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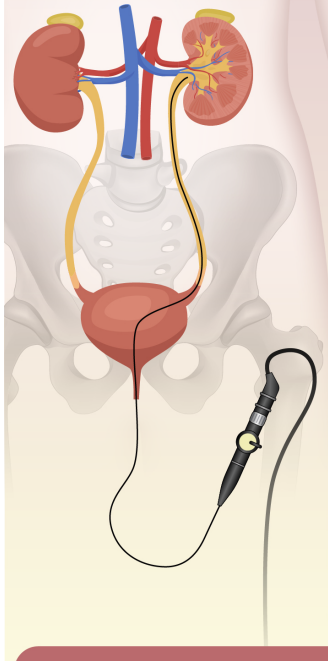
MONTHLY

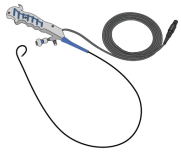
ORIGINAL ARTICLE

Comparing Reusable and Single-use ureteroscope



Comparing Mechanical and Optical characteristics

Storz Flex-XC
Reusable
ureteroscope



Storz Flex-XC1
Single-use
ureteroscope

Results

	XC1		XC
Deflection		<	
Loop diameter		=	
Irrigation flow rate		<	
Resolution		=	
Color		>	

Optical characteristics

Resolution

Color

Mechanical characteristics

Deflection

Loop diameter

Irrigation flow rate

Conclusion: The XC1 offered improved color representation and marginally better resolution in saline.

SCAN FOR FULL TEXT

SMJ SIRIRAJ MEDICAL JOURNAL | Leelathanyakit, et al. *Siriraj Med J* 2025;77(5):313-321.

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In Vitro Comparison of the Mechanical and Optical Characteristics of the Storz Flex-X^{C1} Single-use Ureteroscope and the Storz Flex-X^{C} Reusable Flexible Ureteroscope

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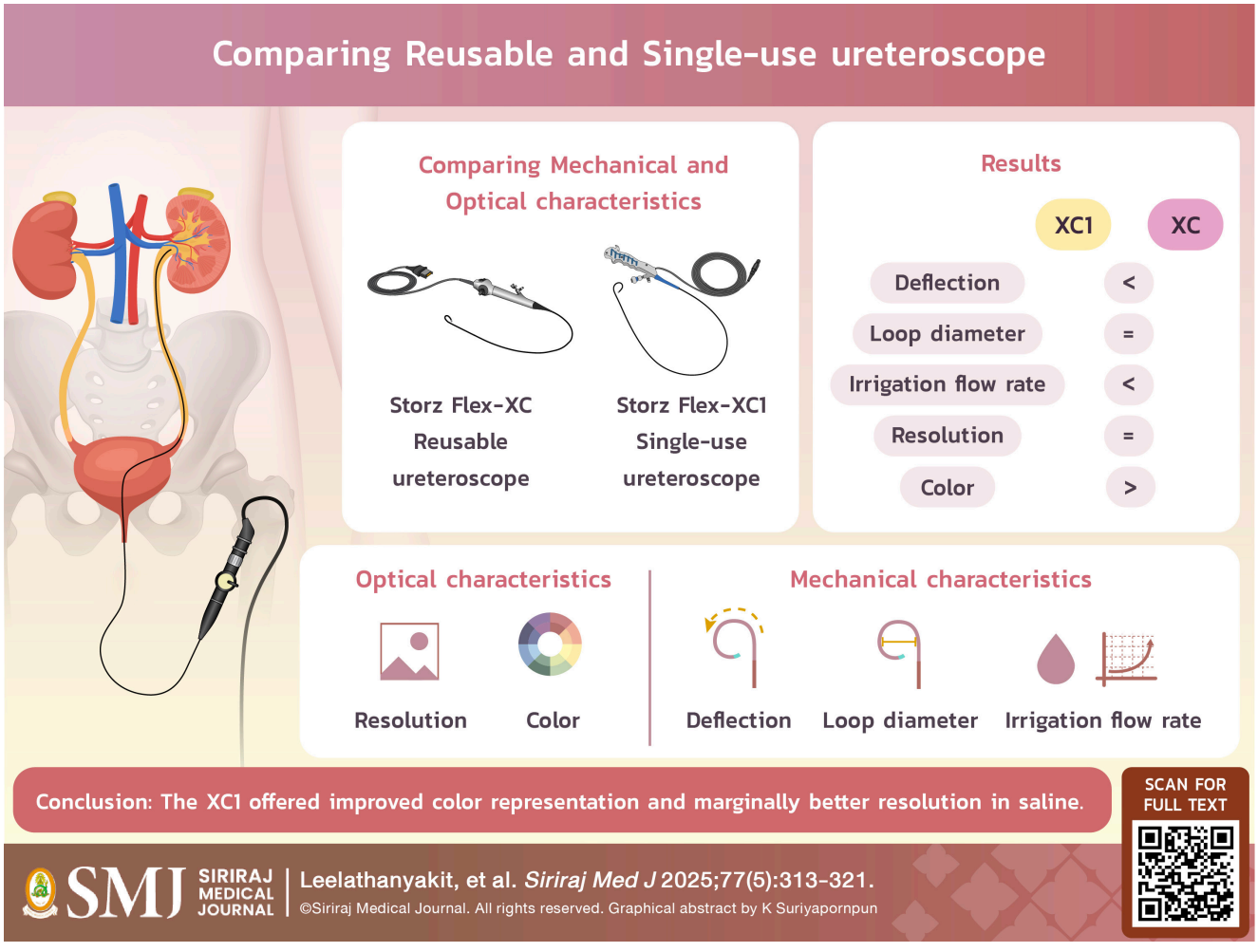

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ABSTRACT

Objective: This study compared the mechanical and optical characteristics of the Storz Flex-X^{C1} single-use ureteroscope and the Storz Flex-X^{C} reusable flexible ureteroscope. The mechanical parameters comprised the upward/downward deflection, loop diameter, and irrigation flow rate. The optical parameters were image resolution and color representation.

Materials and Methods: We conducted an in vitro evaluation of two Karl Storz flexible ureteroscopes. Specifically, we examined the Storz Flex-X^{C1} single-use and Storz Flex-X^{C} reusable scopes for upward/downward deflection angles, loop diameter, irrigation flow rates, image resolution, and color representation. The Storz Professional Image Enhancement System was also applied.

Results: The Storz Flex-X^{C} reusable ureteroscope achieved greater upward/downward deflection angles than did the Storz Flex-X^{C1} single-use ureteroscope when a 200 µm laser or a 1.9 Fr tipless basket was used, with mean differences of 1.9°–2.2° and 2.3°–5.6°, respectively. No clinically significant difference in loop diameter was found. The Storz Flex reusable scope achieved a higher irrigation flow rate with an empty working channel (mean difference of 2.25 ml/min). Both scopes demonstrated identical image resolutions in air and in a normal saline solution, but the Storz Flex single-use device showed superior color representation.

Conclusion: The Storz Flex-X^{C} reusable flexible ureteroscope displayed slight advantages in terms of the deflection angle and irrigation flow rate. The Storz Flex-X^{C1} single-use flexible ureteroscope offered improved color representation and marginally better resolution in saline.

Keywords: Flexible ureteroscopes; reusable; deflection angle; resolution; single use (Siriraj Med J 2025; 77: 313-321)

INTRODUCTION

Nephrolithiasis has a lifetime incidence ranging from 1% to 13% in the general population and between 1% and 5% among Asian individuals.[1,2] In Thailand, the northeastern region exhibits the highest incidence of nephrolithiasis compared to other regions in the country.[3] The renal pelvis is the most common stone location within the urinary tract.[4] Advances in ureteroscope and laser lithotripter technologies have increased the preference for endourology over percutaneous nephrolithotomy and extracorporeal shock wave lithotripsy in treating nephrolithiasis. According to the 2023 European Association of Urology guidelines, endourology is recommended for managing both ureteral and renal calculi across all anatomical locations.

Ureteroscopy, which was introduced in 1912, uses a 9.5 Fr pediatric cystoscope as a flexible instrument. The first fiber-optic flexible ureteroscope without a working channel was developed by Marshall in 1964.[5] In 1979, ureteroscopes equipped with working channels enabled intraureteral lithotripsy via electrohydraulic and ultrasonic lithotripters. However, their application was initially limited to the lower ureter. Therapeutic flexible ureteroscopy, which allows access to the renal pelvis and all calyces, was invented in 1987 and began clinical use in 2008.[6]

A wide range of flexible ureteroscopes are available from many manufacturers. Karl Storz is a leading provider of reusable flexible ureteroscopes. However, single-use ureteroscopes have gained increasing popularity in endourology.[7,8] Although single-use flexible ureteroscopes cost more than reusable models do, they reduce reprocessing and maintenance expenses and minimize the risk of contamination with urinary tract pathogens.[9,10] Moreover, single-use devices may be preferable for managing multiple large stones in the lower renal pole of recurrent stone formers or in patients with a steep infundibulopelvic angle (≤ 50°), since these conditions increase the risk of ureteroscope damage.[11] Compared with reusable ureteroscopes, LithoVue (Boston Scientific) is an early single-use flexible ureteroscope that provides complete visualization, correct identification of calyces, effective stone retrieval, and improved image quality.[12] Karl Storz recently introduced Flex-X^{C1}, a single-use flexible ureteroscope intended to mimic the performance of the established Storz Flex-X^{C} reusable model.

This study aimed to compare the mechanical and optical characteristics of the Storz Flex-X^{C1} single-use ureteroscope and the Storz Flex-X^{C} reusable flexible ureteroscope.

MATERIALS AND METHODS

We conducted an in vitro study at Siriraj Hospital using two Karl Storz flexible ureteroscopes: the Storz Flex-X^{C1} single-use ureteroscope and the Storz Flex-X^{C} reusable ureteroscope. We examined their mechanical and optical characteristics.

The mechanical assessments examined the following items: the upward/downward deflection angles, the loop diameter of the upward/downward deflection, the angle of view, and the irrigation flow rate under three working-channel conditions. The optical evaluations were assessments of image resolution and color representation.

We also applied the Storz Professional Image Enhancement System. This system comprises five software modes that enhance imaging and visualization. "Clara" provides homogeneous illumination at all depths of view. "Chroma" intensifies image contrast; Clara and Chroma can be combined. "Spectra A" filters out red tones, whereas "Spectra B" enhances green and blue light. These filters help endoscopists identify tumor stalks and vessels more easily.

Mechanical characteristics

We evaluated the upward/downward deflection angles under three working-channel conditions: an empty channel, a channel containing a 200 µm laser fiber (TFL-FBX200s), and a channel containing a 1.9 Fr tipless nitinol basket (Boston Scientific Zero Tip). Each ureteroscope was tested 36 times to measure upward/downward deflection angles and loop diameters. Between each test, we allowed the scope to rest for 1 minute while it returned to its neutral position. The loop diameter was defined as the maximum horizontal diameter attained at full deflection.

We then measured the irrigation flow rate via a pressure-regulated irrigation system (Uromat E.A.S.I., Karl Storz, Tuttlingen, Germany) under the same three conditions: an empty channel, a channel with a 200 µm laser fiber, and a channel with a 1.9 Fr tipless nitinol basket. The inflow pressure was 200 mmHg, and the maximum flow rate was 250 ml/min. The total volume of fluid exiting the ureteroscope tip in 1 minute was recorded in milliliters.

Optical characteristics

We assessed resolution using a 1951 U.S. Air Force Test Pattern Card (Edmund Optics, Barrington, NJ, USA) under two conditions: in air and in normal saline solution. The resolution measurements were obtained at distances of 0.5 cm, 1 cm, 2 cm, and 3 cm. The resolution, reported in line pairs per millimeter, was calculated with the following formula:

$$\text{Resolution} = 2^{\text{Group} + (\text{element} - 1)/6}$$

We evaluated color representation via a Gretag Macbeth color checker target (Edmund Optics). Fourteen reviewers (12 urological residents and 2 fellows) graded color quality in a blinded manner. Each reviewer assigned a score from 0 to 2, where "0" indicated no similarity to the reference colors, "1" indicated slight similarity, and "2" indicated strong similarity.

Statistics

The correlation of mechanical characteristics between the two scopes was determined using the Pearson test, and the correlation of optical characteristics was determined using Wilcoxon's signed-rank test. All statistical analyses were performed using IBM SPSS Statistics 25.0. There were 36 observations by one observer for the mechanical comparisons and 14 observers for the optical comparisons.

RESULTS

Mechanical characteristics

The mechanical comparisons between the Storz Flex-X^{C1} single-use ureteroscope and the Storz Flex-X^{C} reusable flexible ureteroscopes assessed through the loop diameter, upward/downward deflection angle, and irrigation flow rate indicated weak to very weak correlations. These findings suggest that the two ureteroscope models differ in their mechanical characteristics as shown in Table 1.

When the working channels were empty, the ureteroscopes presented comparable upward/downward deflection angles. However, the Storz Flex-X^{C} reusable ureteroscope demonstrated significantly greater deflection angles when the working channel contained a laser fiber or a 1.9 Fr tipless nitinol basket (Table 2).

With respect to loop diameter, the Storz Flex-X^{C} reusable ureteroscope performed better under all three conditions (empty, laser, and basket), with mean differences of 0.06–0.27 mm. (Table 3).

For the irrigation flow rate, the Storz Flex-X^{C} reusable ureteroscope achieved higher flow with an empty working channel. Both ureteroscopes experienced reduced irrigation flow when the working channel was occupied (Table 4).

Optical characteristics

The resolution measurements were identical between the Storz Flex-X^{C1} single-use ureteroscope and the Storz Flex-X^{C} reusable flexible ureteroscope at distances of 0.5 cm, 1 cm, 2 cm, 3 cm, and 5 cm (Tables 5 and Fig 3).

With respect to color representation, the Storz Flex-X^{C1} single-use ureteroscope performed better in both air and normal saline. The difference was statistically significant in the normal saline group ($P = 0.002$; Tables 6 and Fig 2).

TABLE 1. Specifications of Storz Flex-X^{C1} single-use and Storz Flex-X^{C} reusable flexible ureteroscopes.

Specification	Storz Flex-X^{C1} single use flexible ureteroscope	Storz Flex-X^{C} reusable flexible ureteroscope
Direction of view	0°	0°
Angle of view	105°	105°
Working length	70°	70°
Outer diameter	9 Fr	8.5 Fr
Working channel	3.5 Fr	3.6 Fr
Deflection	Up 270°; down 270°	Up 270°; down 270°

TABLE 2. Upward and downward deflection angles of ureteroscopes under different conditions.

Ureteroscope		Empty working channel (degree±SD)	200 µm laser fiber (TFL-FBX200s) (degree±SD)	With 1.9 Fr tipless nitinol basket (degree±SD)
Storz Flex-X^{C1} single use	Upward deflection	274.9±1.9	254.6±2.6	256.2±2.2
	Downward deflection	276.8±1.5	258.6±2.6	254.3±2.9
Storz Flex-X^{C} reusable	Upward deflection	274.5±2.2	256.8±2.6	256.8±2.6
	Downward deflection	276.2±2.3	260.5±2.1	260.0±2.3

TABLE 3. Loop diameters of ureteroscopes under various conditions.

Ureteroscope		Empty working channel (cm±SD)	200 µm laser fiber (TFL-FBX200s) (cm±SD)	With 1.9 Fr tipless nitinol basket (cm±SD)
Storz Flex-X^{C1} single use	Upward deflection	2.92±0.04	3.02±0.04	2.96±0.05
	Downward deflection	2.925+0.05	3.00+0.03	2.99+0.03
Storz Flex-X^{C} reusable	Upward deflection	2.91+0.06	2.99+0.09	2.94+0.04
	Downward deflection	2.88±0.05	2.98±0.04	2.95±0.03

TABLE 4. Irrigation flow rates of ureteroscopes under different conditions.

Ureteroscope	Empty working channel (ml/min)	200 µm laser fiber (TFL-FBX200s) (ml/min)	With 1.9 Fr tipless nitinol basket (ml/min)
Storz Flex-X^{C1} single use	69.51±0.75	40.62±0.62	17.96±0.47
Storz Flex-X^{C} reusable	71.77±0.76	41.98±1.08	17.29±0.35
Mean difference (P-value)	-2.26 (0.14)	-1.36 (0.92)	0.67 (0.76)

TABLE 5. Resolution of ureteroscopes in air and normal saline solution.

Ureteroscope		Storz Flex-X^{C1} single use	Storz Flex-X^{C} reusable
0.5 cm (lp/mm)	Air	3.56	3.56
	NSS	3.56	3.56
1 cm (lp/mm)	Air	3.56	3.56
	NSS	3.56	3.56
2 cm (lp/mm)	Air	3.56	3.56
	NSS	3.56	3.56
3 cm (lp/mm)	Air	3.17	3.17
	NSS	3.56	3.56
5 cm (lp/mm)	Air	2	2
	NSS	2.52	2.52

Abbreviations: lp/mm, line pairs per millimeter; NSS, normal saline solution

TABLE 6. Color representation of ureteroscopes in air and normal saline solution.

	Ureteroscope	Median	Range	*P* value
Air	Storz Flex-X^{C1} single use	1.5	0-2	0.058
	Storz Flex-X^{C} reusable	1.0	0-2	
NSS	Storz Flex-X^{C1} single use	1.0	0-2	0.002
	Storz Flex-X^{C} reusable	0.5	0-1	

Abbreviations: NSS, normal saline solution

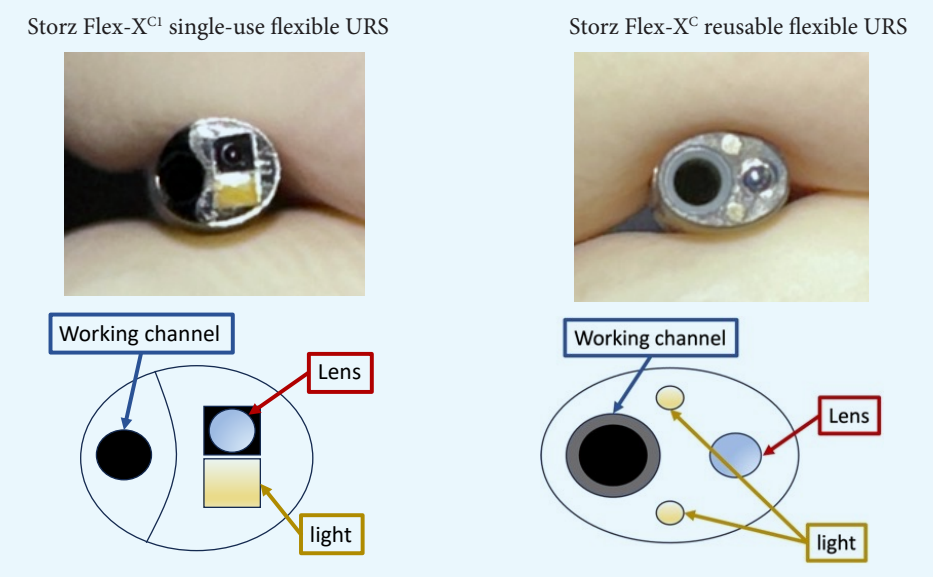

Fig 1. Comparison of Storz Flex-X^{C1} single-use and Storz Flex-X^{C} reusable flexible ureteroscope tips.

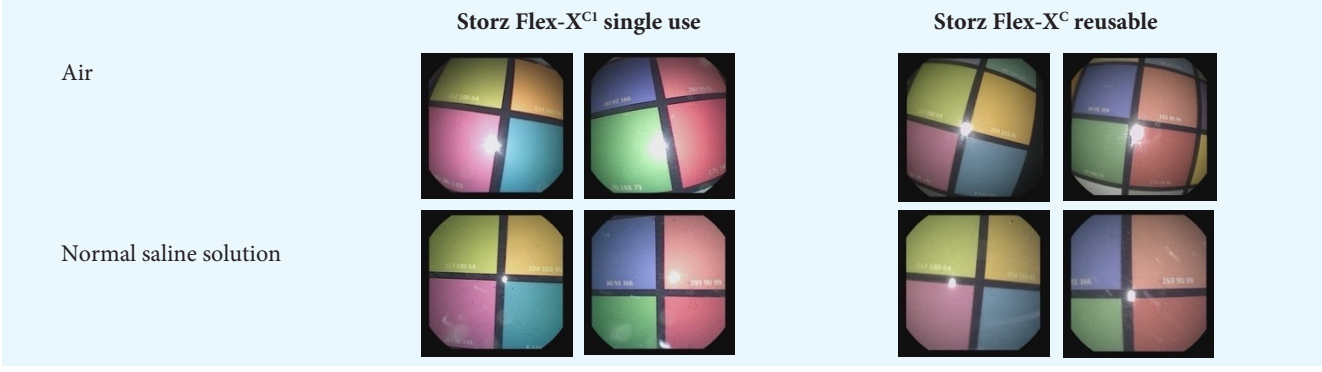

Fig 2. Color representation of Storz Flex-X^{C1} single-use and Storz Flex-X^{C} reusable flexible ureteroscopes in air and normal saline solution.

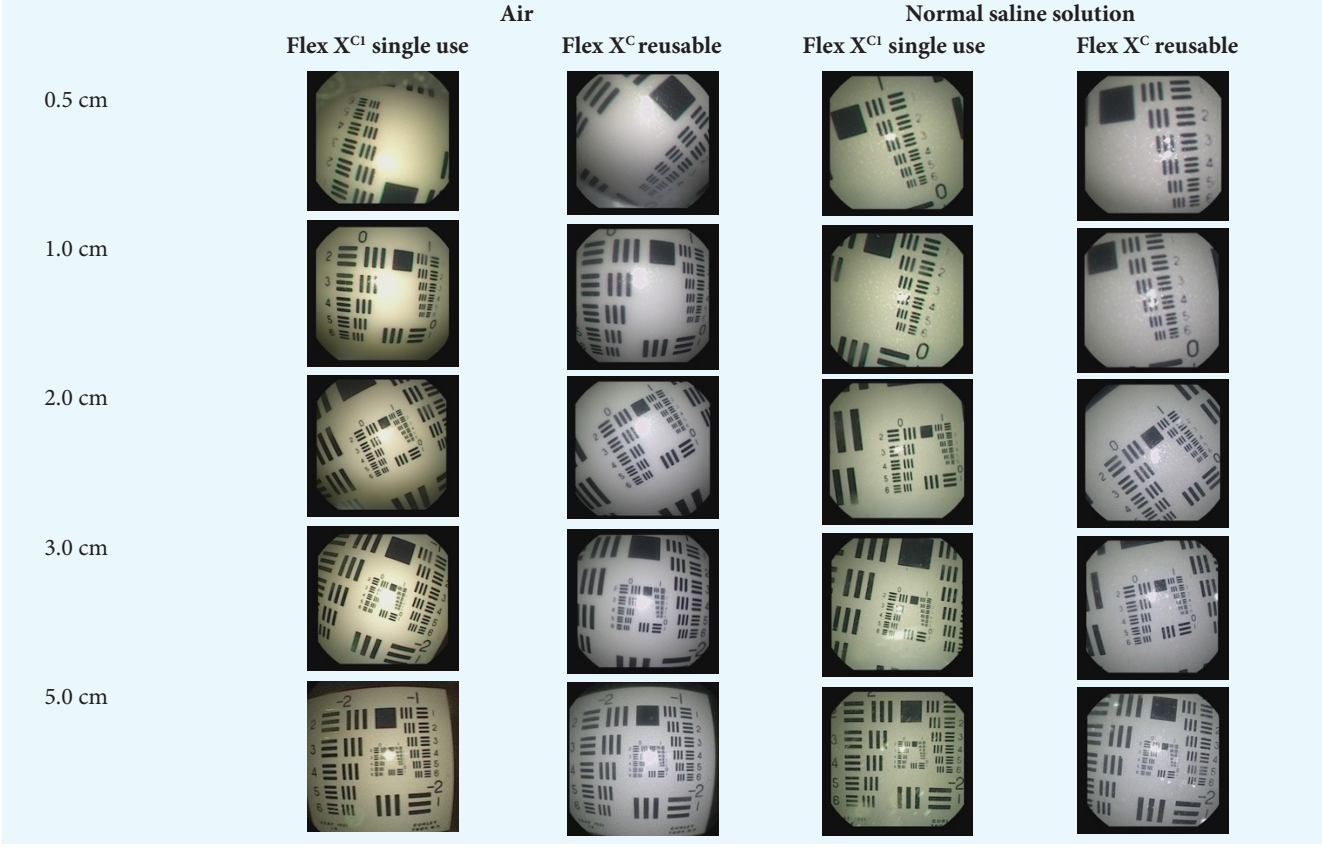

Fig 3. Resolution of Storz Flex-X^{C1} single-use and Storz Flex-X^{C} reusable flexible ureteroscopes in air and normal saline solution.

