surgeries was 66.6%, with a predominance in closedheart and thoracic procedures. Elective status, a preoperative hematocrit level above 35.4%, and intraoperative blood loss under 275 mL were significant factors associated with an inappropriate CT ratio. These findings can help guide and support the development of more appropriate PRC transfusion protocols to reduce excessive crossmatching in CVT surgeries.

Data Availability Statement

The data that support the findings of this study are not publicly available due to privacy and ethical restrictions related to the Personal Data Protection Act (PDPA) of Thailand. Data may be available from the corresponding author (Saranya Harnroongroj) upon reasonable request and with permission from the Siriraj Institutional Review Board.

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DECLARATIONS

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None.

Conflict of Interest

All the authors confirm that they have no personal or professional conflicts of interest to declare relating to any aspect of this research study.

Registration Number of Clinical Trial

None.

Author Contributions

Conceptualization and methodology, S.H.; Investigation, S.H, W.S, R.D; Formal analysis, S.H; Visualization and writing – original draft, S.H. All authors have read and agreed to the final version of the manuscript.

Use of Artificial Intelligence

During the preparation of this work the author(s) did not use generative AI in any writing process.

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Optical Interventions for Myopia Control

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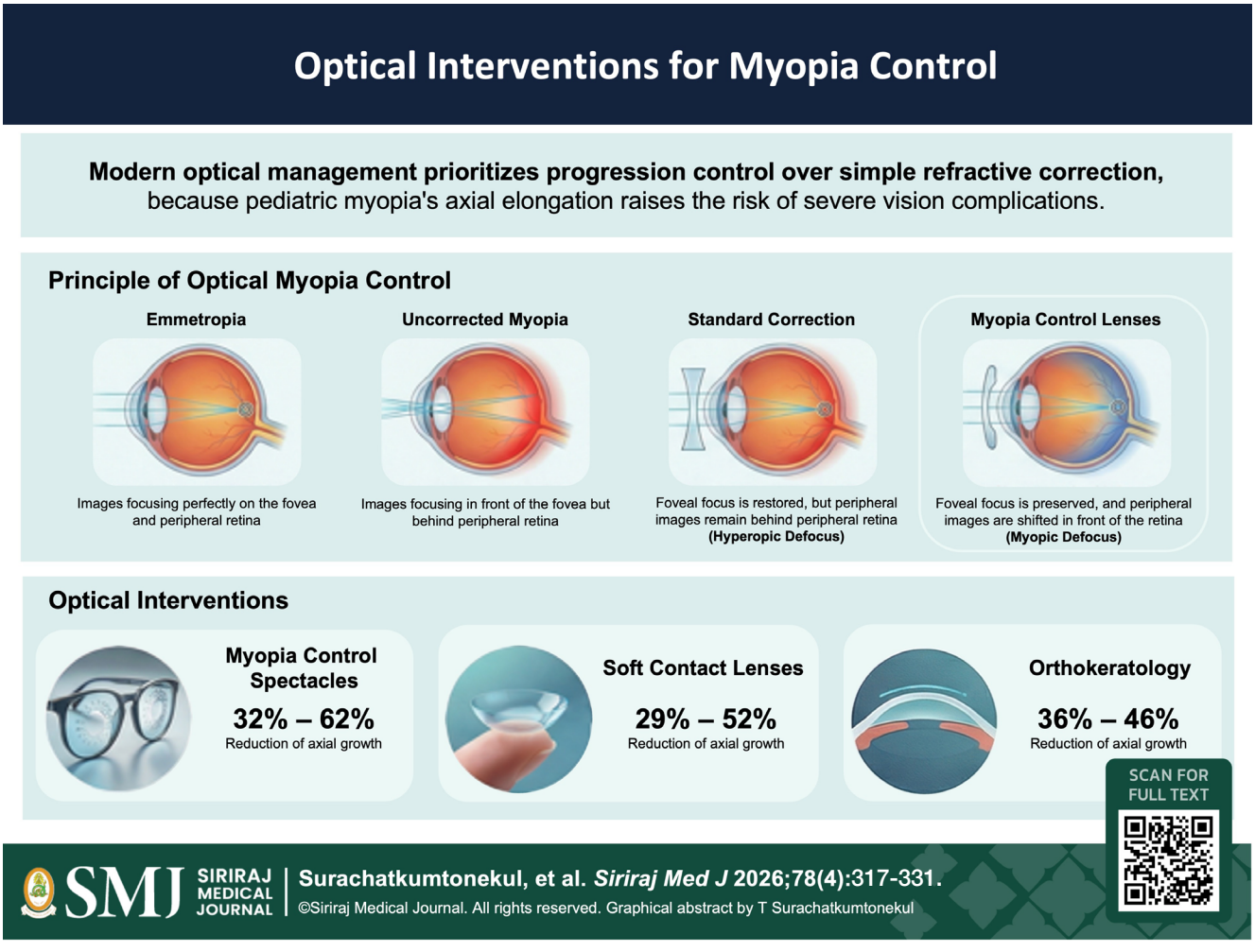

