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Challenge Journal of PERIOPERATIVE MEDICINE

Research Article

The effectiveness of M-TAPA on pain management and quality of recovery after cesarean section: A prospective randomized controlled study

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ABSTRACT

Objective: Moderate-to-severe pain is a common complaint after cesarean section (C/S) and may adversely affect the recovery and well-being of both the mother and the newborn. This prospective randomized controlled trial aimed to determine whether ultrasound-guided modified thoracoabdominal nerve block via the perichondral approach (M-TAPA) improves postoperative analgesia and quality of recovery after cesarean section.

Methods: This single-center study included pregnant women scheduled for elective cesarean section, beyond the 37th week of gestation, with American Society of Anesthesiologists (ASA) physical status II. Participants were randomly allocated to the M-TAPA group or the control group. Postoperative pain was assessed using the numeric rating scale (NRS), and quality of recovery was assessed using the 15-item Quality of Recovery Scale (QoR-15). Primary and secondary outcomes were statistically compared between groups.

Results: Patients who received M-TAPA showed significantly lower pain scores than the control group at rest and with movement at postoperative hours 2, 4, 8, and 16 ($p < 0.05$); however, NRS values at postoperative hour 24 were similar between groups. Opioid consumption was similarly reduced, and QoR-15 scores were higher in the M-TAPA arm compared with the control group ($p = 0.001$).

Conclusion: M-TAPA provides effective analgesic management after cesarean section. M-TAPA is important for supporting recovery and reducing opioid requirements, thereby improving outcomes in women undergoing cesarean section.

Trial Registration: The study was registered at ClinicalTrials.gov (ID: NCT06078475).

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1. Introduction

Cesarean section (C/S) is one of the most common delivery methods worldwide. Approximately one fifth of all births worldwide are performed in this way [1]. A substantial proportion of women experience moderate-to-severe pain after the procedure. This pain prolongs the recovery process and delays the mother's return to daily activities. It may also weaken mother-infant bonding,

complicate breastfeeding, and adversely affect the mother's psychological state [2,3].

Acute pain after surgery develops in response to operative tissue damage and the accompanying inflammatory process, gradually diminishing as tissues heal. When this pain is inadequately treated, the likelihood of hyperalgesia and persistent pain increases [4]. Effective perioperative care therefore relies on a patient-specific multimodal plan [5]. Such regimens typically combine

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opioids with nonsteroidal anti-inflammatory drugs. However, opioids whether administered systemically or neuraxially can cause undesirable effects even at standard doses, including respiratory depression, nausea, vomiting, sedation, pruritus, and opioid-induced hyperalgesia. Various alternative approaches, including interfascial plane blocks, have been adopted to reduce these opioid-related complications.

The perichondral approach to thoracoabdominal nerve block (TAPA), a relatively new interfascial plane technique, produces analgesic coverage over the anterolateral thoracoabdominal wall corresponding to the T5–T12 dermatomal distribution [6]. It was later adapted into a single-injection form and termed M-TAPA; this method has been found effective in numerous minor and major surgeries [7–11]. However, to date no randomized trial has evaluated the efficacy of M-TAPA in postoperative pain control after cesarean section.

Strategies aimed at improving postoperative recovery generally focus on alleviating pain, encouraging early oral intake and mobilization, minimizing complications, and shortening hospital stay. Their effectiveness has traditionally been assessed using concrete clinical outcomes, particularly complication rates and length of hospital stay. However, these metrics do not reflect how patients personally perceive their recovery or experience changes in their well-being. As a result, valid, reliable, patient-centered tools for assessing recovery have become necessary. The Quality of Recovery-15 (QoR-15) questionnaire offers a concise and practical way of capturing recovery from the patient's own perspective. With robust psychometric properties such as strong internal consistency, split-half reliability, and test-retest reproducibility, it serves as a dependable tool that allows clinicians to identify clinically relevant changes in recovery status. These properties have made QoR-15 a sensitive and evaluative endpoint applicable in both routine practice and research studies. Because it takes only about four minutes to complete, this tool encourages patient cooperation and consistently achieves high response and completion rates. Its widespread adoption among patients and practitioners across various healthcare settings further reinforces its real-world usefulness. Scores are consistently lower in patients who develop complications, show an inverse relationship with operative time and length of hospital stay, and have been documented to correlate positively with the patient's own global VAS rating of recovery [12].

The aim of this study was to examine the analgesic performance of ultrasound-guided M-TAPA after cesarean section. Compared with standard care, we hypothesized that ultrasound-guided M-TAPA would reduce postoperative pain scores and opioid consumption and improve quality of recovery after cesarean section. The primary endpoint was the comparison of QoR-15 scores between the M-TAPA and control groups at postoperative hour 24, which served as the time point underlying the sample size calculation. Secondary endpoints were postoperative pain scores at rest and with movement, postoperative opioid consumption, and opioid-related side effects.

2. Materials and Methods

2.1. Study design, ethical approval and setting

The present prospective randomized controlled trial was carried out at a single institution following the ethical standards outlined in the Declaration of Helsinki. Prior to enrollment, each participant received a detailed explanation of the study protocol and provided written informed consent. The trial received ethical clearance from the Ethics Committee of the University of Health Sciences Bursa City Hospital (approval no. 2022-10/13) as well as from the Turkish Medicines and Medical Devices Agency (23-AKD-154). The trial was registered on the ClinicalTrials.gov platform (identifier: NCT06078475; first posted: October 11, 2023).

Eligible participants were ASA II pregnant women scheduled for elective cesarean section beyond the 37th week of gestation. Women who were using anticoagulants, had a bleeding diathesis, had allergy or hypersensitivity to local anesthetics or opioids, had infection at the injection site, reported alcohol or substance dependence, required general anesthesia, or declined to participate were excluded. The remaining patients were assigned to one of two groups: the M-TAPA Group (receiving M-TAPA) or the Control Group, using a computer program.

Before being taken to the operating room, venous access was established with an 18 G cannula. Electrocardiography, non-invasive arterial blood pressure, and peripheral oxygen saturation were monitored throughout surgery. For the spinal block, each woman was placed in a sitting position; after appropriate aseptic and antiseptic preparation, a 26-gauge pencil-point spinal needle (B. Braun, Melsungen, Germany) was advanced into the subarachnoid space via a midline approach at the L3-4 or L4-5 interspace. After free, clear cerebrospinal fluid was observed, 12.5 mg hyperbaric bupivacaine was administered. The block level was confirmed with the pinprick test, and surgery began once an adequate block was achieved.

Once surgery had ended, women allocated to the M-TAPA group were positioned supine for block application. Following skin preparation with an aseptic technique, ultrasound visualization was performed with a high-frequency linear transducer (GE ML6-15-D Matrix Linear, Boston, USA), and an 80 mm block needle (Stimuplex Ultra®, Braun, Melsungen, Germany) was used for injection. The transducer was oriented in the sagittal plane at the intersection of the midclavicular line with the costal cartilage. The lower costochondral angle was then identified sonographically, and under in-plane needle guidance the needle trajectory was directed from caudal to cranial (Fig. 1). Correct needle-tip location was verified by observing appropriate saline hydrodissection, after which 20 mL of 0.25% bupivacaine was deposited on each side, yielding a cumulative volume of 40 mL.

For safety, the needle tip and local anesthetic spread were continuously monitored in real time under ultrasound guidance; negative aspiration was confirmed before each injection to avoid intravascular administration, and the drug was injected incrementally in 5 mL aliquots. The total bupivacaine dose (100 mg, approxi-

mately 1.3-1.5 mg/kg) remained below the maximum safe single-dose threshold widely accepted in the obstet-

ric population; no evidence of local anesthetic systemic toxicity was observed in any patient.

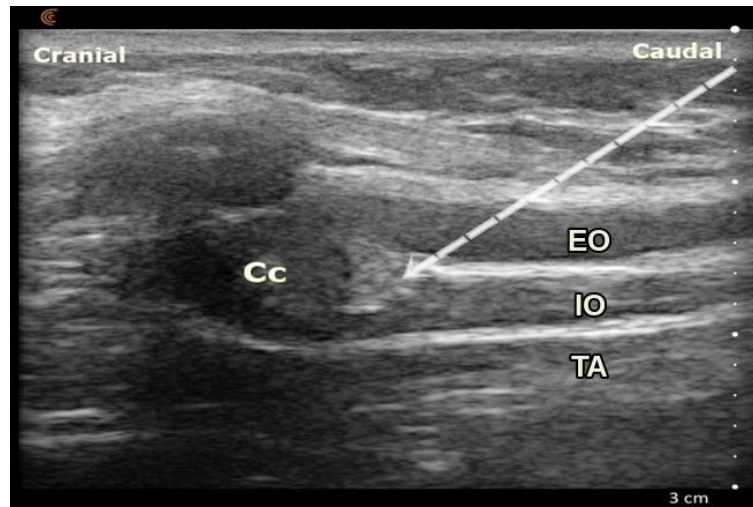


Fig. 1. Sonographic anatomy of the M-TAPA block. Arrows indicate the needle direction. Cc: costal cartilage; EO: external oblique; IO: internal oblique; TA: transversus abdominis.

2.2. Perioperative analgesia management, postoperative analgesia protocol, and pain measurement

After surgery, all participants in both the M-TAPA and Control groups routinely received 1000 mg paracetamol three times daily. Local wound infiltration was not performed by the surgical team in either group. Postoperative assessment was performed by an anesthesiologist who was not involved in the study intervention and was blinded to group allocation; however, because no sham block was performed in the control group, patients and the bedside clinical care team were not blinded to group allocation; this should be considered when interpreting subjective endpoints such as pain scores and QoR-15 results.

Postoperative pain was assessed using a 10 cm numeric rating scale (NRS) ranging from 0 (no pain) to 10 (worst pain imaginable). Both resting (passive) and movement-related (active) scores were recorded at hours 0, 2, 4, 8, 16, and 24. Active NRS assessment was performed during the patient's in-bed movement (coughing or changing position) at hours 0, 2, and 4, and during mobilization at the other time points. When a patient's NRS value was ≥ 4 , intravenous meperidine 0.5 mg/kg was administered as rescue analgesia. Analgesic agents used during the postoperative period, total opioid requirement, and side effects such as nausea, vomiting, and pruritus were recorded.

2.3. Assessment of quality of recovery

Relying exclusively on pain intensity and opioid requirements yields only a partial view of how a patient truly progresses after surgery. To overcome this shortcoming, the QoR-15, a 15-item instrument evaluating five distinct domains, namely pain, physical comfort, physical independence, psychological support, and emotional state, was developed as a concise, dependable, and clinically feasible measure of postoperative recovery [13,14]. For the purposes of the current study, recovery

quality was quantified using the linguistically validated Turkish adaptation of this scale [15].

2.4. Sample size and statistical analyses

The required sample size was derived from a pilot study of 12 individuals. In this pilot study, the mean 24-hour QoR-15 score was 125.67 ± 22.35 in the M-TAPA group and 110.83 ± 13.35 in the control group. Based on these data, 52 patients were required to achieve two-sided $\alpha = 0.05$, a large effect size (0.8), and 80% power. To account for a possible 15% dropout rate, enrollment of 60 patients was planned. The 24-hour QoR-15 score was chosen as both the primary endpoint and the basis for the power calculation, because it is a composite endpoint reflecting the overall analgesic and functional benefit of the block; the 24-hour NRS score was used as a secondary endpoint for between-group comparison of pain intensity.

All statistical analyses were performed using SPSS Statistics for Windows (Version 29.0, IBM Corp., Armonk, NY, USA, 2022). Normality of distribution was examined using the Kolmogorov-Smirnov test. Depending on whether the data followed a normal distribution, continuous variables were compared using Student's t-test or the Mann-Whitney U test, and categorical variables were compared using Pearson's chi-square test or Fisher's exact test, as appropriate. Results are presented as median and 25th-75th percentile, mean and standard deviation (SD), or number and percentage, with $p < 0.05$ considered statistically significant.

3. Results

Patient enrollment and group allocation are summarized in the CONSORT flow diagram (Fig. 2). Sixty patients were enrolled and equally assigned to the M-TAPA group ($n = 30$) and the control group ($n = 30$); all randomized patients completed the study per protocol and were included in the analysis.

CONSORT Flow Diagram

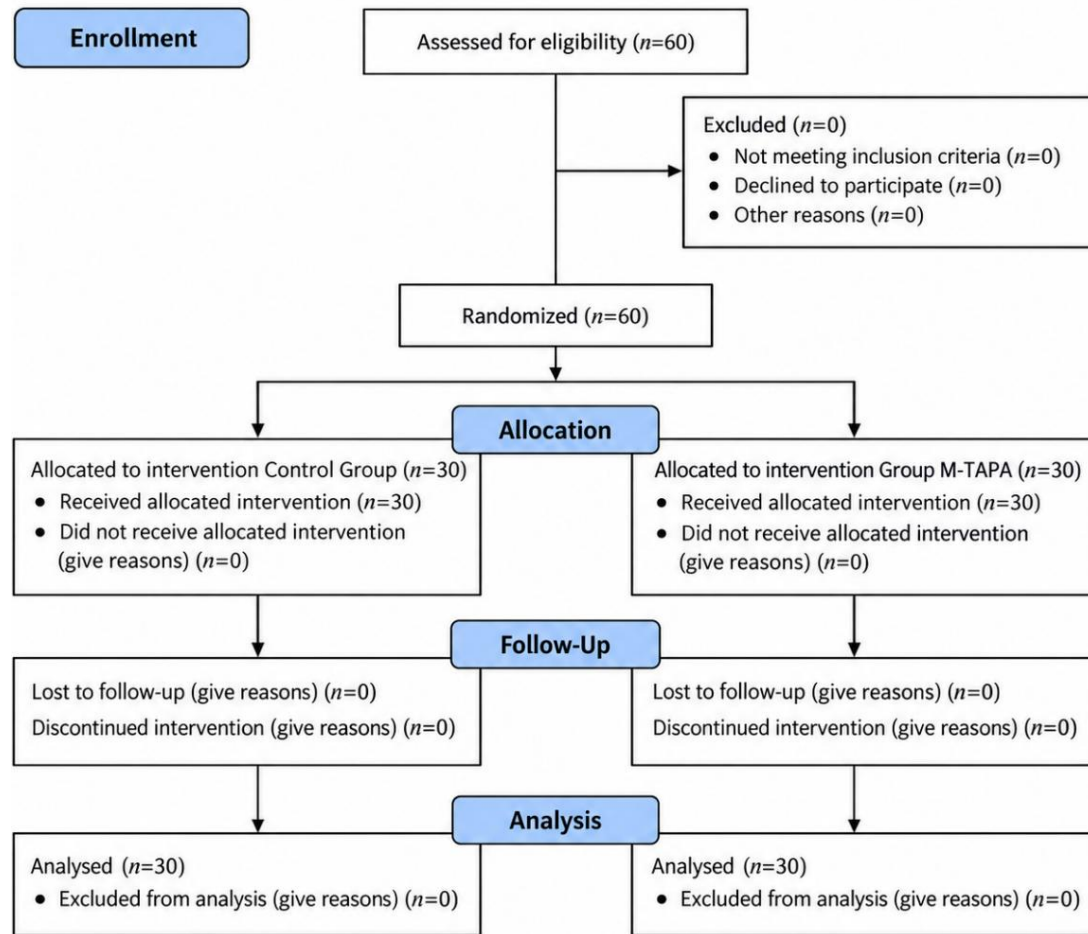


Fig. 2. Study flow diagram.

No statistically significant difference was found between the two groups in age ($p = 0.521$), height ($p = 0.167$), weight ($p = 0.098$), duration of surgery ($p = 0.052$), or duration of anesthesia ($p = 0.075$) (Table 1).

QoR-15 scores measured at postoperative hour 24 were significantly higher in the M-TAPA group than in the control group [128.5 [113.0-136.3] vs. 109.5 [98.0-127.0], $p = 0.001$). When the five subdomains of the QoR-15 scale (pain, physical comfort, physical independence, psychological support, and emotional state) were evaluated together, patients in the M-TAPA group showed a markedly more positive overall perception of recovery compared with the control group. This difference was consistent not only with the reduction in pain scores but also with the overall improvement in patients' physical

and emotional well-being (Table 2).

The need for rescue analgesia ($p = 0.020$) and total meperidine dose ($p = 0.001$) were significantly lower in the M-TAPA group than in the control group (Table 2).

In the M-TAPA group, pain scores measured both at rest and with movement were significantly lower than in the control group at hours 2, 4, 8, and 16 (at rest, respectively $p = 0.002$; $p = 0.003$; $p = 0.003$; $p = 0.024$; with movement, respectively $p = 0.001$; $p < 0.001$; $p < 0.001$; $p = 0.008$). No significant difference between groups was found at hours 0 and 24 (at rest, $p = 0.682$ and $p = 0.349$; with movement, $p = 0.096$ and $p = 0.258$) (Table 3).

The frequency of nausea ($p = 0.766$) and vomiting ($p = 0.612$) were similar between groups, and no patient experienced pruritus (Table 4).

Table 1. Comparison of demographic data and surgical procedures between groups.

	M-TAPA (n = 30)	Control (n = 30)	p value
Age	30.0±5.4	29.1±5.4	0.521
Height (cm)	166.0±5.2	164.0±5.9	0.167
Weight (kg)	78.4±8.5	82.5±10.2	0.098
Duration of surgery (min)	52.4±12.3	59.3±14.5	0.052
Duration of anesthesia (min)	63.6±13.3	70.3±15.3	0.075

Values are expressed as mean ± standard deviation or number. kg: kilogram, cm: centimeter, ASA: American Society of Anesthesiologists, mcg: microgram, min: minute.

Table 2. Comparison of QoR-15 and rescue analgesia between groups.

	M-TAPA (n = 30)	Control (n = 30)	p value
Need for rescue analgesia (+); n (%)	21 (70.0)	28 (93.3)	0.020
Rescue analgesic dose (mg); med (25-75P)	40.0 (0.0 - 60.0)	90.0 (50.0 - 100.0)	0.001
QoR-15; med (25-75P)	128.5 (113.0 - 136.3)	109.5 (98.0 - 127.0)	0.001

Values are expressed as median (interquartile range).

Table 3. Comparison of active and passive NRS assessments between groups.