DISCUSSION

This study compared the mechanical and optical characteristics of two Karl Storz flexible ureteroscopes. According to their specifications, both ureteroscopes share a similar direction of view, angle of view, and working length. However, the single-use Flex-X^{C1} ureteroscope features a slightly larger outer diameter (9 Fr vs 8.5 Fr) and a slightly smaller working channel (3.5 Fr vs 3.6 Fr) than the reusable Flex-X^{C} ureteroscope (Table 1). Both devices have working channels positioned at the 3 o'clock orientation, which generally favors stone ablation in the right kidney. Under gravity, the calyces appear on the left side of the screen, whereas the stones tend to settle on the right side. This arrangement allows the laser, originating from the 3 o'clock direction, to access stones more easily.[13]

Regarding mechanical characteristics, no significant differences emerged in the upward/downward deflection angles when both ureteroscopes were tested with empty working channels. Thus, their suitability for diagnostic procedures is similar. However, when the working channel was occupied by either a 200 µm laser fiber (TFL-FBX200s) or a 1.9 Fr tipless basket, the reusable Flex-X^{C} achieved significantly greater deflection angles (approximately 2°–5°). This difference may be attributed to the more durable materials and craftsmanship of the reusable scope. A greater deflection angle may confer a therapeutic advantage during complex procedures.

A smaller loop diameter can facilitate access to challenging lower-pole calyces, enabling more efficient stone management within difficult anatomical configurations.[13] In this study, the Flex-X^{C} reusable ureteroscope achieved slightly smaller loop diameters under all three testing conditions (empty, laser, and basket), with mean differences ranging from 0.06–0.27 mm. Although these differences are generally minor, they may provide a subtle benefit in highly complex scenarios. Nonetheless, such small variations are unlikely to significantly affect overall performance in most clinical situations.

The irrigation flow rate influences intrarenal pressure and fluid temperature control, which is critical in preventing complications.[14] In our study, the Storz Flex-X^{C} reusable flexible ureteroscope had a modest, although statistically nonsignificant, advantage in terms of the irrigation flow rate compared with the Flex-X^{C1} single-use device. When the working channel was obstructed, both ureteroscopes experienced reduced flow rates without significant differences.

The two ureteroscopes demonstrated identical resolutions under air and normal saline conditions, as shown in Table 5 and Fig 3. However, for color representation, the Flex-X^{C1} single-use ureteroscope performed better in normal saline than did the reusable Flex-X^{C}, as shown in Table 6 and Fig 4.

Furthermore, the Flex-X^{C1} single-use ureteroscope is compatible with various imaging and monitoring systems, allowing flexible integration into existing surgical platforms. It is also the only single-use ureteroscope compatible with visual enhancement features, including the Storz Professional Image Enhancement System. This system's functions such as Chroma, which intensifies pixel-to-pixel brightness, and the two Spectra modes, which enhance image contrast can improve the visualization of blood vessels, mucosa, and small lesions.[15] These enhancements may provide clinical benefits (Fig 4).

CONCLUSION

The Flex-X^{C1} single-use ureteroscope and the Flex-X^{C} reusable flexible ureteroscope showed identical Flexresolutions, with the single-use device offering improved color representation. The reusable Flex-X^{C} ureteroscope demonstrated superior mechanical characteristics in some parameters, but these differences may be minor. Importantly, this was an in vitro study. In clinical practice, surgeon skills and experience may mitigate small mechanical disparities. Many of these variations may not translate into significant clinical differences during kidney stone management.

Data Availability Statement

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

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DECLARATION

Grants and Funding Information

There are no sources of funding to disclose.

Conflict of Interest

There are no conflicts of interest to report.

Registration Number of Clinical Trial

None.

Author Contributions

Conceptualization and methodology, S.S. and E.C.; Investigation, C.L.; Formal analysis, C.L.; Visualization and writing – original draft, C.L., E.C., T.T., K.P., S.J., P.R.,

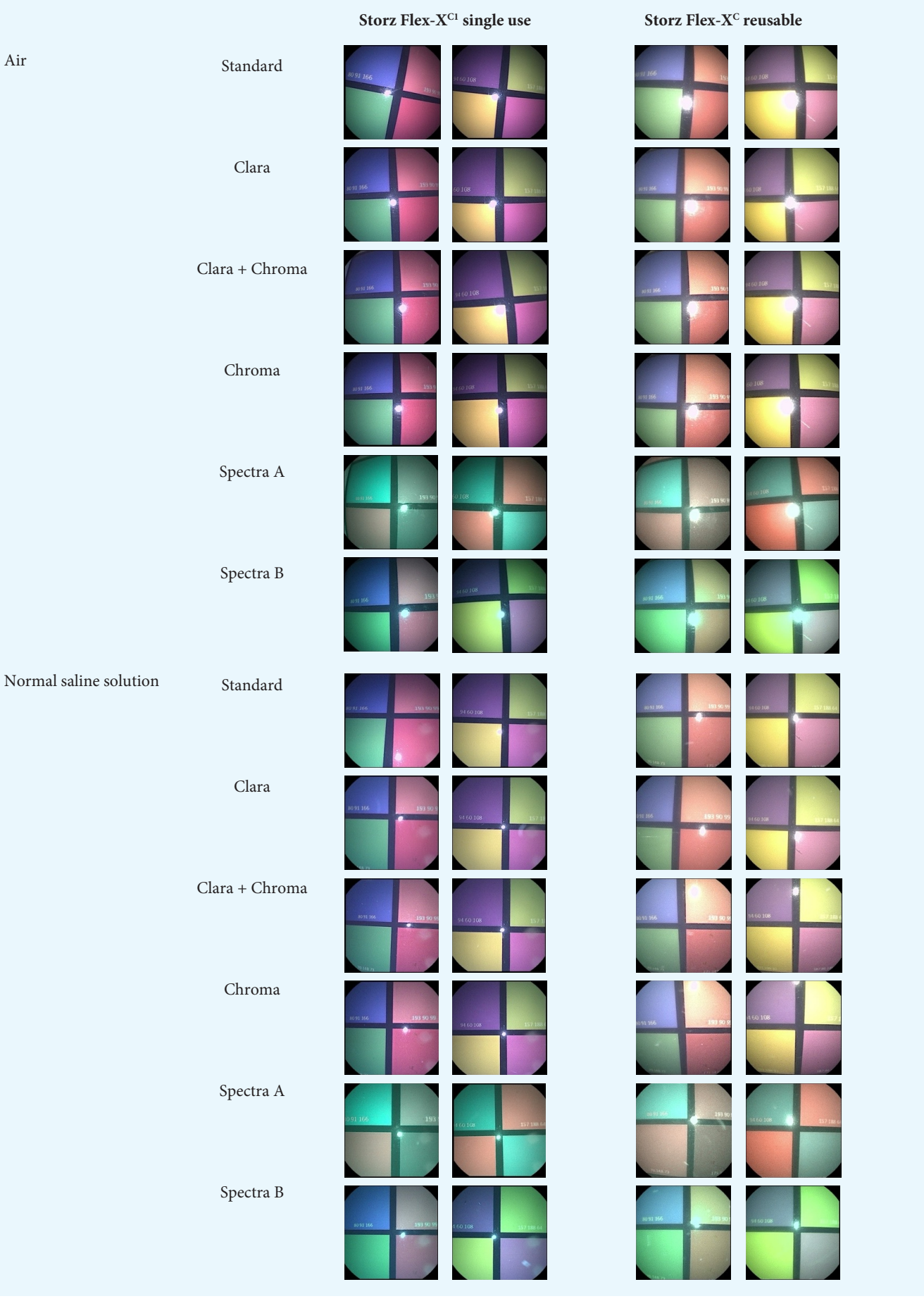

Fig 4. Comparison of color representation modes for Storz Flex-X^{C1} single-use and Storz Flex-X^{C} reusable flexible ureteroscopes in air and normal saline solution.

V.W., T.M., T.H., K.J., and S.S.; Writing – review and editing, S.S. and E.C. ; Supervision, S.S. All authors have read and agreed to the final version of the manuscript.

Use of Artificial Intelligence

No artificial intelligence tools or technologies were used in the writing analysis.

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Effectiveness of Local Wound Infiltration with Morphine, Ketorolac, and Bupivacaine Compared to Bupivacaine Alone Following Tibial Osteotomy in Pediatric Patients: A Randomized Controlled Trial

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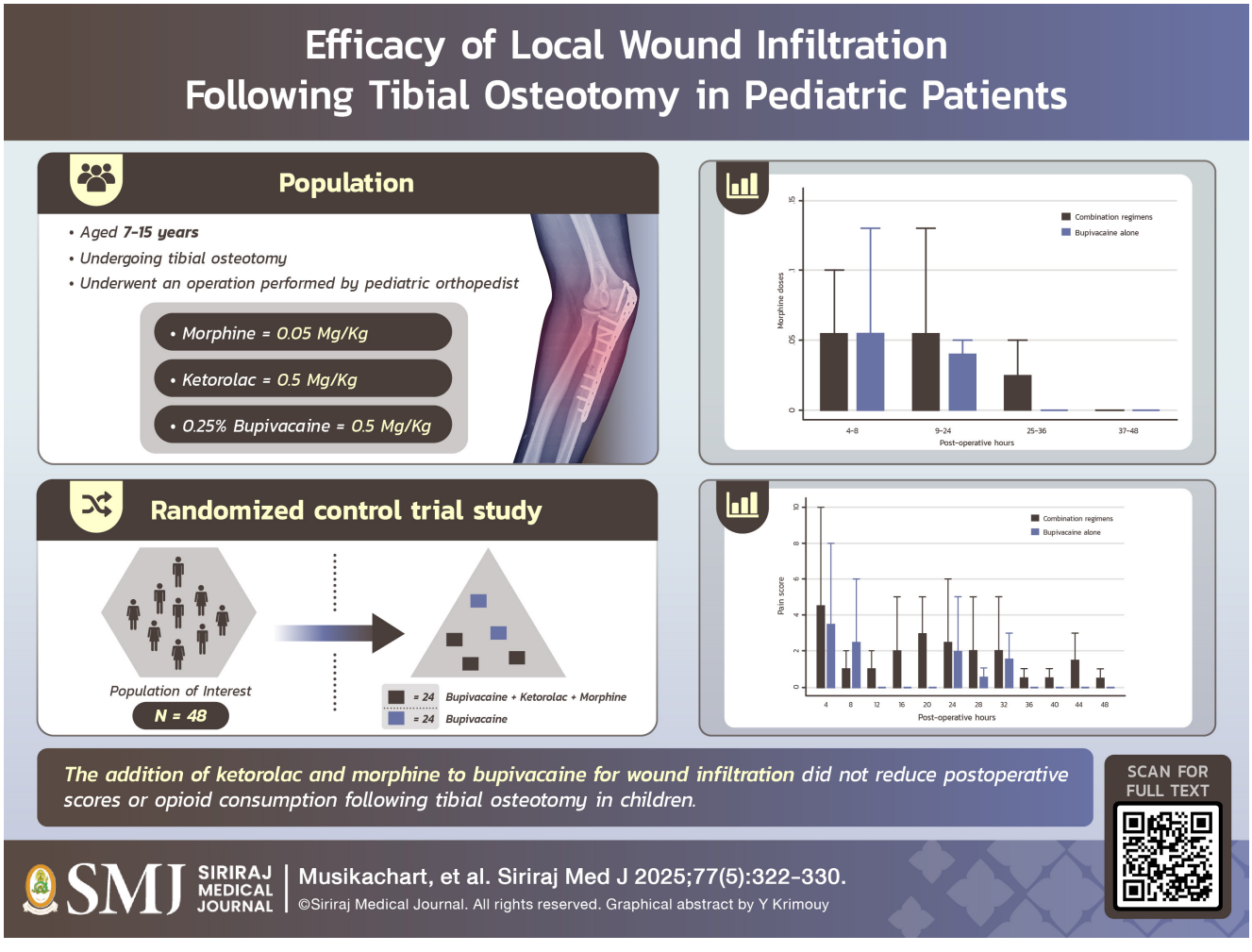

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ABSTRACT

Objective: To compare postoperative pain in children receiving ketorolac plus morphine local wound infiltration as adjunct analgesic agents with bupivacaine for local wound infiltration following tibial osteotomy

Materials and Methods: This randomized, double-blind, placebo-controlled trial included patients aged 7-15 years underwent tibial osteotomy. Participants were allocated into two groups. The combination group received wound infiltration with 0.5 ml/kg bupivacaine 0.25% and 0.5 mg/kg ketorolac and 0.05 mg/kg morphine, while the control group received bupivacaine alone before skin closure. Primary outcomes were Visual Analog Scale (VAS) pain scores measured every 4 hours during the first 48 hours after surgery. Secondary outcomes included morphine consumption and opioid-related complications.

Results: Among the 48 patients included in the study, no significant differences were observed in postoperative VAS pain scores between the two groups at nearly all time points. The combination group showed a trend towards higher mean pain levels compared to the control group at almost every time point from 4-hour to 48-hours post-operation. The maximum mean postoperative pain level in both groups, at four hours, was higher in the combination group, with a maximum mean postoperative pain level of 2.1 vs. 1.9. Higher mean opioid use was noted in the combination group, with a mean of 0.04±0.08 mg/kg vs. 0.03±0.04, at 4-8 hours postoperatively. Also, the cumulative morphine dose was lower in the control group compared to the combination group.

Conclusion: The addition of ketorolac and morphine to bupivacaine for wound infiltration did not reduce postoperative VAS pain scores or opioid consumption following tibial osteotomy in children.

Keywords: Tibial osteotomy; postoperative pain; wound infiltration; morphine; ketorolac; bupivacaine (Siriraj Med J 2025; 77: 322-330)

INTRODUCTION

Operative treatments in pediatric patients, such as orthopedic surgery, often result in significant postoperative pain, placing burden on both children and their caregivers. Accordingly, adequate perioperative pain control is important in operative treatments in children. However, achieving optimal pain control in pediatric patients is challenging due to various factors, including children's limited ability to communicate and cooperate.[1] Consequently, children often experience residual postoperative pain due to insufficient analgesic prescription. Previous studies have emphasized that acute postoperative pain can cause short- and long-term effects on pediatric patients, with up to twenty-two percent of children experiencing moderate to severe chronic postsurgical pain.[2] Moreover, a magnetic resonance imaging (MRI) study demonstrated that nociceptive stimulation in the brains of school-aged children and adolescents who had undergone medical procedures during infancy in the neonatal intensive care unit (NICU) affects long-term pain perception.[3]

Evaluating pain in children is more difficult. Different tools have been developed to assess pain accurately, including self-report measures, questionnaires, and behavioral observational scales. One such tool is the Visual Analogue Scales (VAS), which is a reliable behavioral scale for rating postoperative pain in patients >=5 years.[4]

Local surgical site analgesia infiltration was a popular perioperative analgesic method known for effectively preventing postoperative pain. This analgesic method is cost-effective, demands minimal technical expertise, and has limited potential for adverse effects. The mechanism of local analgesics relies on the reduction of neural transmission and blocking axonal depolarization. This increases the threshold for action potential, decreases nociceptor sensitization, and reduces local inflammatory reactions.[5]

Several local surgical site infiltration regimens have been introduced. Theoretically, combining various analgesic substances could enhance the effectiveness of pain control properties while minimizing the dosage of each substance, resulting in fewer medication-related adverse events. Moreover, the use of combination local surgical site infiltration could reduce postoperative opioid consumption. Commonly used adjuvant analgesic agents were ketorolac, morphine, epinephrine, bupivacaine, dexamethasone and ketamine.[6-9] Although several studies have demonstrated the effectiveness of local surgical site infiltration for postoperative pain control, data on its use in pediatric orthopaedic procedures was limited. Some studies have reported efficacy of postoperative pain and opioid use with local wound infiltration following surgical hip dislocation for management of femoroacetabular impingement (FAI).[10] However, other studies found

that wound infiltration did not significantly reduce pain scores following abdominal surgery in children.[11-13]

The purpose of this study was to compare the efficacy of combined analgesic wound infiltration regimens (bupivacaine, ketorolac, and morphine) with a control group receiving bupivacaine alone for postoperative pain control following tibial osteotomy Moreover, we aimed to assess intravascular opioid consumption following the surgery between these treatment groups.

MATERIALS AND METHODS

Patient population

The study was approved by the Institutional Review Board (IRB) of Siriraj Hospital; COA Si590/2021. Patients aged 7-15 years who underwent unilateral tibial osteotomy were included. Tibial osteotomy was indicated for pediatric patients with tibial malalignment due to various causes, including Blount's disease, physeal arrest, or tibial hemimelia. The operations were performed by a pediatric orthopedist. The exclusion criteria included pre-existing pain (e.g from fractures or infections), loss of sensation, and history of allergies to NSAIDs, morphine, bupivacaine, or paracetamol. All patients that had renal dysfunction (eGFR< 90 mL/min/1.73 m^2) or language barriers were excluded. Informed consent was obtained from all patients and relevant persons (such as parents or legal guardians).

Randomization

Patients were randomized into two groups using a computer-generated block randomization table managed by research assistants. Forty-eight patients were allocated to either the combination group (n=24), which received wound infiltration with bupivacaine, ketorolac, and morphine, or the control group (n=24), which received bupivacaine alone. All patients were blinded to grouping. The envelope containing the group allocation was opened by the surgeon before the operation. Electrical operative notes were entered into a secure computer system accessible only by password to maintain blinding for the nursing staff.

Outcome measurements

The primary outcome was pain at rest scores collected at 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 hours postoperatively using the VAS. The score consisted of a 100 mm straight horizontal line with endpoints representing no pain (left end) and worst pain (right end). A nurse blinded to the two groups evaluated the pain scores. Secondary outcomes included (1) cumulative breakthrough morphine consumption at 8, 24, 36 and 48 hours after surgery; (2) opioid-related side effects (i.e., respiratory depression, urinary retention, nausea/vomiting, skin irritation, hypotension); and (3) hospital length of stay from admission to discharge.

Treatment

All patients were managed under general anesthesia without regional nerve block or epidural block. Antibiotic prophylaxis consisted of a single 25 mg/kg/dose IV bolus dose of cefazolin (or clindamycin 25 mg/kg/dose in cases of allergy). Only our regimen of local wound anesthesia was administered with normal saline dilution to 10 ml. Patients received either a subcutaneous wound injection with a combination of 0.5 ml/kg bupivacaine 0.25% and 0.5 mg/kg ketorolac and 0.05 mg/kg morphine or with 0.5 ml/kg bupivacaine 0.25% alone, allocated at random.

Postoperative Protocol

Postoperative analgesic drugs were prescribed based on the patients' ideal body weight. Both study groups received 0.5 mg/kg/dose of intravenous ketorolac every 8 hours for the first 24 hours, and 10-15 mg/kg/dose of oral paracetamol every 6 hours. Oral ibuprofen 10-15 mg/kg/dose was administered every 8 hours following the last dose of intravenous ketorolac. This regimen continued for 48 hours after surgery. Patients were asked to rate their pain at rest level, starting at 4-hour after surgery, using a 100-mm VAS measurement printed on full A4 paper. The left side of scale represents least pain (pain score = 0) and the right side represented worst pain (pain score = 10). The rating scale was explained to the patients. Data on complications, such as nausea and vomiting, were also collected. If a VAS score ≥ 5 was reported, it was treated with an intravenous morphine bolus 0.03-0.05 mg/kg every 4 hours. Total medication requirements and side effects were recorded over a 48-hour period. Patients were encouraged to limit weight bearing after the surgery. Most patients were discharged on postoperative day 2 or 3, assuming no complications had arisen.

Statistical analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS version 18.0) software, Chicago, IL, USA. Continuous data between groups were compared using the independent *t*-test and ANOVA. Nominal data were analyzed with Chi-square tests and the Mann-Whitney U test for ordinal data. The graph in this study was generated using STATA version 16 (StataCorp LLC, College Station, TX, USA).

Sample size calculation was based on a previous

study,[8] which reported a mean VAS score of 4.5 (standard deviation, 1.9) for patients receiving local wound infiltration with bupivacaine plus epinephrine, and a mean VAS score of 3.2 (standard deviation, 1.8) for those receiving bupivacaine plus epinephrine and morphine plus ketorolac after spinal surgery. According to this, a sample size of 54 patients was needed to detect a difference of 2 (effect size, 0.4) with 90% power and alpha of 0.05.

RESULTS

Between January 2021 and April 2022, 48 patients, aged 7 to 15 years, who underwent elective tibial osteotomy were allocated into two groups. Six patients were excluded for not meeting the study's inclusion criteria. Thus, a total of 48 patients were enrolled (24 in the combination group, and 24 in the control group) in the study. None were excluded from their allocated group, and all patients completed the 48-hour assessment. There were no statistically significant differences in baseline patient characteristic between the groups in term of gender, age, BMI, side, duration of surgery, and length of hospital stay (Table 1). The majority of participants were male in both groups, with 54.2% in the control group and 62.5% in the combination group. The age range was 7 to 15 years in both groups, with mean ages of 10.7±3.1 years in the control group and 11.8±3.1 years in the combination group, respectively. The control group had a mean surgery duration of 68.4±35.8 minutes, compared to 78.9±50.6 in the combination group. The baseline characteristics were illustrated in Table 1.

Table 2 presents the postoperative VAS scores. Although not statistically significant, patients in the combination group tended to report higher mean pain levels compared to the control group at almost every time point from 4 to 48 hours post-operation, except at 8 hours (1.3 vs.1.2 for the control and combination groups, respectively). The maximum mean postoperative pain level in both groups, at four hours, was higher in combination group (2.1) compared to the control group (1.9). Pain levels decreased continuously after four hours. However, patients in the two groups experienced pain differently. The trends in mean VAS scores over time are shown in Fig 1.

In control group, patients reported experiencing intense pain after 24 hours of surgery, with a mean pain VAS score level of 1.3. In contrast, patients in the combination group experienced a continuous increase in pain starting from 16 hours, with the highest pain level recorded at 20 hours, reaching 1.7. Pain levels in the combination group slightly decreased after 28 hours and nearly disappeared by 36 hours post-surgery. In the control group, the results showed a progressive decline in pain and plateau with a mean pain level ranging from 0 to 1. Morphine consumption ranged from 0-1 mg/kg. There was no significant difference between the two groups in postoperative VAS scores at most time points, as shown in Table 2. The trends in VAS scores over time after surgery are illustrated in Fig 1.

TABLE 1. Demographic data.

	Combination Regimens (n=24)		Bupivacaine alone (n=24)		p-value
	Mean	±SD or percent	Mean	±SD or percent	
Gender (n, %)					0.77
Male	15	62.5	13	54.2	
Female	9	37.5	11	45.8	
Age (years)	11.8	3.1	10.7	3.1	0.25
BMI (kg/m^2)	23.8	7.7	22.4	8.2	0.47
Side (n, %)					>0.99
Right	14	58.3	13	54.2	
Left	10	41.7	11	45.8	
Duration of surgery (minutes)	78.9	50.6	68.4	35.8	0.84
Length of stay (day)	5.5	5.3	8.4	14.2	0.63

TABLE 2. Postoperative pain score.