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ABSTRACT

Pediatric myopia is a major public health challenge driven primarily by progressive axial elongation, which substantially increases the lifetime risk of vision-threatening complications, such as myopic macular degeneration. Accordingly, contemporary management emphasizes myopia control rather than simple refractive correction. Current strategies include behavioral modification, low-dose atropine, and — most critically — optical interventions. These interventions encompass a variety of myopia-control spectacle lenses, such as Defocus Incorporated Multiple Segments (DIMS), Highly Aspherical Lenslet (HAL), and newer designs such as Cylindrical Annular Refractive Elements (CARE) and Lenslet-ARray-Integrated (LARI), which use lenslet arrays to project a plane or volume of myopic defocus in front of the peripheral retina. In contrast, Diffusion Optics Technology (DOT) employs microscopic light-scattering elements to reduce retinal image contrast without forming a secondary focal plane. Beyond spectacles, additional modalities, including multifocal soft contact lenses, dual-focus designs, and orthokeratology, rely on the same underlying principle of myopic defocus. All these optical strategies operate by manipulating the peripheral visual profile to suppress pro-elongation signals in the growing eye. Existing evidence demonstrates a 30%–60% reduction in axial elongation, depending on the technology employed. Combination therapy, particularly the integration of optical devices with low-dose atropine, offers superior efficacy compared with monotherapy, especially in children with rapid progression. Standard monitoring includes axial length measurement every six months and cycloplegic refraction one to two times per year. General practitioners play a pivotal role in identifying high-risk children — such as those with early-onset myopia, rapid refractive shifts, or a strong family history of high myopia — and in facilitating timely referral to ophthalmologists for definitive evaluation and evidence-based intervention.

Keywords: Optical interventions; myopia control (Siriraj Med J 2026;78(4):317-331)

INTRODUCTION

Childhood myopia is no longer regarded as a simple refractive error that can be corrected with spectacles. It is now recognized as a major public health concern because of its lifelong association with sight-threatening ocular comorbidities. The global prevalence of myopia continues to rise, particularly across East and Southeast Asia. In Thailand, the reported prevalence of myopia in primary school children is 4.3–11.1%.[1] Among secondary school students, more recent data indicate a prevalence of 24.52%, increasing to 31.36% after a two-year follow-up.[2] Accordingly, myopia management has shifted from purely optical correction toward interventions aimed at slowing refractive progression and axial elongation. This review synthesizes contemporary evidence on optical interventions for myopia control to guide clinicians in selecting and implementing evidence-based options for pediatric patients.

Definition

Myopia is a refractive condition in which light rays from distant objects are focused anterior to the retinal plane rather than directly on the retina, resulting in blurred distance vision. Clinically, the most reliable biometric parameter of myopic progression is axial elongation, a process that typically begins in early childhood and continues progressively with age.[3,4]

Once considered a prevalent refractive error, myopia has now emerged as a global public-health priority. Its prevalence is rising at an unprecedented rate, with projections estimating that by 2050, nearly 5 billion individuals — approximately 50% of the world's population — will be myopic. The burden is particularly severe in East and Southeast Asia, including Thailand, where prevalence rates are among the highest worldwide and continue to escalate at an alarming pace.[5,6]

Assessment of myopia

Accurate evaluation of myopic progression relies on two principal clinical metrics: refractive error and axial length.[7,8]

Refractive error

Refractive error is the clinical metric most familiar to clinicians and caregivers. It represents the eye's optical power, determined primarily by the refractive contributions of the cornea and crystalline lens, and is expressed in diopters (D), with negative values denoting myopia. In children, however, refractive assessment is complicated by the strong influence of accommodation. For this reason, cycloplegic refraction is considered the clinical gold standard for diagnosis. Despite cycloplegia, refractive measurements may still exhibit variability and do not always correlate precisely with structural progression.

Axial length

Childhood myopia progression is fundamentally driven by axial elongation, making axial length measurement the most reliable objective parameter and universally recognized as the gold standard for monitoring disease trajectory. In contrast to refractive error — which may be influenced by lenticular changes — axial length directly reflects the underlying biological process associated with long-term ocular morbidity. Furthermore, certain optical interventions, such as orthokeratology, deliberately alter corneal curvature, rendering refractive error an unreliable indicator of treatment efficacy. In these scenarios, serial axial length measurements provide the most accurate means of assessing therapeutic response.

Clinical significance

The urgency surrounding childhood myopia lies not merely in its prevalence, but in its severity. High myopia, conventionally defined as a refractive error of –6.00 D or worse, is a major risk factor for multiple sight-threatening ocular diseases, including myopic macular degeneration, glaucoma, cataract, and retinal detachment, all of which may result in irreversible visual impairment.

Importantly, each additional –1.00 D of myopia is associated with a significant increase in the lifetime risk of myopic macular degeneration and related complications. Consequently, strategies that slow axial elongation — even to a modest degree — offer meaningful long-term protection against the development of myopia-associated pathology.[9,10]

Approaches to slowing myopia progression

Historically, myopia management focused primarily on visual correction, typically using single-vision spectacles or standard contact lenses. While these modalities restore visual acuity, they do not address the underlying pathophysiology of axial elongation. With growing evidence linking high myopia to serious ocular morbidity, the clinical paradigm has shifted toward myopia control, in which the primary therapeutic objective is to slow refractive progression and axial length growth, thereby reducing the risk of high myopia later in life.[11]

Current myopia-control strategies can be broadly categorized into three evidence-supported modalities:[12]

1. Behavioral and environmental modification,
2. Pharmacologic therapy, particularly low-dose atropine, and
3. Optical interventions, including specialized spectacle lenses, multifocal soft contact lenses, and orthokeratology.

Together, these approaches form the foundation of contemporary, multimodal myopia management in children.