At rest				With movement			
Hour	M-TAPA (n = 30)	Control (n = 30)	p value	Hour	M-TAPA (n = 30)	Control (n = 30)	p value
0	0.0 (0.0 - 1.0)	0.0 (0.0 - 1.3)	0.682	0	0.0 (0.0 - 0.0)	0.0 (0.0 - 1.0)	0.096
2	3.0 (2.0 - 4.0)	4.5 (3.8 - 7.0)	0.002	2	4.0 (3.0 - 5.0)	6.0 (5.0 - 7.3)	0.001
4	3.0 (2.3 - 4.0)	4.0 (3.0 - 5.0)	0.003	4	4.0 (3.8 - 5.0)	6.0 (5.0 - 7.3)	<0.001
8	3.0 (2.0 - 3.0)	4.0 (3.0 - 5.0)	0.003	8	4.0 (4.0 - 4.3)	5.0 (5.0 - 6.3)	<0.001
16	3.0 (1.0 - 3.0)	3.5 (2.0 - 4.0)	0.024	16	4.0 (3.0 - 4.0)	4.0 (3.0 - 5.0)	0.008
24	2.0 (1.0 - 3.0)	2.0 (1.0 - 3.0)	0.349	24	3.0 (2.0 - 3.3)	3.0 (2.0 - 4.0)	0.258

Data are expressed as median (25th-75th percentile). The symbol p is italicized. Note: NRS values recorded at postoperative hours 0 and 2 may have been affected by residual sensory-motor block from spinal anesthesia; these early time points should be interpreted with caution.

Table 4. Comparison of side-effect frequency between groups.

	M-TAPA (n = 30)	Control (n = 30)	p value
Nausea (+); n (%)	8 (26.7)	7 (23.3)	0.766
Vomiting (+); n (%)	1 (3.3)	3 (10.0)	0.612
Pruritus (+); n (%)	0 (0.0)	0 (0.0)	-

Values are expressed as number.

4. Discussion

According to our results, M-TAPA provided effective pain control after cesarean section: compared with the control group, women who received the M-TAPA block had lower pain scores, lower opioid requirements, and better quality of recovery.

Cesarean section is among the most commonly performed surgeries worldwide; in 2018, approximately 20% of deliveries worldwide were performed this way [1]. Data from our country for 2022 show that 60.1% of deliveries were performed by cesarean section [16]. Because women who undergo this procedure generally experience moderate-to-severe pain afterward, adequate analgesia is of great importance for both mother and infant in such a frequently performed surgery. When intrathecal opioids are not used, the Procedure-Specific Postoperative Pain Management (PROSPECT) group recommends the transversus abdominis plane (TAP) block; the literature also describes the effective use of quadratus lumborum (QL) and erector spinae plane (ESP) blocks for analgesia after cesarean section [17].

Each of these techniques has its own advantages and limitations. The classic TAP block is technically simple and widely known, but it primarily covers the T10-T12 dermatomes and may not reliably block the upper abdominal wall. The QL block can provide broader and more visceral coverage owing to posterior spread, but it

is technically more demanding and requires a needle trajectory close to the paraspinal space. The ESP block is easy to perform and has a favorable safety profile because of its distance from major vessels and the peritoneal cavity, but its analgesic mechanism and reliability of abdominal wall coverage remain debated. In contrast, M-TAPA is performed from a single, easily identifiable landmark, is technically reproducible, and, based on cadaveric spread data, may cover a broader craniocaudal dermatomal area (T4-T12) compared with a single-injection TAP block, which may reduce the number of injections needed for bilateral multidermatomal coverage. Considered together with the favorable analgesic and opioid-sparing results observed in the present study, these theoretical advantages suggest that M-TAPA may be a reasonable alternative within multimodal analgesia algorithms for cesarean section; however, direct comparative trials with TAP, QL, and ESP blocks are still needed to establish its comparative position.

M-TAPA, a newer interfascial plane technique described by Tulgar et al., has been reported to provide analgesia across the anterior and lateral abdominal wall along the T7-11 dermatomes [6]. Cadaveric studies have shown dye spread between T4-T12 with both TAPA and M-TAPA [18]; broader staining over the transversus abdominis has been reported with the M-TAPA approach [19]. Another cadaveric study reported that M-TAPA injections adequately stained the T9-T11 segmental nerves [20].

The M-TAPA block is an interfascial plane block that targets the terminal branches of the thoracoabdominal intercostal nerves extending into the abdominal wall, achieved by applying local anesthetic adjacent to the inferior perichondrial surface of the costal cartilage. In this approach, local anesthetic spread is thought to progress craniocaudally along the costal margin, potentially affecting the anterior cutaneous branches and, more variably, the lateral cutaneous branches. Data in the literature on the dermatomal spread of the M-TAPA block are heterogeneous; cadaveric dye studies have reported that nerve branches can be stained over a wide craniocaudal area between T4-T12 after a single injection [18–20]. However, some publications suggest that the M-TAPA block may anatomically target the T4/T5-T12/L1 thoracoabdominal nerves, and thus that spread may extend to the L1 level [21]. Given these differences, the analgesic effect observed in the present study is difficult to explain by a single dermatomal mechanism alone. The analgesic benefit may plausibly arise from blockade of nerve branches at the T12 level contributing to the incision line, reduced somatic afferent transmission of adjacent thoracoabdominal nerves, and/or indirect modulation of visceral afferent input. However, since L1-derived innervation cannot be said to be consistently and predictably covered by the M-TAPA block, the analgesic contribution at this level should be considered variable.

Recent anatomical investigations attempt to offer a plausible explanation for the considerable inter-study variability in the reported dermatomal distribution of M-TAPA. Ohgoshi et al. delineated a previously undescribed fascial compartment situated adjacent to, yet anatomically discrete from, the M-TAPA plane, namely, the space bounded by the endothoracic fascia, diaphragm, and costodiaphragmatic recess (SEDIC), demonstrating through cadaveric dissection that costal cartilage or tendinous structures consistently separate this compartment from the M-TAPA plane. In their volunteer investigation, conventional M-TAPA injection yielded reliable anesthesia of the lateral cutaneous branches (LCBs) in only 3 of 10 participants, and even in these cases the block level extended only as far as T12; by contrast, direct deposition of local anesthetic within the SEDIC, a technique the authors designated re-modified TAPA (RM-TAPA), extended LCB coverage to T8–T12 in the majority of participants [22]. This anatomical demarcation provides a coherent explanation for the inconsistent lateral blockade reported in earlier M-TAPA literature, suggesting that dependable coverage of the LCBs requires the injectate to traverse this fascial or tendinous barrier and gain access to the SEDIC, a passage that does not occur reliably following conventional M-TAPA administration. On this basis, Murata has proposed that, in view of its distinct anatomical substrate, the SEDIC-targeted injection warrants recognition as a discrete, precisely designated technique, the "SEDIC block", rather than being subsumed under successive modifications of the TAPA nomenclature [23].

Clinical evidence on M-TAPA remains limited and is largely restricted to case reports. When the block was applied to 10 women undergoing gynecological surgery, anesthesia in the anterior cutaneous branch region lasted up to a median of 6.5 dermatomes at postopera-

tive hour 24 [24]. In a separate study, M-TAPA was found to reduce postoperative pain scores and significantly lower opioid use compared with the control group in patients undergoing laparoscopic cholecystectomy [25]. Opioid requirement after laparoscopic cholecystectomy has also been shown to be lower with M-TAPA compared with the oblique subcostal transversus abdominis plane block [26]. In a case report, a pediatric patient undergoing laparoscopic cholecystectomy required no postoperative analgesia after M-TAPA [27]. When applied to a patient undergoing sleeve gastrectomy, sensory block lasted up to 56 hours [8]. In another case series, unilateral volumes of 15 and 20 mL produced sensory block between T6–T12 [19].

In the present study, the M-TAPA block reduced both resting and movement-related pain scores in cesarean patients and reduced postoperative opioid requirement. The pain relief effect after cesarean section surgery lasted up to 16 hours. An improvement in the patients' quality of recovery was also observed.

Beyond statistical significance, these findings may carry clinically meaningful implications. Lower movement-related pain scores in the M-TAPA group are particularly important, because the primary barrier to early mobilization after cesarean section is not resting pain but movement-related pain. Better control of dynamic pain may facilitate earlier ambulation, more comfortable holding of the infant, positioning for breastfeeding, and closer mother-infant interaction in the early postpartum period, while the accompanying reduction in opioid consumption may also lower the risk of maternal sedation. Considered together with the improvement in QoR-15 scores, these results suggest that the benefit of M-TAPA extends beyond pain scores alone to functionally meaningful aspects of early postoperative recovery.

Some limitations should be noted. First, the study was conducted at a single center. Second, the sample size was not large enough to detect a difference in opioid-related side effects between the M-TAPA and control groups. Third, although the outcome assessor was blinded, because no sham block was performed in the control group, patients and the bedside clinical care team were not blinded to group allocation; this may have influenced subjective endpoints such as pain scores and QoR-15 results. Fourth, quality of recovery was not assessed preoperatively as a baseline value; this limits our ability to measure the change attributable to surgery and to the block itself, and should be incorporated into future protocols. Finally, this study did not assess long-term outcomes such as chronic postsurgical pain. Nevertheless, this is the first study to test the efficacy of M-TAPA in women undergoing cesarean section, and the findings need to be confirmed by larger, multicenter studies.

5. Conclusions

In conclusion, this prospective randomized controlled trial demonstrates that bilateral M-TAPA provides effective analgesia in women undergoing cesarean section. Compared with standard care, M-TAPA significantly reduced both resting and movement-related pain scores throughout the early postoperative period, lowered the

need for rescue analgesia and total opioid consumption, and was associated with markedly higher QoR-15 scores across the domains of pain, physical comfort, physical independence, psychological support, and emotional state. This reflects a more favorable overall recovery experience. Because the primary barrier to early mobilization after cesarean section is not pain at rest but pain with movement, the block's pronounced effect on dynamic pain may facilitate earlier ambulation, easier handling and positioning of the infant for breastfeeding, and closer mother-infant contact in the early postpartum period, while its opioid-sparing effect may further reduce the risk of maternal sedation. Taken together with the technique's reliance on a single, easily identifiable landmark and its technical reproducibility, these benefits support considering M-TAPA as a practical addition to multimodal analgesia protocols after cesarean section. Solely because of the limitations discussed above, the present findings should be regarded as an initial step rather than a definitive conclusion. Larger, multicenter randomized trials, preferably incorporating baseline recovery assessment and longer follow-up, are therefore needed to confirm these results and to clarify M-TAPA's position relative to established techniques such as the transversus abdominis plane, quadratus lumborum, and erector spinae plane blocks.

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Conflict of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this manuscript.

Data Availability

The datasets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author upon reasonable request.

AI Assistance

During the preparation of this manuscript, ChatGPT was used exclusively for language editing and stylistic refinement. The authors take full responsibility for the content, interpretation, and conclusions of the published article.

Ethics Approval and Consent to Participate

This study was approved by Bursa City Hospital Ethics Committee (Approval Number: 2022-10/13; Date: 16.09.2022). Written informed consent was obtained from all participants. All procedures were conducted in accordance with relevant guidelines and regulations.

Author Contributions

Ahmet Kacıroglu: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, validation, visualization, writing – original draft, writing – review and editing.

Mursel Ekinci: conceptualization, data curation, formal analysis, investigation, methodology, writing – original draft, writing – review and editing.

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Challenge Journal of PERIOPERATIVE MEDICINE

Research Article

Effect of anesthetic choice on ST-segment-defined myocardial ischemia and early postoperative course in monopolar TURP

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ABSTRACT

Objective: This historical cohort, originally collected as a prospective, randomized study was re-analyzed to compare propofol–remifentanyl–based intravenous anesthesia (P-RIA) and sevoflurane-based balanced anesthesia (BA) regarding ST-segment-defined myocardial ischemia and hemodynamic stability in elderly ASA II–III patients with cardiovascular comorbidities undergoing monopolar transurethral resection of the prostate (TURP). As troponin measurements were unavailable, myocardial injury after non-cardiac surgery (MINS) was considered only as a conceptual framework rather than a predefined endpoint.

Methods: Sixty-six patients scheduled for elective monopolar TURP ($n = 33$ per group) were randomized in a single-center, outcome-assessor-blinded design to receive P-RIA or BA. Continuous ST-segment monitoring (leads DII, V5, aVL) was performed from 15 minutes before induction to 15 minutes postoperatively. ECGs were read by a blinded cardiologist, and hemodynamics, electrolytes, and CK-MB/CK were recorded serially.

Results: Baseline demographic and surgical characteristics, as well as overall ischemia incidence and duration, were similar between groups. Blood pressure and heart rate were lower and more stable with P-RIA. At 15 minutes postoperatively, ischemia was less frequent in the P-RIA group than in the BA group (15.2% vs 36.4%; $p = 0.045$), an exploratory finding. CK-MB levels, CK-MB/CK ratios, electrolyte values, and postoperative complications did not differ significantly.

Conclusion: In this elderly, comorbid TURP cohort, P-RIA was associated with a more stable hemodynamic profile and a transiently lower early postoperative ischemia rate, without reducing total perioperative ischemic burden or CK-MB–based myocardial injury. The data are hypothesis-generating and require confirmation in larger troponin-based MINS studies.

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1. Introduction

Transurethral resection of the prostate (TURP) remains one of the principal surgical options for the treat-

ment of symptomatic benign prostatic hyperplasia (BPH) and, with appropriate perioperative optimization, offers an acceptable cardiac risk profile even in elderly patients with cardiovascular comorbidities [1]. How-

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ever, in patients with significant comorbidity or those receiving anticoagulant therapy, minimally invasive techniques such as bipolar TURP and holmium laser enucleation of the prostate (HoLEP) are increasingly recommended because they reduce blood loss, irrigation load, and the risk of TUR syndrome [1–7].

Perioperative cardiac risk assessment has moved beyond traditional symptom- and ECG-based approaches, demonstrating that most myocardial injury after non-cardiac surgery is clinically silent and that elevations in high-sensitivity troponin carry strong prognostic value [8]. Accordingly, contemporary guidelines recommend postoperative troponin surveillance in high-risk patients and advocate integrating the concept of myocardial injury after non-cardiac surgery (MINS) into clinical decision-making algorithms [8–11]. However, because this study was conducted in 2001, high-sensitivity troponin measurements were not available; therefore, MINS was not evaluated as a direct endpoint but was instead used as a conceptual framework to interpret the observed ST-segment changes and CK-MB/CK findings.

The effect of anesthetic technique on myocardial ischemia and hemodynamic stability remains uncertain. Despite the potential cardioprotective properties of volatile agents, recent studies have not demonstrated a clear advantage of sevoflurane–remifentanyl over propofol–remifentanyl, instead emphasizing that hemodynamic stability is the principal determinant of risk [12–14]. In the present study, because nitrous oxide was used in both arms, the propofol–remifentanyl regimen is described as “propofol–remifentanyl–based intravenous anesthesia” rather than classical total intravenous anesthesia (TIVA).

The aim of this study was to compare the effects of propofol–remifentanyl–based intravenous anesthesia and sevoflurane-based balanced anesthesia on ST-segment–defined myocardial ischemia and perioperative hemodynamic stability in elderly ASA II–III monopolar TURP patients with cardiovascular comorbidities. Our hypothesis was that a propofol–remifentanyl–based regimen would provide a more stable hemodynamic profile and thereby modify ischemic patterns. In addition, the ST-segment and hemodynamic findings were planned to be interpreted in light of the MINS literature, not for direct diagnostic purposes, but to offer an interpretative, hypothesis-generating framework.

2. Materials and Methods

2.1. Study design and ethical approval

The study was conducted in accordance with the Declaration of Helsinki after approval by the institutional ethics committee (date: 2001-06-04) as a prospective, randomized, single-center, outcome-assessor-blinded clinical trial. Treatment allocation was known only to the anesthesiologist, whereas patients, surgeons, postoperative clinical assessors, data analysts, and the cardiologist interpreting the ECGs were all blinded to group assignment. Written informed consent was obtained from all participants. Because the study was initiated at a time

when prospective clinical trial registration was not mandatory, no trial registration number is available.

2.2. Patient selection, exclusion criteria and randomization

Between June and November 2001, 80 consecutive male patients aged 50–87 years, classified as ASA II–III and scheduled for elective monopolar TURP due to benign prostatic obstruction, were assessed for eligibility. Fourteen patients were excluded because of missing pre- or postoperative laboratory data ($n = 5$), incomplete postoperative ECG monitoring ($n = 2$), discharge before completion of 24-hour observation ($n = 6$), or withdrawal of consent after preoperative preparation ($n = 1$), leaving 66 patients who completed the protocol and were included in the final analysis. The CONSORT flow diagram of screening, randomization, and analysis is shown in Fig. 1.

Exclusion criteria were severe heart failure, hemodynamically significant valvular heart disease, myocardial infarction within the preceding 6 months, uncontrolled arrhythmia, severe pulmonary/renal/hepatic failure, major conduction disturbances, preoperative hemoglobin < 12 g/dL, age < 50 or > 90 years, and preference for regional anesthesia. Coronary artery disease, hypertension, diabetes mellitus, prior stroke, mild–moderate valvular disease, COPD, obesity, and smoking were recorded as cardiovascular comorbidities but were not exclusion criteria.

Cardiac risk assessment was based on the ASA physical status classification, the Goldman cardiac risk index, and clinical variables (ejection fraction, functional capacity, arrhythmias, and comorbidities). As most patients were elderly with cardiovascular comorbidities and fell into the low–intermediate Goldman risk categories, the cohort was defined as “elderly ASA II–III monopolar TURP patients with cardiovascular comorbidities.”

Patients who provided written informed consent were randomized in a 1:1 ratio to receive either sevoflurane-based balanced anesthesia (BA, $n = 33$) or propofol–remifentanyl–based intravenous anesthesia (P-RIA, $n = 33$). Randomization was performed by a researcher independent of anesthesia management using a computer-generated allocation list concealed in sequentially numbered, opaque, sealed envelopes. Group assignment was disclosed only to the anesthesiologist, while all other clinical and assessment teams remained blinded.