	Combination Regimens (n=24)					Bupivacaine alone (n=24)					p-value
VAS at	Mean	SD	Median	Q1	Q3	Mean	SD	Median	Q1	Q3	
4 hours	2.1	2.9	0.0	0.0	4.8	1.9	2.9	0.0	0.0	3.8	0.66
8 hours	1.2	2.2	0.0	0.0	1.5	1.3	2.3	0.0	0.0	2.8	0.80
12 hours	1.1	2.2	0.0	0.0	1.5	0.4	1.2	0.0	0.0	0.0	0.24
16 hours	1.3	2.4	0.0	0.0	2.0	0.2	1.0	0.0	0.0	0.0	0.02
20 hours	1.7	2.3	0.0	0.0	3.0	0.9	2.1	0.0	0.0	0.0	0.10
24 hours	1.3	2.0	0.0	0.0	2.8	1.3	2.0	0.0	0.0	2.0	0.89
28 hours	1.1	1.8	0.0	0.0	2.0	0.9	2.0	0.0	0.0	0.8	0.54
32 hours	1.3	2.3	0.0	0.0	2.0	1.0	1.9	0.0	0.0	1.8	0.86
36 hours	1.2	2.5	0.0	0.0	0.8	0.4	1.3	0.0	0.0	0.0	0.12
40 hours	1.1	2.4	0.0	0.0	0.8	0.7	1.6	0.0	0.0	0.0	0.67
44 hours	1.0	1.9	0.0	0.0	1.8	0.4	1.2	0.0	0.0	0.0	0.15
48 hours	0.7	1.4	0.0	0.0	0.8	0.4	1.2	0.0	0.0	0.0	0.28

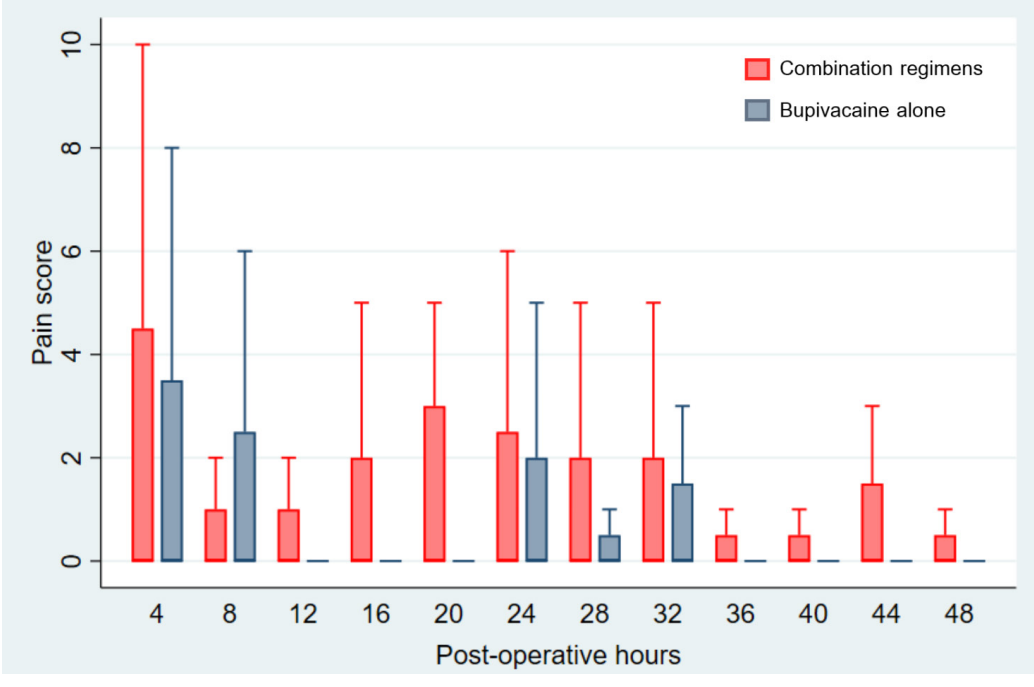

Fig 1. Postoperative pain score.

Opioid consumption after surgery is detailed in Table 3. The combination group had a higher mean morphine usage of 0.04±0.08 mg/kg compared to 0.03±0.04 in the control group at 4-8 hours postoperatively. Similarly, mean morphine consumption in the combination group was higher at 9-24 hours postoperatively (0.11±0.42 vs. 0.03±0.05). After 25 hours, the results aligned with the VAS pain score. Overall, the cumulative morphine dose was lower in the control group compared to the combination group, as shown in Fig 2.

TABLE 3. Postoperative morphine.

	Combination Regimens (n=24)					Bupivacaine alone (n=24)					p-value
Postop time at	Mean	SD	Median	Q1	Q3	Mean	SD	Median	Q1	Q3	
4 – 8 hours	0.04	0.08	0.00	0.00	0.06	0.03	0.04	0.00	0.00	0.06	0.90
9 – 24 hours	0.03	0.05	0.00	0.00	0.06	0.11	0.42	0.00	0.00	0.04	0.74
25 – 36 hours	0.10	0.41	0.00	0.00	0.04	0.01	0.02	0.00	0.00	0.00	0.60
37 – 48 hours	0.01	0.03	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.00	0.27

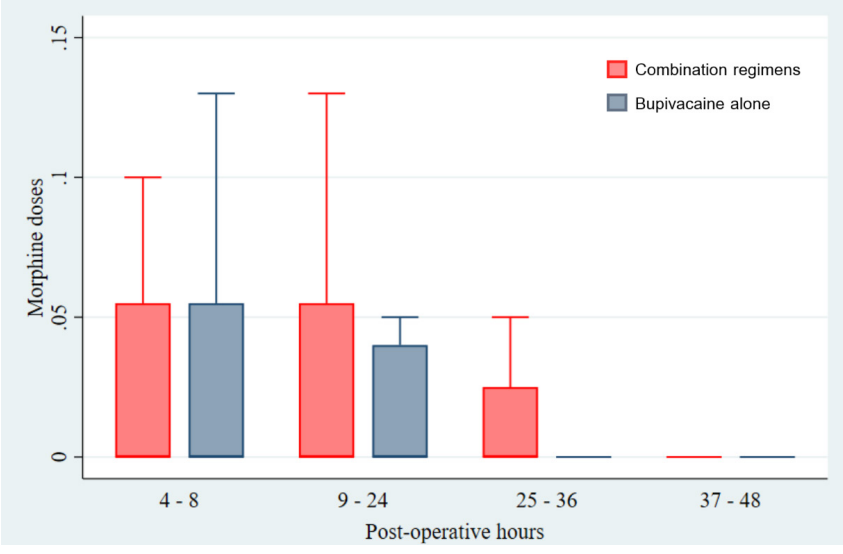

Fig 2. Postoperative morphine.

DISCUSSION

This clinical trial attempted to compare the anesthetic effects of wound infiltration using a combination of bupivacaine, ketorolac, and morphine, versus bupivacaine alone in children undergoing tibial osteotomy. The dosage of bupivacaine was based on European Society for Paediatric Anaesthesiology (ESPA) guidelines. Since there were no reported studies on the use of ketorolac or morphine for local infiltration in children, the dosage regimens for intravenous ketorolac and morphine were applied.[14] An ideal body weight was used to adjust drug dosing to mitigate concerns about adverse effects, especially in children.[15]

The mechanisms of action to reduce pain of the three drugs are different. Morphine exerts its effects by interacting with mu-opioid receptors located in both the central and peripheral nervous systems.[16] Bupivacaine, like other local anesthetics, works by preventing the initiation of action potentials in nerve cells, achieved by raising the threshold for electrical stimulation.[17] Ketorolac works by inhibiting cyclooxygenase (COX) enzymes, which play a key role in transforming arachidonic acid into prostaglandins, thromboxane, and prostacyclin. This action effectively alleviates pain and inflammation.[18]

There was no significant difference in postoperative VAS pain scores or morphine consumption between the two groups. Our findings indicated that bupivacaine alone resulted in lower pain scores compared to the combination group, though the difference was not statistically significant.

Local wound filtration was commonly used to optimize postoperative pain due to its simplicity, low cost, and low risk of side effects. Bupivacaine has a long history of use as a primary agent for local wound infiltration, acting by inhibiting sodium channels and NMDA receptors.[19] The 2018 guidance from the Pain Committee of ESPA emphasizes the use of bupivacaine for managing limb fractures in patients aged> 1 month.[17]

Based on different mechanisms for blocking nerve conduction, combining various infiltration drugs with

anesthetic agents has garnered interest for improving pain managements and reducing opioid consumption after surgery.[20,21] Clinical trials following lumbar discectomy have shown that the use of combination drug infiltration significantly reduces the need for postoperative analgesics.[22,23] Recent studies also indicate that patients receiving a combination of local drug infiltration required less IV-PCA compared to those in the control group.[24,25] However, *Singhatanadgige et al.* observed no significant difference in pain management between patients treated with a combination of bupivacaine and epinephine, with or without ketorolac and morphine.[8] Although many studies have demonstrated the efficacy of combination drug infiltration in adults, evidence supporting its effectiveness in pediatric orthopaedic patients remains limited.

Previous studies have shown that the onset of bupivacaine injection occurs within 10±5 minutes,[26] with a duration of action of up to 12 hours.[27] However, research involving pediatric patients after spinal surgery indicated that bupivacaine wound infiltration only reduces pain for the first 4 hours after surgery.[28] In our study, pain scores were first evaluated at four hours post-operation to ensure that all patients had been fully transferred from the recovery room to the ward. As shown in Fig 1, pain decreased after 4 hours post-operation in both groups. This reduction in pain may be attributed to the administration of oral paracetamol and intravenous ketorolac injection. The efficacy of NSAIDs in reducing pain after surgery in children was evaluated by *Raslan N et al.* In a randomized clinical trial study involving 66 pediatric patients aged 6-8 years who underwent tooth extraction, pain scores significantly decreased in patients who received preoperative ibuprofen compared to those who received a placebo, immediately after injection, after extraction, and 5 hours after extraction ($P<0.05$).[29]

In the present study, the combination analgesia group exhibited higher VAS scores compared to the control group. One plausible explanation for this observation is the lower concentration of local anesthetic agents resulting from the dilution in normal saline that occurs when they are combined with adjunct medications. Both study groups also experienced a decrease in pain during the first 20 hours postoperatively, followed by a rapid increase at 24 hours. The initial pain relief may be attributed to the effect of intravenous ketorolac, which was routinely administered every 8 hours for first 24 hours after surgery. The increase in pain scores at 24 hours could be due to the decrease in serum NSAID levels when switching from IV to oral medication. Few studies have reported on the efficacy of intravenous ketorolac in pediatric orthopaedic surgery. *CP Eberson et al.* conducted a study with 27 patients aged between 6 months and 18 years who underwent long-bone osteotomies or foot procedures. They compared ketorolac 0.5 mg/kg every 6 hours postoperatively versus placebo. Patients receiving ketorolac required significantly lower doses of morphine and had a shorter length of stay.[30] Similarly, intravenous ketorolac was associated with lower pain scores and reduced morphine consumption after spinal fusion at 24 and 48 hours postoperatively.[33] However, the conclusions could not be fully supported due to lack of a control group without kelotorac IV injection data.

The secondary objectives of the study were to compare opioid consumption and complications between the two groups. No statistically significant differences in opioid use was observed, which was consistent with the postoperative pain scores noted in primary outcomes. Additionally, complications such as nausea, vomiting, skin irritation, and hypotension were not detected in either group.

Most patients reported higher pain levels on the first day after surgery. This finding aligns with previous studies on postoperative pain in children aged ≤ 18 years undergoing various types of surgery. The results indicate that the type of operation was a significant factor influencing pain levels in patients aged ≥ 4 years. In the orthopedic surgery group, pain scores were highest on the first day after surgery, averaging approximately 2 points on the pain scale.[32] *Kart et al.* also observed increased pain and analgesic requirements following tibial osteotomy maximum on first day as well.[21]

No previous studies have documented the effects of local wound infiltration on post-osteotomy pain control in pediatric patients. Our findings suggest that neither ketorolac nor morphine, when added to bupivacaine, significantly reduced VAS scores or opioid use after tibial osteotomy. This is consistent with other surgical fields involving children. For instance, a recent study on postoperative pain management in pediatric patients (30 patients, aged 8-17, randomized into two groups) undergoing spinal deformity correction found no significant difference in opioid use between the control group and those receiving 0.25% bupivacaine wound infiltration group four hours post-operation ($p= 0.54$). Additionally, bleeding was more frequently observed in the bupivacaine group compared to the control group. The authors did not recommend using bupivacaine wound infiltration as a standard management protocol following spinal surgery in children.[25] However, no studies have yet examined the use of morphine or ketorolac for local wound infiltration in pediatric patients.

CONCLUSION

Multidrugs for local wound infiltration drug regimens involving bupivacaine, morphine, and ketorolac do not reduce postoperative VAS pain scores or opioid consumption following tibial osteotomy in children compared to bupivacaine alone. Future research should focus on conducting studies to explore alternative combination modalities for postoperative pain control following tibial osteotomy in pediatric patients. Given that surgical procedures involving bone procedure can result in significant pain, relying on local wound infiltration may be insufficient to adequately manage postoperative discomfort.

Limitations

There were several limitations to this study. Firstly, assessing pain levels in children can be particularly challenging due to their developmental stage and ability to communicate effectively. Secondly, our study showed only a modest decrease in pain scores, which may not be clinically relevant. Thirdly, since most pain scores recorded were below 5 on the VAS, the study may have been underpowered to detect statistical significance, especially when using a minimal clinically important difference (MCID) of 2.

Data Availability Statement

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

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Conflict of Interest

None

Registration Number of Clinical Trial

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Author Contributions

The authors confirm contribution to the paper as follows: study conception and design: PE; data collection: PM; analysis and interpretation of results: SC and PM; draft manuscript preparation and critical revision: PE. All authors reviewed the results and approved the final version of the manuscript.

Use of Artificial Intelligence

None

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Impact of Social Determinants of Health on Postoperative Health-Related Quality of Life Among Patients Undergoing Colorectal Cancer Surgery

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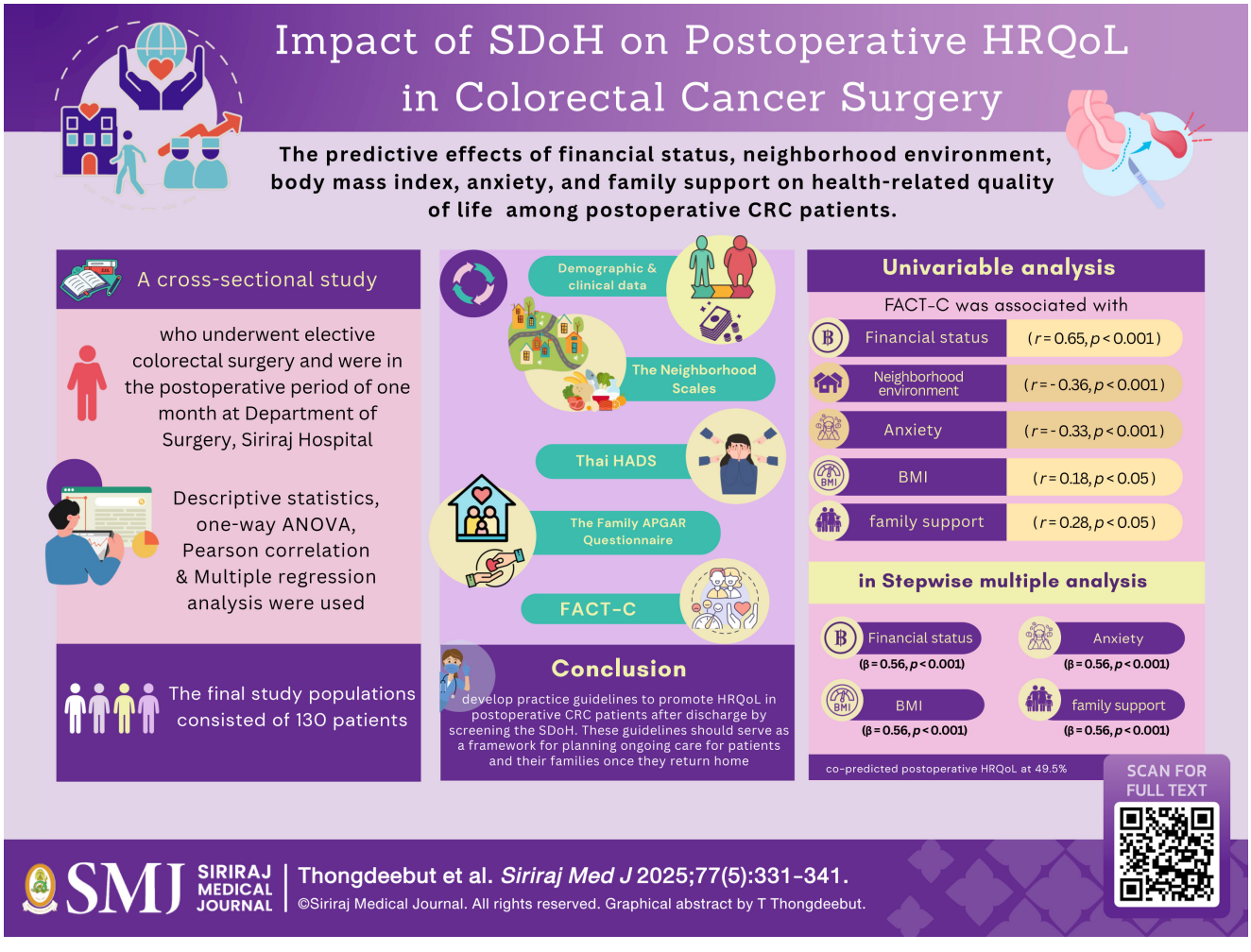

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ABSTRACT

Objective: This study aimed to investigate the predictive effects of social determinants of health–specifically financial status, neighborhood environment, body mass index, anxiety, and family support–on the health–related quality of life (HRQoL) among patients undergoing colorectal cancer (CRC) surgery.

Materials and Methods: A cross-sectional study was conducted with patients who underwent elective colorectal surgery and were in the postoperative period of one month in a super-tertiary hospital in Thailand. Data were collected using questionnaires and analyzed with descriptive statistics, one-way ANOVA, Pearson correlation, and multiple regression analysis.

Results: A total of 130 patients were enrolled, with 71 patients (54.6%) having fewer complications. Patients who have undergone CRC surgery had an average HRQoL score of 111.9 ± 11.9. Notably, the HRQoL after surgery was higher than before, reflecting an increase of 78.5%. The significant predictive factors of HRQoL were financial status ($\beta = 0.56$, $p < 0.001$), followed by anxiety ($\beta = -0.172$, $p = 0.011$), body mass index ($\beta = 0.171$, $p = 0.008$), and family support ($\beta = 0.15$, $p = 0.022$).

Conclusion: Nurses should develop practice guidelines to promote HRQoL in postoperative CRC patients after discharge by screening financial status, body mass index, anxiety, and family support. These guidelines should serve as a framework for planning ongoing care for patients and their families once they return home, ensuring that their physical, emotional, and social needs are effectively addressed during their recovery process.

Keywords: Quality of life; social determinants of health; financial status; body mass index; anxiety; family support; colorectal cancer (Siriraj Med J 2025; 77: 331-341)

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer-related deaths globally.[1] With advancements in early detection and treatment, the number of CRC survivors has risen substantially.[2] Colorectal surgeries are among the most common treatments for removing cancerous tumors.[3] Following surgery, additional treatments may be required based on the cancer's stage and the patient's overall health[4,5], resulting in better outcomes and an improved quality of life of the patient.[6] However, patients after CRC surgery may face long-term physical, psychological, and social challenges that persistently impact their health-related quality of life (HRQoL).[7-9]

The HRQoL of postoperative CRC patients is influenced by a complex interplay of factors that extend beyond the biological implications of the disease, individual factors, symptoms, complications arising from surgery and its clinical management.[10,11] Nevertheless, the social determinants of health (SDoH) are the concept of WHO; the World Health Organization suggests that health conditions are influenced not only by individual factors, genetics, or symptoms but also by social factors and environmental resources.[12]

SDoH are non-medical factors that play a crucial role in shaping health outcomes and overall well-being of individuals.[13] These include the conditions in which individuals are born, grow, live, and work, as well as the systems established to manage illness.[14] SDoH significantly influence the health outcomes of patients with cancer. For example, income, economic stability, neighborhood environment, Body Mass Index (BMI), anxiety, and family support.[16-23] In the literature, socioeconomic disparities have been associated with differences in cancer care, with factors such as financial security, lack of insurance, and limited access to transportation identified as major obstacles to achieving optimal health outcomes.[24] Furthermore, factors such as economic stability and the neighborhood environment have been linked to a reduced likelihood of poor mental and physical health in cancer survivors.[25] Moreover, food security was an important part of promoting an improved HRQoL, which could be measured by the BMI, indicating a person's overweight or underweight.[12,26]

In addition, CRC survivors exhibit an anxiety rate of 20.9%, primarily resulting from the challenges of coping with illness, treatment expectations, and decreased financial status. These factors are correlated to a deterioration in overall HRQoL.[21,27] Lastly, family support encourages patients to adopt healthy behaviors, leading to quality recovery after surgery.[28] Positive family support has a significant impact on improving quality of life in all dimensions.[22] Therefore, the purpose of this study is to investigate the predictors of HRQoL, including financial status, neighborhood environment, BMI, anxiety, and family support among patients undergoing CRC surgery.

Recognizing the impact of these factors on CRC patients is essential for developing tailored guidelines to improve their HRQoL. Despite the growing recognition of these factors, there is limited research focused on the impact of SDoH on HRQoL among postoperative CRC patients, mostly from studies focusing on long-term cancer survivors, particularly in countries with socioeconomic disparities. The results of this study would improve our comprehension of the social context of postoperative CRC patients and guide the creation and execution of effective support strategies.

MATERIALS AND METHODS

Study design and setting

This study was based on a cross-sectional study design in a super-tertiary hospital in Bangkok, Thailand, from April to July 2024. The study was approved by the Human Research Ethics Committee, Faculty of Nursing, Mahidol University, and the Faculty of Medicine Siriraj Hospital (MU-MOU CoA No. IRB-NS2023/843.1903).

Participants

The participants comprised patients aged 18 and older, both male and female, who underwent colorectal cancer surgery and received post-operative follow-up care at the surgical unit. To be eligible, patients had to meet the following inclusion criteria: (1) a first-time diagnosis of CRC at stages 1 to 3B; (2) a post-operative period of 4 to 6 weeks; 3) having a Mini-Cog score ≥ 3 (patients aged ≥ 60 years); and 4) the ability to understand and communicate in Thai (speaking, listening, reading, and writing). The exclusion criteria included: (1) previous treatment with chemotherapy or radiation therapy; (2) a diagnosis of recurrent or metastatic cancer; (3) severe psychiatric disorders that could not be controlled, such as panic disorder, major depressive disorder, or schizophrenia; and (4) severe clinical symptoms, such as significant dyspnea or high fever.

The sample size for this study was determined using the G*Power software, with power of test 90%, a significance level (α) of 5%, and 5 independent variables. As no related studies were found in the literature review, the R^2 value could not be determined. An effect size of 0.15, representing a medium effect size, was selected based on the guidelines of Polit and Beck.[29] This effect size is considered appropriate for nursing research involving multiple predictors. The G*Power analysis determined that a sample size of 116 participants was required. To account for potential data incompleteness during collection, the sample size was increased by 10%, leading to a final total of 130 participants.

Data collection

After patients agreed to participate in the study, they were asked to sign a written consent form. The data were collected using questionnaires and patient files. After obtaining informed consent and ascertaining eligibility, participants were asked to complete a demographic characteristic assessment. The Functional Assessment of Cancer Therapy-Colorectal (FACT-C) was administered at two timepoints: preoperatively (i.e., baseline), where patients were asked to recall their condition prior to surgery, and postoperatively (i.e., follow-up), four to six weeks after their elective CRC surgery. The Neighborhood Scales, Hospital Anxiety and Depression Scale (HADS), and Family APGAR questionnaires were administered simultaneously, taking approximately 45 to 60 minutes for each participant.

Measurement

Baseline characteristics and clinical data: Part 1 demographic characteristics were obtained, including sex, age, body mass index, marital status, educational attainment, occupation, average monthly household income, financial status of household income, healthcare coverage, primary caregiver support, smoking status, alcohol consumption, and exercise habits. Part 2 clinical data were obtained, including diagnosis, stage of cancer, surgical approach, CEA tumor marker, complications, length of stay, presence of a stoma, and comorbidity.

The Neighborhood Scales by Auchincloss et al.[30] were used to evaluate neighborhood environment. This instrument was translated into Thai by Pawitra Jariyasakulwong and colleagues. This scale consists of 9 items, assessing two aspects: the walking environment and the availability of healthy food. It was interpreted from its scoring system (9-45 points) as high resources (9-21), moderate resources (22-33), and low resources (34-45). Cronbach's alpha coefficient of Thai version was 0.85.[31]

The Hospital Anxiety and Depression Scale (HADS) by Zigmond & Snaith[32] was used to evaluate only the anxiety subscale. This instrument was translated into Thai by Thana Nilchaikovit and colleagues. This scale consists of 7 items. It was understood from its scoring system (0-21 points) as non-anxiety (0-7), doubtful anxiety (8-10), confirm anxiety (11-21). Cronbach's alpha coefficient of Thai version was 0.85.[33]

The Family APGAR Questionnaire by Smilkstein et al.[34] was used to evaluate satisfaction from receiving family support and was translated into Thai by Pornthip Malatham and colleagues. This scale consists of 5 items. Scores are categorized as follows: high satisfaction (14-20),

moderate satisfaction (7-13), and low satisfaction (0-6). The questionnaire is used for family support in patients undergoing breast cancer surgery.[35] Cronbach's alpha coefficient of Thai version was 0.91.[36]

Functional Assessment of Cancer Therapy-Colorectal (FACT-C) by Cella et al.[37] was used to evaluate health-related quality of life. This instrument was translated into Thai under the license of the Facit group.[38] This tool comprises 36 items that correspond to five domains: physical well-being, emotional well-being, social and family well-being, functional well-being, and colorectal cancer subscale. Scores range from 0 to 136, with higher scores reflecting better HRQoL. The Cronbach's alpha coefficient for the Thai version was 0.87.[39]

The Neighborhood Scales, HADS, Family APGAR Questionnaire, and FACT-C were applied to 30 patients with similar characteristics to the participants in this study, using Cronbach's alpha coefficient for these scales were 0.80, 0.81, 0.87 and 0.87, respectively.