Behavioral and environmental interventions

Increased outdoor activity

Spending time outdoors is one of the most effective behavioral measures for reducing the onset of myopia. Robust evidence demonstrates that increased outdoor exposure can reduce incident myopia by approximately 50%. Current recommendations suggest a minimum of two hours of outdoor activity per day to achieve meaningful preventive benefit.[13]

Reduction of excessive near work

Prolonged near work represents a significant, modifiable risk factor for myopia. The risk is particularly elevated in children who engage in activities at a working distance shorter than 30 cm or who perform uninterrupted near tasks for more than 30 minutes at a time. Encouraging regular breaks and maintaining proper reading distance are therefore essential strategies to reduce accommodative stress and hyperopic defocus during near work.[14]

Pharmacologic therapy

Low-Dose atropine

Low-dose atropine (0.01%–0.05%) is a well-established pharmacologic intervention for slowing myopia progression and is widely used in pediatric practice. Multiple randomized controlled trials have demonstrated its efficacy in significantly reducing both refractive progression and axial elongation.[15,16]

A study from Siriraj Hospital, Thailand, reported results from a retrospective cohort of 247 children (493 eyes), showing that both 0.01% and 0.05% atropine effectively slowed myopia progression over a one-year period. In the 0.01% group, the spherical equivalent (SE) change improved from –0.87 D in the year preceding treatment to –0.38 D after one year. Similarly, the 0.05% group showed an improvement from –0.50 D to –0.25 D over the same interval. Although 0.05% atropine exhibited a slightly greater numerical reduction in myopic progression, the between-group difference was not statistically significant.[17,18]

Evidence across multiple studies indicates a dose-dependent effect of atropine on axial elongation. Treatment with 0.01% atropine has been shown to reduce axial elongation by approximately 0.08 mm in the first year and 0.12 mm in the second year, despite diminished efficacy over time. Higher concentrations (0.025–0.05%) provide greater therapeutic benefit and approach the effect sizes observed with optical interventions. However, adverse

events occur substantially more frequently at 0.05% than at 0.01% (37.5% vs. 1.7%), with photophobia and near blur being the most reported side effects. These effects are consistent with increased pupillary dilation and reduced accommodative amplitude at higher atropine concentrations.

Current evidence suggests that optimal atropine concentration is not universal and may vary depending on ethnicity, baseline rate of axial elongation, individual sensitivity to atropine and tolerance of visual side effects. Thus, pediatric ophthalmologists should individualize treatment strategies, balancing efficacy with comfort and adherence when selecting atropine concentration.[12]

Optical interventions

Optical therapy refers to the use of specially designed lenses aimed not only to correct refractive error but also to modify ocular growth signals to slow myopia progression. These interventions can be broadly classified into three major categories:[19]

- Myopia-control spectacle lenses
- Soft contact lenses
- Orthokeratology lenses

Principles of optical myopia control

Modern optical interventions are designed to do more than simply produce a clear retinal image. Instead, they intentionally deliver specific optical signals to the eye to regulate axial elongation. Two key mechanisms underpin their therapeutic efficacy:

Modulation of peripheral retinal defocus

A widely accepted concept in contemporary myopia research is that the nature and quality of defocus at the peripheral retina play a critical role in refractive development, even when foveal vision remains clear.[20] Several fundamental findings support this mechanism:

1. Visual signals arising from the peripheral retina play a dominant role in regulating ocular growth compared with those originating from the central retina.[21,22]

2. Peripheral defocus is a key driver of axial growth regulation. Peripheral hyperopic defocus — where images are focused behind the peripheral retina — stimulates compensatory axial elongation as the eye attempts to reposition the image plane onto the retina, thereby exacerbating myopic progression. The standard single-vision refractive correction only addresses central vision; it inadvertently maintains peripheral hyperopic defocus, failing to halt axial elongation. Conversely, peripheral myopic defocus — where images fall in front of the peripheral retina — provides inhibitory cues that suppress further axial elongation. Based on this principle, the intentional induction of peripheral myopic defocus has become a central mechanism in current myopia-control strategies (Fig 1).[23-25]

Insufficient accommodative response

It has been hypothesized that children with myopia may exhibit an insufficient accommodative response, commonly referred to as accommodative lag, during sustained near-work activities such as reading or digital device use. When accommodation is inadequate, the image focal plane is positioned posterior to the retina, generating signals that promote axial elongation. Certain therapeutic approaches — such as multifocal spectacles and contact lenses — are specifically designed to reduce accommodative demand and mitigate these pro-elongation cues.[26,27]

Myopia-control spectacle lenses

Early optical strategies for slowing myopia progression primarily involved undercorrection and the use of bifocal