For all randomized patients, demographic data, ASA class, Goldman index, preoperative ejection fraction, surgical and anesthesia durations, calculated irrigation fluid absorption, and resected prostate weight were recorded prospectively.

2.3. Anesthesia protocol

All patients were monitored using standard modalities, including heart rate, noninvasive arterial blood pressure, SpO₂, ETCO₂, and five-lead ECG (DII, V5, aVL). Premedication consisted of 0.03 mg/kg IV midazolam and 7 ml/kg 0.9% NaCl, followed by 2–3 minutes of preoxygenation with 100% oxygen. Induction was achieved

in both groups with remifentanyl (0.5–1 µg/kg), combined with etomidate (0.15–0.25 mg/kg) in the BA group and propofol (1–2 mg/kg) in the P-RIA group; all patients received vecuronium 0.1 mg/kg to facilitate tracheal intubation. Anesthesia was maintained with 1–3%

sevoflurane in the BA group and with remifentanyl (0.1–0.5 µg/kg/min) plus propofol (3–6 mg/kg/h) in the P-RIA group, using a 66% N₂O/33% O₂ gas mixture in both groups; supplemental vecuronium (0.02 mg/kg) was given as needed.

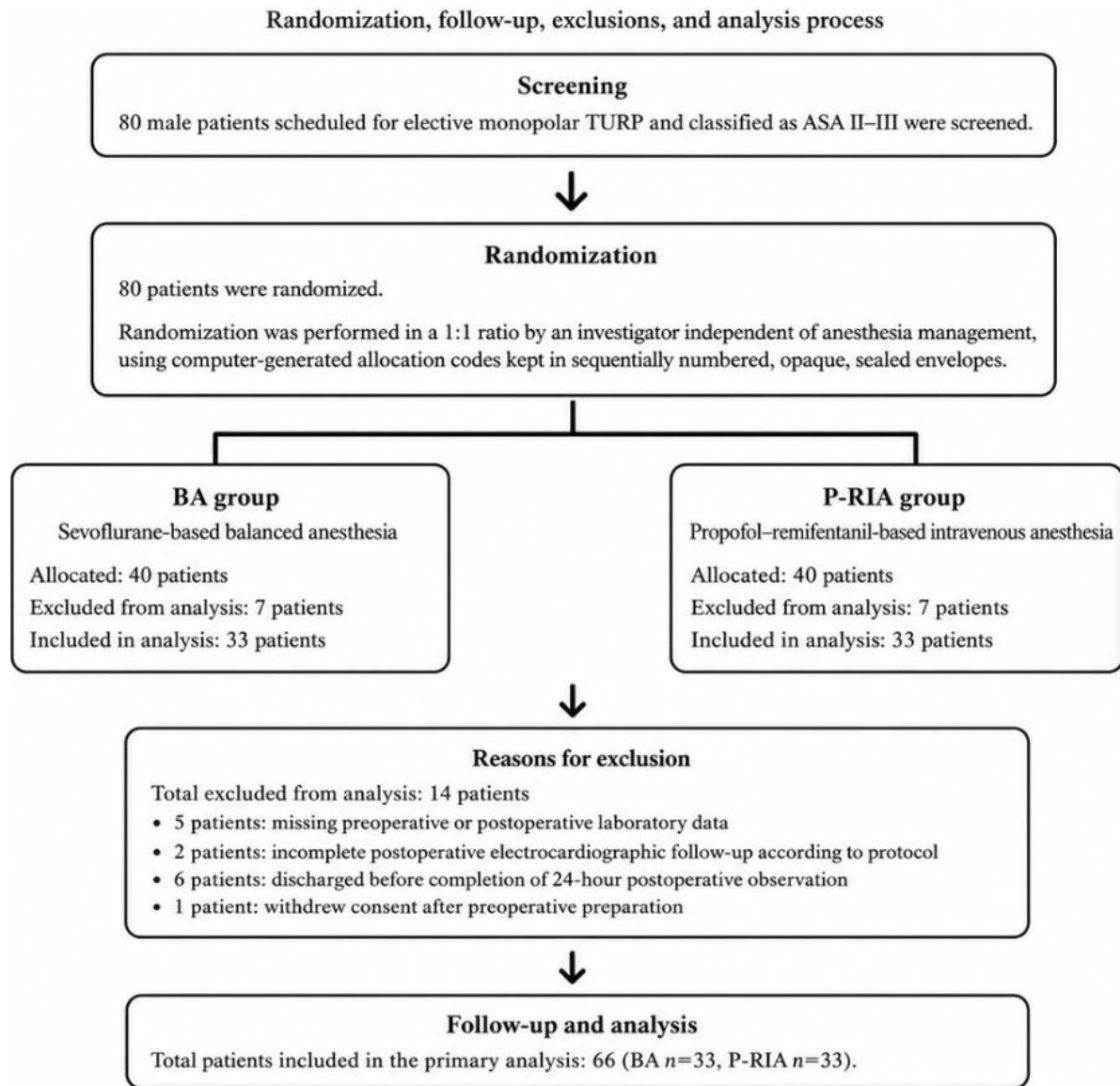


Fig. 1. This CONSORT flow diagram shows the screening, randomization, group allocation, exclusion from analysis, and final analysis process, assuming that randomization occurred before post-randomization exclusions in ASA II–III patients scheduled for elective monopolar TURP.

Depth of anesthesia was assessed clinically rather than with processed electroencephalography (EEG) monitoring, and hypnotic/analgesic doses were titrated accordingly. Hypotension (systolic blood pressure < 85 mmHg) or bradycardia (heart rate < 50 beats/min) triggered a stepwise response: anesthetic dose reduction and optimization of intravascular volume as the first-line measure, followed by an increased crystalloid infusion rate if the response was insufficient. As a result of this stepwise approach, no patient required a vasopressor for persistent hypotension or atropine (0.01 mg/kg) for bradycardia; these episodes were therefore not quantified as a separate variable.

Postoperative analgesia was standardized with intramuscular tramadol (1–1.5 mg/kg) given 10–20 minutes

before the end of surgery. Because pain scores were not recorded systematically, the relationship between early postoperative pain and sympathetic responses could not be analyzed. Neuromuscular block was reversed with neostigmine (0.02–0.08 mg/kg) plus atropine (0.01 mg/kg); anesthetic agents were discontinued, patients were extubated, and then transferred to the recovery unit with 100% oxygen.

2.4. Surgical technique and fluid absorption

All TURP procedures were performed in the lithotomy position using a standard resectoscope and 1.5% glycine irrigation; the irrigation bags were positioned approximately 60 cm above the level of the pubic sym-

physis. Surgical, resection, and anesthesia durations, as well as the total volume of irrigation fluid administered and the calculated volume absorbed, were recorded prospectively. Irrigation fluid absorption was estimated using a standard formula based on the change in serum sodium concentration and the initial extracellular fluid volume (ECF, assumed to be 20% of body weight) [15].

$$\text{Volume Absorbed} = \left(\frac{\text{Preoperative serum Na}}{\text{Postoperative serum Na}} \cdot \text{ECF} \right) - \text{ECF} \quad (1)$$

During the intraoperative period, crystalloid solutions were infused at a rate of 4–6 ml/kg/h, and both the total fluid volume administered and urine output were recorded. Transfusion requirements were standardized according to predefined hemoglobin targets, with thresholds of ≥ 12 g/dL preoperatively and ≥ 10 g/dL postoperatively.

2.5. Definition of myocardial ischemia and ECG monitoring

In all patients, left ventricular ejection fraction was assessed by transthoracic echocardiography within 24 hours before surgery, and myocardial ischemia screening was performed with a 12-lead ECG; all tracings were reviewed by a blinded cardiologist. During intraoperative monitoring, continuous ST-segment surveillance was carried out in leads DII, V5, and aVL from 15 minutes before induction until 15 minutes after the end of surgery. Myocardial ischemia was defined as ≥ 1 mm ST-segment depression or ≥ 2 mm ST-segment elevation lasting at least 1 minute, measured 80 ms after the J point.

In the postoperative period, 12-lead ECGs were repeated at 6 and 24 hours, and all recordings were evaluated by the same cardiologist. For each patient, ischemia incidence, total ischemia duration, number of ischemic episodes, and maximal ST deviation were calculated. The primary endpoint was the overall incidence of perioperative ST-segment-defined myocardial ischemia, defined as the occurrence of at least one ischemic episode during the predefined monitoring period. Secondary endpoints included total ischemia duration, number of ischemic episodes, maximal ST-segment deviation, and hemodynamic variables (systolic and mean arterial pressure and heart rate) measured at predefined intraoperative and early postoperative time points. Exploratory analyses focused particularly on the frequency of ischemia at the early postoperative 15th minute.

2.6. Clinical and laboratory variables

In all patients, baseline laboratory evaluation included complete blood count (Hb, Hct), cardiac biochemistry (CK, CK-MB), serum electrolytes (Na, K), and arterial blood gas analysis; these measurements were repeated at 0 and 24 hours postoperatively. The maximum decrease in Hb/Hct was calculated as the difference between the preoperative value and the lowest postoperative value. Changes in CK-MB concentration and the CK-MB/CK ratio were assessed as biochemical indicators of myocardial injury, with upper reference limits defined as 25 IU/L for CK-MB and 5% for the CK-MB/CK

ratio.

The presence of hypertension, diabetes, COPD, atrial fibrillation, smoking, heart failure, previous stroke, exercise limitation, mild valvular heart disease, coronary artery disease, and obesity was recorded to derive the overall comorbidity burden. During the postoperative period, atrial fibrillation, ischemic stroke, TUR syndrome, chest pain, ventricular premature beats, pulmonary thromboembolism, electrolyte disturbances, and severe anemia (Hb < 9 g/dL) were prospectively monitored.

2.7. Hemodynamic monitoring and subgroup analysis by myocardial ischemia

Systolic and mean arterial pressure and heart rate were recorded at predefined standard time points (baseline, after premedication, during induction-intubation, after positioning, at the start of resection, as an intraoperative mean value, before and after reversal, at the end of anesthesia, at extubation, and immediately before transfer to the recovery unit). Temporal changes were analyzed both within and between groups.

In addition, patients were stratified according to the occurrence of myocardial ischemia (ischemia: $n = 29$; no ischemia: $n = 37$), and these subgroups were compared with respect to demographic characteristics, cardiac risk scores, overall comorbidity burden, perioperative variables, irrigation volume, laboratory findings, and postoperative complications.

2.8. Sample size calculation

The sample size was prospectively calculated based on the primary hypothesis that propofol-remifentanyl-based intravenous anesthesia (P-RIA) would reduce the incidence of perioperative ST-segment-defined myocardial ischemia compared with sevoflurane-based balanced anesthesia (BA). In high-risk TURP series, the incidence of ischemia under volatile anesthesia has been reported to be approximately 40–50%, and for this study a reduction from 50% to 15% (an absolute decrease of 35 percentage points) was considered clinically meaningful.

Assuming a two-sided comparison of two independent proportions with $\alpha = 0.05$ and 80% power, the required sample size was calculated as at least 30 patients per group. To compensate for potential dropouts and protocol deviations, the target sample size was increased to 33 patients in each arm, yielding a total of 66 randomized patients.

2.9. Statistical analysis

All statistical analyses were performed using SPSS version 27.0 (IBM Corp., Armonk, NY, USA), and a two-sided p value < 0.05 was considered the threshold for statistical significance. Given the exploratory nature of the study and the relatively small sample size, no formal adjustment for multiple comparisons was applied; p values were interpreted descriptively, with the risk of false-positive findings due to multiple testing taken into account.

Continuous variables are presented as mean $\pm$ standard deviation, and categorical variables as counts and percentages. For comparisons between two independent groups, the Student t test was used for normally distributed continuous data and the Mann–Whitney U test for non-normally distributed data; categorical var-

iables were analyzed using the chi-square test or Fisher's exact test, as appropriate. Repeated-measures analysis of variance (ANOVA) was applied to assess time-dependent changes, and, when a significant main effect was detected, suitable post-hoc tests were conducted.

Table 1. Demographic, preoperative cardiac risk, comorbidities and postoperative complications in the balanced anesthesia and P-RIA groups.

	BA (n = 33)	P-RIA (n = 33)	p
Age (years)	67.7 $\pm$ 8.5	69.5 $\pm$ 5.8	0.286
Weight (kg)	70.3 $\pm$ 13.2	70.9 $\pm$ 15.2	0.856
Height (m)	1.64 $\pm$ 0.07	1.61 $\pm$ 0.06	0.057
BMI (kg/m ²)	25.97 $\pm$ 4.2	27.21 $\pm$ 5.2	0.349
ASA II / III	25 (75.8) / 8 (24.2)	23 (69.7) / 10 (30.3)	0.580
Goldman cardiac risk index – Low / intermediate / high	22 (66.7) / 8 (24.2) / 3 (9.1)	18 (54.5) / 11 (33.3) / 4 (12.1)	0.602
Resection time (min)	46.94 $\pm$ 20.1	47.27 $\pm$ 18.1	0.700
Anesthesia time (min)	55.91 $\pm$ 21.3	57.21 $\pm$ 19.3	0.686
Total glycine used (L)	14.73 $\pm$ 6.02	15.99 $\pm$ 6.6	0.302
Glycine absorbed (L)	0.62 $\pm$ 0.6	1.1 $\pm$ 0.9	0.041
Resected prostate weight (g)	18.85 $\pm$ 13.1	21.91 $\pm$ 14.6	0.267
Preoperative ejection fraction (%)	65.7 $\pm$ 5.8	60.3 $\pm$ 11.2	0.034
Myocardial ischemia incidence, n (%)	16 (48.5)	13 (39.4)	0.457
Comorbidities			
Number of comorbidities	2.27 $\pm$ 1.15	2.76 $\pm$ 1.82	0.301
Hypertension	14 (42.4)	10 (30.3)	0.306
Diabetes mellitus	4 (12.1)	4 (12.1)	1
COPD	13 (39.4)	16 (48.5)	0.457
Atrial fibrillation	1 (3)	2 (6.1)	0.555
Smoking history	19 (57.6)	18 (54.5)	0.804
Heart failure	6 (18.2)	7 (21.2)	0.757
Previous stroke	1 (3)	5 (15)	0.087
Exercise limitation	5 (15.2)	10 (30.3)	0.142
Mitral regurgitation (mild)	3 (9.1)	7 (21.2)	0.170
Aortic regurgitation (mild)	1 (3)	3 (9.1)	0.302
Coronary artery disease	5 (15.2)	2 (6.1)	0.230
Obesity	6 (18.2)	8 (24.2)	0.547
Complications			
Atrial fibrillation	1 (3)	0 (0)	0.500
Ischemic stroke	1 (3)	1 (3)	1
TUR syndrome	0 (0)	2 (6.1)	0.246
Chest pain	1 (3)	0 (0)	0.500
Ventricular premature beats	0 (0)	1 (3)	0.500
Pulmonary thromboembolism	0 (0)	1 (3)	0.500
Hyponatremia			
Mild	11 (33.3)	7 (21.2)	0.269
Moderate	3 (9.1)	9 (27.3)	0.056
Severe	4 (12.1)	6 (18.2)	0.492
Hypokalemia	14 (42.4)	17 (51.5)	0.459
Anemia (Hb < 9 g/dL)	8 (24.2)	7 (21.2)	0.769

Abbreviations: BA, balanced anesthesia; P-RIA, propofol–remifentanyl-based intravenous anesthesia, BMI, body mass index; ASA, American Society of Anesthesiologists, COPD, chronic obstructive pulmonary disease; TUR, transurethral resection of the prostate. Values are presented as mean $\pm$ SD or n (%). Statistical significance was defined as $p < 0.05$.

An additional post hoc analysis was performed to evaluate the statistical power for the primary endpoint, the overall incidence of perioperative ST-segment-defined myocardial ischemia. The ischemia incidence was 48.5% in the BA group and 39.4% in the P-RIA group (absolute difference $\approx 9.1\%$; $n = 33$ per group). Using these observed proportions and a two-sided comparison of two independent proportions at $\alpha = 0.05$ with a normal

approximation, the post hoc power was estimated at approximately 12%. Because this observed effect size was much smaller than the prospectively assumed absolute risk reduction of 35%, the study was considered underpowered to detect small-to-moderate differences in global ischemic burden or rare cardiac events; accordingly, the findings are interpreted as exploratory and hypothesis-generating rather than confirmatory.

Table 2. Perioperative systolic and mean arterial pressure and heart rate profiles in the balanced anesthesia and P-RIA groups.