Statistical analysis

The data were analyzed using SPSS version 27. Descriptive statistics and one-way ANOVA were used to analyze baseline characteristics and clinical data, while Pearson correlation was used to assess the relationships between variables. Multiple regression analysis was used to analyze the power of predictive variables, with a significance level set at 0.05. Statistical analyses were performed according to the necessary assumptions for each test.

RESULTS

Baseline characteristics and relevant clinical data of HRQoL among postoperative CRC patients (n = 130)

The study sample consisted of 130 postoperative CRC patients. Their characteristics and clinical data are included in the univariate analysis, which was described in Table 1.

The correlation between financial status, neighborhood environment, BMI, anxiety, family support, and HRQoL

Financial status was positively correlated with HRQoL at high level (r = 0.65, p < 0.001). The neighborhood environment and anxiety were negatively correlated with HRQoL at medium level (r = - 0.36, p < 0.001), (r = - 0.33, p < 0.001). BMI and family support were positively correlated with HRQoL at a low level (r = 0.18, p < 0.05), (r = 0.28, p < 0.05). However, family support was found to be correlated with financial status (r = 0.19, p < 0.05) and anxiety (r = - 0.07, p < 0.05), as shown in Supplementary content 1.

Neighborhood environment, anxiety, family support, and HRQoL

More than half of the participants had a high neighborhood environment (89.2%), Additionally, 76.2% of participants reported no symptoms of anxiety, while 63.1% expressed high levels of satisfaction with family support. The overall HRQoL after CRC surgery had a mean score of 111.9±11.9. In addition, when comparing the quality of life before and after surgery, it was found that more than half of participants showed an increase in HRQoL based on the FACT-C, with 78.5% (Table 2).

Stepwise multiple regression model

According to the results from stepwise multiple regression analyses, financial status, anxiety, body mass index and family support co-predicted postoperative HRQoL at 49.5% (R^2 = 0.495, F = 30.632, p < 0.001). Financial status had the highest significance in predicting postoperative HRQoL in CRC patients (Table 3).

DISCUSSION

This study aimed to investigate the predictive effects of SDoH on postoperative HRQoL among patients undergoing CRC surgery. The findings of this study indicated that HRQoL in CRC patients was at a favorable level. Notably, HRQoL after surgery was higher than before surgery, reflecting an increase of 78.46%. This may be due to the CRC symptoms, where patients experience abdominal pain, alternating diarrhea and constipation, fatigue, weight loss, easy tiredness, and pallor.[40] Additionally, when they were unwell, they may have experienced a sense of losing their position as the family's primary caregiver[41], which resulted in a lower HRQoL. Additionally, 59 (55.4%) of the participants developed one or two grades of postoperative complications. A previous study found that more postoperative complications were related to poorer HRQoL than for patients without complications.[23,42,43] The experience of only minimal postoperative adverse effects, or none at all, led to a better HRQoL.[44] This is consistent with previous studies by Li et al.[45] as their study of patients after CRC surgery at 1, 3, and 5 months (n = 70). The HRQoL of the discharged CRC patients in the study was at an adequate level and stayed fairly consistent over time, as indicated by FACT-C (102.5; 102.9; 103.0). Moreover, Chutikamo et al.[46] also found that the HRQoL of postoperative CRC patients, three months after surgery, was at a moderate to high level. Reudink et al.[47] also found that quality of life improves over time (p <0.001), with recovery reaching pre-illness levels within a period of 6 months, as indicated by the EQ-5D index scores (0.82, p = 0.01).

TABLE 1. Baseline characteristics and relevant clinical data of HRQoL among postoperative CRC patients. (n = 130)

Variables	Total n (%)	*F*	*p*-value
Sex		**0.55**	**0.58**
Male	79 (60.8)		
Female	51 (39.2)		
Age (years)		**0.01**	**0.99**
20-39	6 (4.6)		
40-59	34 (26.2)		
≥ 60	90 (69.2)		
Mean ±SD (years)	**63.03±11.80**		
BMI (kg/m²)			
< 18.5	11 (8.5)		
18.5 – 22.9	47 (36.2)		
23 – 24.9	28 (21.5)		
25 – 29.9	34 (26.2)		
≥ 30	10 (7.6)		
Mean ±SD (kg/m²)	**23.8±4.7**		
Status		**0.30**	**0.74**
Single	11 (8.5)		
Married	101 (77.7)		
Divorce	18 (13.8)		
Educational attainment		**15.01**	**<0.001***
Elementary	19 (14.6)		
High school graduate	33 (25.4)		
Associate degree/ Vocational Certificate	18 (13.9)		
≥ Bachelor's degree	60 (46.1)		
Healthcare coverage		**12.47**	**<0.001***
Universal Health Coverage	61 (46.9)		
Civil Service Medical Benefits Scheme	49 (37.7)		
Social Security Scheme	11 (8.5)		
Private	9 (6.9)		
Household income (Thai baht/month)		**34.80**	**<0.001***
≤ 10,000	18 (13.8)		
10,001 - 20,000	15 (11.5)		
20,001 - 30,000	17 (13.2)		
> 30,000	80 (61.5)		
Mean ±SD (THB)	**52,906.2±55,689.2**		
Financial status			
Adequate	74 (57.0)		
Inadequate	56 (43.0)		

TABLE 1. Baseline characteristics and relevant clinical data of HRQoL among postoperative CRC patients. (n = 130) (Continue)

Variables	Total n (%)	*F*	*p*-value
Primary caregiver support		**3.79**	**0.003***
None	8 (6.2)		
Child/Grandchild	58 (44.6)		
Husband/Wife	53 (40.7)		
Parents	4 (3.1)		
Siblings	4 (3.1)		
Friends	3 (2.3)		
Alcohol consumes		**0.82**	**0.44**
Never	82 (63.1)		
Ex-alcohol	33 (25.4)		
Current alcohol	15 (11.5)		
Smoking status		**3.98**	**0.02***
Never	92 (70.8)		
Ex-smoker	34 (26.1)		
Current smoker	4 (3.1)		
Exercise	81 (62.3)	**0.44**	**0.66**
Colon cancer	81 (62.3)	**6.88**	**0.01***
Staging of cancer		**2.58**	**0.08**
I	16 (12.3)		
II	68 (52.3)		
III	46 (35.4)		
Surgical approach		**2.82**	**0.007***
Open	102 (78.5)		
Laparoscopy	28 (21.5)		
CEA tumor maker		**1.40**	**0.16**
0 - 5 ng/mL	95 (73.1)		
> 5 ng/mL	35 (26.9)		
The Clavien-dindo classification of surgical complication		**0.04**	**0.96**
No complication (grade 0)	71 (54.6)		
Grade 1	49 (37.7)		
Grade 2	10 (7.7)		
Postoperative length of stay (days)		**0.58**	**0.63**
< 5	6 (4.6)		
5 – 7	66 (50.8)		
8 – 10	42 (32.3)		
> 10	16 (12.3)		
Mean±SD (days)	**8.14±0.3**		
Stoma	**59 (45.4)**	**6.45**	**<0.001****
Comorbidity	**89 (68.5)**	**0.01**	**0.99**

**p < 0.001, *p < 0.05

TABLE 2. Health-related quality of life, neighborhood environment, anxiety, and family support in postoperative CRC patients. (n = 130)

Variables	Mean±SD	Median (IQR)	Min	Max
HRQoL before surgery (i.e. baseline)	95.12±16.13	94.5 (88-103)	52	123
HRQoL after surgery	111.93±11.89	110 (98.8-127)	77	136
Neighborhood environment	16.2±4.6	15 (13-19)	9	38
Anxiety	5.2±3.2	4 (3-7)	0	15
Family support	14.1±4.5	15 (12.8-17.3)	3	20

Abbreviations: HRQoL; Health-related quality of life, IQR; inter quartile range

TABLE 3. Parameters of the generalized stepwise multiple linear regression analysis for exploring the potential influences of the study variables on health-related quality of life. (n = 130)

Variables	b	SE	β	t	*p* value
Constant	65.841	7.080		9.300	<0.001
Financial status	9.871	1.182	0.564	8.350	<0.001**
BMI	0.591	0.220	0.171	2.684	0.008*
Anxiety	-0.878	0.340	-0.172	-2.587	0.011*
Family support	0.540	0.233	0.150	2.315	0.022*

SE_b = 11.643, R = 0.704, R^2 = 0.495, Adjusted R^2 = 0.479, F = 30.632, $p < 0.05$*, $p < 0.01$**

In the present study, we observed the influence of the SDoH factors—including financial status, neighborhood environment, BMI, anxiety, and family support—in improving the HRQoL of patients undergoing CRC surgery. This result indicates that more than 80 (61.5%) reported a monthly household income of at least 30,000 baht, and 74 (57%) participants with adequate financial status reported a significantly better HRQoL, indicating a positive correlation between financial stability and well-being.[2] Moreover, the majority of the participants held a bachelor's degree or higher (46.1%), use the universal health coverage (46.9%), and have a family member as a caregiver (91.5%). The support from these sources enabled the participants to have adequate income to access quality healthcare and essential resources that promote health after CRC surgery.[48] Similarly, Han et al.[49] found that for gastrointestinal cancer survivors in the US, low economic stability and poor health care access significantly contributed to poor HRQoL. Furthermore, Robinson et al.[15] found that CRC survival in the US with average household income less than $30,000 and lower neighborhood socioeconomic status, was associated with a poor HRQoL.

Furthermore, the majority of the participants were married (77.7%), and more than half of the participants (63.1%) reported a high level of satisfaction with family support. Marital status, often considered a proxy for family support, was found to be significantly associated with better general and mental HRQoL.[50] Family support is an important determinant for the ability of patients undergoing CRC to cope with illness situations.[51] Studies have found that social support, especially from family, is closely related to patients' quality of life.[52] Furthermore, it plays a crucial role in promoting good health behaviors, as

well as promoting the post-treatment rehabilitation process, and self-efficacy, thereby contributing to the improvement of HRQoL.[53] Similarly, a study by Costa et al.[54] examined 144 patients with CRC treatment and found that family support and professional social support are important factors that contributed to the improvement of HRQoL. In addition, psychosocial interventions effectively reduce distress and enhance quality of life. Conversely, lower family support is associated with poorer psychological well-being and QOL in CRC patients.[55] This result may indicate that 10 (7.7%) participants experienced anxiety, with the mean HADS score being 5.2±3.2 during their postoperative periods. It can be stated that family support and mild postoperative complications prevented the patients from experiencing psychological distress, resulting in a high HRQoL.[56] Anxiety was found to be associated with poorer postoperative HRQoL in our study. Similarly, a study by Siddiqui et al.[57] which examined CRC patients who received any form of treatment, found that anxiety significantly affected HRQoL. Mols et al.[27] also found that anxiety symptoms in CRC survivors were inversely associated with all EORTC QLQ-C30 scales, with the smallest correlation observed in physical functioning and the largest for role functioning.

Previous findings have suggested that high BMI was protective against HRQoL deterioration, but BMI > 30 kg/m^2 is associated with lower physical function in CRC,[58,59] on the other hand, postoperative CRC patients who were underweight (BMI <18.5 kg/m^2) reported worse quality of life.[60] The results of this study showed a significant increase in BMI; individuals more than 75 (57.7%) were normal to overweight (BMI 18.5-24.9 kg/m^2) with the average BMI being classified as overweight. Most cancer patients demonstrate positive health behaviors, such as making healthy dietary choices following surgery,[61] and effectively managing their BMI, which in turn plays a significant role in enhancing their overall HRQoL. The findings are consistent with Li et al.[45] who reported that patients who underwent CRC surgery at 1, 3, and 5 months showed an increase in BMI over time, and that patients with moderate obesity were likely to have better HRQoL.

The neighborhood environment was not recognized as a major factor influencing HRQoL in this study. This may be attributed to the fact that the majority of participants (89.2%) reported a high level of neighborhood environment. Moreover, most of the participants live in urban areas, which allows them access to resources that facilitate postoperative recovery, with no significant differences. However, previous studies found that the neighborhood environment has a positive impact on HRQoL regarding CRC survivors.[22] Therefore, it is important to promote the availability of neighborhood environment that supports HRQoL among postoperative CRC in both urban and rural communities.

However, there are some limitations that should be noted. Our analyses on predictive of HRQoL were cross-sectional, precluding causal inferences, and the findings may not be generalizable due to its single-setting nature and the exclusion of patients receiving chemotherapy or radiation therapy. Additionally, the data on clinical and HRQoL baseline were based on self-report, which is why we cannot completely exclude the possibility of recall bias. The neighborhood environment was only partially assessed. However, the validation of this factor in a subset of 30 patients revealed a concordance of about 80%.

CONCLUSION

This study highlighted the impact of SDoH on HRQoL in postoperative CRC patients after discharge. Financial status was the most significant factor in predicting HRQoL. Therefore, it is essential for nursing practitioners to develop practice guidelines aimed at enhancing HRQoL for postoperative CRC patients after discharge. This can be achieved by implementing screening protocols to assess financial status, BMI, anxiety levels, and family support. The results of these assessments should guide the creation of personalized care plans that address the unique needs of patients and their families as they transition back home.

Data Availability Statement

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

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DECLARATION

Grants and Funding Information

None

Conflict of Interests

The authors declare no conflict of interest.

Registration Number of Clinical Trial

None

Author Contributions

Conceptualization and methodology: T.T., S.D., W.P., V.L.; Data collection, data acquisition and data analysis: T.T., S.D., W.P.; Drafting the manuscript T.T., S.D. All authors have read and agreed to the final version of the manuscript.

Use of artificial intelligence

Not applicable

Ethics Statement

The study was approved by Human Research Ethics Committee, Faculty of Nursing, Mahidol University, and the Faculty of Medicine Siriraj Hospital (MU-MOU CoA no. IRB-NS2023/843.1903).

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Efficacy and Safety of Dual Antiplatelet Therapy Using Cilostazol with Aspirin or Clopidogrel to Reduce the Rate of Recurrent Ischemic Stroke in Asia: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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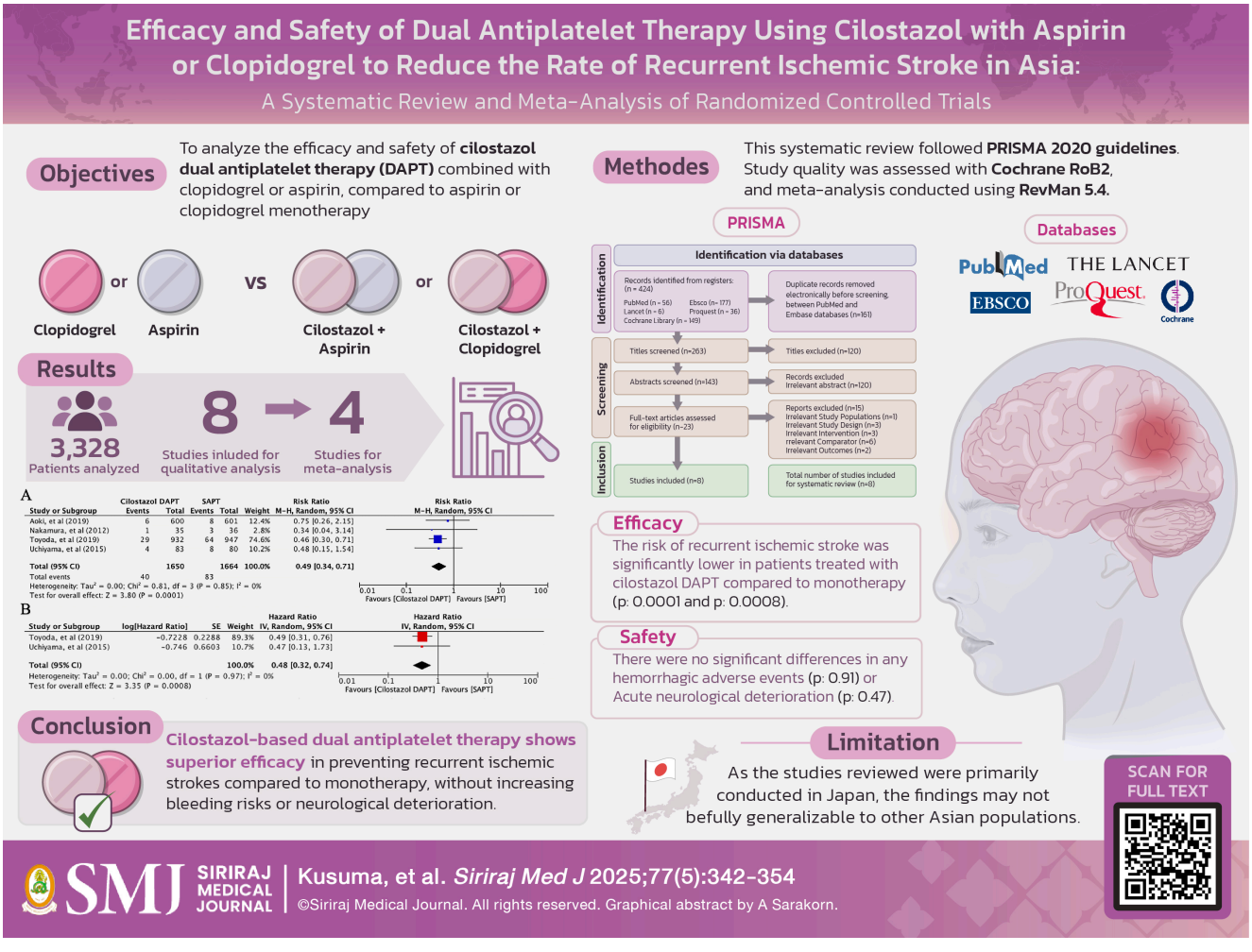

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ABSTRACT

Objective: The stroke mortality rate in Asia is higher than in other regions worldwide. As an antiplatelet medication and phosphodiesterase-3 inhibitor, cilostazol lacks approval for use in ischemic stroke. We intended to analyze the efficacy and safety of cilostazol dual antiplatelet therapy (DAPT) with clopidogrel or aspirin compared to aspirin or clopidogrel monotherapy.

Materials and Methods: This review was carried out under the PRISMA 2020 guidelines, using sources from PubMed, Cochrane Library, EBSCOhost, Proquest, and the Lancet database. The Cochrane Risk of Bias 2 (RoB2) tool for randomized controlled trials was used to grade the quality of studies and Review Manager (RevMan) 5.4 for the meta-analysis.

Results: Eight studies were included in this analysis, with four undergoing quantitative evaluation through meta-analysis, involving 3,328 patients. The risk of recurrent ischemic stroke for patients treated with cilostazol DAPT was significantly lower compared to those receiving monotherapy (risk ratio, RR: 0.49; 95% CI: 0.32–0.71; p: 0.0001) and (hazard ratio, HR: 0.48; 95% CI: 0.32–0.74; p: 0.0008). There were no significant differences in any hemorrhagic adverse events between the treatment groups (RR: 0.98; 95% CI: 0.71-1.36; p: 0.91). Acute neurological deterioration showed no significant differences (RR: 0.55; 95% CI: 0.11-2.77; p: 0.47).

Conclusion: Cilostazol DAPT is more effective than clopidogrel or aspirin alone in preventing recurrent ischemic strokes without significantly increasing hemorrhagic risks or acute neurological decline. However, the study's exclusive focus on a Japanese population limits the generalizability of the findings, highlighting the need for more diverse clinical trials across Asia.

Keywords: Aspirin; cilostazol; clopidogrel; dual antiplatelet; ischemic stroke (Siriraj Med J 2025; 77: 342-354)

INTRODUCTION

Stroke continues to be the second leading cause of death in Asia despite the global establishment of guidelines. It is also the third most prevalent cause of years lost due to disability on a global scale.[1] Stroke affects not just the patient; it also imposes considerable strain on their family and caregivers.[2] Epidemiological studies have shown that Asia had a higher stroke mortality rate compared to other regions, such as Western Europe, America, and Australia, with East Asia holding the highest prevalence worldwide (including Japan, China, and Taiwan).[3] Ischemic stroke, especially those involving large vessel occlusion, continues to be a significant contributor to long-term disability.[4] Understanding of stroke remains lacking, particularly among individuals in high-risk groups.[5] Furthermore, the stroke recurrence incidence is 26% over a period of five years.[6] Previous studies showed that recurrent stroke patients had a higher mortality rate compared to first-time patients.[7] Motor and functional recovery are critical for improving patient outcomes following a stroke. Motor recovery typically occurs within the first 3-6 months post-stroke. During this period, pharmacological interventions are crucial in optimizing the effectiveness of rehabilitation therapies, enhancing both motor function and overall functional recovery.[8]

Studies have shown that the aspirin and clopidogrel regimen effectively decreased the possibility of recurrent cerebrovascular accidents and was recommended in clinical practices. Clopidogrel inhibits platelet aggregation by targeting the P2Y12 receptor pathway, which shares a mechanism with aspirin in platelet aggregation. Despite its use in clinical settings, patients prescribed both aspirin and clopidogrel as dual antiplatelet therapy significantly increased the chance of experiencing massive bleeding within 90 days compared to those prescribed only aspirin.[9] Studies also showed an increased likelihood of both significant and moderate bleeding in those administered both clopidogrel and aspirin. Therefore, there is still a need for an alternative dual antiplatelet therapy.[9,10]

Cilostazol is a phosphodiesterase III (PDE3) inhibitor. It is metabolized by the hepatic cytochrome P450 system, specifically through the CYP3A4 and CYP2C19 enzymes. It does not depend on the cyclooxygenase or platelet P2Y12 receptor pathways for its action.[10] Cilostazol's active metabolites have a reversible effect on phosphodiesterase 3 (PDE3), which inhibits cyclic adenosine monophosphate (cAMP) from breaking down. This mechanism leads to a decrease in platelet reactivity and aggregation. Additionally, cilostazol has a decreased incidence of hemorrhagic events.[10] Some studies have demonstrated that cilostazol significantly reduces the incidence of stroke while also decreasing the risk of cerebral hemorrhage and other forms of bleeding. Moreover, its usage does not increase the number of vascular deaths or mortality events.[10,11]

Few studies have investigated the efficacy and safety measures of cilostazol combined therapy, specifically in the Asian population, which has a high prevalence of stroke. Therefore, this systematic review and meta-analysis sought to evaluate the use of cilostazol in combination with either clopidogrel or aspirin for preventing recurrent ischemic stroke within the Asian population in terms of safety and efficacy. It is anticipated that the results will help to enhance the guidelines for the prevention of recurrent ischemic stroke in Asia. This would lead to a decline in the death rate and disability associated with ischemic stroke.

MATERIALS AND METHODS

Search strategy

This systematic review of randomized controlled trials (RCTs) followed the 2020 guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[12] Furthermore, PubMed, Cochrane library, EBSCOhost, Proquest, and Lancet databases were searched up to the year 2024, using the following keywords or terms: "cilostazol", "pletaal", "citaz", "naletal", "stazol", "aggravan", "antiplat", "aspirin", "acetylsalicylic acid", "clopidogrel", "plavix", "ischemic stroke", "non hemorrhagic stroke", "cerebral infarction", "brain infarction", "cerebral ischemia", "brain ischemia", "ischemic cerebrovascular accident", and "cerebrovascular ischemia". There were no restrictions on language. The complete search strategy is shown in Supplementary File 1.

Inclusion and exclusion criteria

The inclusion criteria were (a) RCTs that assessed the efficacy and safety of dual antiplatelet therapy (DAPT), combining cilostazol with either aspirin or clopidogrel as the experimental group, compared to single antiplatelet therapy (SAPT) using either aspirin or clopidogrel as the control group for preventing stroke recurrence, (b) studies conducted on the Asian population, and (c) efficacy and safety as the outcome. All non-experimental and non-randomized investigations (including cohort, cross-sectional, or case-control studies), reviews, animal studies, preclinical studies, conference abstracts, book chapters, and commentaries were excluded from this review. Articles without full text and those on irrelevant topics were also excluded. RCTs comparing cilostazol with anticoagulants or a placebo were likewise excluded.

Outcome measures

The efficacy outcome was the risk of recurrent ischemic stroke. Additionally, safety outcomes focused on analyzing any hemorrhagic adverse events and any acute neurological deterioration occurring within 14 days of treatment, as indicated by an increase in the NIHSS score.