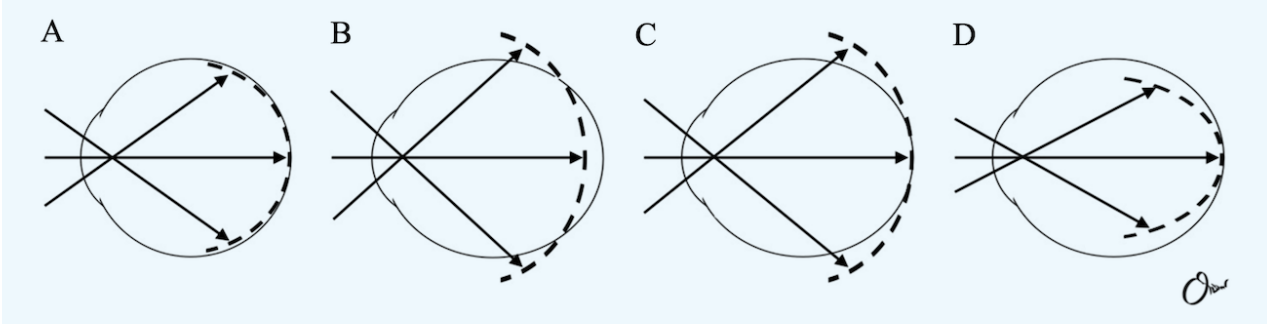

Fig 1. **(A)** Emmetropia: Images are focused on both the fovea and the peripheral retina. **(B)** Uncorrected myopia: Images focus in front of the fovea while falling behind the peripheral retina, resulting in peripheral hyperopic defocus. **(C)** Myopia corrected with single-vision lenses: Foveal focus is restored; however, images continue to fall behind the peripheral retina, maintaining peripheral hyperopic defocus. **(D)** Myopia corrected with myopia-control lenses: Foveal focus is preserved, while images are shifted to fall in front of the peripheral retina, inducing peripheral myopic defocus.[23–25] *(Image by Arnan Limmahachai)*

spectacles. However, contemporary systematic reviews have found no convincing evidence that either undercorrection or overcorrection provides a clinically meaningful benefit in reducing myopia progression. As a result, the current consensus is that children receive full refractive correction to optimize visual acuity, alongside the use of evidence-based myopia-control treatments.[28,29]

Lenslet-based (multiple-segment) spectacle designs

Over the past decade, spectacle lenses incorporating multiple segments or lenslets have gained widespread adoption due to their demonstrated ability to slow myopia progression in clinical trials. These designs operate on the principle of inducing peripheral myopic defocus while preserving clear central distance vision.

Although several commercial designs exist, they share a common structural framework:

- A central optical zone (approximately 10 mm in diameter) providing standard myopic correction for clear distance vision.
- A surrounding region populated with arrays of small, positive-powered lenslets, typically occupying about 50% of the annular treatment area.

The lenslet arrays generate controlled myopic defocus across the mid-peripheral retina, delivering a sustained inhibitory signal against axial elongation while preserving visual comfort and stability.

Defocus Incorporated Multiple Segments (DIMS)

Design: DIMS lenses incorporate a 9-mm central optical zone for conventional distance correction, surrounded by a 33-mm annular treatment zone configured in a honeycomb-like pattern. This treatment zone contains numerous 1-mm positive-powered lenslets (+3.50 D), which are uniformly distributed across the surface.

Mechanism: When worn, the central zone provides clear foveal vision, while light entering through the +3.50 D lenslets creates peripheral myopic defocus extending from the parafoveal region to the mid-peripheral retina. This continuous defocus signal suppresses axial elongation.

Efficacy: In children aged 8–13 years, DIMS lenses have been shown to reduce myopia progression by 52% and axial elongation by 62% compared with single-vision spectacles over a 2-year period. The mean reduction in axial elongation was 0.34 mm over two years, with sustained benefits observed into the third year.[12] Notably, 21% of children experienced no myopia progression throughout the two-year study period. Long-term follow-up data indicates that the therapeutic effect is maintained for up to six years, with no significant adverse effects reported.[30,31]

Highly Aspherical Lenslet (HAL)

Design: HAL lenses incorporate a 9-mm central correction zone surrounded by 11 concentric rings of densely packed, highly aspherical 1.1-mm lenslets. Each ring contains lenslets with differing positive powers, creating a graded asphericity profile across the treatment area.

Mechanism: The highly aspherical lenslets generate a three-dimensional volume of myopic defocus rather than defocus confined to a single focal plane. This sustained, deep-field myopic defocus is delivered to the peripheral retina, providing a potent inhibitory signal against axial elongation.

Efficacy: HAL lenses slow myopia progression by 55% and axial elongation by 51% compared with single-vision lenses over two years, corresponding to 0.35 mm less axial elongation.[12] Treatment efficacy is strongly dose-dependent: children who wear HAL lenses more than 12 hours per day experience a 67% reduction in refractive progression and a 60% reduction in axial elongation. Continuous daily wear is therefore recommended to achieve optimal therapeutic outcomes.

In long-term follow-up, children who wore HAL lenses for five years demonstrated myopia progression comparable to that observed in the single-vision control group after only three years, indicating sustained protective benefit.[32,33]

Importantly, HAL lenses have received U.S. FDA approval for use in children aged 6–12 years, making them the first spectacle lens design authorized for slowing myopia progression.

Cylindrical Annular Refractive Elements (CARE)

Design: CARE lenses feature a 9.4-mm central optical zone surrounded by a treatment annulus containing numerous microcylinders. These elements possess a +8.00 D cylindrical power and are arranged concentrically around the center at a fixed radial spacing of 1.2 mm.

Mechanism: The microcylinders intentionally introduce higher-order aberrations (HOAs) that create controlled peripheral blur. This optical disruption generates peripheral myopic defocus, which acts as a signal to reduce axial elongation.