	BA ($n = 33$)	P-RIA ($n = 33$)	Between-group p	Within BA p	Within P-RIA p
Systolic arterial pressure (mmHg)					
Preoperative	153.03 $\pm$ 20.3	155.33 $\pm$ 24.7	0.680		
After premedication	139.88 $\pm$ 21.3	138.82 $\pm$ 21	0.839	0.001	0.001
After induction	114.76 $\pm$ 22.3	85.24 $\pm$ 20.7	0.001	0.001	0.001
After intubation	168.18 $\pm$ 35	122.94 $\pm$ 34.9	0.001	0.019	0.001
After lithotomy	158.88 $\pm$ 31.1	123.27 $\pm$ 28.3	0.001	0.269	0.001
At start of resection	144.94 $\pm$ 35.3	113.09 $\pm$ 27.2	0.001	0.125	0.001
Intraoperative mean	127.45 $\pm$ 24.7	108.15 $\pm$ 24.1	0.002	0.001	0.001
Pre-reversal	121.09 $\pm$ 29	106.85 $\pm$ 24.1	0.034	0.001	0.001
Post-reversal	126.18 $\pm$ 33.3	106.52 $\pm$ 23.2	0.007	0.001	0.001
At end of anesthesia	124.42 $\pm$ 29.3	105.85 $\pm$ 27.5	0.010	0.001	0.001
Supine	137.42 $\pm$ 33.1	118.64 $\pm$ 30.8	0.020	0.008	0.001
After extubation	163.33 $\pm$ 33.2	140 $\pm$ 28.7	0.003	0.052	0.007
Before recovery	161.33 $\pm$ 28.5	141.24 $\pm$ 26.6	0.004	0.057	0.007
Mean arterial pressure (mmHg)					
Preoperative	110.51 $\pm$ 11.8	112.87 $\pm$ 13.5	0.452		
After premedication	100.14 $\pm$ 12.1	101.28 $\pm$ 12.1	0.703	0.001	0.001
After induction	85.18 $\pm$ 14.5	65.1 $\pm$ 16.4	0.001	0.001	0.001
After intubation	125.66 $\pm$ 23.70	95.36 $\pm$ 23.4	0.001	0.001	0.001
After lithotomy	119.46 $\pm$ 25.6	93.43 $\pm$ 17.9	0.001	0.04	0.001
At start of resection	110.64 $\pm$ 26.5	87.09 $\pm$ 19.2	0.001	0.973	0.001
Intraoperative mean	97.96 $\pm$ 17.2	82.09 $\pm$ 16.6	0.001	0.001	0.001
Pre-reversal	92.93 $\pm$ 20.6	81.09 $\pm$ 17.9	0.015	0.001	0.001
Post-reversal	97.68 $\pm$ 23.00	82.36 $\pm$ 17.9	0.004	0.001	0.001
At end of anesthesia	95.82 $\pm$ 19.4	80.98 $\pm$ 20.7	0.004	0.001	0.001
Supine	105.42 $\pm$ 25.6	91.61 $\pm$ 21.9	0.022	0.207	0.001
After extubation	122.40 $\pm$ 24.2	107.78 $\pm$ 21.6	0.012	0.003	0.138
Before recovery	114.79 $\pm$ 18.2	105.53 $\pm$ 19.3	0.049	0.130	0.035
Heart rate (bpm)					
Preoperative	80.88 $\pm$ 14.3	89.42 $\pm$ 17.6	0.034		
After premedication	80.58 $\pm$ 12.9	89.06 $\pm$ 13	0.010	0.760	0.810
After induction	72.45 $\pm$ 12.1	76.82 $\pm$ 11.5	0.138	0.001	0.001
After intubation	87.36 $\pm$ 17.2	87.70 $\pm$ 15.7	0.935	0.020	0.519
After lithotomy	79.91 $\pm$ 15.1	82.91 $\pm$ 14.5	0.414	0.722	0.024
At start of resection	73.42 $\pm$ 15.4	73.70 $\pm$ 13.4	0.939	0.004	0.001
Intraoperative mean	67.48 $\pm$ 11.8	61.39 $\pm$ 10.4	0.030	0.001	0.001
Pre-reversal	64.27 $\pm$ 11.1	56.88 $\pm$ 9.2	0.04	0.001	0.001
Post-reversal	77.97 $\pm$ 13.7	64.09 $\pm$ 13.4	0.001	0.375	0.001
At end of anesthesia	68.24 $\pm$ 13.6	58.73 $\pm$ 11.6	0.003	0.001	0.001
Supine	69.33 $\pm$ 13.8	64.12 $\pm$ 13.1	0.121	0.001	0.001
After extubation	78.55 $\pm$ 12.8	74.88 $\pm$ 14.8	0.286	0.453	0.001
Before recovery	73.15 $\pm$ 13.9	75 $\pm$ 16.3	0.621	0.019	0.001

Abbreviations: BA, balanced anesthesia; P-RIA, propofol-remifentanyl-based intravenous anesthesia; bpm, beats per minute. Values are presented as mean $\pm$ SD. Statistical significance was defined as $p < 0.05$.

3. Results

Baseline demographic characteristics, body size, BMI, ASA class, Goldman score, surgical and anesthesia durations, total glycine volume, resected prostate weight, and overall myocardial ischemia incidence were similar between the BA and P-RIA groups. However, preoperative ejection fraction was higher in the BA group, whereas calculated glycine absorption was greater in the P-RIA group (65.7 ± 5.8 vs $60.3 \pm 11.2\%$ [BA vs P-RIA] and 1.1 ± 0.9 vs 0.62 ± 0.6 L [P-RIA vs BA], respectively; $p = 0.034$, $p = 0.041$). These variables were considered potential confounders, but because the sample size was insufficient for robust multivariable modelling, the results were interpreted in an exploratory manner. No significant between-group differences were observed in overall comorbidity burden or postoperative complications ($p > 0.05$) (Table 1)

Pre- and postoperative Hb/Hct values were compara-

ble, although the maximal decrease was more pronounced in the P-RIA group. In contrast, CK-MB levels, CK-MB/CK ratios, and electrolyte concentrations were similar between groups and remained within normal limits, and no clinically relevant elevation above CK-MB thresholds was detected.

Hemodynamic assessment showed lower and more stable systolic and mean arterial pressures and heart rates in the P-RIA group, a pattern confirmed by repeated-measures analysis (Table 2).

The total incidence of myocardial ischemia, ischemia duration, and number of ischemic episodes did not differ between groups. A higher ischemia rate was observed only at 15 minutes postoperatively in the BA group compared with the P-RIA group (36.4% vs 15.2%), a secondary/exploratory finding that was interpreted cautiously in view of multiple comparisons. Maximal ST-segment deviations and postoperative ECG findings were otherwise similar (Table 3).

Table 3. Myocardial ischemia incidence, duration and timing in the balanced and P-RIA groups.

	BA (n = 33)	P-RIA (n = 33)	p
Myocardial ischemia incidence, n (%)	16 (48.5)	13 (39.4)	0.457
Total ischemia duration (min)	16.09 ± 23.95	11.06 ± 18.43	0.301
Preoperative ischemia duration (min)	1.39 ± 2.83	1.21 ± 2.25	0.778
Intraoperative ischemia duration (min)	12.18 ± 20.38	9.24 ± 15.98	0.714
Postoperative ischemia duration (min)	2.52 ± 4.04	0.76 ± 1.73	0.063
Number of ischemic time points	1.76 ± 2.03	1.39 ± 2.18	0.352
Preoperative ischemia episodes, n (%)	6 (18.2)	8 (24.2)	0.547
Ischemia at induction, n (%)	9 (27.3)	8 (24.2)	0.778
Ischemia at intubation, n (%)	10 (30.3)	8 (24.2)	0.580
Ischemia at extubation, n (%)	10 (30.3)	6 (18.2)	0.251
Ischemia at 15 min postoperatively, n (%)	12 (36.4)	5 (15.2)	0.045
Ischemia on ECG at 6 h postoperatively, n (%)	6 (18.2)	5 (15.2)	0.741
Ischemia on ECG at 24 h postoperatively, n (%)	5 (15.2)	5 (15.2)	1.000
Maximum ST depression amplitude (mm)	1.58 ± 0.29	1.57 ± 0.30	0.987
Maximum ST elevation amplitude (mm)	2.76 ± 0.59	2.72 ± 0.40	0.876

Abbreviations: BA, balanced anesthesia; P-RIA, propofol–remifentanyl-based intravenous anesthesia. Values are presented as mean $\pm$ SD or n (%). Statistical significance was defined as $p < 0.05$.

Among patients who developed ischemia, the proportion with ASA III status was higher, and significant associations were observed with hypertension and heart failure ($p = 0.005$ and $p = 0.007$, respectively) (Table 4). Most ST-segment changes were asymptomatic, and no episodes requiring urgent clinical intervention occurred.

Examination of the temporal distribution of ischemic episodes indicated clustering around airway manipulation and periods of surgical stress in the BA group, whereas in the P-RIA group episodes occurred more often after intubation and during prolonged or intensive resection. In both anesthetic techniques, episodes appeared multifactorial in origin, but hemodynamic fluctuations were attenuated under P-RIA.

4. Discussion

This study is based on a re-evaluation of a historical cohort originally enrolled in a prospective, randomized, outcome-assessor-blinded trial conducted in 2001, with

the findings interpreted in the context of contemporary concepts of perioperative myocardial injury (MINS). At the time, high-sensitivity troponin assays were not available, so the analyses relied on ST-segment changes and CK-MB/CK measurements. The study population consisted of elderly ASA II–III TURP patients with cardiovascular comorbidities, predominantly within the low-intermediate Goldman cardiac risk categories; accordingly, the findings should be viewed as hypothesis-generating for this specific group.

The results indicate that P-RIA was associated with lower and more stable hemodynamic parameters and with a reduced ischemia rate only at the postoperative 15th minute; however, because this difference pertains to a single time point and shows borderline statistical significance ($p = 0.045$), it should not be interpreted as definitive evidence of superiority. The absence of differences in total ischemic burden and CK-MB–based injury is consistent with current literature suggesting that perioperative myocardial damage is driven more by hemodynamic imbalance than by the specific anesthetic agent used [1–3,16–18].

Table 4. Demographic, perioperative and postoperative characteristics in patients with and without myocardial ischemia.

	Myocardial ischemia present (n = 29)	Myocardial ischemia absent (n = 37)	p
Age (years)	68.72 ± 7.9	68.46 ± 6.9	0.885
Weight (kg)	68.69 ± 14.5	72.19 ± 13.8	0.321
Height (m)	1.63 ± 0.1	1.63 ± 0.1	0.941
BMI (kg/m ²)	25.83 ± 5	27.19 ± 4.5	0.251
ASA II / III	17 (58.6) / 12 (41.4)	31 (83.8) / 6 (16.2)	0.023
Goldman cardiac risk index – Low / intermediate / high	14 (48.3) / 11 (37.9) / 4 (13.8)	26 (70.3) / 8 (21.6) / 3 (8.1)	0.193
Resection time (min)	48.45 ± 20.1	46.05 ± 18.2	0.615
Anesthesia time (min)	56.76 ± 20.8	56.41 ± 19.9	0.944
Total glycine used (L)	16.17 ± 6.8	14.72 ± 5.9	0.357
Glycine absorbed (L)	0.76 ± 0.68	0.93 ± 0.89	0.382
Resected prostate weight (g)	20.72 ± 13.3	20.11 ± 14.4	0.859
Preoperative ejection fraction (%)	61.24 ± 10.8	64.38 ± 7.7	0.174
Comorbidities			
Number of comorbidities	2.9 ± 1.8	2.2 ± 1.2	0.890
Hypertension	16 (55.2)	8 (21.6)	0.005
Diabetes mellitus	3 (10.3)	5 (13.5)	0.695
COPD	14 (48.3)	15 (40.5)	0.530
Atrial fibrillation	1 (3.4)	2 (5.4)	0.592
Smoking history	15 (51.7)	22 (59.5)	0.530
Heart failure	10 (34.5)	3 (8.1)	0.007
Previous stroke	2 (6.9)	4 (10.8)	0.583
Exercise limitation	8 (27.6)	7 (18.9)	0.404
Mitral regurgitation (mild)	7 (24.1)	3 (8.1)	0.071
Aortic regurgitation (mild)	3 (10.3)	1 (2.7)	0.197
Coronary artery disease	3 (10.3)	4 (10.8)	0.951
Obesity	6 (20.7)	8 (21.6)	0.927
Complications			
Atrial fibrillation	1 (3.4)	0 (0)	0.439
Ischemic stroke	0 (0)	2 (5.4)	0.500
TUR syndrome	0 (0)	2 (5.4)	0.500
Chest pain	0 (0)	1 (2.7)	0.561
Ventricular premature beats	1 (3.4)	0 (0)	0.439
Pulmonary thromboembolism	0 (0)	1 (2.7)	0.561
Hyponatremia			
Mild	11 (37.9)	7 (18.9)	0.085
Moderate	7 (24.1)	5 (13.5)	0.267
Severe	3 (10.3)	7 (18.9)	0.335
Hypokalemia	15 (51.7)	16 (43.2)	0.493
Anemia (Hb < 9 g/dL)	9 (31)	6 (16.2)	0.154

Abbreviations: BMI, body mass index; ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; TUR, transurethral resection of the prostate. Values are presented as mean ± SD or n (%). Statistical significance was defined as $p < 0.05$.

Although the BA group had a higher baseline ejection fraction—typically indicative of better left ventricular function and cardiac reserve—the overall ST-segment-defined ischemic burden did not differ from that observed with P-RIA. This finding suggests that hemodynamic control may be an important determinant of ischemia independent of ejection fraction. Similarly, the P-RIA group exhibited greater calculated glycine absorption and a more pronounced yet clinically silent decrease

in Hb/Hct, both of which could potentially disturb the myocardial oxygen supply-demand balance; however, no significant differences were detected in total ischemia duration or CK-MB-based myocardial injury despite these factors.

Taken together, these observations indicate that the impact of anesthetic technique and irrigation load is multifactorial and closely intertwined with hemodynamic stability and baseline cardiac reserve. Although

baseline EF was higher in the BA group and glycine absorption was greater in the P-RIA group, neither variable correlated clearly with global ischemia burden, supporting the notion that the observed ischemic and hemodynamic patterns are driven primarily by perioperative blood pressure and heart rate control. Because the sample size was limited, multivariable adjustment including ejection fraction, ASA class, and glycine absorption could not be reliably performed; these variables were therefore treated as potential confounders. Consequently, while the influence of these baseline differences cannot be fully disentangled, the available data nonetheless reinforce the predominant role of hemodynamic stability in determining perioperative cardiovascular outcomes.

These findings, when considered alongside contemporary data indicating that HoLEP, bipolar TURP, and other laser enucleation techniques offer a more favorable safety profile—particularly in elderly BPH patients with substantial comorbidity, with lower blood loss, reduced transfusion requirements, and shorter hospital stays—underscore the need to optimize surgical and anesthetic strategies in parallel. However, the limited availability of detailed data on cardiac-risk subgroups and on comprehensive ischemia monitoring (high-sensitivity troponin, continuous ST-segment surveillance) in HoLEP and related series further highlights the value of the present TURP cohort. The extensive hemodynamic and ST-segment information from this historical dataset, reinterpreted in light of current concepts, provides a useful reference framework that may help inform monitoring strategies in newer surgical techniques [4,5,7,8,19].

The historical nature of this study should be emphasized; its design, data collection period, and outcome definitions differ substantially from contemporary MINS research based on high-sensitivity troponin assays. Consequently, the findings should not be interpreted as directly representative of modern perioperative practice, but rather as a re-evaluation of an ST-segment-based cohort in the light of current concepts.

In both groups, ST-segment changes were similar in magnitude (± 1 –3 mm) and short in duration, suggesting that most episodes were subclinical and predominantly hemodynamic in origin. This is consistent with evidence that perioperative myocardial injury after non-cardiac surgery is frequently asymptomatic and often detected only by elevations in high-sensitivity troponin, despite its strong association with mortality.

Nevertheless, because high-sensitivity troponin was not measured in this study, MINS could not be formally diagnosed and contemporary definitions could not be directly assessed. Although CK-MB and ST-segment findings cannot be mapped one-to-one onto modern MINS criteria, the observed patterns of hypotension, tachycardia, and anemia/hemodilution align closely with the key pathophysiological mechanisms described in the current literature [1,2].

In this context, the findings suggest that P-RIA may attenuate sympathetic activation and hemodynamic fluctuations, particularly in the early postoperative period, and indicate that such an approach should, in contemporary practice, be evaluated in conjunction with systematic high-sensitivity troponin monitoring [1–3,10,16–

18]. Consequently, this study should not be viewed as a direct assessment of MINS but rather as a historical, hypothesis-generating dataset in which ST-segment and CK-MB/CK patterns are interpreted within the framework of mechanisms known to be associated with MINS.

Although a greater volume of glycine absorption was estimated in the P-RIA group, serum sodium and potassium levels were similar between groups. Nevertheless, TURP syndrome was reported in 2 patients in the P-RIA group, and severe hyponatremia was reported in a total of 10 patients across both groups. Thus, similar serum electrolyte levels between groups do not imply the absence of clinically important electrolyte disturbances in individual patients. These findings differ from those of contemporary bipolar TURP and HoLEP series reporting that, with improved irrigation techniques and optimized fluid and electrolyte management, classical TURP syndrome has become rare and hyponatremia is generally mild (Clavien–Dindo grade I–II) [4].

When the more pronounced yet clinically silent decrease in Hb/Hct in the P-RIA group is interpreted alongside MINS literature indicating that anemia and hemodilution can contribute to perioperative myocardial injury but are generally manageable factors, these findings support the notion that the balance between hemodynamic stability and controlled hemodilution plays a key role in cardiac risk management [1,2,5,7,17,18].

In terms of risk profile, the higher prevalence of ASA class III status, hypertension, and heart failure among patients who developed ischemia in the cohort is consistent with the reported determinants of MINS/PMI in large non-cardiac surgical series (Table 4; hypertension $p = 0.005$, heart failure $p = 0.007$). These findings parallel the literature indicating that advanced age and ASA ≥ 3 are independent risk factors, whereas diabetes and COPD make a more limited contribution [17,20]. This concordance supports a reserve-oriented approach that emphasizes the central role of ASA class, blood pressure control, and left ventricular function in cardiac management [12,17,20].

Evidence from noncardiac surgery suggests that differences in hemodynamic responses between sevoflurane- and propofol-based anesthesia do not necessarily translate into differences in major cardiac outcomes. In a randomized trial involving elderly patients with coronary heart disease, Zhang et al. found no significant between-group differences in troponin I or BNP concentrations at the measured time points; however, the 24-hour area under the curve for troponin I was lower and intraoperative hemodynamic stability was better with sevoflurane than with propofol–remifentanyl. Similarly, in their systematic review and meta-analysis, An et al. found no significant differences in postoperative major adverse cardiac events or mortality between sevoflurane and propofol anesthesia, despite lower early postoperative troponin I concentrations and a lower incidence of myocardial ischemia with sevoflurane [21,22].

These findings provide indirect context rather than direct evidence for the comparison of the two regimens used in our TURP population. In the present study, although arterial pressures were higher in the BA group during extubation, the incidence of ischemia was similar between groups. Thus, the observed differences in arte-

rial pressure were not accompanied by a detectable difference in ischemia incidence; however, this observation alone establishes neither cardiac equivalence between the regimens nor a mechanism mediated by modulation of the overall stress response.

Because nitrous oxide was used in both groups, the P-RIA regimen should be described not as classical “total intravenous anesthesia” but as an intravenous anesthesia technique based on propofol–remifentanyl. The hemodynamic advantage of P-RIA rests on serial rather than single measurements; repeated assessments showed lower and less variable systolic and mean arterial pressures, as well as heart rates. This pattern underscores the key role of sustained hemodynamic control in maintaining myocardial oxygen supply–demand balance in high-risk TURP patients.