Data retrieval and assessment of bias

Data were gathered from the selected studies, which included details such as the author and year of publication, sample size, study design, settings, mean or median age of the study subjects, follow-ups, and outcomes expressed as event counts and hazard ratios (HR) along with their respective 95% confidence intervals (95% CIs). The included studies were evaluated for bias using the Cochrane Risk of Bias 2 (RoB2) tool for RCTs. This tool assessed bias across five domains: the randomization process, variations from intended interventions, bias in outcome measurement, missing outcome data, and selection bias in the reported findings. It also guided reviewers through each domain to facilitate the assessment. In addition, quality assessment was conducted by all five authors, and discrepancies were resolved through consultation with the sixth reviewer until an agreement was reached. We did not conduct an evaluation of publication bias because the meta-analysis comprises fewer than 10 studies.[13]

Statistical analysis

The meta-analysis was performed using Review Manager (RevMan) version 5.4. The efficacy and safety outcomes were evaluated and displayed as dichotomous data to show the risk ratios (RR) and their corresponding 95% CIs. Additionally, the recurrence rate of ischemic stroke was reported using pooled HRs and 95% CIs gathered from each applicable study. A p-value will be included for each item to demonstrate the significance of the results. If there were any sub-analyses or extension studies derived from the same RCTs, the efficacy and safety data for the meta-analysis were gathered exclusively from the core RCT to prevent data duplication.

Several studies presented their primary outcomes using various evaluation and calculation methods. As a result, meta-analyses were performed using a random effects model. This model assumed that treatment effects might vary across specific populations and treated each study with equal weight. Combined effect measures such as HRs were computed using the inverse variance method and the Mantel-Haenszel method for RRs.

The heterogeneity across different research studies was evaluated through the I^2 statistic. A value under 25% signifies minimal variability, while values ranging from 25% to 50% denote small variability. Moderate variability is indicated by scores between 50% and 75%, and high

variability is suggested when the score exceeds 75%. Furthermore, any p-value lower than 0.05 is considered statistically significant.

RESULTS

Study selection

The preliminary search approach uncovered a total of 424 studies. Titles, abstracts, and full texts were independently screened. Studies that did not correspond with the objectives of this review were excluded. The detailed exploration and selection methodology are shown in Fig 1.

Study characteristics and outcomes

This review encompassed eight studies for qualitative evaluation, of which four[14–17] were quantitatively analyzed through meta-analysis. All studies involved patients with noncardioembolic strokes in Japan. The study durations ranged from three months to 3.5 years. Five of these studies[17–21] were part of the Cilostazol Stroke Prevention Study for Antiplatelet Combination (CSPS.com) Trial, with Toyoda et al. (2019)[17] serving as the core RCT. Hoshino et al. (2021)[18] conducted a subgroup analysis comparing the types of dual antiplatelet agents used (cilostazol combined with either aspirin or clopidogrel) against monotherapy within the CSPS.com trial. Uchiyama et al. (2021)[19] focused on specific populations with ischemic stroke and over 50% intracranial arterial stenosis (ICAS). Toyoda et al. (2022)[20] categorized patients according to when they began treatment in the CSPS.com trial, while Nishiyama et al. (2023)[21] analyzed only those with lacunar stroke from the same trial. Among the five studies from the CSPS.com trial included in this review, only data from the core RCT were utilized for meta-analysis; the others were assessed through systematic review. Three studies specifically examined cilostazol and aspirin as combination therapy, whereas the CSPS.com trial evaluated both cilostazol plus either aspirin or clopidogrel as dual therapy. The meta-analysis incorporated data from four studies[14–17], totaling 3,328 patients. Table 1 presents the features of the studies that are part of this review.

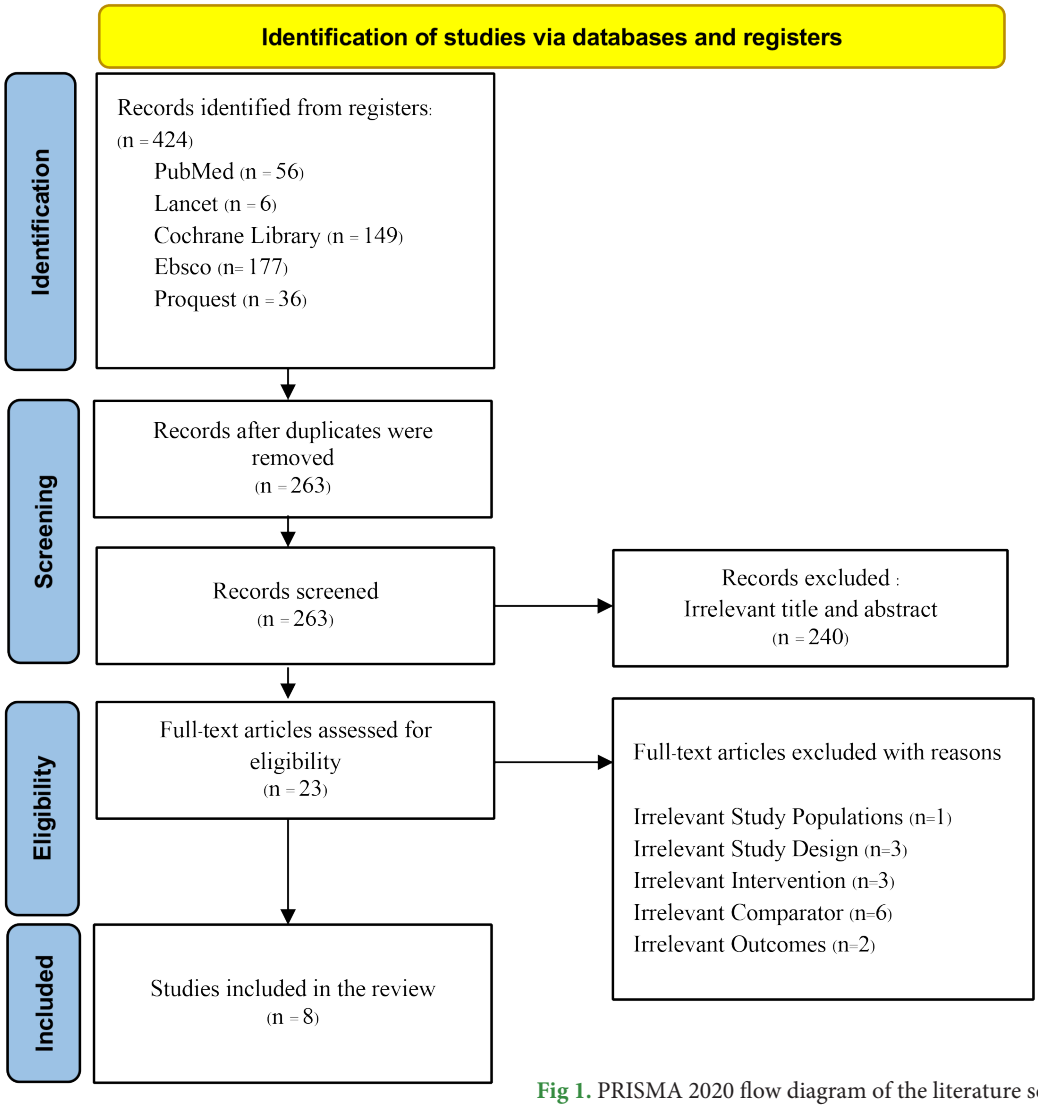

Fig 1. PRISMA 2020 flow diagram of the literature search strategy.

TABLE 1. Demographic and clinical characteristics of this current study.

No	Author, year, country	Subject Number of participants	Age in Mean (SD)/ Median (range) (years)	Study period	Characteristic	Method	Outcome Efficacy	Outcome Safety	Follow-up	Significance
1	Nakamura et al.[16] 2012, Japan	76 patients	66 (12)	6 months	Non-cardioembolic ischemic stroke	Open-labeled, randomized study. Patients are divided into two groups: 1. SAPT: Aspirin 1x300 mg 2. DAPT: Cilostazol 2x100 mg + Aspirin 1x300 mg	Ischemic stroke recurrence and patients with NIHSS score deterioration after 14 days were greater in the SAPT, while mRS at 6 months was better in the DAPT.	No significant difference in major hemorrhagic events.	MRI and MRA upon admission, NIHSS and mRS score on day 14, and month 6.	**Efficacy outcome:** 1. Stroke recurrence was higher in the SAPT compared to the DAPT (RR: 0.34, 95% CI: 0.04–3.14) 2. The number of patients experiencing neurological deterioration in the NIHSS score after 14 days was greater in the SAPT than DAPT (RR: 0.21, 95% CI: 0.05–0.87, p: 0.013) 3. At month 6, patients in the DAPT had more favorable functional status (mRS 0–1) (RR: 1.48, 95% CI: 1.07–2.06, p: 0.0048). **Safety Outcome:** No significant difference in any hemorrhagic events (1 in SAPT, 0 in DAPT) (RR: 0.33, 95% CI: 0.01–7.93)
2	Uchiyama et al[15]. 2015, Japan	165 patients	68.3 (45–84)	2 years	Non-cardioembolic ischemic stroke patients with >50% intracranial artery stenosis	Open-label, multicenter, randomized controlled trial. Patients were randomized into two groups: 1. DAPT: Cilostazol 200 mg/day + Aspirin 100 mg/day (n = 83) 2. SAPT: Aspirin 100 mg/day (n = 82)	1. Progression of intracranial arterial stenosis was lower in the DAPT group but not statistically significant. 2. The combination therapy tended to reduce vascular events and silent brain infarctions.	No significant difference in major hemorrhagic events.	Clinical and laboratory assessment, MRA, serious adverse events at baseline, 3, 6, 12, and 24 months.	**Efficacy outcome:** 1. Progression of intracranial artery stenosis: DAPT: 9.6%, SAPT: 5.6% (p = 0.53) 2. Emergence of new silent brain infarcts: DAPT 4.8%, SAPT 10.0% (RR: 0.48, 95% CI: 0.04–3.14), mean annual recurrence rate of ischemic stroke (HR: 0.47, 95% CI: 0.13–1.73) **Safety Outcome:** No significant difference in any hemorrhagic events (4 in DAPT, 3 in SAPT) (RR: 1.29, 95% CI: 0.30–5.56)

TABLE 1. Demographic and clinical characteristics of this current study. (Continue)

No	Author, year, country	Subject Number of participants	Age in Mean (SD)/ Median (range) (years)	Study period	Characteristic	Method	Outcome		Follow-up	Significance
							Efficacy	Safety		
3	Aoki et al.[14] 2019, Japan	1208 patients	69 (61-77)	3 months	Non-cardioembolic ischemic stroke	Open label: block randomization scheme, 1. DAPT: 200 mg of cilostazol + 80 to 200 mg of aspirin per day for 14 days, continued by 200 mg of cilostazol per day until three months after onset. 2. SAPT: 80 to 200 mg of aspirin per day for 14 days, followed by 200 mg of cilostazol per day until three months after onset	Patients in both groups showed no notable differences regarding NIHSS deterioration within 14 days, and their mRS status at three months was also comparable. Ischemic stroke recurrence was higher in the SAPT	The incidence of hemorrhagic events and their severity were similar in both groups.	MRI and MRA upon admission and day 7. NIHSS and mRS upon admission, day one, day two, day seven, day 14, 3 months.	**Efficacy outcome:** 1. Recurrent ischemic stroke was higher in the SAPT compared to the DAPT (RR: 0.75, 95% CI: 0.26–2.15). 2. The number of patients experiencing neurological deterioration in the NIHSS score after 14 days was similar between the two groups (RR: 1.09, 95% CI: 0.78–1.53, p: 0.632) 3. The secondary efficacy outcome showed that the prevalence of mRS 0-1 at 3 months was similar between the two groups (RR: 1.07, 95% CI: 0.98–1.16, p: 0.087) **Safety outcome:** No significant difference in any hemorrhagic events (6 in SAPT, 9 in DAPT) (RR: 1.50, 95% CI: 0.54–4.20)
4	Toyoda et al.[17] 2019. Japan (CSPS.com Trial)	1879 patients	71 (64-76)	3.5 years	High-risk non-cardioembolic ischemic stroke	Open label: block randomization scheme, The SAPT (947 patients) received either 81 mg/100 mg aspirin or 50 mg/75 mg clopidogrel once daily. The DAPT (932 patients) received cilostazol (50-100 mg twice daily) along with either aspirin (81 mg or 100 mg) or clopidogrel (50 mg or 75 mg) once daily.	The DAPT group experienced a reduced rate of ischemic stroke recurrence compared to the SAPT group	Safety measures were similar between the DAPT and SAPT groups.	MRI and MRA upon admission in 1, 3, 6 months, and every 6 months thereafter.	**Efficacy outcome:** Ischemic stroke recurrence (RR: 0.46, 95% CI: 0.30–0.71) and mean annual recurrence rate of ischemic stroke (HR 0.49, 95% CI: 0.31–0.76, p = 0.0010) were higher in the SAPT. **Safety outcomes:** No significant difference in any hemorrhagic events (49 in SAPT, 54 in DAPT) (RR: 0.93, 95% CI: 0.65–1.33)

TABLE 1. Demographic and clinical characteristics of this current study. (Continue)

No	Author, year, country	Subject Number of participants	Age in Mean (SD)/ Median (range) (years)	Study period	Characteristic	Method	Outcome Efficacy	Outcome Safety	Follow-up	Significance
5	Hoshino et al.[18] 2021, Japan (subanalysis of CSPS.com Trial)	1879 patients	71 (64-76)	3.5 years	High-risk and non-cardiembolic ischemic stroke	Open label: block randomization scheme; SAPT using aspirin 81 mg/100 mg (380 patients) or clopidogrel 50 mg/75 mg (567 patients) once daily; and DAPT using cilostazol 2x 50-100 mg combined with aspirin 81 mg/100 mg (383 patients) or clopidogrel 50 mg/75 mg (549 patients) once daily. The subgroup analysis was conducted according to the types of antiplatelet agents used.	1. Ischemic stroke recurrence/annual event rate was significantly lower in the dual regimen with cilostazol and clopidogrel 2. Ischemic stroke recurrence/annual event rate reduction was insignificant between the monotherapy groups	There was no significant difference in severe or life-threatening hemorrhage between the two groups	MRI and MRA upon admission in 1, 3, 6 months, and every 6 months thereafter.	**Efficacy outcome:** Annual event rate 1. Clopidogrel DAPT vs SAPT : HR 0.447 [95% CI, 0.258, 0.774] 2. Aspirin DAPT vs SAPT : HR 0.569 [95% CI, 0.273, 1.189] **Safety outcome:** Severe or life-threatening hemorrhage 1. Clopidogrel DAPT vs SAPT : HR 0.730 [95% CI, 0.206, 2.588] 2. Aspirin DAPT vs SAPT : HR 0.595 [95% CI, 0.174, 2.034]
6	Uchiyama et al.[19] 2021, Japan (subanalysis of CSPS.com Trial)	547 patients	70 (65-76)	3.5 years	High-risk and non-cardiembolic ischemic stroke and more than 50% ICAS in major intracranial artery	Open-label block randomization scheme: SAPT group (272 patients) using aspirin 81 mg/100 mg or clopidogrel 50 mg/75 mg once daily, and DAPT (275 patients) using cilostazol at 2x 50-100 mg combined with aspirin 81 mg/100 mg or clopidogrel 50 mg/75 mg	Ischemic stroke recurrence rate was lower in the DAPT.	Severe bleeding occurrence between two groups remained comparable in ICAS patients.	MRI and MRA upon admission in 1, 3, 6 months, and every 6 months thereafter.	**Efficacy outcomes:** 1. Any stroke: DAPT vs SAPT-HR 0.47 [95% CI, 0.24–0.93] 2. Ischemic stroke: DAPT vs SAPT-HR 0.47 [95% CI, 0.23–0.95] 3. Composite vascular events: DAPT vs SAPT-HR 0.48 [95% CI, 0.26–0.90] **Safety outcome:** Major or life-threatening bleeding: DAPT vs SAPT-HR 0.72 [95% CI, 0.12–4.30]

TABLE 1. Demographic and clinical characteristics of this current study. (Continue)

No	Author, year, country	Subject Number of participants	Age in Mean (SD)/ Median (range) (years)	Study period	Characteristic	Method	Outcome		Follow-up	Significance
							Efficacy	Safety		
7	Toyoda et al.[20] 2022. Japan (subanalysis of CSPS.com Trial)	1879 patients	69.8 (9.0)	3.5 years	High-risk and non-cardiembolic ischemic stroke	Open-label block randomization scheme: patients receiving SAPT (aspirin 81 mg/100 mg or clopidogrel 50 mg/75 mg once daily) and DAPT (cilostazol 2x 50-100 mg combined with aspirin 81 mg/100 mg or clopidogrel 50 mg/75 mg once daily). The subgroup analysis categorized patients into groups based on the timing of starting trial treatment (8–14 days, 15–28 days, and 29–180 days after stroke onset).	Ischemic stroke recurrence decreased in the DAPT during the 15–28 days and 29–180 day intervals, while remaining similar during the 8–14 day period.	Rates of massive hemorrhage were similar across all categorized groups.	MRI and MRA upon admission in 1, 3, 6 months, and every 6 months thereafter.	**Efficacy outcomes:** The recurrence of ischemic stroke: DAPT vs. SAPT in any of the three groups: - 8–14 days: HR 1.02 [0.51–2.04] - 15–28 days: HR 0.34 [95% CI 0.12–0.95]) - 29–180 days: HR 0.27 [0.12–0.63] **Safety outcome:** Major or life-threatening bleeding: DAPT vs. SAPT in any of the three groups: - 8–14 days: HR 0.22 [95% CI 0.03–1.88] - 15–28 days: HR 1.07 [95% CI 0.15–7.60] - 29–180 days: HR 0.76 [95% CI 0.24–2.39]
8	Nishiyama et al.[21] 2023, Japan (subanalysis of CSPS.com Trial)	925 patients	69.5 (9.15)	3.5 years	High-risk and non-cardioembolic lacunar stroke	Open-label block randomization scheme: SAPT group (461 patients) using aspirin 81 mg/100 mg or clopidogrel 50 mg/75 mg once daily, and DAPT (464 patients) using cilostazol 2x 50-100 mg combined with aspirin 81 mg/100 mg or clopidogrel 50 mg/75 mg once daily.	Ischemic stroke recurrence rate is lower in the DAPT than in the SAPT.	Insignificant events of severe bleeding between the two groups.	MRI and MRA upon admission in 1, 3, 6 months, and every 6 months thereafter.	**Efficacy outcomes:** Ischemic stroke recurrence was significantly lower in DAPT group (HR 0.43 [95% CI, 0.22, 0.84; P = 0.013]) **Safety outcome:** Safety outcome did not differ significantly (HR 0.35 [95% CI, 0.07, 1.75]; P = 0.201)

*N/A = Not Available

Abbreviations: MRI = Magnetic Resonance Imaging; MRA = Magnetic Resonance Angiography; ICAS = Intracranial Artery Stenosis; DAPT = Dual Antiplatelet Therapy; SAPT = Single Antiplatelet Therapy; NIHSS = National Institutes of Health Stroke Scale; mRS = Modified Ranking Score. CSPS.com=Cilostazol Stroke Prevention Study Combination; HR: Hazard Ratio, 95%CI: 95% Confidence Interval, RR: Risk Ratio

Risk of bias assessment

The included studies were evaluated for possible bias using the RCT-specific RoB2 assessment. Fig 2 illustrates the outcomes of the risk assessments conducted across the studies included. Among the eight studies analyzed, seven raised certain concerns, while one exhibited a high risk of bias. The studies were all open-labeled, meaning both participants and study personnel were aware of the treatment, so the results should be interpreted with caution.

Outcome of efficacy analysis

In our efficacy analysis examining the recurrence of ischemic stroke, we evaluated four studies.[14–17] Among these, only the CSPS.com trial employed a cilostazol combination therapy and monotherapy with either clopidogrel or aspirin;[17] the other studies exclusively used aspirin.[14–16] Fig 3A shows that the cilostazol combination treatment significantly reduced the relative risk of recurrent stroke compared to SAPT treatment (RR: 0.49; 95% CI: 0.32–0.71; p: 0.0001), with no significant heterogeneity observed (I^2=0.0%). Additionally, we combined estimates of the incidence of recurrent ischemic stroke into HRs and 95%CIs from two studies. Fig 3B shows that the pooled event rate estimates (HR: 0.48; 95% CI: 0.32–0.74; p: 0.0008; I^2=0%) showed a similar magnitude of the cilostazol combination's positive effect.

Outcome of safety analysis

The pooled analyses aimed to assess the safety of cilostazol DAPT compared to SAPT. Fig 4A shows that neither significant heterogeneity nor significant differences in hemorrhagic adverse events were found between the two groups (RR: 0.98; 95% CI: 0.71-1.36; p: 0.91; I^2=0.0%). Fig 4B illustrates the significantly high heterogeneity (I2: 80%) and lack of significant differences between the two groups when acute neurological deterioration occurred within 14 days of treatment, as indicated by an increase in the NIHSS score (RR: 0.55, 95%CI: 0.11-2.77, p:0.47).

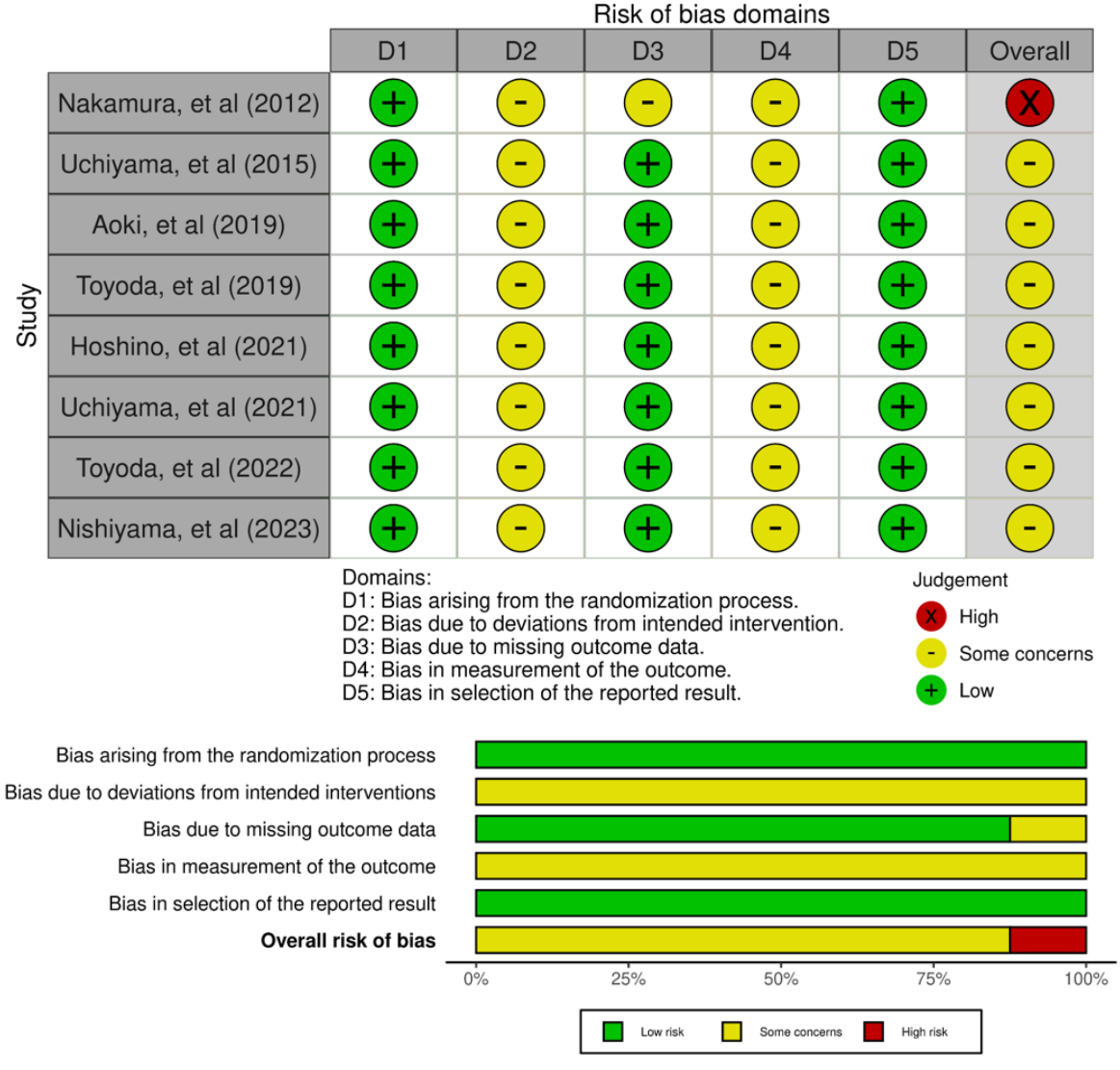

Fig 2. Assessment of bias risk in included studies utilizing the cochrane risk of bias 2 tool.