Efficacy: Compared with single-vision lenses, CARE lenses reduce myopia progression by 37% and axial elongation by 32% over 2 years.[34]

Diffusion Optics Technology (DOT)

Design: DOT lenses incorporate a 5-mm central optical zone, surrounded by a treatment region composed of numerous micro-diffusers. Each diffuser softly scatters

incoming light, producing a subtle reduction in peripheral retinal contrast.[35]

Mechanism: DOT lenses are based on the principle of retinal contrast normalization. Excessively high contrast — whether genetically determined or associated with modern visual environments — may overstimulate retinal neurons and promote axial elongation. By slightly reducing contrast toward physiological norms, DOT lenses aim to decrease excessive neural stimulation and thereby reduce the visual signals that drive myopic eye growth.

Efficacy: DOT lenses reduce myopia progression by 59% and axial elongation by 38% over 2 years, with sustained therapeutic effectiveness observed up to 4 years.[36,37] They also slow axial elongation by 0.13 mm over 3 years.[12]

Lenslet-ARray-Integrated (LARI)

Design: LARI lenses utilize non-coaxially arranged hexagonal lenslet arrays and are available in two configurations:

- Positive LARI (PLARI): +3.00 D lenslets
- Negative LARI (NLARI): –3.00 D lenslets

Mechanism: Both configurations induce higher-order aberrations that create peripheral myopic defocus. Notably, similar defocus patterns are observed with both positive and negative configurations, supporting the concept that the presence of peripheral myopic signaling — rather than the sign of lenslet power — is the key determinant of myopia-control efficacy.

Efficacy: At one year, PLARI lenses demonstrated a 55% reduction in myopia progression and a 44% reduction in axial elongation, while NLARI lenses achieved a 68% reduction in myopia progression and a 50% reduction in axial elongation (approximately 0.17–0.19 mm).[12] Despite numerical differences, no clinically significant distinction has been identified between the two designs, supporting the conclusion that peripheral myopic defocus remains the primary therapeutic mechanism.[38,39]

Bifocal and progressive addition spectacles

Bifocal and progressive addition lenses (PALs) were historically considered for myopia control based on their ability to reduce accommodative demand — a factor associated with myopia progression. However, multiple controlled studies have failed to demonstrate clinically meaningful benefit, and these lenses are therefore not recommended as effective myopia-control strategies.[40-42]

Newer generations of progressive lenses specifically engineered for myopia control are currently under development, including designs that manipulate peripheral defocus, such as radial refractive gradient lenses[43], as well as asymmetrical configurations including U-shaped perifocal lenses[44] and T-shaped asymmetrical myopic-defocus lenses.[45]

These emerging lenses aim to address the limitations of earlier PALs by integrating peripheral defocus induction, a mechanism with proven biological plausibility in slowing axial elongation.

Soft contact lenses

Soft contact lenses designed with a central distance-correction zone and peripheral optical add power have demonstrated significant efficacy in slowing myopia progression. Various optical configurations are currently available, each engineered to induce controlled peripheral myopic defocus while maintaining central visual acuity.

Progressive peripheral add (multifocal) soft lenses

Design: These lenses incorporate progressively increasing peripheral plus-power zones, with treatment optics positioned closer to the visual axis to enlarge the effective area delivering myopic defocus.

Mechanism: The design provides accurate central foveal correction while simultaneously generating peripheral myopic defocus through added plus power, thereby diminishing the peripheral hyperopic blur that drives axial elongation and ultimately slows ocular growth.

Efficacy: Across studies, higher add powers have been associated with greater control of myopic progression. A +2.00 D add resulted in a 50% reduction in myopia progression and a 29% reduction in axial elongation over two years,[46] while a +2.50 D add achieved a 43% reduction in myopia progression and a 36% reduction in axial elongation over three years.[47] The highest tested add power, +3.00 D, produced a 66% reduction in myopia progression and a 63% reduction in axial elongation over 18 months.[48] Collectively, these findings demonstrate a clear dose–response relationship, whereby increasing add power produces stronger inhibition of axial elongation.

Concentric ring (bifocal) soft contact lenses

Dual-focus concentric ring design

Design: Dual-focus lenses incorporate a central optical zone for distance correction, surrounded by alternating concentric rings. The treatment rings contain +2.00 D add power and are interspersed with distance-correction zones to maintain stable on-eye performance.[49]

Mechanism: Similar to other multifocal designs, dual-focus optics correct central refractive error while simultaneously generating peripheral myopic defocus. This creates a continuous inhibitory signal to the peripheral retina.

Efficacy: Clinical trials have shown a 59% reduction in myopia progression and a 52% reduction in axial elongation over three years compared with single-vision soft lenses.[50]

Importantly, this therapeutic effect has been shown to persist through six years of follow-up, supporting long-term safety and durability.[51]

Dual-focus soft contact lenses have received approval from the U.S. Food and Drug Administration as the first optical therapy indicated specifically for slowing myopia progression in children, marking a significant milestone in pediatric myopia management.

Orthokeratology

Design: Orthokeratology employs rigid gas-permeable (RGP) lenses with high oxygen transmissibility, specifically engineered for overnight wear. The lenses are removed upon waking, allowing clear unaided daytime vision.

Mechanism: During sleep, the lens reshapes the anterior corneal surface by flattening the central cornea to correct myopic refractive error, while simultaneously redistributing epithelial cells toward mid-periphery, resulting in mid-peripheral corneal thickening and a relative steepening profile that induces peripheral myopic defocus — the primary mechanism responsible for limiting axial elongation.