These findings provide a meaningful framework for re-examining a historical ST-segment and hemodynamic cohort in the light of contemporary MINS concepts; however, the data collection period, the outcome measures employed, and the absence of troponin data limit the extent to which the results can be interpreted as directly representative of a modern perioperative MINS study. Within this context, the study suggests that P-RIA may be associated with a more stable hemodynamic profile in TURP patients at cardiac risk, and further indicates that the lower ST-segment ischemia rate observed at the 15th minute of the early postoperative period is a hypothesis-generating finding that remains uncertain and requires confirmation, given the multiple comparisons and limited sample size.

This prospectively collected, randomized dataset, when re-interpreted from a contemporary MINS perspective, provides a conceptual foundation that may help define target hemodynamic parameters for less invasive BPH procedures such as HoLEP and bipolar TURP [4,5,8,16,19,23]. In this respect, the study can be regarded as a historical data source of reference value for troponin-based MINS research.

This study suggests that a propofol–remifentanyl-based approach may be associated with a more controlled hemodynamic course in elderly ASA II–III TURP patients with cardiovascular comorbidities. However, no clear difference was demonstrated between the two anesthetic techniques in terms of overall ischemic burden or CK-MB-based myocardial injury.

The modest reduction in ischemia observed in the early postoperative period should be regarded as a signal that warrants further investigation rather than as evidence of a definite effect, given the methodological limitations. The absence of troponin data prevents a direct linkage of the results to contemporary MINS definitions. Accordingly, the study should be considered not as a source of findings that can be directly generalized to clinical practice, but as a historical dataset that highlights the importance of perioperative hemodynamic control and provides a foundation for future troponin-based research.

4.1. Limitations

The single-center design and limited sample size leave the study underpowered for rare clinical endpoints

such as MI and mortality, and the absence of troponin measurements raises the possibility that silent injuries meeting contemporary MINS criteria may have been missed. Multiple time-point analyses yielded only one significant finding (at 15 minutes postoperatively), which increases the likelihood of a false-positive result and relegates this outcome to a hypothesis-generating level. Hemodynamic assessment was based on mean values and patterns; however, because episodes of hypotension/bradycardia and the frequency of interventions were not systematically recorded, the results may reflect the combined impact of anesthetic technique and clinical management rather than anesthesia alone. The use of different induction agents (etomidate versus propofol) also limits the extent to which the observed hemodynamic differences can be attributed solely to the maintenance regimen. The observation of smaller-than-anticipated effect sizes indicates that the study was underpowered to detect differences in overall ischemic burden and biochemical endpoints. In addition, the lack of multivariable analyses prevented clear delineation of the potential confounding effects of variables such as ejection fraction, glycine absorption, and comorbidities. Because the study population consisted predominantly of patients in the low-to-intermediate Goldman risk categories, the findings cannot be generalized to individuals at cardiac risk and should be interpreted as applicable to a specific comorbid patient subgroup.

5. Conclusions

In this study, propofol–remifentanyl-based intravenous anesthesia was associated with a more stable hemodynamic profile than sevoflurane-based balanced anesthesia in ASA II–III patients with cardiovascular comorbidities undergoing monopolar TURP. However, no superiority was demonstrated in terms of overall ST-segment ischemic burden or CK-MB–defined myocardial injury. The lower incidence of ischemia observed at 15 minutes postoperatively should be regarded as a hypothesis-generating finding rather than definitive evidence, given the multiple comparisons and limited sample size.

Although the prospective, randomized design is a strength of the study, the absence of troponin measurements limits the interpretation of the findings within the contemporary MINS framework. Furthermore, an independent association between hemodynamic stability and myocardial injury could not be established because no multivariable adjustment was performed. Accordingly, the findings should be interpreted as exploratory and should not be used to draw a causal conclusion that hemodynamic stability is the primary determinant of myocardial injury or is more important than anesthetic agent selection. The clinical significance of the hemodynamic advantages observed with propofol–remifentanyl-based intravenous anesthesia should be evaluated in larger, multicenter studies using contemporary surgical techniques and incorporating troponin-based MINS endpoints and appropriate multivariable analyses.

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Presentation at a Meeting

This research has previously been presented at the Anesthesiology and Reanimation Specialists' Society Congress, ARUD 2019, Balkan States Anesthesia Days – VI Trauma, Anesthesia and Intensive Care, held in İzmir, Türkiye, on 3-6 April 2019.

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Conflict of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this manuscript.

Data Availability

The datasets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author upon reasonable request.

AI Assistance

No AI-based tools were used in the preparation of this manuscript.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Ankara Numune Education and Research Hospital (Approval Number & Date: 2001-06-04). Written informed consent was obtained from all individual participants prior to their inclusion in the study. Participants were fully informed about the study's aims, procedures, potential risks and benefits, and their rights-including the right to withdraw at any time without consequence. All participants voluntarily signed a written informed consent form. All procedures were conducted in accordance with the Declaration of Helsinki.

Author Contributions

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Research Article

Factors associated with new-onset atrial fibrillation after coronary stent implantation: A single-center retrospective cohort study

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ABSTRACT

Background: New-onset atrial fibrillation is a clinically relevant complication that may occur after coronary stent implantation. Although several clinical and echocardiographic factors have been associated with post-procedural atrial fibrillation, the relationship between coronary anatomical disease burden and early new-onset atrial fibrillation remains incompletely characterized. Therefore, this study aimed to investigate the association between coronary anatomical disease burden and early new-onset atrial fibrillation in patients undergoing coronary stent implantation.

Methods: We retrospectively evaluated 450 patients who underwent coronary stent implantation between January 2018 and December 2025. Patients with a previous history of atrial fibrillation, permanent pacemaker implantation, moderate-to-severe valvular heart disease, or incomplete clinical data were excluded. Patients were monitored for the occurrence of documented new-onset atrial fibrillation during the seven-day observation period. Clinical, laboratory, echocardiographic, and angiographic characteristics were compared between patients who developed atrial fibrillation and those who did not. Coronary anatomical complexity was assessed using the SYNTAX score. Multivariable logistic regression analysis was performed to identify factors independently associated with new-onset atrial fibrillation.

Results: New-onset AF was documented in 37 patients (8.2%). Patients who developed AF were older and had larger left atrial diameter and higher SYNTAX scores than those without AF. In multivariable logistic regression analysis, increasing age (adjusted OR, 1.07; 95% CI, 1.03–1.11; $p = 0.001$), larger left atrial diameter (adjusted OR, 1.15; 95% CI, 1.07–1.24; $p < 0.001$), and higher SYNTAX score (adjusted OR, 1.09; 95% CI, 1.04–1.15; $p < 0.001$) were independently associated with new-onset AF. Given the limited number of AF events, these associations should be interpreted cautiously.

Conclusion: In this retrospective cohort of patients undergoing coronary stent implantation, older age, larger left atrial diameter, and higher SYNTAX score were independently associated with documented new-onset atrial fibrillation within seven days. These findings suggest that both atrial structural characteristics and coronary anatomical disease burden may be relevant to early post-procedural atrial fibrillation. However, the findings are exploratory and should be confirmed in larger prospective studies incorporating systematic rhythm monitoring.

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1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in the adult population and is

strongly associated with stroke, heart failure, and increased mortality [1]. Current epidemiological data indicate that the prevalence of AF in the general population is 1–2% and increases exponentially with age [2]. The

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prevalence of AF is higher in patients with coronary artery disease, and these two conditions frequently coexist [3].

New-onset AF after percutaneous coronary intervention (PCI) represents an important clinical problem. Population-based studies have demonstrated that this condition is associated with increased mortality [4]. In addition, AF occurring after coronary intervention has been linked to long-term major adverse cardiac events [5].

The pathophysiology of new-onset AF after coronary stent implantation is complex and multifactorial. Advanced age, structural changes of the left atrium, increased atrial pressure, and inflammatory activity are considered key components [6]. Procedure-related microvascular injury, myocardial ischemia, and reperfusion injury may also increase atrial electrical instability and facilitate arrhythmia development [7]. Moreover, the increased ischemic burden related to diffuse and complex coronary artery disease may trigger electrical remodelling in atrial tissue.

Previous studies have investigated the incidence and predictors of new-onset atrial fibrillation after primary percutaneous coronary intervention, although the contribution of individual angiographic and procedural characteristics remains incompletely defined [8].

In this context, identifying the determinants of new-onset AF after coronary stent implantation is of major importance for early risk stratification and the development of individualized follow-up strategies. The aim of this study was to evaluate the clinical and angiographic predictors of new-onset AF in a single-center cohort.

Although previous studies have identified several clinical and structural factors associated with new-onset AF after coronary intervention, the relative contribution of angiographic disease burden in conjunction with established clinical and echocardiographic characteristics remains incompletely defined [9–12]. In particular, it is unclear whether the extent of angiographic coronary disease provides additional information regarding the occurrence of new-onset AF beyond conventional risk factors and atrial structural characteristics. Therefore, the present study aimed to evaluate the clinical, echocardiographic, laboratory, and angiographic factors associated with documented new-onset AF within seven days after coronary stent implantation. By simultaneously assessing these different domains, this study seeks to provide a more comprehensive characterization of factors associated with early post-procedural AF and to identify variables that may help clinicians recognize patients who warrant closer rhythm surveillance.

2. Materials and Methods

2.1. Study design and patient selection

This single-center, retrospective cohort study included patients who underwent coronary stent implantation between January 2018 and December 2025. Medical records were reviewed retrospectively after ethics committee approval on December 10, 2025 (Approval No. 2025/12-296). Patients with a previous history of

atrial fibrillation (AF), permanent pacemaker implantation, moderate-to-severe valvular heart disease, or incomplete clinical data were excluded. The final study population consisted of 450 patients.

New-onset AF was defined as a newly documented episode occurring within seven days after coronary stent implantation in patients without a documented history of AF before the index procedure. AF was identified by 12-lead electrocardiography or continuous telemetry during hospitalization. An episode was considered diagnostic of AF if it lasted at least 30 seconds and demonstrated an irregularly irregular ventricular rhythm without consistent, discernible P waves and with variable atrial activity.

The study aimed to evaluate clinical, laboratory, echocardiographic, and angiographic factors associated with documented new-onset AF within seven days after coronary stent implantation.

2.2. Data collection

Demographic data, comorbidities, laboratory findings, echocardiographic measurements, and angiographic data were obtained retrospectively from the hospital electronic medical records. Age, sex, hypertension, diabetes mellitus, chronic kidney disease, heart failure, and smoking status were recorded. Laboratory parameters included hemoglobin, creatinine, C-reactive protein, and troponin levels.

2.3. Echocardiographic assessment

All patients underwent transthoracic echocardiography before the procedure. Left ventricular ejection fraction was calculated using the Simpson method, and left atrial diameter was measured from the parasternal long-axis view.

2.4. Angiographic and interventional characteristics

Coronary angiography was performed using standard projections. The number of diseased vessels, total number of stents, total stent length, and angiographic disease severity scores were recorded. All procedures were performed by experienced interventional cardiologists. Coronary anatomical complexity was assessed using the SYNTAX score, whereas multivessel disease, number of implanted stents, and total stent length were recorded as separate angiographic and procedural characteristics. These variables were considered distinct measures of coronary disease extent and procedural complexity, although potential overlap between these measures was recognized during interpretation of the multivariable analysis.

2.5. Outcome measure

The primary endpoint was the occurrence of new-onset AF confirmed by electrocardiography or continuous monitoring within the first seven days after coronary stent implantation.

During hospitalization, all patients were monitored with continuous telemetry for at least the first 48 hours

after the procedure. In addition, daily 12-lead electrocardiograms were routinely performed, and additional ECG recordings were obtained if patients developed symptoms suggestive of arrhythmia. For patients discharged before day seven, outpatient clinical evaluation and ECG review were performed when clinically indicated.

2.6. Statistical analysis

Statistical analyses were performed using SPSS software. Continuous variables are presented as mean $\pm$ standard deviation, and categorical variables as numbers and percentages. Group comparisons were performed using the Student's *t*-test or Mann–Whitney *U* test for continuous variables and the chi-square test for categorical variables. Candidate variables for the multivariable logistic regression model were selected based on both clinical relevance and findings from the univariate analyses. Variables showing a statistically significant association with new-onset atrial fibrillation in the univariate analysis and variables considered clinically relevant based on established risk factors were considered for multivariable analysis. The final multivariable model included age, left atrial diameter, hypertension, heart failure, C-reactive protein, total stent length, multivessel disease, and angiographic disease severity score. Odds ratios (ORs) with 95% confidence intervals (CI) were calculated. A two-sided *p* value < 0.05 was considered statistically significant.

Because only 37 patients developed new-onset AF, the number of events available for multivariable analysis

was relatively limited. Candidate variables were therefore selected on the basis of clinical relevance and findings from the univariate analyses rather than by indiscriminate inclusion of all measured variables. The multivariable results were interpreted cautiously, particularly for variables representing related aspects of coronary disease burden.

Given the relatively small number of outcome events (37 patients with new-onset AF), the multivariable logistic regression analysis was considered exploratory. Variables were selected based on clinical relevance and the results of the univariate analyses rather than including all available covariates simultaneously. The resulting odds ratios and confidence intervals were interpreted cautiously, and no claim of development or validation of a clinical prediction model was made.

3. Results

A total of 450 patients were included. New-onset AF occurred in 37 patients (8.2%) within seven days after coronary stent implantation. The mean age was 71 ± 9 years in patients who developed AF and 62 ± 11 years in those who did not ($p < 0.001$). The prevalence of hypertension was 78% versus 56% ($p = 0.01$), and heart failure was 41% versus 18% ($p = 0.002$), respectively. The baseline clinical, echocardiographic, and angiographic characteristics of the study population are summarized in Table 1.

Table 1. Baseline clinical, echocardiographic and angiographic characteristics.

Variable	AF (+) (<i>n</i> = 37)	AF (–) (<i>n</i> = 413)	<i>p</i> value
Age (years)	71 $\pm$ 9	62 $\pm$ 11	< 0.001
Hypertension, <i>n</i> (%)	29 (78)	231 (56)	0.01
Heart failure, <i>n</i> (%)	15 (41)	74 (18)	0.002
Left atrial diameter (mm)	41 $\pm$ 4	36 $\pm$ 5	< 0.001
Left ventricular ejection fraction (%)	51 $\pm$ 8	53 $\pm$ 7	0.18
C-reactive protein (mg/L)	9.2 $\pm$ 3.1	4.6 $\pm$ 2.4	< 0.001
Multivessel disease, <i>n</i> (%)	24 (65)	157 (38)	0.004
Total stent length (mm)	48 $\pm$ 16	32 $\pm$ 14	< 0.001
Number of stents	2.3 $\pm$ 0.9	1.6 $\pm$ 0.7	< 0.001
Angiographic disease severity score	24 $\pm$ 7	16 $\pm$ 6	< 0.001

Data are presented as mean $\pm$ standard deviation or number (percentage). AF: atrial fibrillation. *p* values were calculated using Student's *t*-test or Mann–Whitney *U* test for continuous variables and chi-square test for categorical variables.

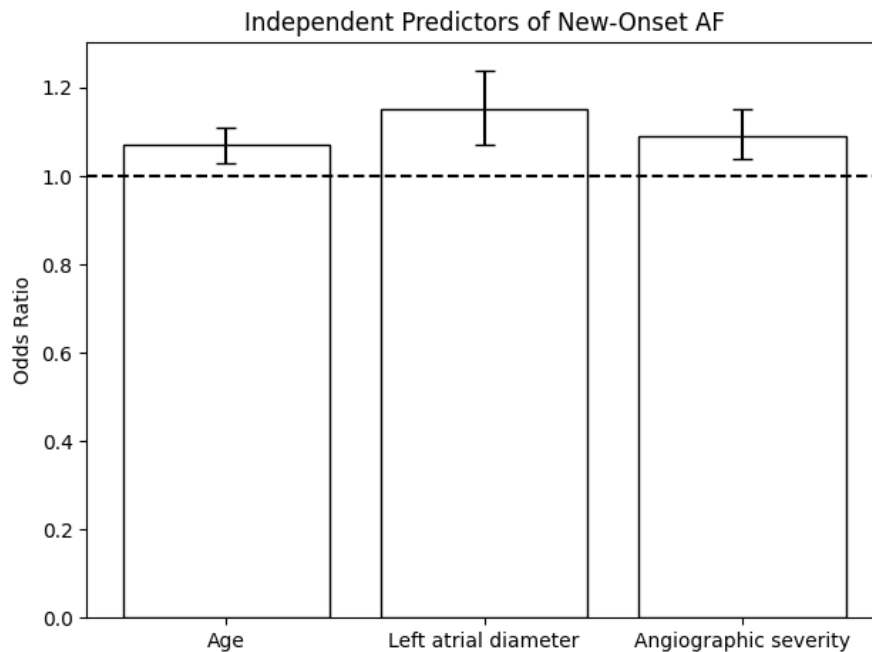
Left atrial diameter was significantly larger in the AF group (41 $\pm$ 4 mm vs. 36 $\pm$ 5 mm, $p < 0.001$). Left ventricular ejection fraction was similar between groups (51 $\pm$ 8% vs. 53 $\pm$ 7%, $p = 0.18$). C-reactive protein levels were higher in patients with AF (9.2 $\pm$ 3.1 mg/L vs. 4.6 $\pm$ 2.4 mg/L, $p < 0.001$). Multivessel disease was more frequent in patients who developed AF (65% vs. 38%, $p = 0.004$). Total stent length was 48 $\pm$ 16 mm versus 32 $\pm$ 14 mm ($p < 0.001$). The mean number of stents was 2.3 $\pm$ 0.9 versus 1.6 $\pm$ 0.7 ($p < 0.001$). The mean SYNTAX score was significantly higher in patients who developed new-onset AF than in those who did not develop AF (24 $\pm$ 7 vs. 16 $\pm$ 6, respectively; $p < 0.001$). In multivariable logistic regres-

sion, advanced age (OR 1.07; 95% CI 1.03–1.11; $p = 0.001$), left atrial diameter (OR 1.15; 95% CI 1.07–1.24; $p < 0.001$), and angiographic disease severity (OR 1.09; 95% CI 1.04–1.15; $p < 0.001$) were independent predictors of new-onset AF. Independent predictors of new-onset AF identified in the multivariable model are shown in Table 2 and graphically illustrated in Fig. 1.