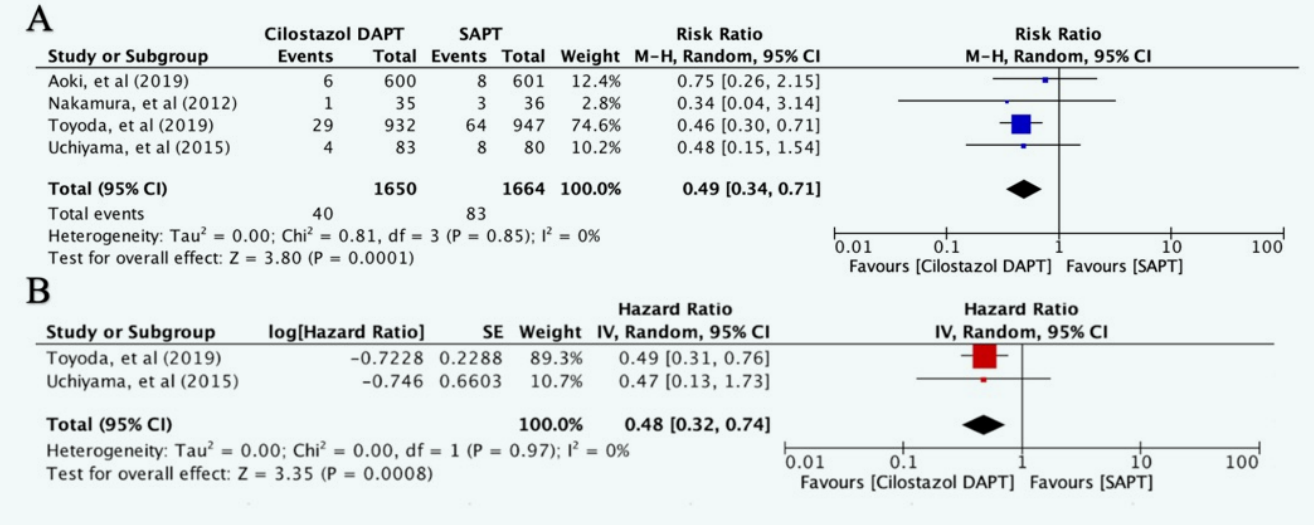

Fig 3. Meta-analysis forest plots: (A) Pooled RR of recurrent ischemic stroke; (B) Pooled HR of recurrent ischemic stroke.

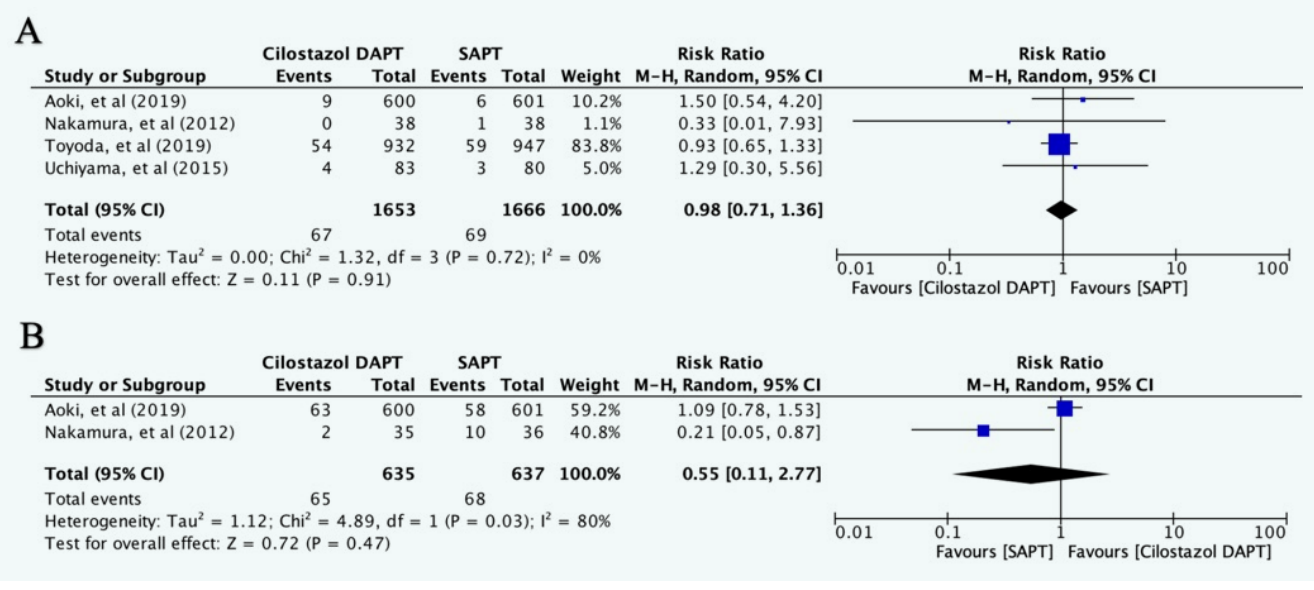

Fig 4. Meta-analysis forest plots: (A) Any hemorrhagic adverse events; (B) Acute neurological deterioration (NIHSS score increase) within 14 days of drug administration.

DISCUSSION

We found that dual antiplatelet therapy with cilostazol significantly reduced the incidence of recurrent ischemic strokes in our meta-analysis comparing the safety and efficacy of cilostazol in combination therapy to monotherapy with aspirin or clopidogrel. Importantly, this approach did not elevate the risk of any hemorrhagic complications or lead to acute neurological deterioration.

For our qualitative analysis, we also included several sub-analysis studies from the clinical investigation of cilostazol for stroke prevention, known as the CSPS combination trial. The CSPS combination trial revealed that DAPT incorporating cilostazol significantly lowers the probability of recurrent ischemic stroke in comparison to SAPT. In this multicenter, randomized controlled study, cilostazol's safety and efficacy in combination with either clopidogrel or aspirin were assessed in patients who had high-risk non-cardioembolic ischemic strokes.[17] Additionally, Hoshino et al.'s CSPS sub-analysis showed that cilostazol plus clopidogrel is a more effective combination than either cilostazol alone or cilostazol plus aspirin in lowering the risk of ischemic stroke recurrence.[18] Nishiyama et al. conducted a subanalysis study on the CSPS combination trial specifically for patients with only lacunar stroke, resulting in a similar result to its core experiment.[21] A subanalysis of the CSPS.com trial by Toyoda et al. showed that DAPT with cilostazol is more effective than monotherapy in preventing recurrent noncardioembolic strokes in patients who start treatment 15 days or more after the onset of a stroke, while not raising

the risk of bleeding.[20] This suggests that a continuous DAPT strategy could be feasible after a stroke, transitioning from aspirin and clopidogrel during the acute and subacute phases to a combination of cilostazol with either aspirin or clopidogrel beginning 15 days post-stroke or later.[20] In a RCT involving 1,201 participants, Aoki et al. reported that starting cilostazol in combination with aspirin within 48 hours of stroke onset did not reduce the frequency of a composite outcome that encompassed worsening neurological function, recurrent symptomatic strokes, and transient ischemic attacks (TIAs) within 14 days. Additionally, when compared to aspirin alone, a non-significant trend ($p = 0.086$) indicated a similar incidence of hemorrhagic stroke and a higher rate of favorable modified Rankin Scale scores (0–1) at three months.[14] Consequently, additional clinical trials are required to assess the efficacy and safety of cilostazol's DAPT in comparison to standard DAPT, particularly focusing on the timing of administration.

Cilostazol is not advised for the prevention of secondary strokes in the guidelines of the European Stroke Organization. In the United States, it has received a less favorable recommendation for use in patients who have had a stroke or transient ischemic attack (TIA) associated with moderate to severe stenosis of intracranial arteries. In contrast, cilostazol is considered the primary antiplatelet agent for preventing secondary strokes in Japan and several other countries in Asia. The Japan Stroke Society's prevention guidelines recommend that cilostazol DAPT using either aspirin or clopidogrel is a valid option for patients with noncardioembolic stroke or TIA, especially those with cervical or intracranial artery stenosis or multiple vascular risk factors.[10] The CSPS and CATHARSIS trials both demonstrated that cilostazol in combination therapy is effective and safe for preventing recurrent strokes in patients with stenosis of intracranial arteries.[15,19]

There are several limitations to this review. The potential for bias due to the absence of blinding in the included RCTs significantly impacts the reliability of both efficacy and safety outcomes in this review. The open-label design introduces potential biases in outcome assessment, particularly for subjective endpoints like neurological improvement and adverse event reporting. This limitation must be considered when interpreting the results, as it may lead to overestimation of benefits or underestimation of risks associated with cilostazol-based dual antiplatelet therapy. For example, in the Nakamura et al. study, primary and secondary endpoints relied heavily on subjective NIHSS and mRS assessments, raising concerns about evaluator bias, especially for subtle improvements or marginally significant outcomes.[16] The Uchiyama et al. study on intracranial arterial stenosis patients could be influenced in the interpretation of imaging studies and assessment of stroke recurrence.[15] The study by Aoki et al., despite having a large sample size, may have been influenced by issues in assessing early neurological deterioration and reporting adverse events.[14] The Toyoda et al. CSPS.com trial, which forms the core of several included studies, may have been influenced by knowledge of treatment allocation in assessing both efficacy and safety outcomes.[17] Sub-analyses from this trial inherit this limitation, potentially affecting assessment of outcomes across different antiplatelet combinations and patient subgroups.[18–21] Seven studies raised concerns during the risk of bias assessment, while one study showed a high risk. This systemic limitation in the current evidence base for cilostazol-based dual antiplatelet therapy in stroke prevention must be considered when interpreting the findings. Future studies should use double-blind designs to reduce biases and provide stronger evidence. It is also important to standardize outcome measures and ensure objective evaluation of clinical and radiological results to improve the reliability of future research.

Another limitation of the review is its focus on East Asian populations, particularly Japanese patients, which may restrict the applicability of the findings to other Asian subpopulations due to the significant diversity across the region. Stroke epidemiology, risk factors, and healthcare systems vary substantially among Asian countries, influencing the applicability of these results. For example, stroke incidence and prevalence vary widely, with Japan and Taiwan reporting some of the highest rates, while Malaysia has notably lower rates. Similarly, the distribution of stroke subtypes differs significantly; hemorrhagic strokes are more prevalent in countries like India and Vietnam compared to East Asian nations, where ischemic strokes are more common.[3] This difference is critical, as cilostazol-based therapies are primarily targeted at ischemic strokes, potentially limiting their effectiveness in regions with a higher burden of hemorrhagic strokes.

Socioeconomic and cultural factors also play a role in affecting stroke risk and treatment responses. For instance, dietary habits, lifestyle patterns, and ongoing economic transitions differ significantly across Asian countries, further complicating the generalization of findings. While East Asian populations share some similarities, the broader Asian region encompasses considerable heterogeneity, making it difficult to apply the review's findings universally.[3] Additionally, the prevalence of stroke risk factors shows significant regional variation. Hypertension is most common in Mongolia and Pakistan,

while diabetes mellitus is more frequently observed in Papua New Guinea and India.[3] These variations in risk factor profiles could influence the outcomes of cilostazol-based treatment, as the interaction between these conditions and therapeutic efficacy may differ across populations. Furthermore, disparities in healthcare systems exacerbate these challenges. Advanced healthcare infrastructure in Japan and South Korea facilitates timely and effective treatment, while resource limitations in Nepal and Bangladesh may delay or restrict access to cilostazol-based therapies, thereby reducing their potential impact.[3]

Importantly, we have not identified any studies specifically investigating the effectiveness and safety of dual antiplatelet therapy with cilostazol in combination with aspirin or clopidogrel in Asian subpopulations other than Japan. The small number of studies included in this review also poses a challenge regarding limited statistical power, preventing us from conducting subgroup analyses to further refine outcomes related to factors such as treatment timing after stroke onset, dosage, gender, or age. Further studies are needed to evaluate cilostazol-based therapy throughout all of Asia, considering regional differences in stroke rates, risk factors, and healthcare systems to provide stronger evidence for improved treatment strategies for recurrent ischemic stroke in diverse Asian populations.

CONCLUSION

In summary, dual antiplatelet therapy that includes cilostazol has demonstrated greater effectiveness than clopidogrel or aspirin alone in preventing recurrent ischemic strokes. Additionally, this combination therapy did not significantly increase the risk of hemorrhagic complications or cause acute neurological deterioration. However, since the studies reviewed were primarily conducted in Japan, the findings may not be directly applicable to other Asian populations. Given the regional variations in stroke rates, risk factors, and healthcare systems, further clinical trials are needed to assess cilostazol-based therapy across diverse Asian populations, which would provide stronger evidence and inform more effective treatment strategies for ischemic stroke in Asia.

Data Availability Statement

The evidence for the findings in this review article comes from the primary sources mentioned. No new data was created or examined for this study.

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DECLARATION

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Conflict of Interest

There was no conflict of interest.

Registration Number of Clinical Trial

There is no clinical trial number since this study is not classified as a clinical trial or experimental study.

Author Contributions

All the authors contributed to the conceptualization, methodology, resources, writing - original draft, writing - review and editing. H.C.K, G.Y., E.I., H.K., P.V. contributed to the formal analysis, data curation and investigation. Supervision and validation were done by H.C.K., A.G. All authors have read and agreed to the final version of the manuscript.

Use of Artificial Intelligence

None

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Characteristics of Injuries in Road Traffic Accident Victims: An Autopsy Study at Srinagarind Hospital, Khon Kaen University, Thailand

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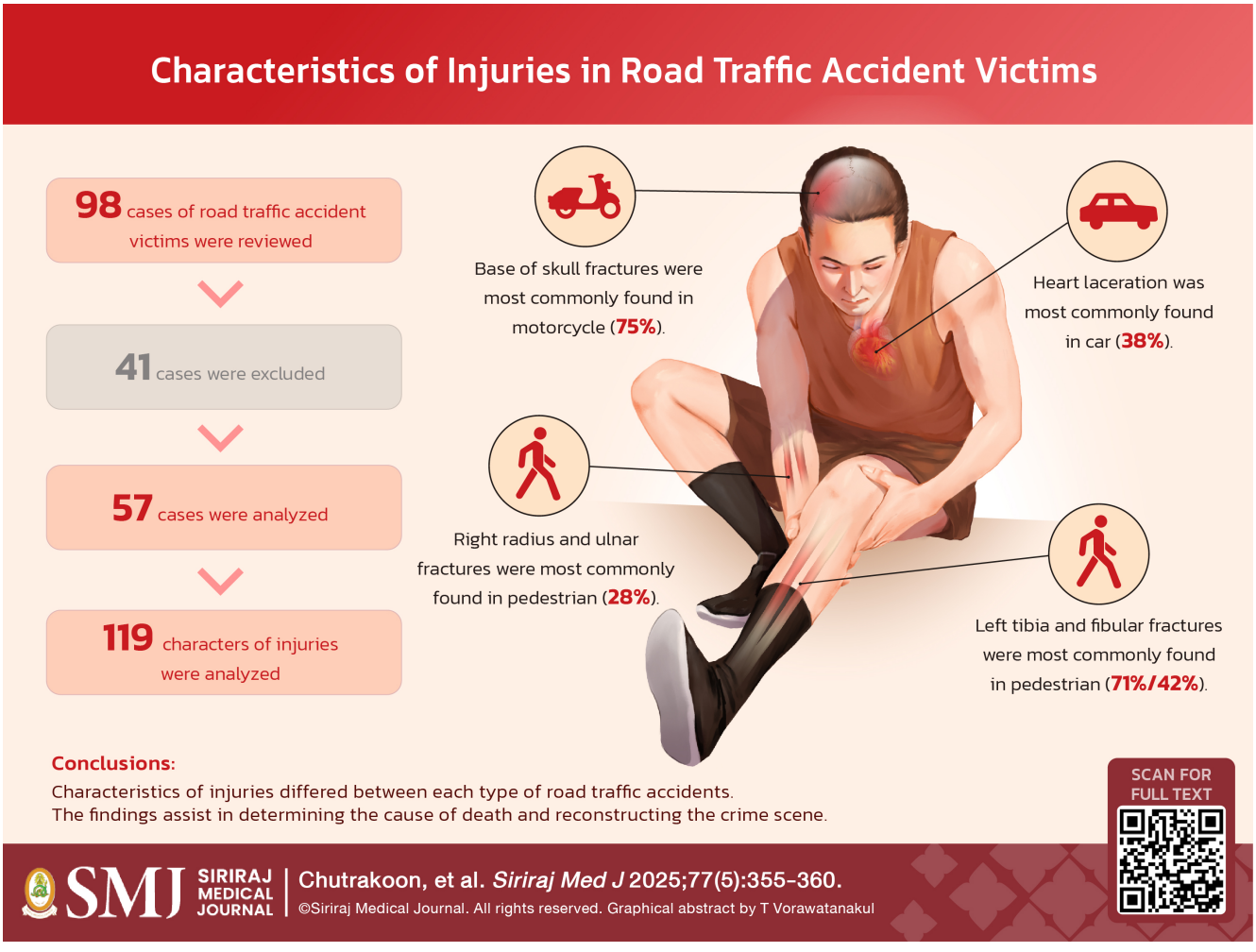

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ABSTRACT

Objective: This ambidirectional cohort study aimed to investigate injury characteristics in road traffic accident (RTA) victims based on autopsy cases at the Department of Forensic Medicine, Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Thailand.

Material and Methods: Autopsy cases from September 2022 to August 2024 were reviewed, with data collected from autopsy reports and crime scene photographs. Injury characteristics, types of RTAs, time of accidents, and victim demographics were analyzed in 57 RTA cases.

Results: The results revealed noteworthy differences in injury patterns between types of RTAs. Fractures at the skull base (Car 38%, Motorcycle 75%, Pedestrian 28%; $p < 0.01$), heart lacerations (Car 46%, Motorcycle 10%, Pedestrian 28%; $p < 0.05$), and fractures of the right radius (Car 7.7%, Motorcycle 2.7%, Pedestrian 28%; $p < 0.05$), right ulna (Car 7.7%, Motorcycle 2.7%, Pedestrian 28%; $p < 0.05$), left tibia (Car 23%, Motorcycle 8%, Pedestrian 71%; $p = 0.001$), and left fibula (Car 23%, Motorcycle 8%, Pedestrian 71%; $p < 0.05$) were associated with specific accident types.

Conclusion: This study highlights the observed differences in injury characteristics across various types of RTAs at Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Thailand. Key injuries, including fractures at the base of the skull, heart lacerations, and fractures of the right radius, right ulna, left tibia, and left fibula, were significantly associated with particular types of accidents. These results can serve as a guide for determining the causes of death, especially in RTA cases, particularly in areas lacking forensic pathologists.

Keywords: Road traffic accident; characteristic of injury; autopsy; forensic medicine; trauma (Siriraj Med J 2025; 77: 355-360)

INTRODUCTION

Road traffic accidents (RTAs) are a major public health problem due to their being a major cause of morbidity and death.[1] They account for about 2.37% of all deaths worldwide. Approximately 1.19 million people die annually from traffic accidents, with nearly 50 million individuals sustaining injuries.[2] In Thailand, injuries from RTAs have been identified as a significant public health issue, contributing to high rates of mortality, morbidity, and disability, which impact individuals, families, and society. RTAs not only affect public health but also have significant financial implications. In 2002, the economic losses from traffic crashes, injuries, disabilities, and fatalities were estimated to exceed 168 billion Baht.[3]

Since deaths resulting from RTAs are classified as unnatural, RTAs present significant challenges for forensic pathologists tasked with determining the manner and cause of death. RTAs caused by different mechanisms typically exhibit specific injury patterns and characteristics.[4] For example, head injuries and fractures are frequently observed in motorcycle accidents, while thoracic trauma may be more common in car accidents due to the forceful impact of steering wheels or dashboards.[5,6] However, most studies on the patterns and characteristics of injuries resulting from RTAs have been conducted outside of Thailand; currently, there are no reports specific to the northeastern region of Thailand. Therefore, studying the characteristics of injuries specific to RTAs in the northeastern region of Thailand is essential to establish baseline data for assessing the cause and manner of death, particularly in areas lacking specialized forensic pathologists.

The examination of injury patterns and characteristics across different types of accidents, vehicles, and participants provides valuable insights that can contribute to ongoing efforts to reduce RTA-related mortality and enhance forensic investigations in Thailand. Therefore, the present study aimed to investigate the patterns and characteristics of injuries in RTA victims through a detailed analysis of autopsy cases referred to the Department of Forensic Medicine, Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Thailand.

MATERIALS AND METHODS

Study population and study design

This ambidirectional cohort study included all RTA autopsy cases who were declared dead at the scene and referred to the Department of Forensic Medicine, Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Thailand, for autopsy from September 2022 to August 2024. Cases were excluded based on the following exclusion criteria: if they tested positive for COVID-19 using the Antigen Test Kit, presented with minimal external injuries, were completely decomposed (characterized by full skin discoloration, bloating, and the presence of purge fluid), or were suspected to be homicides.

Study data

The data for RTA cases, including age, gender, body weight, height, time and date of the accident, type of vehicles (e.g., car, motorcycle, bicycle, bus, truck, motorcycle trailer, agricultural vehicle, etc.), type of participant (driver, passenger, pedestrian), type of accident (e.g., vehicle hitting a pedestrian crossing the road, vehicle hitting a pedestrian on the footpath, vehicle hitting a fixed object, vehicle rollover, vehicle collision), type of litigant vehicles (e.g., car, motorcycle, bicycle, bus, truck, motorcycle trailer, agricultural vehicle, etc.), crime scene location, underlying diseases, and occupation, were included for statistical analysis.

The characteristics of injuries in RTA cases from autopsy reports were classified by anatomical region as follows:

Head: Abrasion wounds, contusion wounds, laceration wounds, skull fractures, maxillofacial fractures, base of skull fractures, epidural hemorrhage, subdural hemorrhage, subarachnoid hemorrhage, intraparenchymal brain hemorrhage, intraventricular hemorrhage, brain contusion, brain laceration, brainstem contusion, and brainstem laceration.

Neck: Abrasion wounds, contusion wounds, laceration wounds, neck muscle injuries, blood aspiration, upper airway injuries, esophageal injury, and cervical spine fractures or dislocation.

Chest and back: Abrasion wounds, contusion wounds, laceration wounds, chest or back muscle injuries, clavicle fractures, scapular fractures, rib fractures, thoracic spine fractures or dislocation, pneumothorax, hemothorax, hemopericardium, lung contusions, lung lacerations, heart contusions, heart lacerations, intrathoracic great vessel injuries, diaphragm injury, esophageal injury, and sternum fractures.

Abdomen: Abrasion wounds, contusion wounds, laceration wounds, abdominal muscle injuries, lumbar spine fractures or dislocation, liver injury, spleen injury, kidney injury, large intestine injury, small intestine injury, stomach injury, intraperitoneal hemorrhage, retroperitoneal hemorrhage, intra-abdominal great vessel injury, and mesentery injury.

Pelvis: Abrasion wounds, contusion wounds, laceration wounds, muscles of the hip injury, pelvis fracture, urinary bladder injury, colorectum injury, intrapelvic hemorrhage, and genital organ injury.

Right upper limb: Abrasion wounds, contusion wounds, laceration wounds, upper limb muscle injuries, humerus fracture, radius fracture, ulnar fracture, carpal bone fractures, metacarpal or phalanx fractures, vascular injury, shoulder dislocation, elbow dislocation, and wrist dislocation.

Left upper limb: Abrasion wounds, contusion wounds, laceration wounds, upper limb muscle injuries, humerus fracture, radius fracture, ulnar fracture, carpal bone fractures, metacarpal or phalanx fractures, vascular injury, shoulder dislocation, elbow dislocation, and wrist dislocation.

Right lower limb: Abrasion wounds, contusion wounds, laceration wounds, lower limb muscle injuries, femur fracture, patellar fracture, tibia fracture, fibula fracture, tarsal bone fractures, metatarsal or phalanx fractures, vascular injury, hip dislocation, knee dislocation, and ankle dislocation.

Left lower limb: Abrasion wounds, contusion wounds, laceration wounds, lower limb muscle injuries, femur fracture, patellar fracture, tibia fracture, fibula fracture, tarsal bone fractures, metatarsal or phalanx fractures, vascular injury, hip dislocation, knee dislocation, and ankle dislocation.

Ethical clearance

The experimental design and protocol were approved by The Khon Kaen University Ethics Committee for Human Research (HE661607).