Through these combined effects on corneal contour and peripheral focus, orthokeratology delivers both refractive correction and biologically effective myopia control.[52,53]

Efficacy: Studies in predominantly Asian cohorts demonstrate that orthokeratology lenses reduce axial elongation by 36–46% over two years compared with single-vision controls.[54-56] Additional evidence indicates mean axial elongation inhibition of approximately 0.17 mm at one year and 0.30 mm at two years.[12]

These findings confirm orthokeratology as one of the most established optical approaches to slowing myopic eye growth.

Emerging technologies

Light-based therapies

Light-based modalities — including red light, blue light, and ultraviolet-light–related approaches — are being investigated as novel strategies for modulating refractive development. These interventions target both image-forming and non–image-forming visual pathways, which are believed to interact with ocular growth regulation.

At present, light therapy remains an emerging treatment, with limited long-term data and limited availability in Thailand.[12]

Red-Light therapy

Design: Low-level red-light therapy generally employs wavelengths in the 600–650 nm range delivered at low energy to the retina. Clinical protocols commonly involve two daily treatment sessions of three minutes each, spaced at least four hours apart. This regimen is designed to provide consistent inhibitory signaling to suppress axial elongation.

Mechanism: Although the precise biological mechanisms are not fully established, proposed pathways include mitochondrial modulation that enhances cellular bioenergetics, choroidal thickening that improves perfusion, and reduction of scleral hypoxia, an identified contributor to scleral remodeling and axial elongation. Collectively, these effects may suppress the biomechanical cascade underlying progressive myopia.

Efficacy: Clinical studies report reductions in axial elongation of approximately 0.16 mm at three months, 0.21 mm at six months, and 0.31 mm at twelve months, with treated children also demonstrating significantly smaller increases in spherical equivalent refraction, supporting red-light therapy as a biologically active modality for myopia control.[57]

Spatio-temporal optical phase (S.T.O.P.) kits

S.T.O.P. kits represent a novel optical approach in which a specialized optical film is applied to single-vision spectacle lenses to induce dynamic optical cues for myopia control. Current evidence is derived primarily from studies in Chinese children aged 6–14 years; data in Thai populations are not yet available.[58]

Design: Each S.T.O.P. kit includes two pairs of spectacles, each equipped with a transparent, ultra-thin optical film containing approximately 30 large optical elements (1.7–3.0 mm) with a maximum lens power of about +3.00 D. The elements are arranged asymmetrically to generate non-uniform blur patterns across different gaze directions. Children alternate between the two pairs on a weekly basis to expose the retina to varying optical signal patterns.

Mechanism: The large, irregularly distributed elements generate multidirectional myopic defocus. Weekly alternation between the two film designs introduces a temporal component that produces continually shifting spatial blur patterns and dynamic optical stimuli to which the visual system is less able to adapt. This spatiotemporal variability reduces neural adaptation, a recognized limitation of fixed-defocus therapies, thereby sustaining the inhibitory effect on axial elongation.

Efficacy: Compared with controls, S.T.O.P. kits significantly reduce axial elongation by 0.091 mm with

Kit 1 and 0.090 mm with Kit 2 at six months, while also attenuating refractive progression, with spherical equivalent increasing approximately +0.13 D less than in controls. These findings indicate a therapeutic effect comparable to established modalities such as DIMS, HAL, and CARE lenses.[59] (Table 1)

Combination therapy

Growing evidence supports the combined use of optical interventions and low-dose atropine in children at high risk of rapid myopic progression. Although the precise mechanism underlying this synergistic effect remains uncertain, several hypotheses have been proposed. The two therapies may act through complementary biological pathways, or atropine-induced pupillary dilation may allow a greater proportion of incoming light to pass through the treatment zones of myopia-control lenses, thereby enhancing peripheral myopic defocus.[60]

Spectacle lenses combined with atropine

Co-administration of 0.01% atropine with DIMS lenses has demonstrated superior efficacy compared with either therapy alone.[60,61] Similarly, children who respond inadequately to atropine monotherapy derive additional benefit when HAL lenses are added, suggesting the value of dual-mechanism intervention in rapid progressors.[59,62]

TABLE 1. Efficacy of optical interventions for myopia control.[30,32,34,37,38,46–48,54–56]

Treatment	Design	Principle	Myopia-control efficacy*		Follow-up duration
			Refractive error	Axial length	
Myopia-control spectacles					
DIMS	Honeycomb-like ring composed of multiple +3.50 D micro-lens elements	Myopic defocus	52%	62%	2 years
HAL	Eleven aspheric micro-lens rings	Myopic defocus	55%	51%	2 years
CARE	Micro-cylinder lens ring with +8.00 D power	HOAs-induced blur	37%	32%	2 years
DOT	Micro-diffusion dots	Reduced contrast	59%	38%	2 years
PLARI NLARI	+3.00 D micro-lens elements –3.00 D micro-lens elements	HOAs-induced blur	55% 68%	44% 50%	1 year 1 year
Soft contact lenses					
Multifocal +2.00 +2.50 +3.00	Peripheral annular zones incorporating varying levels of plus add power	Myopic defocus	50% 43% 67%	29% 36% 63%	2 years 3 years 1.5 years
Dual focus	Alternating +2.00 D treatment rings with distance-correction zones	Myopic defocus	59%	52%	3 years
Orthokeratology					
Orthokeratology	Applies pressure to the corneal surface, causing the peripheral cornea to steepen	Myopic defocus	-	36-46%	2 years