OR: odds ratio; CI: confidence interval. Variables included in the multivariable model were age, left atrial diameter, angiographic disease severity score, hypertension, heart failure, C-reactive protein, total stent length, and multivessel disease. A *p* value < 0.05 was considered statistically significant.

Table 2. Multivariable logistic regression analysis for new-onset atrial fibrillation.

Variable	Odds ratio (OR)	95% confidence interval	p value
Age (per year)	1.07	1.03–1.11	0.001
Left atrial diameter (per mm)	1.15	1.07–1.24	< 0.001
SYNTAX score	1.09	1.04–1.15	< 0.001

**Fig. 1.** Factors independently associated with new-onset atrial fibrillation.

(Bars represent odds ratios; error bars indicate 95% confidence intervals. The dashed horizontal line indicates OR = 1.)

4. Discussion

In this single-center retrospective study, the incidence of new-onset AF within seven days after coronary stent implantation was 8.2%. Previous studies have reported rates ranging from 5% to 12% [13]. These differences may be explained by variations in patient characteristics, follow-up duration, and definitions of AF.

Age was independently associated with new-onset atrial fibrillation in the multivariable analysis. Multicenter analyses in patients with ST-elevation myocardial infarction have also shown that age is one of the most important predictors of new-onset AF [14]. Age-related atrial fibrosis, conduction slowing, and electrical heterogeneity create a substrate for arrhythmogenesis.

Left atrial diameter was another independent predictor, supporting the role of atrial stretch and structural remodeling in AF pathogenesis [15]. Pre-procedural echocardiographic assessment may therefore be useful for risk stratification.

Angiographic disease severity was independently associated with new-onset AF, suggesting that increased ischemic burden and complex coronary anatomy may promote atrial electrical instability. New-onset AF after primary PCI has been linked to multivessel disease and high-risk lesions [16]. The independent association between SYNTAX score and new-onset AF is a potentially important finding of the present study. The SYNTAX score reflects the anatomical extent and complexity of

coronary artery disease and may therefore serve as an indirect marker of overall coronary atherosclerotic burden. More extensive and complex coronary disease may be associated with a greater ischemic burden, systemic inflammation, endothelial dysfunction, and adverse ventricular or atrial remodeling, all of which may facilitate the development of atrial arrhythmias. However, given the observational nature of our study, this association should not be interpreted as evidence of a direct causal relationship.

The relatively small number of patients who developed new-onset AF ($n = 37$) represents an important limitation of the multivariable analysis. Although several clinically relevant variables were considered, the number of outcome events was limited relative to the number of candidate covariates. Consequently, model overfitting and instability of the estimated associations cannot be completely excluded. The multivariable findings should therefore be considered exploratory and hypothesis-generating rather than definitive estimates of independent predictive effects. Larger prospective studies with adequate numbers of AF events are required to confirm these associations and to determine whether they provide incremental value for clinical risk stratification. With 37 AF events and eight covariates included in the multivariable model, the events-per-variable ratio was relatively low. Therefore, the possibility of overfitting and imprecision of the regression coefficients should be acknowledged when interpreting the observed associations.

The association between larger left atrial diameter and new-onset AF is biologically plausible and is consistent with previous clinical observations. In a cohort of 1,603 patients with STEMI undergoing primary PCI, new-onset AF occurred in 6.1% of patients, and left atrial diameter was identified as an independent factor associated with AF. These findings support the concept that pre-existing atrial structural remodeling may contribute to susceptibility to AF during the acute or early post-interventional period. Our findings extend this observation to a broader population of patients undergoing coronary stent implantation [17].

Our findings are broadly consistent with more recent studies evaluating new-onset AF after PCI. In a contemporary cohort of patients undergoing PCI for acute myocardial infarction, increasing age and larger left atrial diameter were independently associated with new-onset AF, while the type of PCI was also associated with AF risk. These findings support the importance of age and atrial structural remodeling as clinically relevant determinants of post-PCI AF [18].

Our study extends these observations by evaluating clinical, echocardiographic, and angiographic characteristics together in a broader cohort of patients undergoing coronary stent implantation. In particular, the independent association between angiographic disease severity and new-onset AF suggests that the extent of coronary atherosclerotic burden may provide additional information beyond conventional clinical and echocardiographic variables. This association should nevertheless be interpreted cautiously, as angiographic disease severity may partly reflect overall ischemic and procedural complexity rather than a direct causal mechanism.

From a practical standpoint, early identification of patients at high risk for new-onset atrial fibrillation may allow closer rhythm surveillance, optimization of volume status, stricter control of blood pressure, and consideration of tailored antithrombotic strategies. Such an approach may potentially reduce arrhythmia-related complications and improve short- and long-term outcomes after coronary intervention.

The independent association between the SYNTAX score and new-onset AF should be interpreted with caution. Several angiographic and procedural variables, including SYNTAX score, multivessel disease, number of stents, and total stent length, may be interrelated and may partly represent the same underlying construct of coronary disease burden. In addition, only 37 patients developed new-onset AF, resulting in a relatively limited number of outcome events for multivariable modeling. Therefore, residual confounding, model instability, and potential overfitting cannot be completely excluded. The present findings should consequently be regarded as hypothesis-generating rather than as a validated prediction model.

Future prospective studies with larger sample sizes and a greater number of AF events should evaluate whether angiographic disease complexity provides incremental prognostic information beyond established clinical and echocardiographic risk factors.

This study has several limitations. First, its retrospec-

tive, single-center design limits the generalizability of the findings and precludes conclusions regarding causality. Second, the relatively small number of patients who developed new-onset AF ($n = 37$) limited the number of outcome events available for multivariable analysis. With eight covariates considered in the final model, the events-per-variable ratio was relatively low; therefore, model instability and potential overfitting cannot be completely excluded. The multivariable findings should consequently be interpreted as exploratory and hypothesis-generating rather than as a validated prediction model. Third, rhythm surveillance was not uniform throughout the entire seven-day observation period. Continuous telemetry was routinely performed for at least the first 48 hours during hospitalization, whereas post-discharge rhythm assessment was clinically driven. Consequently, asymptomatic episodes of AF occurring after hospital discharge may have remained undetected, potentially resulting in an underestimation of the incidence of documented new-onset AF. In addition, previously unrecognized paroxysmal AF could not be completely excluded because systematic prolonged ambulatory rhythm monitoring before or after the index procedure was not performed. Fourth, several angiographic and procedural variables, including SYNTAX score, multivessel disease, number of stents, and total stent length, may represent overlapping aspects of coronary disease burden and procedural complexity. Although these variables were considered separately in the analysis, residual interrelationships among them may have influenced the estimated associations. Therefore, the independent association between SYNTAX score and new-onset AF should be interpreted cautiously. Finally, because the study focused on clinically documented AF during the defined observation period, the findings should not be interpreted as representing the complete burden of post-PCI atrial arrhythmia. Prospective multicenter studies incorporating systematic and prolonged rhythm monitoring, larger sample sizes, and appropriately powered multivariable or prediction analyses are needed to validate these findings.

5. Conclusions

In patients undergoing coronary stent implantation, older age, larger left atrial diameter, and higher SYNTAX score were independently associated with documented new-onset AF within seven days of the procedure. These findings suggest that early post-procedural AF may be related to both pre-existing atrial structural substrate and the extent of coronary anatomical disease. However, given the retrospective single-center design, the limited number of AF events, the potential overlap among measures of coronary disease burden, and the possibility of undetected asymptomatic AF after hospital discharge, these findings should be considered exploratory rather than definitive. Larger prospective studies with systematic prolonged rhythm monitoring are warranted to determine whether these factors provide clinically meaningful incremental information for identifying patients at increased risk of post-PCI AF.

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Conflict of Interest

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Data Availability

The datasets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author upon reasonable request.

AI Assistance

No AI-based tools were used in the preparation of this manuscript.

Ethics Approval and Consent to Participate

This study was approved by the ethics committee of Erzurum Faculty of Medicine, University of Health Sciences, Türkiye (Approval Number: 2025/12-296; Date: 10.12.2025). Written informed consent was obtained from all participants. All procedures were conducted in accordance with relevant guidelines and regulations.

Author Contributions

Esma Selva Ateş Ceyhun: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, validation, visualization, writing – original draft, writing – review & editing.

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Research Article

Health literacy, decisional conflict, and body image in patients eligible for breast-conserving surgery: A comparison between mastectomy and breast-conserving surgery groups

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ABSTRACT

Objective: The aim was to evaluate the relationship between health literacy, decision conflict, and body image in early-stage breast cancer patients eligible for breast-conserving surgery (BCS) who opted for either breast-conserving surgery or mastectomy.

Methods: This prospective, cross-sectional study included 60 female patients eligible for BCS (30 mastectomy, 30 BCS). Health literacy was assessed using the European Health Literacy Survey Questionnaire-6 (HLS-EU-Q6); decision conflict was evaluated using the SURE and the Decision Conflict Scale (DCS); and body image was assessed using the Body Image Scale. The groups were compared using appropriate statistical methods, and factors associated with decisional conflict were explored using logistic regression analysis.

Results: The groups were similar in terms of age, marital status, and education level ($p > 0.05$). The level of health literacy was significantly higher in the mastectomy group compared to the BCS group (median 3.52 vs. 2.36; $p < 0.001$). In contrast, body image satisfaction was higher in the BCS group (3.50 vs. 2.00; $p < 0.001$), while body image-related anxiety was lower (2.00 vs. 4.00; $p < 0.001$). While SURE scores were higher in the mastectomy group (4.00 vs. 2.00; $p < 0.001$), the total DCS score was higher in the BCS group (47.65 vs. 14.66; $p < 0.001$). In the multivariable analysis, age and health literacy were not found to be significant independent predictors of decision conflict ($p > 0.05$).

Conclusion: Health literacy, decisional conflict, and body image differed significantly between patients who underwent mastectomy and those who underwent breast-conserving surgery. Because these variables were assessed after the surgical decision had already been finalized, these findings should be interpreted as associations rather than causal determinants of surgical choice; larger, longitudinal studies assessing these factors before the decision is made are needed to clarify their role in shared decision-making.

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1. Introduction

Breast cancer is the most common malignancy in women, and thanks to advances in diagnosis and treat-

ment, the rate of early-stage detection is steadily increasing. Long-term studies have demonstrated that breast-conserving surgery (BCS) followed by radiation therapy in early-stage breast cancer yields oncological

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outcomes equivalent to those of mastectomy; therefore, breast-conserving surgery is recommended as the standard treatment approach in current guidelines for appropriate patients [1,2].

Nevertheless, a significant proportion of patients who meet the criteria for breast-conserving surgery opt for mastectomy. In the literature, factors influencing this preference include tumor characteristics, educational level, socioeconomic status, the surgeon's recommendation, family influence, and, in particular, fear of recurrence. However, these variables alone are insufficient to explain patients' surgical preferences, and it is believed that psychosocial factors also play an important role in the decision-making process [3,4].

In recent years, with the widespread adoption of a patient-centered care approach, the concept of shared decision-making has gained importance in breast cancer surgery. The effectiveness of this process is closely related to the level of health literacy—which refers to patients' ability to access, understand, and evaluate health information. It has been reported that low health literacy makes it difficult to understand treatment options, increases uncertainty in the decision-making process, and leads to higher levels of decision conflict [5,6]. More recent evidence continues to underscore this relationship: qualitative syntheses have identified persistent barriers to fully shared decision-making in breast cancer surgical care [7]. Furthermore, a recent study found that, although health literacy was not independently associated with the choice between breast-conserving surgery and mastectomy, it was associated with the receipt of contralateral prophylactic mastectomy and breast reconstruction, as well as with survival outcomes in breast cancer [8].

The choice of surgical treatment directly affects not only clinical outcomes but also patients' quality of life and body image. It has been shown that breast-conserving surgery yields more positive outcomes in terms of body image, perception of femininity, and psychosocial well-being, whereas body image disturbances and psychological distress are more pronounced in patients who undergo mastectomy [9,10].

However, in the current literature, there are very few studies that jointly assess health literacy, decision conflict, and body image perceptions in patients who opt for mastectomy even though they are eligible for BCS. Elucidating this relationship could contribute to a better understanding of the surgical decision-making process and the improvement of patient counseling, and may help generate hypotheses relevant to reducing potentially avoidable mastectomies that future interventional research could test. Therefore, the aim of this study was to evaluate the relationship between health literacy levels, decision conflict, and body image perceptions in patients eligible for breast-conserving surgery, comparing those who opted for breast-conserving surgery with those who opted for mastectomy.

2. Materials and Methods

2.1. Study design and patient selection

This study is a single-center, prospective, cross-sectional study evaluating the relationship between health

literacy, decision conflict, and body image in patients diagnosed with early-stage breast cancer who, despite being oncologically eligible for breast-conserving surgery (BCS), underwent either total mastectomy or breast-conserving surgery. The study was planned and reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.

The study was conducted at the Breast Surgery Unit of the Department of General Surgery, Faculty of Medicine, Atatürk University. This study was approved by the Atatürk University Faculty of Medicine Clinical Research Ethics Committee (Date: 06.02.2026, Number:5/48). After patients were evaluated by a multidisciplinary breast council and a decision was made regarding their suitability for breast-conserving surgery, they were divided into groups according to their preference for mastectomy or breast-conserving surgery. Written informed consent was obtained from all participating patients prior to enrollment in the study.

2.2. Inclusion criteria

Patients meeting the following criteria were included in the study:

- Female patients aged 18 years or older,
- Having received a histopathological diagnosis of invasive breast carcinoma or ductal carcinoma in situ,
- Being deemed eligible for breast-conserving surgery according to current NCCN and ESMO guidelines [11,12]
- Having undergone primary total mastectomy or breast-conserving surgery as surgical treatment,
- Having fully completed the health literacy, decision conflict, and body image scales prior to surgical treatment,
- Voluntarily agreeing to participate in the study.

2.3. Eligibility criteria for breast-conserving surgery

Eligibility for breast-conserving surgery was evaluated by a multidisciplinary breast team based on the following criteria:

- Presence of a single-focus tumor,
- Prediction that negative surgical margins can be achieved,
- The possibility of an acceptable cosmetic outcome,
- No clinical conditions that would preclude the administration of radiation therapy,
- Absence of inflammatory breast cancer and widespread microcalcifications.

Both mastectomy and breast-conserving surgery were confirmed as oncologically feasible options for all included patients by a multidisciplinary breast tumor board comprising at least two breast surgeons and one radiologist. Within this framework, the treating surgeon discussed both options with the patient, and the final surgical procedure reflected the patient's informed preference between the two oncologically equivalent options rather than a clinical restriction or a board recommendation for one specific procedure.

2.4. Exclusion criteria

Patients with any of the following characteristics

were excluded from the study:

- Male breast cancer,
- Stage IV disease or the presence of distant metastases,
- Locally advanced inflammatory breast cancer,
- Prophylactic bilateral mastectomy due to BRCA1/BRCA2 or other high-penetrance hereditary mutations,
- A history of prior ipsilateral breast surgery or breast radiation therapy,
- Cases deemed unsuitable for breast-conserving surgery following neoadjuvant therapy,
- Patients unable to reliably complete questionnaires due to psychiatric illness or cognitive impairment,
- Patients with incomplete clinical data or missing scale forms.

2.5. Data collection

Demographic and clinical data, including age, education level, marital status, and the surgical method performed, were recorded. Health literacy was assessed using the Turkish HLS-EU-Q6, a six-item instrument scored from 1 (very difficult) to 4 (very easy), with higher mean scores indicating higher health literacy [13]. Decisional conflict was assessed with the Turkish-adapted SURE test and the 16-item Decisional Conflict Scale (DCS) [14]. On the SURE test, each “yes” response scores 1 and each “no” response scores 0; total scores range from 0 to 4, and a score < 4 screens positive for decisional conflict. In contrast, the DCS is transformed to a 0–100 scale, with higher scores indicating greater decisional conflict; scores > 37.5 have been associated with clinically relevant decisional conflict. Body-image perceptions were assessed using the satisfaction and anxiety dimensions of the Turkish-validated body-image instrument used in the study [15]. All scales were administered to patients prior to surgical treatment, after the decision to undergo surgery had been finalized. Because assessment occurred after the surgical decision was already made, the scale scores reflect the psychological state of patients who had already chosen a given procedure; the study design therefore allows evaluation of associations between surgical group and these variables, but does not permit inference that these factors caused or determined the surgical choice, and reverse causality (e.g., the surgical decision itself shaping subsequent decisional-conflict or body-image responses) cannot be excluded.

2.6. Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics 27.0 (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was assessed using the Shapiro-Wilk test. Variables that did not follow a normal distribution were presented as the median and interquartile range (IQR), while categorical variables were presented as counts and percentages.

The Mann-Whitney U test was used to compare two independent groups, while the Pearson chi-square test or Fisher’s exact test was used for categorical variables. Multivariable logistic regression analysis was performed to identify factors associated with decisional conflict, and the results were reported as adjusted odds ratios

(OR) with 95% confidence intervals (CI). Because the surgical-group variable showed complete/quasi-complete separation with respect to decisional conflict, conventional maximum-likelihood logistic regression coefficients for this variable could not be reliably estimated; this limitation, and the resulting instability of the wider model, is addressed in the Discussion and Limitations. No a priori sample size or power calculation was performed for this study; statistical significance was set at a two-tailed $p < 0.05$.

3. Results

When the demographic characteristics of the patients participating in the study were examined, the median age was 51.00 (IQR: 41.25–61.00) in the mastectomy group, and 48.00 (IQR: 43.25–56.75) years in the breast-conserving surgery (BCS) group; no statistically significant difference was found between the two groups ($p = 0.524$). The distributions of marital status ($p = 0.671$) and educational levels ($p = 0.056$) were similar between the groups. The health literacy score (HLS-EU-Q6) was statistically significantly higher in the mastectomy group (Median: 3.52) compared to the BCS group (Median: 2.36) ($p < 0.001$). Basic patient characteristics are shown in Table 1.

Significant statistical differences were found between the surgical methods performed on patients and the body image and decision conflict parameters. Body Image: Satisfaction scores were significantly higher in the BCS group (Median 3.50 vs. 2.00, $p < 0.001$), while Body Image: Anxiety scores were higher in the mastectomy group (Median 4.00 vs. 2.00, $p < 0.001$).