Statistical analysis

The data were statistically analyzed using IBM SPSS Statistics for Windows, version 28.0.0 (SPSS, Chicago, IL, USA). The proportions of injuries and ordinal demographic data across different types of road traffic accidents were compared using the Chi-squared test. The distributions of age and body weight for each type of road traffic accident were tested using the Kolmogorov-Smirnov (K-S) test. The comparison of mean age across different types of road traffic accidents was conducted using the Kruskal-Wallis H test, as age data did not follow a normal distribution. For body weight, the comparison of means across groups was performed using one-way ANOVA.

RESULTS

Sociodemographic characteristics

A total of 98 registries from road traffic accident (RTA) victims were reviewed, with 57 cases meeting the inclusion criteria. Among these cases, 73.68% were male, and 26.32% were female. The average age of the cases was 39.11 years, and the average body weight was 67.36 kilograms.

The timing of accidents was reported for 44 out of 57 cases. A statistically significant distribution was observed ($p < 0.001$), with 45.45% of accidents occurring during Q1 (00:00–06:00), 20.45% during Q2 (06:00–12:00), 6.82% during Q3 (12:00–18:00), and 29.55% during Q4 (18:00–00:00).

Of the 57 cases, 13 involved cars, 37 involved motorcycles, and 7 involved pedestrians. Regarding participant roles, 45 were drivers, 5 were passengers, and 7 were pedestrians. Accident types included vehicle-pedestrian collisions (8 cases), vehicles striking fixed objects (11 cases), vehicle rollovers (6 cases), and vehicle collisions (30 cases). Vehicle types included 23 cars, 2 motorcycles, 11 trucks, and 1 bus.

Characteristics of injuries in RTAs

As shown in Table 1, among the 119 types of injuries recorded, six patterns were statistically significant in their association with specific types of RTAs. These included fractures at the base of the skull, heart lacerations, and fractures of the right radius, right ulna, left tibia, and left fibula. Base of skull fractures were the most common injury (75%) in motorcycle accidents. Heart lacerations were observed in 46% of cases in car accidents. Common injuries in pedestrian accidents included fractures of the right radius (28%), right ulna (28%), left tibia (71%), and left fibula (42%).

DISCUSSION

There are few publications that have demonstrated the characteristics of injuries in RTAs. This study was the first to report on the specific characteristics of injuries in RTAs in the northeastern region of Thailand. The majority of RTA cases were found in males. This distribution was similar to the previous report, which shows a higher incidence of traffic-related injuries and fatalities among men.[7] In Australia, young men have a higher incidence of crashes, with rates 1.25 to 2.07 times greater than women for various crash types.[7] This was likely due to greater exposure to risky driving behaviors and more frequent vehicle operations.[7,8] The average age of 39.11 years reflects a population segment commonly involved in RTAs due to increased mobility and exposure to road traffic.

The increased incidence of RTA cases at night aligns with the literature. For example, Akerstedt and colleagues observed a significant increase in the risk of injury in traffic accidents during the night, especially around 04:00, with an odds ratio of 5.7 for total accidents and 11.4 for fatal accidents.[9] This observation can be attributed to factors such as reduced visibility[10] driver fatigue[11] and impaired driving due to alcohol consumption.[12] Moreover, environmental factors such as poor road conditions and adverse weather also contribute significantly to the occurrence and severity of RTAs.[13]

Of the 57 cases, 13 involved cars, 37 involved motorcycles, and 7 involved pedestrians. These findings were similar to those of previous studies, which found that motorcycles represented the majority of vehicles involved in RTAs in Thailand.[14] This trend may be attributed to the high prevalence of motorcycle use as a primary mode of transportation in Thailand. In addition, significant factors influencing motorcycle crash severity in Thailand include exceeding the speed limit, non-helmet use, road surface conditions, mobile phone use, and road lighting conditions.[15,16]

Base of skull fractures were most prevalent in motorcycle accidents caused by direct head impact. This observation confirmed a report from Vietnam[17], where basilar skull fractures were found in 60.6% of

TABLE 1. Observed associations between injury types and road traffic accident categories.

Types of Injuries	Car (n = 13)	Motorcycle (n = 37)	Pedestrian (n = 7)	p-value
Base of skull fracture	5 (38.46%)	28 (75.68%)	2 (28.57%)	0.008
Heart laceration	6 (46.15%)	4 (10.81%)	2 (28.57%)	0.017
Right radius fracture	1 (7.69%)	1 (2.70%)	2 (28.57%)	0.041
Right ulnar fracture	1 (7.69%)	1 (2.70%)	2 (28.57%)	0.041
Left tibia fracture	3 (23.08%)	3 (8.11%)	5 (71.43%)	0.001
Left fibular fracture	2 (15.38%)	2 (5.41%)	3 (42.86%)	0.018

fatal motorcycle accident cases. This injury has been associated with high morbidity and mortality rates.[18] Therefore, base of skull fractures are a significant concern in motorcycle accidents.

Injury patterns in car crashes vary significantly depending on the type of collision, the position of the occupant, and the use of safety devices. In the present study, heart lacerations were common injuries found in car accidents. In frontal impact collisions, heart ruptures often occur due to collisions against the steering wheel or dashboard.[19] This finding was consistent with a study in Milan, Italy.[4] Autopsy studies reveal that cardiac ruptures can occur even without significant external injuries, highlighting the importance of thorough internal examinations in forensic investigations. In this study, heart injuries were classified into two categories, including heart contusion and heart laceration. However, a previous study reported traumatic ventricular septal defects without heart lacerations or heart contusions.[20] This finding highlights the necessity for further research to explore additional types and mechanisms of cardiac injuries to improve understanding and forensic practices.

Injuries of pedestrians in RTAs exhibit distinct patterns influenced by various factors. Our results indicated that pedestrians showed higher incidences of fractures in the right radius, ulna, left tibia, and fibula, which may suggest defensive postures during collisions. However, these fractures could also result from other mechanisms, such as energy transmission during impact or subsequent falls after the collision. A report in the U.S. demonstrated an increase in thorax and pelvis and hip injuries among pedestrians, while head injuries remained the most common.[21] The differences among each type of RTAs found in this study are consistent with findings from hospitals participating in TraumaRegister DGU, which found significant differences between pedestrians and motor vehicle occupants.[22]

There are several limitations in the present study, particularly the small sample size, which may have impacted the reliability of the results. In addition, the unavailability of injury severity score (ISS) and abbreviated injury scale (AIS) data, as all RTA cases were declared dead at the scene, restricted the ability to systematically assess injury severity and its correlation with accident outcomes. Research with larger datasets or multi-center studies could provide more robust insights into RTA trends. Moreover, further investigation into the role of environmental factors (e.g., weather conditions, road design) and driver behavior (e.g., alcohol consumption) would provide a more comprehensive understanding of the causes of accidents.

CONCLUSION

This study provides critical insights into the specific injury patterns associated with different types of RTAs in the northeastern region of Thailand. These injury patterns include skull base fractures in motorcycle accidents, heart lacerations in car crashes, and a high incidence of lower limb fractures in pedestrians, reflecting the unique impact dynamics of each accident type. These findings can guide strategies for improving road safety and reducing traffic-related fatalities. In addition, the study supports forensic investigations by identifying injury patterns specific to each vehicle type, aiding in determining the mechanism of injury and clarifying accident circumstances. These insights strengthen forensic reports and contribute to targeted road safety strategies.

Data Availability Statement

The data of this study is available upon request.

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DECLARATION

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Conflict of Interest

The authors declare that they have no conflicts of interest.

Registration Number of Clinical trial

Not applicable

Author Contributions

Conceptualization and methodology, NC, WK, TW, and WS; Investigation, NC and WS; Formal analysis, NC; Visualization and writing—original draft, NC; Writing—review and editing, WS; Supervision, WK, TW, and WS. All authors have read and agreed to the final version of the manuscript.

Use of Artificial Intelligence

This manuscript used artificial intelligence tools, including ChatGPT (OpenAI, version GPT-4) and QuillBot for language enhancement and grammar correction. These tools were applied exclusively to improve the quality of the English writing and did not influence the scientific content, analysis, or interpretation of the findings. All final decisions regarding the text were made by the authors.

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The Role of Intraprostatic Injection of Epinephrine in Reducing Perioperative Blood Loss during Transurethral Resection of the Prostate (TURP) in Patients with Benign Prostatic Hyperplasia (BPH): A Systematic Review & Meta-Analysis

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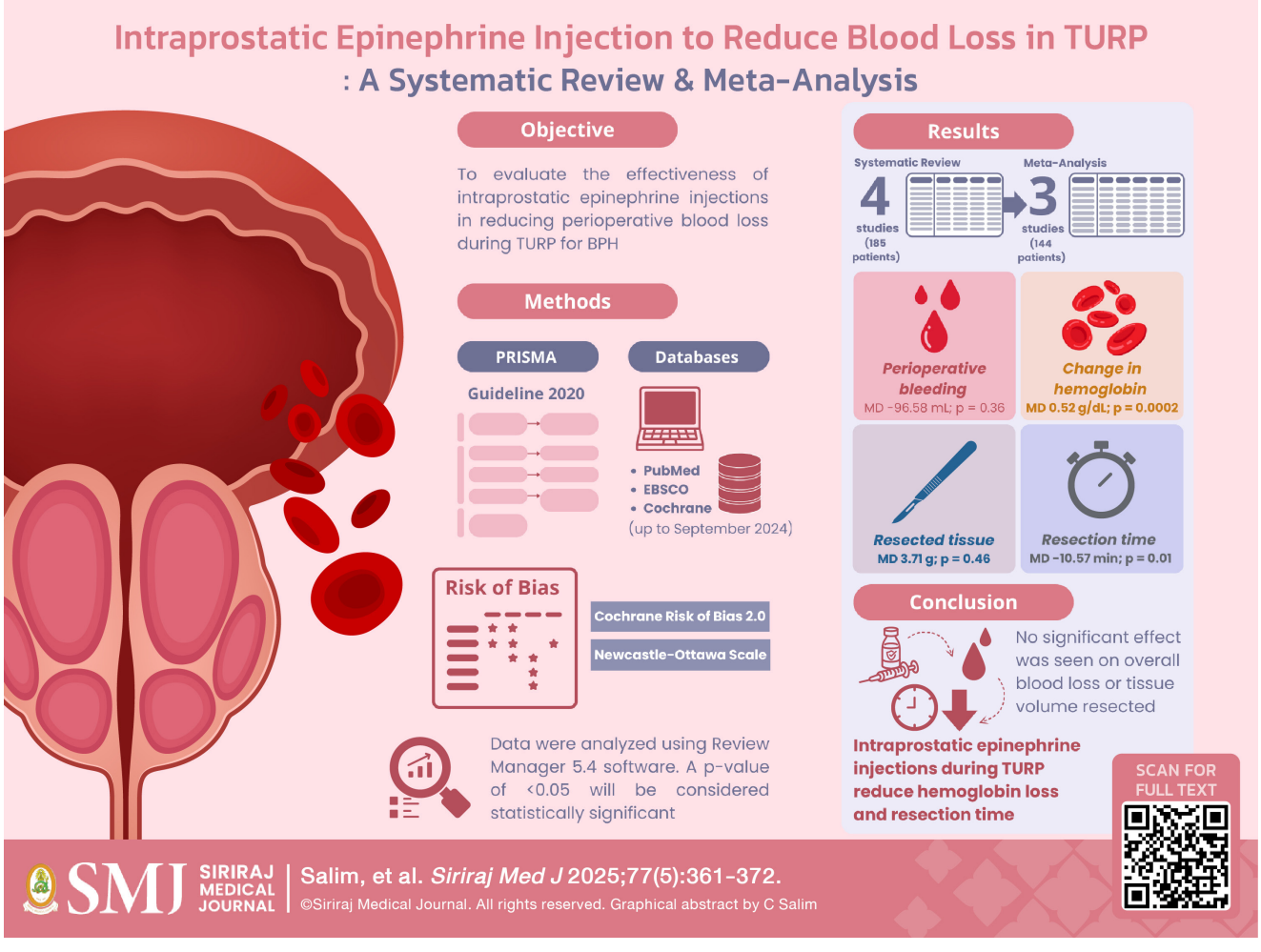

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ABSTRACT

Objective: This systematic review and meta-analysis aims to evaluate the effectiveness of intraprostatic epinephrine injections in reducing perioperative blood loss during TURP for BPH.

Materials and Methods: A systematic review and meta-analysis was conducted by searching the PubMed, EBSCO, and Cochrane databases up to September 2024. Randomized controlled trials (RCTs) and observational studies involving the use of intraprostatic epinephrine during TURP were included. The primary outcome assessed was perioperative blood loss, while secondary outcomes included hemoglobin changes, resected tissue volume, and resection time. Data analysis was performed using Review Manager 5.4 software.

Results: A total of 185 patients from three RCTs and one comparative retrospective study were included in the systematic review. Among these, 144 patients from the RCTs were included in the meta-analysis. Intraprostatic epinephrine was associated with a significant reduction in hemoglobin decline (mean difference [MD]: 0.52 g/dL, $p = 0.0002$) and shorter resection time (MD: -10.57 minutes, $p = 0.01$). However, no significant differences were observed in perioperative blood loss (MD: -96.58 mL, $p = 0.36$) or the volume of resected tissue (MD: 3.71 g, $p = 0.46$).

Conclusion: Intraprostatic epinephrine injections during TURP effectively reduce hemoglobin loss and resection time, improving surgical efficiency. However, no significant effects were observed on total perioperative blood loss or tissue volume resected. Variability in surgical techniques and patient factors likely contributed to inconsistent outcomes, underscoring the need for standardized protocols in future research.

Keywords: Benign prostatic hyperplasia; intraprostatic epinephrine; meta-analysis; perioperative blood loss; TURP
(Siriraj Med J 2025; 77: 361-372)

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a common condition in older men, significantly affecting their quality of life. Approximately 50% of men in their 50s and 60s and up to 90% of men in their 70s experience lower urinary tract symptoms (LUTS) associated with BPH.[1,2] While medical treatments, such as alpha-1-adrenoceptor antagonists, are the first-line options for managing moderate-to-severe symptoms, many patients eventually require surgical intervention, particularly those with larger prostate glands (>80 g) who do not respond adequately to medication.[3]

Transurethral resection of the prostate (TURP) has long been considered the gold standard for the surgical treatment of LUTS caused by BPH.[4] However, TURP is associated with a 15-20% complication rate, with hematuria and perioperative blood loss being among the most common complications.[5] Blood transfusion rates during TURP have been reported to reach as high as 2.9%.[6] Additionally, excessive bleeding can obstruct the surgeon's view, complicating the procedure and increasing the risk of other complications, including fluid absorption and hyponatremia, which can lead to transurethral resection (TUR) syndrome.[7]

To address these challenges, various technologies and techniques have been developed to minimize bleeding during TURP. Among these advancements is the bipolar resection technique, which reduces the risks of fluid absorption and TUR syndrome compared to the traditional monopolar method. However, evidence regarding its effectiveness in reducing bleeding remains inconsistent.[8-10]

A promising adjunctive approach for controlling bleeding during TURP is the intraprostatic injection of epinephrine, a vasoconstrictor that effectively reduces blood flow to the prostate, helping to manage perioperative blood loss.[11] This approach has been successfully utilized in other surgical fields, such as ear, nose, and throat (ENT) surgery, where epinephrine is routinely employed to minimize bleeding during tissue resection.[4]

This systematic review aims to evaluate the effectiveness of intraprostatic epinephrine injections in reducing perioperative blood loss. By synthesizing the available evidence, this review will also explore whether the use of epinephrine as a hemostatic agent can improve surgical efficiency by increasing the amount of tissue resected and reducing resection time, while minimizing the need for blood transfusion and perioperative complications, and ensuring safety compared to conventional TURP.

MATERIALS AND METHODS

Protocol registration and literature search

This systematic review and meta-analysis was registered in PROSPERO under the registration number CRD42024588452 and adhered to the PRISMA 2020 guidelines. A comprehensive literature search was conducted

across electronic databases, including PubMed, EBSCO, and Cochrane, up to September 2024. The search strategy employed a combination of MeSH terms and keywords, such as "epinephrine" OR "adrenaline" AND "transurethral resection of prostate" AND "prostatic hyperplasia" OR "benign prostatic obstruction" AND "surgical blood loss" OR "postoperative blood loss." Only studies published in English were included.

Eligibility criteria

The inclusion criteria comprised studies involving patients who underwent transurethral resection of the prostate (TURP) for benign prostatic hyperplasia (BPH) and received intraprostatic epinephrine injections to reduce perioperative blood loss. Eligible studies included randomized controlled trials (RCTs), observational studies, cohort studies, and case-control studies published in English. Studies were excluded if they lacked sufficient data, were unavailable as full texts, or were categorized as case reports, letters to the editor, or conference abstracts.

Data extraction

Data extraction was independently performed by three reviewers. Extracted information included study details (authors, publication year, country, and study design), participant characteristics (inclusion/exclusion criteria, sample size, and median/mean age), and intervention details. Outcome measures collected included perioperative blood loss, changes in hemoglobin levels, resected tissue volume, resection time, and the number of blood transfusions required. Complications, irrigation methods, prostate volume, and statistical significance of intergroup differences were also recorded. This meticulous process ensured comprehensive data collection and comparability across studies.

Quality assessment

The risk of bias in the included studies was independently assessed by four reviewers. For the three RCTs, the Cochrane Risk of Bias Tool 2.0 was utilized, evaluating five key domains: randomization process, deviations from intended interventions, incomplete outcome data, outcome measurement, and reporting bias. For the comparative retrospective study, the Newcastle-Ottawa Scale (NOS) was applied to assess the quality of non-randomized studies. This rigorous assessment ensured high methodological standards across all included studies.

Statistical analysis

Quantitative data analysis was conducted using the Cochrane Collaboration's Review Manager 5.4 software. Data reported as medians and ranges were converted into means and standard deviations (SDs) using formulas provided by Luo et al. (2018) and Wan et al. (2014).

$$\bar{X}(w) \approx \left(\frac{4}{4+n^{0.75}}\right)\frac{a+b}{2} + \left(\frac{n^{0.75}}{4+n^{0.75}}\right)m$$

$$S \approx \frac{b-a}{2\Phi^{-1}\left(\frac{n-0.375}{n+0.25}\right)}.$$

a = the minimum value, b = the maximum value, m = median, n = sample size

When data were reported as medians and interquartile ranges (IQRs), these were also converted to means and SDs. Since the study providing the IQR data explicitly mentioned that the data were skewed, we assumed that this dataset might exhibit right-skewness. Therefore, we approximated the first ($q1$) and third quartiles ($q3$) from the IQR using the following formulas:

$$q1 \approx m - \frac{IQR}{3}$$

$$q3 \approx m + \frac{2 \times IQR}{3}$$

These approximations are consistent with the general approaches in applied statistics, particularly for skewed data distributions, where the median and IQR are robust statistical measures. The formulas serve as approximations when the data are not symmetric, aiming to better estimate the quartiles by adjusting for skewness. The values of $q1$ and $q3$ were then substituted into the formula below to estimate the mean:

$$\bar{X}(w) \approx \left(0.7 + \frac{0.39}{n}\right)\frac{q_1+q_3}{2} + \left(0.3 - \frac{0.39}{n}\right)m$$

The SD was estimated using the formula provided by Wan et al. (2014):

$$S \approx \frac{q_3 - q_1}{2\Phi^{-1}\left(\frac{0.75n-0.125}{n+0.25}\right)}.$$

**$q1$ = the first quartile, $q3$ = the third quartile, m = median, IQR = interquartile range, n = sample size

Outcomes were analyzed by calculating mean differences (MDs) with 95% confidence intervals (CIs). A p-value of <0.05 was considered statistically significant. Heterogeneity was assessed using I^2 statistics and categorized as high ($I^2 > 50\%$), moderate ($26\% < I^2 \leq 50\%$), or low ($I^2 \leq 26\%$).

RESULTS

Literature search

Fig 1 illustrates the detailed flow of study selection, outlining the exclusion process throughout the review. A total of 94 studies were identified through searches across three databases. After removing duplicates, 60 unique records were screened, and 19 were further assessed for eligibility. Ultimately, four full-text from three countries (Sweden, Mexico, and Pakistan) were included in the systematic review, all of which were published in English. Of these, three studies were incorporated into the meta-analysis.

Data extraction

This systematic review included three randomized controlled trials (RCTs) and one comparative retrospective study, encompassing a total of 185 participants. The intervention involved intraprostatic epinephrine injections during TURP, compared to control groups undergoing TURP without epinephrine.

Stenmark et al. observed a 40% reduction in bleeding per resected weight, with no significant differences in overall bleeding, hemoglobin levels, resected tissue volume, or complications. Lira-Dale et al. reported significantly lower blood loss in the epinephrine group, although resection time and resected tissue volume were similar between the groups. Zohaib et al. found reduced blood loss, shorter operative times, and increased tissue resection in the epinephrine group. Schelin demonstrated a 70% reduction in perioperative and total blood loss with minimal impact on operative time and no adverse events attributed to epinephrine use.

Risk of bias assessment

Fig 2 provides the risk of bias assessment for the included RCTs. Two studies demonstrated a low risk of bias, while one study had some concerns.

The comparative retrospective study's risk of bias assessment, conducted using Newcastle-Ottawa Scale (NOS), indicated a low risk of bias (Table 2).

Meta analysis

Data conversion

Table 3 presents the mean and standard deviation (SD) values for the analyzed variables. These values were derived from various reported statistics, including

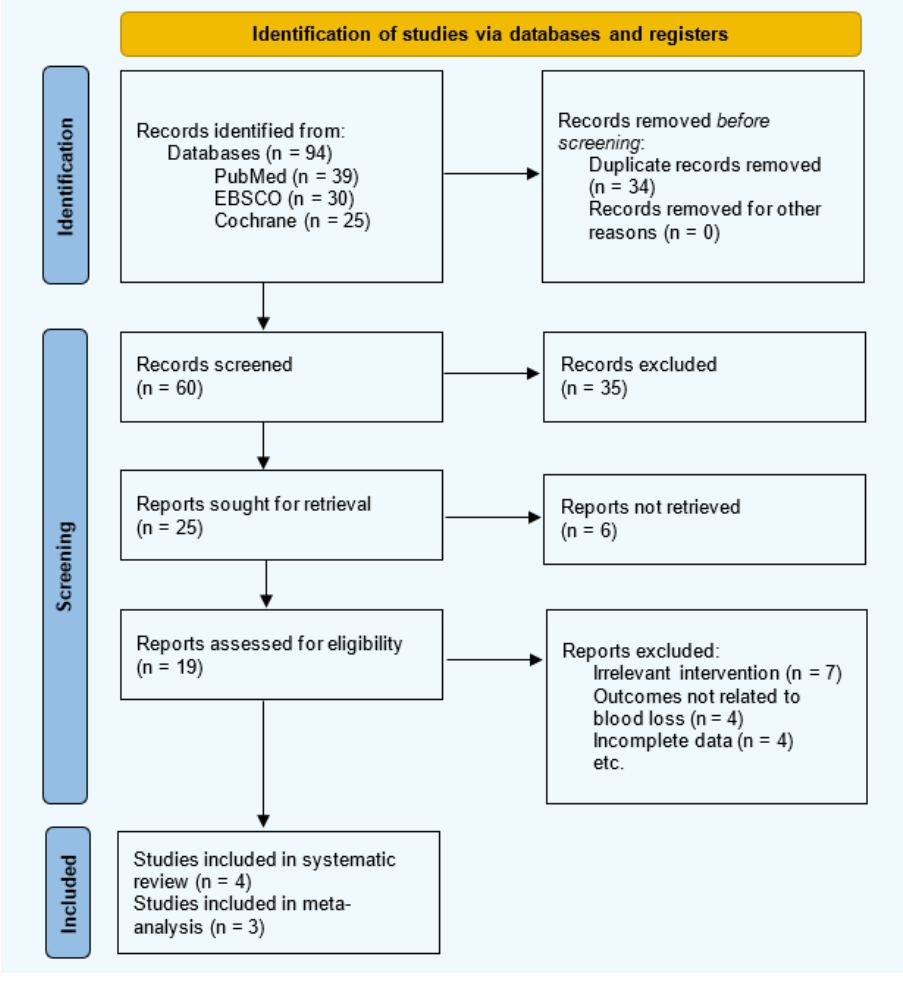

Fig 1. PRISMA flowchart 2020 depicting the selection process of included studies.

TABLE 1. Characteristics of the included studies and outcomes of the intervention using intraprostatic epinephrine during TURP compared to controls.