**Compared with single-vision spectacles or contact lenses*

Soft contact lenses combined with atropine

The combination of soft multifocal contact lenses with 0.05% atropine further enhances myopia control in children exhibiting fast progression.[63] In contrast, studies evaluating soft contact lenses together with 0.01% atropine have not demonstrated significant additive benefit, indicating that the synergistic effect may be atropine dose dependent.[64]

Orthokeratology combined with atropine

Combining orthokeratology with either 0.01% or 0.05% atropine consistently provides greater inhibition of axial elongation than orthokeratology alone.[65-67] In a two-year randomized study, axial elongation in the combined-treatment group was 0.12 mm less than in the orthokeratology-only group. Year-by-year reductions of 0.10 mm in the first year and 0.09 mm in the second year further support the enhanced efficacy of dual therapy.[12]

Key clinical considerations

Safety

The primary safety concern in myopia-control interventions is the risk of infectious keratitis, particularly with contact lens wear. Typical presenting symptoms include ocular pain, redness, decreased vision, focal corneal opacity, or excessive discharge.

Myopia-control spectacle lenses

Spectacle-based myopia-control interventions carry no risk of infectious keratitis and therefore represent the safest option from an ocular health standpoint.

Soft contact lenses

In adults, the incidence of microbial keratitis associated with soft lenses — especially daily disposables — is extremely low.[68,69] Large pediatric studies involving children aged 8–12 years have reported no cases of infectious keratitis.[70,71] Additional studies indicate that infection rates in children are lower than in adults, likely due to increased parental supervision and better compliance.[72] Collectively, these findings support the high safety profile of soft contact lenses in children when used appropriately.

Orthokeratology

Orthokeratology lenses are associated with a higher risk of infectious keratitis relative to soft daily lenses. This risk is particularly notable in children and in East and Southeast Asia, where multiple reports have documented severe microbial keratitis.[73] The incidence exceeds that of daily-wear soft lenses, necessitating strict adherence to hygiene and careful patient selection.[74,75]

Visual quality

Because myopia-control lenses involve complex optical designs, their impact on visual quality must be considered.

Myopia-control spectacle lenses

Lenslet-based designs such as DIMS and HAL generally provide good overall visual performance, with HAL lenses associated with less contrast reduction than DIMS. Both designs may cause mild reductions in visual quality under low-light conditions; however, most children adapt within approximately one week of wear.[32,76]

Soft contact lenses

Most studies indicate that children maintain excellent visual acuity while wearing soft myopia-control lenses. Patient-reported outcomes consistently demonstrate good comfort, rapid adaptation, and minimal interference with daily activities.[50,77]

Orthokeratology

Orthokeratology lenses provide stable daytime acuity under normal lighting conditions. However, induced higher-order aberrations may reduce visual quality in dim light, more so than other modalities.[78]

Rebound effects after treatment discontinuation

Rebound—defined as accelerated myopic progression following the cessation of therapy—is a concern across all myopia-control modalities, but particularly with pharmacological interventions. While rebound effects were found to be clinically small among low-dose atropine concentrations, higher concentrations of atropine potentially induce a greater rebound effect.[16] Regarding optical myopia-control methods, current limited data suggest there is little to no rebound effect, with the notable exception of orthokeratology.

Spectacle lenses

Long-term follow-up studies of children who discontinued DIMS lenses found no evidence of rebound, with progression rates returning to expected baseline levels.[31]

Soft contact lenses

The therapeutic effect of soft myopia-control lenses appears to be largely maintained after discontinuation, with no significant rebound noted.[79]

Orthokeratology

Evidence regarding rebound after discontinuation

of orthokeratology is mixed. The myopia-control effect of orthokeratology appears to diminish gradually over time, with a distinct rebound effect frequently observed upon the sudden cessation of lens wear. Specifically, discontinuing orthokeratology before the age of 14 years may precipitate a rapid acceleration in axial length elongation. Ongoing monitoring following cessation is therefore recommended.[80] (Table 2)

Accessibility and cost-effectiveness

The real-world application of optical myopia interventions is heavily dictated by socio-economic factors. Globally, annual costs range from 120 to 1,000 USD for low-dose atropine, 500 to 1,000 USD for novel spectacles like DIMS or HAL, and 1,500 USD for multifocal soft contact lenses, with orthokeratology reaching up to 3,000 USD.[81] Consequently, evaluating cost-effectiveness is a critical public health dimension. Recent analyses show low-dose atropine provides the greatest economic value, presenting an incremental cost-effectiveness ratio (ICER) of 220 to 275 USD per SE reduction. Myopia-control spectacles also offer reasonable economic value with an ICER of 352 to 735 USD per SE reduction, whereas contact lenses—including multifocal soft contact lenses

TABLE 2. Clinical considerations for optical interventions in myopia control.[31,32,50,68-80]