When decision conflict was assessed, SURE scores were statistically significantly higher in the mastectomy group (Median: 4.00) compared to the BCS group (Median: 2.00) ($p < 0.001$). In contrast, patients’ total DCS scores were found to be significantly higher in the BCS group (Median: 47.65) compared to the mastectomy group (Median: 14.66) ($p < 0.001$). While the proportion of patients experiencing “Decisional Conflict” at the clinical level (using the ≥ 37.5 DCS threshold defined in Methods) was 13.3% ($n = 4$) in the mastectomy group, decisional conflict was present in all patients (100.0%, $n = 30$) in the BCS group ($p < 0.001$). This complete separation between groups is an unusually large effect; data entry, scale scoring (including reverse-coded items), and the applied cutoff were rechecked, and the result is presented as observed.

A multivariable logistic regression model was constructed to explore factors associated with the presence of decisional conflict (“Decisional Conflict = Present”). Because 100% of patients in the BCS group had decisional conflict, the surgical-group variable produced complete/quasi-complete separation, making the resulting coefficients, odds ratios, and confidence intervals for that variable unstable and uninterpretable; this instability also affects the precision of the other coefficients estimated within the same model. Within this constrained model, Age (OR = 1.06, 95% CI: 0.98–1.15, $p = 0.103$) and Health Literacy (OR = 0.36, 95% CI: 0.01–9.97, $p = 0.551$) did not reach statistical significance, but given the sepa-

ration problem and the small sample size, this finding should be regarded as preliminary; a penalized-likelihood approach (e.g., Firth logistic regression) or a de-

scriptive/univariable-only analysis would be more appropriate and is recommended before this result is relied upon. The findings are summarized in Table 2.

Table 1. Demographic and clinical characteristics of patients by surgical group.

Variables	Total mastectomy (<i>n</i> = 30)	Breast-conserving surgery (<i>n</i> = 30)	<i>p</i> -value
Age (years), median (IQR)	51.00 (41.25–61.00)	48.00 (43.25–56.75)	0.524 ^a
Educational status, <i>n</i> (%)			0.056 ^b
- Elementary school and below	7 (23.3)	16 (53.3)	
- Middle school / high school	9 (30.0)	5 (16.7)	
- College and above	14 (46.7)	9 (30.0)	
Marital status, <i>n</i> (%)			0.671 ^b
- Married	26 (86.7)	28 (93.3)	
- Single / widowed / divorced	4 (13.3)	2 (6.7)	
Health literacy (HLS-EU-Q6), median (IQR)	3.52 (3.35–3.90)	2.36 (1.99–2.69)	< 0.001 ^a
Body image: satisfaction, median (IQR)	2.00 (1.00–2.00)	3.50 (3.00–4.00)	< 0.001 ^a
Body image: anxiety, median (IQR)	4.00 (4.00–5.00)	2.00 (2.00–2.00)	< 0.001 ^a
SURE score (IQR)	4.00 (4.00–4.00)	2.00 (2.00–2.75)	< 0.001 ^a
Total DCS, median (IQR)	14.66 (10.06–24.84)	47.65 (42.21–51.20)	< 0.001 ^a
- Information-value clarity	25.00 (1.04–41.67)	8.33 (0.00–31.25)	0.110 ^a
- Support	0.00 (0.00–31.25)	0.00 (0.00–25.00)	0.955
- Uncertainty	0.00 (0.00–18.75)	0.00 (0.00–37.50)	0.216 ^a
- Effective decision making	22.50 (15.00–35.00)	20.00 (10.00–33.75)	0.887 ^a
Decision conflict situation, <i>n</i> (%)			< 0.001 ^b
- No decision conflict	26 (86.7)	0 (0.0)	
- Decision conflict present	4 (13.3)	30 (100.0)	

Note: IQR: interquartile range (25th–75th percentile). Statistical significance: *p* < 0.05.

^a Mann–Whitney *U* test; ^b chi-square / Fisher’s exact test.

Table 2. Multivariable logistic regression analysis of factors predicting the presence of decision conflict.

Independent variables	Adjusted OR (odds ratio)	95% confidence interval (CI)	<i>p</i> -value
Surgical group (BCS vs. mastectomy)*	–	–	–
Age (years; continuous variable)	1.06	0.98 – 1.15	0.103
Health literacy score	0.36	0.01 – 9.97	0.551

*Note: As all 30 patients (100%) in the BCS group had decisional conflict (DCS > 37.5), the surgical group variable produced quasi-complete separation in the logistic regression model. Because this resulted in inflated and unstable estimates, the OR, 95% CI, and *p* value for this variable were not reported (–). *p* < 0.05 was considered statistically significant.

4. Discussion

In this study, the relationship between surgical group (mastectomy vs. breast-conserving surgery) and health literacy, decisional conflict, and body image was evaluated in breast cancer patients eligible for breast-conserving surgery (BCS). The most notable finding of the study is that surgical group was associated not only with clinical characteristics but also with cognitive and psychosocial factors. Because health literacy, decisional conflict, and body image were all measured after the surgical decision had already been made, these associations cannot be interpreted as evidence that such factors influenced or predicted the decision; a measurement obtained after an outcome has occurred cannot function as

a predictor of that outcome. While the level of health literacy was found to be significantly higher in the mastectomy group compared to the BCS group (3.52 vs 2.36; *p* < 0.001), body image satisfaction was higher and body image-related anxiety was lower in the BCS group (*p* < 0.001). These findings suggest that treatment decisions in early-stage breast cancer cannot be explained solely by “having the right information,” but are also closely related to how patients interpret this information and perceive risks.

One of the notable findings in our study is that the level of health literacy was higher in the mastectomy group. At first glance, this result contradicts the expectation that as health literacy increases, patients would tend to opt for more conservative treatments. One possible

explanation is that while health literacy enables individuals to access information, it may also lead to a greater information load and an increased perception of risk. In particular, easy access to the internet, social media, and patient experiences might lead patients to perceive the likelihood of recurrence as higher than it actually is and to view more radical treatments as “safer.” However, as information load, perceived risk, and the interpretation of information were not measured in the present study, these explanations should be regarded as hypotheses to be tested in future research. Therefore, our findings suggest that high health literacy does not always translate into a preference for breast-conserving surgery, and that how information is interpreted may be at least as important as the level of knowledge itself [1].

Findings supporting this view are also present in the literature. In a prospective study by Li and colleagues involving 1,136 patients with early-stage breast cancer, the rate of breast-conserving surgery was found to be only 19.9%; the study showed that a strong recommendation from the surgeon increased the likelihood of breast-conserving surgery by 12.38 times, while high trust in the surgeon increased it by 2.94 times [3]. Similarly, Ephraim et al. reported that the proportion of patients who initially preferred breast-conserving surgery was 15.5%, but this proportion rose to 89.3% following structured counseling. The same study showed that the primary reason cited by 90% of patients who continued to prefer mastectomy was fear of recurrence [16]. When these studies are evaluated together, it becomes clear that the surgical decision is shaped not so much by the level of information as by how that information is perceived by the patient and the quality of patient-physician communication.

Our findings regarding decision conflict also support this approach. Patients diagnosed with breast cancer are forced to choose between two different surgical options with similar survival outcomes. The uncertainty experienced during this process can affect not only treatment selection but also long-term psychological adjustment and quality of life. The fact that our study found significant differences in decision conflict scales between the two surgical groups indicates that the surgical decision-making process imposes a significant psychological burden on patients. However, it is difficult to say that decision conflict stems solely from a lack of information. Patients’ personal values, family influence, concerns about cancer recurrence, and expectations regarding body image are also important components of this process.

This observation is also supported by the current literature. In a multicenter study by Zhuang et al. covering the survival outcomes of 448 breast cancer patients, 79% of the patients underwent mastectomy, while only 21% underwent breast-conserving surgery. It was demonstrated that decision conflict ($p = 0.015$ – 0.028) and decision regret ($p = 0.013$; $p < 0.001$) were significantly higher in patients who underwent mastectomy compared to the BCS group, and that there was a moderate negative correlation between decision conflict and quality of life ($r = -0.430$) [17]. In contrast, a randomized controlled trial by Lin et al. involving 151 patients reported that patient decision-aid tools alone did not reduce decision conflict [18]. These findings suggest that

decision conflict cannot be resolved through information alone; rather, effective communication, a shared decision-making approach, and consideration of individual psychosocial needs are more critical. The findings of our study also support this view, demonstrating that patient-centered counseling should be an integral part of the standard preoperative evaluation in breast cancer surgery.

Another important finding of our study is that body image satisfaction was significantly higher, and body image-related anxiety was markedly lower, in patients who had chosen breast-conserving surgery compared with those who had chosen mastectomy ($p < 0.001$). Because these scales were administered before surgery, this finding reflects preoperative differences in body-image perceptions and expectations between the two groups rather than a postoperative effect of either procedure; the study did not measure how body image actually changed after surgery. It is plausible that anticipated body-image concerns preceded and were associated with the surgical choice, or alternatively that patients with more favorable baseline body-image perceptions were more inclined toward breast-conserving surgery; the cross-sectional, preoperative design cannot distinguish between these possibilities. Postoperative studies in the literature, discussed below, provide contextual support for the general association between mastectomy and body-image concerns, but they should not be read as directly confirming the present, preoperative findings.

Our preoperative findings are broadly in line with the direction reported in postoperative literature, although the two are not directly comparable given the difference in assessment timing. In a case-matched study by Kelsall et al. involving 567 patients, body image scores after surgery were significantly better in patients who underwent oncoplastic BCS compared with those who underwent mastectomy and simultaneous reconstruction ($p = 0.002$) [19]. Similarly, Latifee and colleagues identified impaired body image in 66% of 159 patients evaluated after mastectomy, an impairment strongly associated with a diminished sense of attractiveness, avoidance of looking in the mirror, and changes in intimate relationships ($p < 0.001$) [10]. Taken together, these postoperative studies and our preoperative findings raise the hypothesis that breast-conserving surgery may be associated with more favorable body-image outcomes across the treatment course, but confirming this would require a longitudinal design that follows the same patients from before to after surgery.

One of the notable aspects of our study is the joint assessment of health literacy, decision conflict, and body image. These three variables are not independent of one another; rather, they are components of an interrelated decision-making process. A patient with high health literacy having access to more information does not necessarily mean they will experience less decision conflict. Similarly, as the importance placed on body image increases, deciding between surgical options can become more complex. Therefore, the surgical decision-making process should not be reduced to mere information transfer; the patient’s anxieties, expectations, and individual values must also be assessed. The findings of our study suggest that incorporating psychosocial counseling into the standard patient assessment in multidisciplinary

nary breast cancer boards may be beneficial. This is consistent with a recent study using the Capability-Opportunity-Motivation-Behavior (COM-B) model, which found that shared decision-making behavior in breast cancer surgery was associated with multiple participatory and psychosocial factors, including participation competence, perceived social support, and self-care self-efficacy, rather than with any single determinant. Notably, according to the published correction of that study, perceived social support was not uniformly protective and was associated with greater decisional hesitation in one patient subgroup, possibly owing to family and social considerations [20]. These findings support the joint assessment approach used in the present study.

This approach is also supported by the current literature. Li and colleagues demonstrated that high trust in the surgeon increased the likelihood of breast-conserving surgery by approximately 3-fold, while a strong recommendation from the surgeon increased it by 12-fold [3]. Similarly, Ephraim et al. reported that the preference rate for breast-conserving surgery rose from 15.5% to 89.3% following repeated counseling sessions [16]. These results suggest that patient education is not merely about providing information; rather, effective communication and a shared decision-making approach appear to be important components of surgical preference in the cited literature. Our cross-sectional findings are consistent with this broader picture, though our data cannot themselves demonstrate that patient-centered counseling reduces mastectomy rates; this remains a hypothesis for future interventional research rather than a conclusion of the present study.

This study has several important limitations. First, it was conducted at a single center and included only 60 patients, which limits statistical power and generalizability; the small sample size, combined with the complete separation observed for the surgical-group variable, also limits how many variables can reasonably be included in a multivariable model, and the reported multivariable results should be regarded as preliminary (see Methods and Results). Second, because of the cross-sectional design and because all scales were administered after the surgical decision had already been finalized, the study cannot establish causal or temporal relationships among the variables; the findings represent associations between surgical group and health literacy, decisional conflict, and body image, and reverse causality cannot be excluded. Third, several clinically and psychosocially relevant confounders were not collected and could not be adjusted for, including tumor size and stage, tumor-to-breast volume ratio, genetic risk, access to radiotherapy, reconstruction preferences, socioeconomic status, fear of recurrence, anxiety, depression, family influence, and the surgeon's specific recommendation for each patient; because these factors may independently affect both surgical choice and psychosocial outcomes, their absence limits how confidently the observed group differences can be attributed to health literacy, decisional conflict, or body image alone. Fourth, this study did not assess information overload, internet or social media exposure, recurrence-risk perception, patient satisfaction, decision regret, postoperative quality of life, or the effect of any shared decision-making intervention; any statements

regarding these constructs in this manuscript should be read as hypotheses for future research rather than as conclusions supported by the present data. Nevertheless, the study's strongest aspect is its joint, preoperative examination of health literacy, decisional conflict, and body image within the same cohort, which can inform the design of future longitudinal studies.

5. Conclusions

In conclusion, in this cohort of patients eligible for BCS, health literacy, decisional conflict, and body image differed significantly between patients who underwent mastectomy and those who underwent breast-conserving surgery. Because these variables were assessed after the surgical decision had already been made, these findings should be interpreted as associations rather than evidence that these factors determined or caused the surgical choice. Systematically evaluating health literacy, decisional conflict, and body image earlier in the decision-making process—before the surgical decision is finalized—may be a valuable focus for shared decision-making interventions, and whether doing so improves patient satisfaction or reduces potentially avoidable mastectomies remains an open question for future research. Larger, multicenter, prospective, longitudinal studies that assess these factors before the surgical decision is made, account for the clinical and psychosocial confounders noted above, and use regression methods appropriate for small or separated samples (e.g., Firth penalized logistic regression) are needed to clarify the role of these factors in patient-centered surgical decision-making.

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Conflict of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this manuscript.

Data Availability

The datasets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author upon reasonable request.

AI Assistance

During the preparation of this manuscript, ChatGPT was used exclusively for language editing and stylistic refinement. The authors take full responsibility for the content, interpretation, and conclusions of the published article.

Ethics Approval and Consent to Participate

The study was conducted at the Breast Surgery Unit of the Department of General Surgery, Faculty of Medicine, Atatürk University. This study was approved by the Atatürk University Faculty of Medicine Clinical Research Ethics Committee (Date: 06.02.2026, Number:5/48). All procedures were conducted in accordance with relevant guidelines and regulations.

Author Contributions

İdeal Beraa Yilmaz Kartal: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, validation, visualization, writing – original draft, writing – review and editing.

Furkan Şakiroğlu: investigation, methodology, writing – original draft, writing – review and editing.

Mehmet Akif Nas: conceptualization, data curation, formal analysis, investigation, methodology.

Furkan Bingöl: conceptualization, data curation, formal analysis, investigation, methodology.

Murat Kartal: validation, visualization, writing – original draft, writing – review and editing.

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Research Article

Short-term perfusion and respiratory effects of dexketoprofen, tramadol, and their combination in renal colic: A prospective randomized capnography study

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ABSTRACT

Objective: Intravenous non-steroidal anti-inflammatory drugs (NSAIDs) and opioids, including dexketoprofen trometamol and tramadol, remain the primary analgesic options for treating acute renal colic in emergency departments. However, concerns about respiratory depression associated with opioids can limit the use of tramadol with confidence, and there are limited data on the short-term respiratory and perfusion effects of these agents. The present study aimed to evaluate the short-term effects of intravenous dexketoprofen trometamol, tramadol, and their combination on tissue perfusion and respiratory function. The study assessed these effects using EtCO₂ and related physiological parameters. The study population comprised hemodynamically stable emergency department patients presenting with acute renal colic.

Methods: In this prospective, randomized, controlled trial conducted in an academic emergency department, adults aged 18–55 with acute renal colic received one of three intravenous regimens: dexketoprofen trometamol (50 mg), tramadol (100 mg), or their 50 mg/50 mg combination. Vital signs, SpO₂, and EtCO₂ were recorded at baseline, 30, and 60 minutes; arterial blood gases, including lactate, were drawn at baseline and 60 minutes. The primary endpoint of the study was the EtCO₂ trajectory over time.

Results: In a study of 102 patients (with 34 patients in each group), EtCO₂, heart rate, and blood pressure were found to be similar between the groups at all measured time points. Furthermore, analysis using mixed-effects models revealed no significant group-by-time interactions. SpO₂ levels were found to be lower in the combination group compared to the dexketoprofen group at the 60-minute mark (93.8% vs. 95.4%; ANOVA $p = 0.018$; post hoc $p = 0.016$). In the present study, seven patients, all in tramadol-containing arms, exhibited transient SpO₂ levels below 90%, though none of these patients required oxygen supplementation. The blood-gas parameters demonstrated stability, while lactate levels exhibited a significant decrease across all groups, without any observed between-group variation.

Conclusion: In patients with renal colic who were hemodynamically stable, the three treatment plans resulted in similar short-term effects on EtCO₂, hemodynamics, and blood-gas parameters. The findings of this study demonstrate that modest SpO₂ declines, accompanied by transient desaturations in the tramadol-containing arms, provide substantiated support for the implementation of pulse oximetry and capnography monitoring when tramadol is administered. It should be noted that the study was not designed to assess comparative safety, and thus the findings should be considered physiological observations only. The lactate reduction may be indicative of a resolution of pain-related stress; however, this remains a hypothesis that requires further investigation.

Trial Registration: The study was registered at ClinicalTrials.gov (ID: NCT07386288). Registration was retrospective.

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1. Introduction

Acute renal colic is a prevalent cause of emergency department visits, characterized by its intense and debilitating pain. Patients frequently report it to be one of the most severe pain experiences they have ever endured. The majority of cases are attributable to an obstructing ureteral stone, which leads to elevated intraluminal pressure, the occurrence of ureteral spasm, and the stimulation of visceral nociceptors. The resultant flank pain is often accompanied by symptoms such as nausea, vomiting, and agitation [1,2]. Given its high prevalence among young and middle-aged adults, renal colic constitutes a substantial clinical and operational burden for emergency departments worldwide [3,4]. Consequently, the provision of rapid and effective analgesia constitutes a fundamental element of initial management.