No	Author (year)	Country	Study design	Inclusion criteria	Exclusion criteria	Sample size
1	Stenmark F, et al. (2023)	Sweden	RCT	Patients with verified prostate enlargement deemed suitable for TURP, TRUS >30 mL, IPSS >12, Qmax <13 mL/s	Known intolerance of mepivacaine or adrenaline or patients unfit to tolerate TURP (e.g. severe bleeding disorders or high ASA score)	81
2	Lira-Dale A, et al. (2012)	Mexico	RCT	Patients with diagnosis of obstructive BPH that were surgery candidates and patients programmed for TURP	• Past history of high blood pressure • Heart disease • Blood dyscrasia • Anticoagulant medications • Treatment in the last 3 months with 5-ARIs • Genitourinary cancer • Urinary tract lithiasis • Urological surgery within the last 3 months	23
3	Zohaib A, et al. (2023)	Pakistan	RCT	All symptomatic males with BPH requiring TURP	• Abnormally high blood pressures • Ischemic heart disease • Blood dyscrasia • Urinary lithiasis • Anticoagulant medications • Any urological surgical intervention in the previous 3 months	40
4	Schelin S (2009)	Sweden	Comparative retrospective study	Consecutive and unselected TURP patients, compared with the previous consecutive regular TURP patients, performed by the same doctor. Indication for surgery: outflow obstruction by prostate enlargement due to BPH	N/A	41

TABLE 1. Characteristics of the included studies and outcomes of the intervention using intraprostatic epinephrine during TURP compared to controls (Continued).

No	Group	Irrigation	Sample	Age (years)	Prostate volume (g)	Perioperative bleeding (mL)	*p*
1	**Control:** regular TURP	Mannitol + ethanol	41	68 (54-90)[a]	50.0 (31.0-98.0)[a]	100 (15-595)[a]	0.247
	Case: TURP with intraprostatic injections of mepivacaine/adrenaline - 40 mL of Carbocaine-Adrenaline 0.5% (= 200 mg of mepivacaine and 200 mcg of epinephrine) - Infiltrating injections using the Schelin catheter to 8, 11, 1, 4 o'clock positions (10 mL at each)		40	73 (57-90)[a]	51.0 (35.0-90.0)[a]	90 (10-700)[a]	
2	**Control:** 20 mL of saline solution	Sterile water	10	62.2 ± 9.75[b]	65.08 ± 13.4[b]	336.63 ± 185.6[b]	<0.05
	Case: intraprostatic epinephrine, 200 mcg in 20 mL of saline solution - 10 mL was applied at the prostatic floor level, 5 mL in each lateral lobe (total 20 mL) - Williams endoscopic needle		13	66.23 ± 9.89[b]	68.9 ± 16.1[b]	127.48 ± 77[b]	
3	**Control:** 20 mL of 0.9% normal saline injection	Not described	20	65.65 ± 7.43[b]	64.00, 21[c]	NA	NA
	Case: intraprostatic epinephrine injection, 200 mcg in 20 mL normal saline - 10 mL was injected into the median lobe, 5 mL in both lateral lobes (total 20 mL) - 20G metal needle		20	66.30 ± 9.24[b]	68.00, 15[c]	NA	
4	**Control:** former, regular, and consecutive TURP	Mannitol + alcohol	30	NA	NA	354 (67-1500)[d]	NA
	Case: TURP with intraprostatic injections of mepivacaine epinephrine (as in study 1)		11	NA	NA	108 (<20-302)[d]	

a = median (range), b = mean ± standard deviation (SD), c = median with interquartile range (IQR), d = mean (range)

TABLE 1. Characteristics of the included studies and outcomes of the intervention using intraprostatic epinephrine during TURP compared to controls (Continued).

No	Group	Change in hemoglobin (g/dL)	*p*	Bleeding per resected weight (mL/g)	*p*	Resected tissue (g)	*p*	Resection time	*p*
1	Control Case	– 1.1 (–2.7-1.1)[a] – 0.6 (–2.1-0.8)[a]	0.254	5.2 (0.4-31.4)[a] 3.5 (0.4-17.6)[a]	0.030	19 (8-69)[a] 25 (10-60)[a]	0.067	NA NA	NA
2	Control Case	NA NA	NA	NA NA	NA	26.2 ± 23.6[b] 14 ± 8.2[b]	not reported (no statistically significant differences)	45.1 ± 21.1[b] (min) 40.92 ± 20.3[b] (min)	not reported (no statistically significant differences)
3	Control Case	– 1.87 ± 1.04[b] – 1.15 ± 0.42[b]	0.007	NA NA	NA	30.00, 12[c] 41.00, 18[c]	0.017	42.50, 19[c] (min) 30.00, 19[c] (min)	0.024
4	Control Case	NA NA	NA	15.4 (5.6-44.4)[d] 4.8 (0-8.3)[d]	NA	23.6 (5-54)[d] 21.3 (15-37)[d]	NA	2.2 (1-5)[d] (min/g) 2.0 (1.5-3.0)[d] (min/g)	NA

a = median (range), b = mean ± standard deviation (SD), c = median with interquartile range (IQR), d = mean (range)

No	Group	Transfusion (n)	*p*	Complications	*p*
1	**Control**	0	NA	4 - 1 resorbed minor volumes of irrigation fluid during surgery (no TUR syndrome) - 1 resorbed minor volumes of irrigation fluid during surgery (no TUR syndrome) + urinary tract infection - 1 urinary tract infection only - 1 pancreatitis and prolonged bladder irrigation (>48 h) which extended his hospital stay	0.349
	Case	0		1 (an episode of hypertension and bradycardia during surgery that resolved spontaneously)	
2	**Control**	NA	NA	0	NA
	Case	NA		1 (transitory high blood pressure up to 190/110 mmHg that was managed with oral nifedipine, resulting in remission at 30 min	
3	**Control**	6	0.010	NA	NA
	Case	0		NA	
4	**Control**	NA	NA	1	NA
	Case	NA		0	

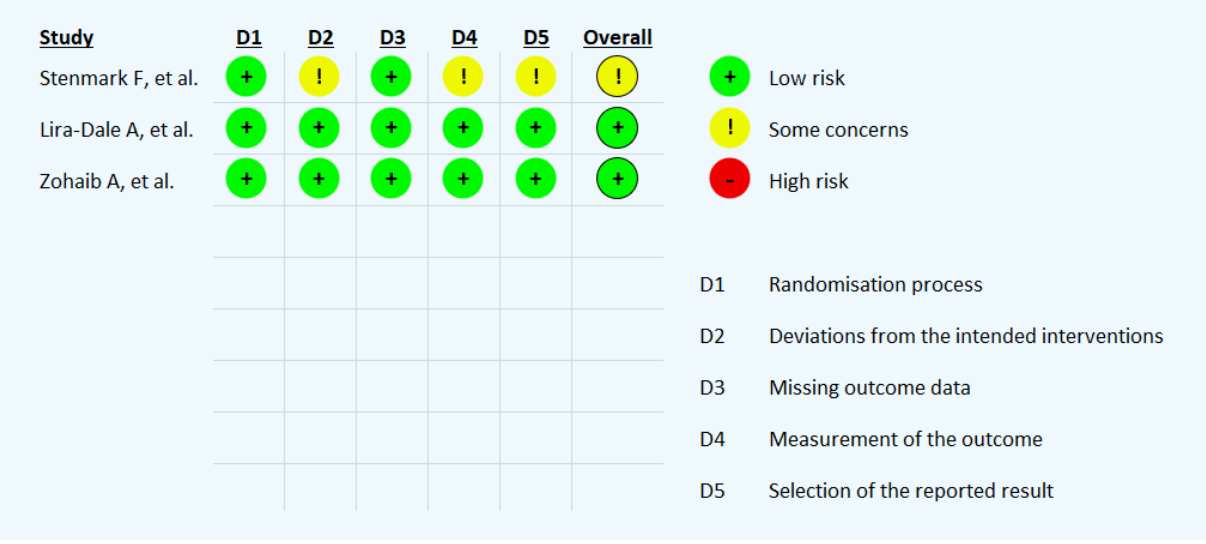

Fig 2. Risk of bias assessment for three studies using the Cochrane Risk of Bias Tool (RoB 2).

TABLE 2. Risk of bias assessment for the comparative retrospective study using the Newcastle-Ottawa Scale (NOS)

Study	Selection				Comparability	Outcome			Total Score
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome of interest not present at start	Comparability of cohorts	Assessment of outcome	Follow-up long enough	Adequacy of follow-up	
Schelin S	1	1	1	1	1	1	1	1	8/9

TABLE 3. Mean ± SD values comparing intraprostatic epinephrine (case) versus control groups after data conversion.

No	Group	Sample	Perioperative bleeding (mL) (Mean ± SD)	Change in hemoglobin (g/dL) (Mean ± SD)	Resected tissue (g) (Mean ± SD)	Resection time (min) (Mean ± SD)
1	**Control**	41	140.588 ± 133.880	– 1.040 ± 0.877	22.860 ± 14.080	NA
	Case	40	143.251 ± 159.992	– 0.61 ± 0.672	27.860 ± 11.593	NA
2	**Control**	10	336.63 ± 185.6	NA	26.2 ± 23.6	45.1 ± 21.1
	Case	13	127.48 ± 77	NA	14 ± 8.2	40.92 ± 20.3
3	**Control**	20	NA	– 1.87 ± 1.04	31.439 ± 9.574	44.778 ± 15.159
	Case	20	NA	– 1.15 ± 0.42	43.158 ± 14.361	32.278 ± 15.159

median with range, median with interquartile range (IQR), and mean with range. Data conversions followed established statistical methods outlined in the Materials and Methods section, ensuring consistency across studies for inclusion in the meta-analysis.

Perioperative bleeding

Two studies compared perioperative bleeding between intraprostatic epinephrine and control groups. Although the epinephrine group exhibited lower perioperative bleeding (MD -96.58; 95% CI, -303.74 to 110.58), the difference was not statistically significant (p = 0.36). High heterogeneity was observed (I^2 = 89%). A detailed analysis of perioperative bleeding is shown in Fig 3A, with the funnel plots for bias illustrated in Fig 4A.

Change in hemoglobin

Two studies evaluated changes in hemoglobin levels between the two groups. The epinephrine group showed a significantly smaller reduction in hemoglobin compared to the control group, with a mean difference of 0.52 g/dL (95% CI, 0.24 to 0.80; p = 0.0002). No heterogeneity was detected (I^2 = 0%). A detailed analysis of hemoglobin changes is presented in Fig 3B, with corresponding funnel plots in Fig 4B.

Resected tissue

Three studies assessed the amount of resected tissue. The pooled analysis indicated a mean difference of 3.71 g (95% CI, -6.06 to 13.48), slightly favoring the epinephrine group, though this difference was not statistically significant (p = 0.46). Substantial heterogeneity was noted (I^2 = 74%). Detailed results are shown in Fig 3C, with funnel plots for bias in Fig 4C.

Resection time

Two studies analyzed resection time during TURP procedures. The epinephrine group exhibited a significantly shorter resection time, with a mean difference of -10.57 minutes (95% CI, -18.81 to -2.34; p = 0.01). No heterogeneity was observed (I^2 = 0%), indicating consistency in findings. The detailed analysis of resection time is illustrated in Fig 3D, with the funnel plot presented in Fig 4D.

DISCUSSION

This meta-analysis provides valuable insights into the use of intraprostatic epinephrine during transurethral resection of the prostate (TURP). While the pooled analysis reveals a significant advantage for the epinephrine group in terms of changes in hemoglobin and resection time, no statistically significant differences were observed

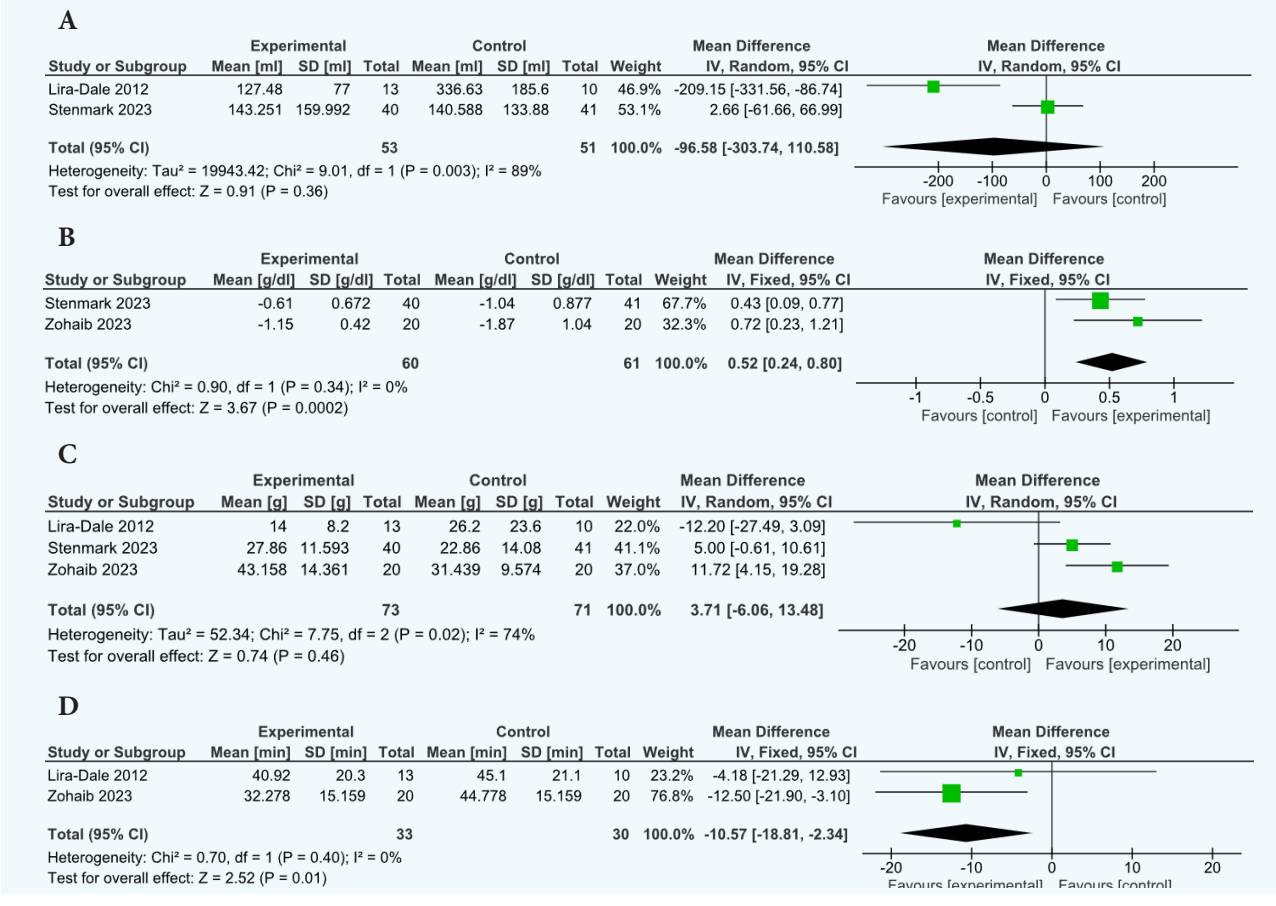

Fig 3. Forest plot comparing intraprostatic epinephrine during TURP versus control. A: Perioperative bleeding; B: Change in hemoglobin; C: Resected tissue; D: Resection time.

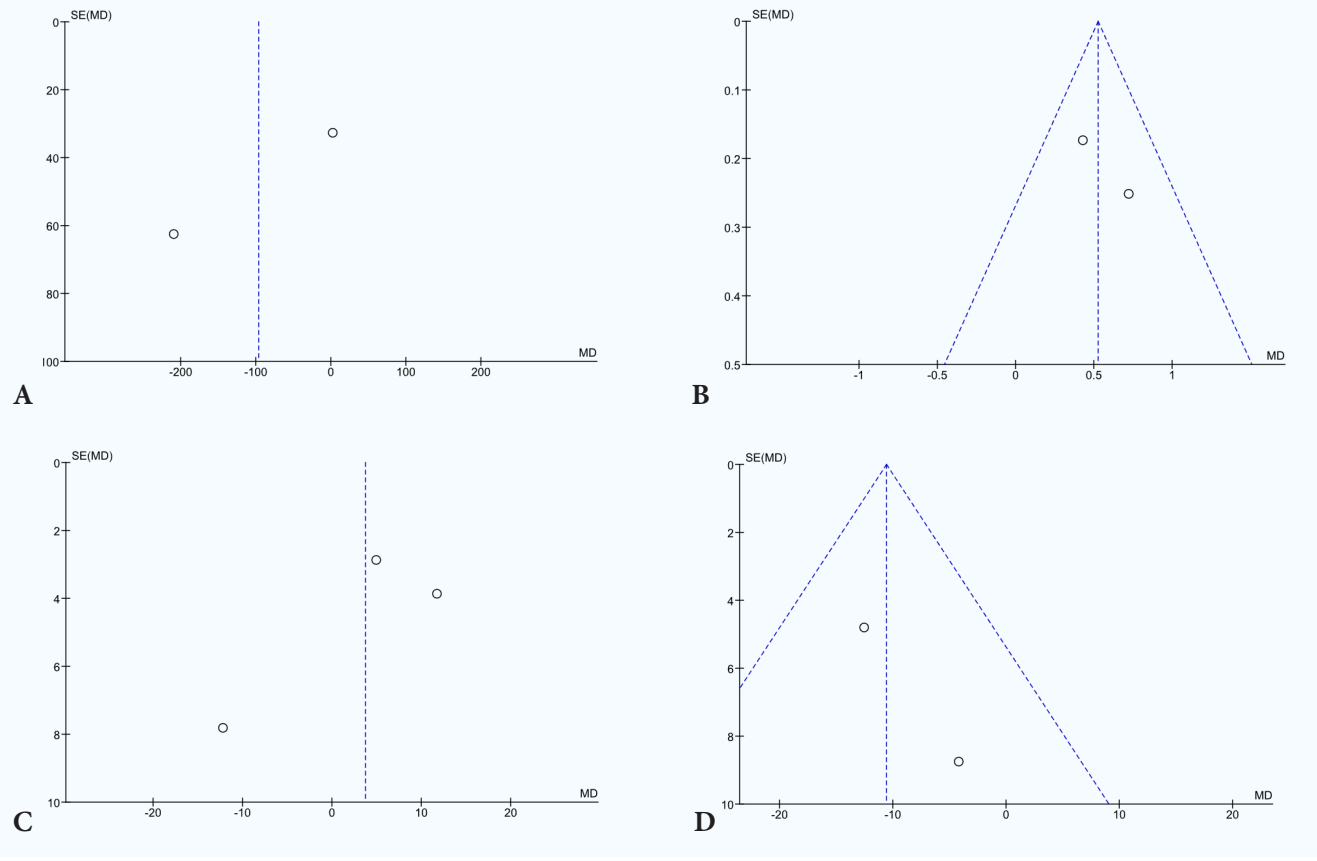

Fig 4. Funnel plot comparing intraprostatic epinephrine during TURP versus control. A: Perioperative bleeding; B: Change in hemoglobin; C: Resected tissue; D: Resection time.

between the epinephrine and control groups regarding perioperative bleeding or the amount of resected tissue in grams.

The significant reduction in hemoglobin decline in the epinephrine group suggests that intraprostatic epinephrine effectively minimizes hemoglobin loss during TURP. This reduction may lower the risk of postoperative anemia and decrease the need for blood transfusions. Additionally, the shorter resection time observed in the epinephrine group may reflect enhanced surgical efficiency, potentially due to improved visibility and reduced coagulation requirements, as suggested by Schelin et al.[4]

However, the lack of significant differences in perioperative bleeding and resected tissue volume warrants further discussion. High heterogeneity among the included studies likely contributed to variability in these outcomes. One plausible explanation is the variation in surgical experience across studies. Inexperienced urologists typically have a bleeding rate of 25-30 mL per gram of resected tissue, compared to approximately 15 mL/g for experienced urologists.[12,13] The studies by Stenmark et al. and Zohaib et al. involved multiple surgeons with varying preferences, potentially influencing outcomes.[3,7] In contrast, Lira-Dale et al. did not provide details on surgeon experience, further complicating the interpretation of findings.[14]

Moreover, the inclusion of patients taking medications such as 5-alpha reductase inhibitors (5-ARIs) or nonsteroidal anti-inflammatory drugs (NSAIDs) may have confounded the results. These medications are known to influence bleeding risk. For instance, 5-ARIs reduce prostate size and vascular density, which might independently decrease bleeding.[15] NSAIDs, on the other hand, impair platelet function and could exacerbate perioperative bleeding, skewing outcomes.[16]

The lack of correlation between perioperative bleeding and changes in hemoglobin may also be attributed to perioperative fluid irrigation and intraoperative intravenous fluid administration, which dilute blood and mask immediate hemoglobin changes. Hahn et al. have described how hemodilution and fluid redistribution complicate the assessment of blood loss based on hemoglobin levels.[17] Additionally, the timing of postoperative hemoglobin measurement may obscure the relationship between blood loss and hemoglobin changes. Blandy and Notley

emphasized that compensatory mechanisms during surgery further delay hemoglobin changes.[12]

Furthermore, Tantanate's review of bleeding time tests underscores how preanalytical variables, such as patients' hematological status and test methods, can affect bleeding assessments, highlighting the importance of standardized diagnostic approaches to reduce variability.[18] The variability in perioperative bleeding during TURP highlights the challenges in standardizing hemostatic interventions. Advanced diagnostic tools like thromboelastography (TEG) and rotational thromboelastometry (ROTEM) offer more accurate coagulation assessments. Wannatoop et al.'s pilot study showed that these tools enable goal-directed therapy based on real-time parameters, which could improve bleeding management in variable settings like TURP. Integrating these methods into TURP protocols may reduce outcome inconsistencies and enhance patient care.

The lack of correlation between resected tissue and resection time can be explained by variability in surgical techniques and patient-specific factors. Surgeon experience greatly influences resection efficiency, with experienced surgeons often able to remove more tissue in less time.[12] Prostate characteristics such as size, density, and vascularity also affect resection difficulty. Larger or more vascular prostates may require additional time for resection regardless of the tissue volume. Aus et al. highlighted that prostate morphology significantly impacts the relationship between resected weight, blood loss, and operative time.[13]

Differences in injection techniques across studies may also have influenced outcomes. Stenmark et al. and Schelin used the Schelin catheter for epinephrine delivery, injecting into all four quadrants of the prostate for consistent distribution.[4,7] In contrast, Lira-Dale employed a Williams endoscopic needle, delivering 10 mL at the prostatic floor and 5 mL into each lateral lobe.[14] Zohaib utilized a 20G metal needle, administering 10 mL to the median lobe and 5 mL to both lateral lobes.[3] Although all studies used a fixed dose of 200 mcg of epinephrine, these differences in technique and injection sites likely impacted the hemostatic effect.

These limitations underscore the need for more rigorous study designs and standardized protocols. Future research should control for confounding factors, such as preoperative medication use, and provide detailed information on surgeon experience and technique to improve the consistency and applicability of outcomes. Additionally, the fixed epinephrine dose of 200 mcg warrants future investigation to determine whether dose adjustments based on prostate volume could enhance treatment efficacy, particularly in patients with larger glands.

In terms of safety, none of the included studies reported significant adverse events associated with epinephrine use, suggesting that the intervention is both effective and safe for managing perioperative bleeding in TURP. Nonetheless, larger studies are necessary to confirm these findings and explore the long-term effects of intraprostatic epinephrine in a broader TURP patient population.

CONCLUSION

This systematic review and meta-analysis demonstrates that the use of intraprostatic epinephrine during TURP significantly reduces hemoglobin decline and resection time, contributing to improving surgical efficiency. However, it does not significantly decrease perioperative bleeding or the volume of resected tissue. The high variability among studies highlights the need for standardized techniques and better control of confounding factors to ensure consistency in outcomes. The safety profile of intraprostatic epinephrine is favorable, with no significant adverse events reported. Future research should focus on conducting larger, well-designed studies to confirm these findings and optimize the use of intraprostatic epinephrine in TURP.

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request. All data extracted for the systematic review and meta-analysis were obtained from previously published studies, which are cited accordingly in the reference list.

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DECLARATION

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None.

Conflict of Interest

None.

Registration Number of Clinical Trial

This systematic review and meta-analysis was registered with the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD42024588452.

Author Contributions

Conceptualization and methodology, C.S., and N.S. ; Selection and data extraction, C.S., N.S., and A.R. ; Formal analysis, C.S., W.A., and R.H. ; Visualization and writing – original draft, C.S., A.R., W.A., and R.H. ; Writing – review and editing, C.S., N.S., A.R., R.H., W.A. ; Supervision, E.M. All authors have read and agreed to the final version of the manuscript.

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