Considerations	Myopia-control spectacles	Soft contact Lenses	Orthokeratology
Safety	High safety profile with no direct contact with the ocular surface.	Carries a risk of corneal infection and may induce dry-eye symptoms.	Carries a higher risk of corneal infection compared with soft contact lenses.
Visual quality	Provides clear distance vision while simultaneously slowing myopia progression.	Provides clear distance vision while simultaneously slowing myopia progression.	Provides clear distance vision throughout the entire day without the need for spectacles or contact lenses, while also slowing myopia progression.
Visual limitations	May cause temporary visual disturbances during adaptation, including reduced clarity and decreased peripheral contrast.	May cause temporary visual disturbances during adaptation, including reduced clarity and decreased peripheral contrast.	Increases higher-order aberrations and induces irregular astigmatism, along with reduced contrast sensitivity.
Convenience	Requires no daily maintenance, though frames may break or be lost in highly active children.	Suitable for children who prefer not to wear spectacles or who engage in high-activity sports; daily disposable options are available.	Highly suitable for children with high levels of daily activity, as no daytime eyewear or contact lenses are required.
Clinical limitations	Requires a short period of visual adaptation.	Requires parental supervision for insertion, removal, and lens care.	Requires parental supervision for lens insertion, removal, and care.
Prescribing limitations	Limited applicability in cases with myopia exceeding –10.00 D or astigmatism greater than –4.00 D.	Limited applicability in cases with myopia greater than –7.00 D or astigmatism exceeding –0.75 D.	Limited applicability in cases with myopia greater than –4.50 D or astigmatism exceeding –1.50 D. Requires practitioner expertise in corneal imaging and lens fitting.

and orthokeratology—are considerably less cost-effective at 788 to 1,187 USD per SE reduction.[82]

These substantial expenses result in significant barriers to care, particularly in developing healthcare scenarios. In Thailand, this creates a distinct dichotomy in myopia management: while low-dose atropine is Thai FDA-approved and free under the national universal healthcare scheme, optical interventions remain strictly an out-of-pocket expense. Even though local consumer costs may be slightly lower than global estimates, advanced optical therapies remain prohibitively expensive compared to standard spectacles for the general pediatric population. Practitioners must therefore weigh this financial burden against clinical benefits when recommending optical interventions to parents.

Referral guidelines for general practitioners

General practitioners play a pivotal role in early identification and timely referral of children at risk of progressive myopia. Key responsibilities and recommended clinical actions include the following:[12,83-85]

Screening and risk assessment

Children who develop myopia at a young age — particularly before 8–9 years — are at high risk of accelerated progression due to a longer window of ocular growth. A family history of myopia, especially high myopia, is a strong predictor of both onset and rapid axial elongation. Early identification of at-risk children enables timely intervention and reduces the risk of future sight-threatening complications.

Communication and counseling

General practitioners should counsel parents that the objective of treatment extends beyond achieving clear visual acuity and focuses on reducing the risk of long-term complications associated with high myopia. Counseling should emphasize increasing outdoor activity to at least two hours per day, reducing prolonged near work — particularly continuous tasks performed without breaks — and clarifying that traditional approaches such as undercorrection, bifocal spectacles, and conventional progressive lenses are ineffective in slowing myopia progression. Parents should be informed of evidence-based treatment options and the importance of initiating therapy early.

Referral indicators

Children should be referred to an ophthalmologist when any of the following criteria are met:

1. Onset of myopia at a young age (e.g., <8 years)
2. Presence of high myopia (≤–6.00 D)
3. Rapid progression, defined as >–0.50 D increase within one year
4. Strong family history of high myopia
5. Associated symptoms or signs, such as blurred vision despite correction, strabismus, or nystagmus
6. Parental concern or desire for targeted myopia-control therapy

Selection of treatment modality

Treatment selection should account for age, level of cooperation, parental readiness, potential risks, and financial considerations. Younger children with rapid progression are typically suitable candidates for specialized myopia-control spectacle lenses such as HAL or DIMS, or for overnight orthokeratology. Older children, or those less comfortable with spectacles, may benefit from soft multifocal contact lenses.

While monotherapy is effective for many patients, combination therapy is a critical strategy for 'fast progressors'—typically defined clinically as those progressing more than 1.00 D per year or experiencing axial elongation greater than 0.50 mm per year. For these high-risk children, combination therapy may be initiated immediately as a first-line treatment. Additionally, it can be utilized as a step-up approach when a single modality provides insufficient control despite initial interventions.

Follow-up recommendations

Regular monitoring is essential, with axial length measured every six months and cycloplegic refraction performed one to two times per year. These metrics provide objective and reliable markers of treatment efficacy and guide the timely adjustment of the management plan.[12] While refraction remains a fundamental metric, axial length is now the gold standard for monitoring disease progression because true refractive changes are frequently masked by the optical profiles of myopia-control interventions. Consequently, monitoring progression solely by refractive error is inadequate.

When to stop treatment

Discontinuation of myopia-control therapy may be considered when axial length elongation is less than 0.01 mm per year or when refractive progression is less than 0.25 D per year. Although most individuals reach refractive stability by approximately 18 years of age, persistent progression into the third decade of life (20–30 years) has been reported in up to 30% of cases.[86,87] Discontinuing treatment at an older age and at lower concentrations is associated with a smaller rebound effect. For children

treated with higher doses of atropine, a gradual tapering schedule to lower concentrations is recommended to minimize this risk. Consequently, even after complete treatment cessation, continued routine monitoring for at least one year remains crucial to promptly detect any myopia progression.

CONCLUSION

The management of pediatric myopia has advanced from simple refractive correction to active slow progression strategies. Modern optical interventions — including specialized spectacle lenses and soft or rigid contact lenses — demonstrate robust efficacy in slowing myopia progression. A solid understanding of these technologies, coupled with evidence-based clinical decision-making, is essential for reducing the long-term public health burden of high myopia. Early detection, appropriate referral, and informed treatment selection are critical components in safeguarding visual outcomes for future generations.

Data Availability Statement

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

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