Non-steroidal anti-inflammatory drugs (NSAIDs) and opioid analgesics remain the principal pharmacological options for the management of acute renal colic [5–7]. The analgesic effect of NSAIDs is primarily attributable to their capacity to inhibit cyclooxygenase-mediated prostaglandin synthesis, a process that results in a reduction in ureteral smooth muscle tone, intrarenal pressure, and inflammatory-mediated pain [5]. A substantial body of research, encompassing numerous systematic reviews and meta-analyses, has demonstrated the analgesic efficacy of parenteral NSAIDs to be comparable to, and in some cases superior to, that of opioids. Furthermore, these studies have shown that parenteral NSAIDs are associated with reduced rates of vomiting and a decreased requirement for rescue analgesia [3,6–9]. Opioids remain a treatment of choice when NSAIDs are contraindicated or insufficient. Contemporary guidance, including the European Association of Urology recommendations and NICE guideline NG118, positions NSAIDs as first-line analgesia when not contraindicated, with opioids such as tramadol reserved for second-line or rescue use; the present study therefore evaluated tramadol both alone and in combination with dextketoprofen as a physiological safety comparison rather than as a first-line efficacy recommendation [3,10]. However, conventional opioids are associated with well-recognised adverse effects, including nausea, vomiting, respiratory depression, and dependence. Tramadol, a synthetic opioid with weak μ -opioid receptor agonism and additional monoaminergic activity, is often considered an intermediate option with a more favourable respiratory safety profile compared with stronger opioids. Dextketoprofen trometamol, the active S(+)-enantiomer of ketoprofen, is a rapidly acting NSAID that has demonstrated efficacy and good tolerability in the intravenous treatment of acute pain, including renal colic [9,11]. Despite the extensive literature comparing the analgesic efficacy and adverse-event profiles of these agents, data regarding their short-term effects on systemic hemodynamics and tissue perfusion are limited. It is acknowledged that acute pain itself is known to increase sympathetic activity, elevate heart rate and blood pressure, and alter regional blood flow. Conversely, effective analgesia has been demonstrated to attenuate these responses. However, sedative or opioid-based therapies have been demonstrated to impair ventilation and gas exchange [12].

EtCO₂, measured noninvasively via capnography, reflects the integrated relationship between ventilation, cardiac output, and carbon dioxide production. It has been proposed as a surrogate marker of global tissue perfusion. Reduced EtCO₂ levels have been demonstrated to be associated with decreased cardiac output, elevated lactate concentrations, and adverse outcomes in critically ill patients. Nevertheless, the clinical usefulness of EtCO₂ in detecting more subtle perfusion changes during analgesic treatment in hemodynamically stable ED patients remains unclear [13–15]. To the best of our knowledge, no prospective randomised study has specifically evaluated the effects of intravenous dextketoprofen trometamol, tramadol, or their combination on EtCO₂ and other physiological markers of tissue perfusion in spontaneously breathing patients presenting with renal colic. The primary objective of this study was therefore to compare the short-term effects of these three analgesic regimens on EtCO₂, vital signs, and arterial blood-gas parameters, including lactate, in adult ED patients with renal colic. It was hypothesised that none of the three regimens would induce clinically significant changes in EtCO₂ or other global perfusion and respiratory surrogates during the first hour of treatment.

Beyond its established role as a global perfusion surrogate, EtCO₂ has increasingly been recognized as an early, continuous, and non-invasive indicator of opioid-induced ventilatory impairment, capable of detecting hypoventilation before changes become apparent on pulse oximetry [16,17]. In emergency department settings where opioids such as tramadol are administered alongside NSAIDs for acute pain, this early-warning capacity has direct relevance to bedside safety monitoring, independent of any demonstrable perfusion effect. The evaluation of EtCO₂ trajectories following dextketoprofen trometamol, tramadol, and their combination is a pragmatic approach to addressing a salient safety concern. This concern pertains to the question of whether commonly utilized ED analgesic regimens carry any discernible respiratory risk signal. This approach diverges from conventional testing methods that focus exclusively on perfusion physiology.

2. Materials and Methods

2.1. Study design and setting

This prospective, randomized, single-center study was conducted in the emergency department of Atatürk University Faculty of Medicine, Yakutiye Research Hospital, Erzurum, Türkiye between November 2024 and April 2025; the first participant was enrolled on 10 November 2024. Adults aged 18–55 years presenting with flank pain and a clinical and imaging-confirmed diagnosis of renal colic were eligible. The study received approval from the Erzincan Binali Yıldırım University Clinical Research Ethics Committee (Decision No. 2024-16/01, dated 7 November 2024), and written informed consent was reported for all enrolled participants. The trial was registered retrospectively at ClinicalTrials.gov (NCT07386288; first submitted on 20 January 2026).

In order to qualify for inclusion in the study, patients

were required to have a Glasgow Coma Scale score of 15, intact spontaneous breathing, and the ability to give informed consent themselves. Individuals who met any of the following criteria were excluded from the study: those who were pregnant or breastfeeding, those with chronic kidney or respiratory disease, those with a known allergy to any of the study drugs, those with hemodynamic instability, those with acute intoxication, those with poorly controlled epilepsy, or those who had recently taken a monoamine oxidase inhibitor.

2.2. Randomisation and interventions

The randomisation process employed a sealed-envelope technique, wherein equal numbers of opaque envelopes, labelled 1–3 (one per treatment arm), were prepared by a physician not involved in treatment administration and drawn sequentially by the treating physician. This ensured allocation concealment and balanced group sizes. The administration of the study drugs was conducted via intravenous infusions, with each infusion being administered over a period of 20 minutes. Utilising a 1:1:1 randomisation scheme, participants were assigned to receive one of three intravenous treatments: dexketoprofen trametamol 50 mg as an individual treatment, tramadol 100 mg as a standalone treatment, or a combination of both drugs at a ratio of 50 mg and 50 mg, respectively. Prior to infusion, each dose was diluted in 100 mL of normal saline. In the event that the treating physician deemed it necessary, intravenous morphine (5 mg) could be administered as rescue analgesia. Participants were blinded to treatment allocation, as all regimens were diluted in 100 mL of normal saline and administered as identical-appearing infusions; the physician who ordered the treatment and the nurse who prepared the infusions were not blinded.

2.3. Data collection and monitoring

The following parameters were recorded: blood pressure, heart rate, oxygen saturation, and EtCO₂. These were recorded at three time points: baseline (T0), 30 minutes (T30), and 60 minutes (T60). Arterial blood gases were only drawn at T0 and T60. The primary outcome of the study was the change in EtCO₂ over time, with vital signs and blood gas trajectories designated as secondary outcomes. It is notable that no participant received supplemental oxygen during the observation period, and no concomitant analgesics other than rescue morphine were administered.

The primary outcome was defined as the pattern of EtCO₂ change across T0, T30, and T60, which was then compared between the three analgesic arms. The continuous monitoring of EtCO₂ was conducted using a Nihon Kohden Vismo bedside monitor, with the sampling cannula employed for this purpose being of the sidestream nasal type. This was undertaken as an indirect measure of global perfusion. The secondary outcomes encompassed the time-course of heart rate, blood pressure, and SpO₂; the shift in arterial blood gas values (pH, bicarbonate, PCO₂, lactate, base deficit) from T0 to T60; and the comparison of these physiological responses across the treatment groups.

2.4. Sample size and statistical analysis

The required sample size was calculated using G*Power based on a previous study comparing the respiratory effects of tramadol and oxycodone [18], in which EtCO₂ was 45 ± 4 mmHg before and 43 ± 4 mmHg after administration. To detect a within-group difference of 2 mmHg (SD 4 mmHg; effect size $d_z = 0.5$) using a two-tailed paired *t* test with an alpha level of 0.05 and 80% power, 34 patients per arm were required, for a total of 102 patients.

All analyses were performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp.; Armonk, NY, USA). The normality of the data was checked using both a histogram inspection and the Shapiro–Wilk test. Continuous variables were reported as the mean ± standard deviation or as the change over time, and categorical variables were reported as counts with percentages. The alterations in vital signs and blood-gas measures within and between the groups were subjected to analysis using a repeated-measures ANOVA, while the between-group disparities were assessed through the implementation of a one-way ANOVA, complemented by Tukey post hoc comparisons. Paired *t* tests were used to analyze within-group T0-to-T60 comparisons, and categorical data were analyzed with χ^2 tests. For the purpose of this study, a *p* value of less than 0.05 was taken to indicate statistical significance.

As a sensitivity analysis, EtCO₂, heart rate, systolic and diastolic blood pressure, and SpO₂ were additionally re-analyzed using linear mixed-effects models with group, time, and group × time interaction as fixed effects and a random intercept for participant, in order to directly evaluate the group × time interaction for each repeatedly measured parameter. The analysis population comprised all randomized participants, with no post-randomization exclusions and no missing data at any timepoint.

3. Results

3.1. Participant characteristics

A total of 102 patients were enrolled in the study and randomly assigned equally to one of three treatment groups ($n = 34$ per group). The baseline sociodemographic and clinical characteristics of the patients are presented in Table 1.

Across the three designated time points (T0, T30, and T60), no statistically significant between-group disparities were observed in EtCO₂, heart rate, systolic or diastolic blood pressure. The study found that SpO₂ levels were comparable between the groups at T0 ($p = 0.584$) and T30 ($p = 0.635$). However, a statistically significant between-group variation was observed at T60 (one-way ANOVA, $F = 4.19$, $p = 0.018$). Further post-hoc Tukey testing revealed that this variation was attributable to the combination group compared to the dexketoprofen group ($93.82 \pm 2.02\%$ vs. $95.44 \pm 2.64\%$, $p = 0.016$). No pairwise comparison involving the tramadol group reached significance. Nineteen patients (Group 1: $n = 4$, Group 2: $n = 9$, Group 3: $n = 6$) had at least one SpO₂

measurement below 92% during the observation period, and seven patients (Group 2: $n = 4$, Group 3: $n = 3$) had at least one measurement below 90%. No patient received supplemental oxygen or required a respiratory intervention. Subsequent within-group analyses revealed no significant alterations in EtCO₂ across any of the study arms. However, a significant decrease in heart rate and systolic and diastolic blood pressure was observed from T0 to T30 in all three groups, with no further alterations between T30 and T60. The study revealed a transient decrease in SpO₂ at T30 in the dexketoprofen group ($p = 0.024$), with a subsequent return to the baseline level by T60 ($p = 0.932$ vs. T0). In the tramadol group, a decrease in SpO₂ was observed at T30 ($p = 0.009$), with a persistent lower level recorded at T60 ($p = 0.004$). In the combination group, a significant decrease in SpO₂ was noted

at T60 ($p = 0.003$). The hemodynamic values remained within clinically acceptable ranges throughout the observation period (see Table 2 and Figs. 1 and 2).

A sensitivity analysis using linear mixed-effects models confirmed these findings: no statistically significant group $\times$ time interaction was observed for EtCO₂, heart rate, systolic blood pressure, diastolic blood pressure, or SpO₂ (likelihood-ratio test, all $p \geq 0.24$), indicating that the trajectories of these parameters did not differ meaningfully between treatment groups over the observation period. A significant main effect of time was evident for heart rate, systolic and diastolic blood pressure, and SpO₂ (all $p < 0.001$), reflecting a decline associated with analgesia across all three groups equally; no significant main effect of group was found for any parameter (Fig. 3).

Table 1. Baseline demographic and clinical characteristics of the study population.

Variable		Group 1 ($n = 34$)	Group 2 ($n = 34$)	Group 3 ($n = 34$)	p value
Age (years), mean $\pm$ SD		34.7 $\pm$ 10.3	36.8 $\pm$ 10.2	35.5 $\pm$ 9.4	0.697
Sex, n (%)	Male	22 (64.7)	17 (50.0)	29 (85.3)	0.008
	Female	12 (35.3)	17 (50.0)	5 (14.7)	
History of stone passage, n (%)	Yes	20 (58.8)	23 (67.6)	26 (76.5)	0.298
	No	14 (41.2)	11 (32.4)	8 (23.5)	
Family history of nephrolithiasis, n (%)	Yes	21 (61.8)	18 (52.9)	20 (58.8)	0.755
	No	13 (38.2)	16 (47.1)	14 (41.2)	
Analgesic use in previous 24 h, n (%)	Yes	13 (38.2)	11 (32.4)	12 (35.3)	0.879
	No	21 (61.8)	23 (67.6)	22 (64.7)	

Group 1: 50 mg dexketoprofen; Group 2: 100 mg tramadol; Group 3: 50 mg dexketoprofen + 50 mg tramadol

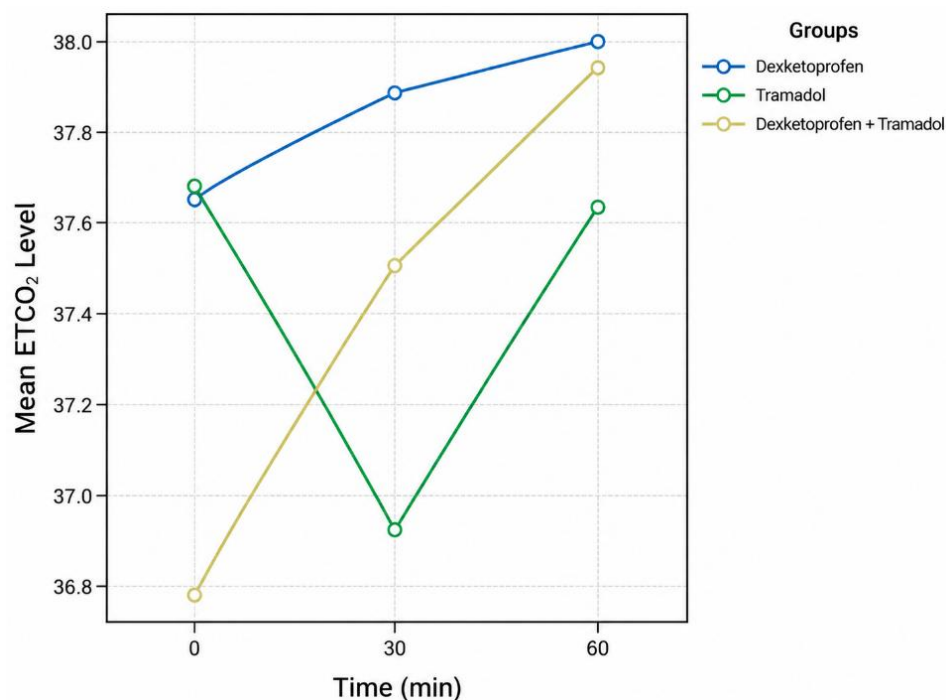


Fig. 1. Changes in end-tidal carbon dioxide levels over time; mean end-tidal carbon dioxide (EtCO₂) values measured at baseline (T0), 30 minutes (T30), and 60 minutes (T60) following intravenous administration of dexketoprofen, tramadol, or their combination. EtCO₂ levels remained within a narrow physiological range across all treatment groups throughout the observation period, with no evidence of clinically relevant deterioration in ventilation or global perfusion.

Table 2. Comparison of perfusion-related vital signs between treatment groups.

	Group 1 (n = 34)		Group 2 (n = 34)		Group 3 (n = 34)	
		p value		p value		p value
End-tidal CO ₂ (mmHg)						
T0	37.65 ± 3.65	0.820	37.68 ± 3.21	0.345	36.76 ± 4.02	0.182
T30	37.88 ± 4.15		36.91 ± 3.60		37.50 ± 2.94	
T60	38.0 ± 3.67		37.65 ± 4.17		37.94 ± 4.04	
Heart rate (beats/min)						
T0	86.50 ± 12.17	0.035 ^a	85.32 ± 14.60	< 0.001 ^a	82.29 ± 13.28	0.002 ^a
T30	81.53 ± 12.70	0.003 ^b	77.26 ± 11.29	0.001 ^b	76.56 ± 11.18	0.004 ^b
T60	80.32 ± 10.95	1.0 ^c	77.44 ± 12.30	1.0 ^c	75.91 ± 11.53	1.0 ^c
Systolic BP (mmHg)						
T0	131.68 ± 14.79	0.001 ^a	130.53 ± 15.31	0.004 ^a	130.53 ± 15.64	< 0.001 ^{a,b}
T30	122.53 ± 12.85	< 0.001 ^b	121.15 ± 16.66	< 0.001 ^b	119.06 ± 13.63	1.0 ^c
T60	122.71 ± 10.92	1.0 ^c	117.82 ± 14.48	0.518 ^c	117.32 ± 15.49	
Diastolic BP (mmHg)						
T0	79.94 ± 11.59	0.002 ^a	83.29 ± 15.13	0.014 ^a	79.82 ± 10.35	0.001 ^a
T30	74.09 ± 8.57	0.013 ^b	74.88 ± 11.87	< 0.001 ^b	72.53 ± 9.57	0.015 ^b
T60	74.15 ± 7.93	1.0 ^c	72.06 ± 11.39	0.378 ^c	73.15 ± 12.24	1.0 ^c
SpO ₂ (%)						
T0	95.94 ± 1.78	0.024 ^a	95.59 ± 2.50	0.009 ^a	95.41 ± 2.08	0.078 ^a
T30	94.74 ± 2.59	0.932 ^b	94.12 ± 3.09	0.004 ^b	94.35 ± 2.34	0.003 ^b
T60	95.44 ± 2.64	0.209 ^c	94.29 ± 2.41	1.0 ^c	93.82 ± 2.02	0.432 ^c

T0: prior to the initiation of the analgesic infusion. T30: 30 minutes after the analgesic infusion T60: 60 minutes after the analgesic infusion.

Between-group comparison of SpO₂ (one-way ANOVA): T0 $p = 0.584$; T30 $p = 0.635$; T60 $p = 0.018$ (Tukey post hoc: combination vs. dexketoprofen, $p = 0.016$).

^a: comparison between T0 and T30; ^b: comparison between T0 and T60; ^c: comparison between T30 and T60.

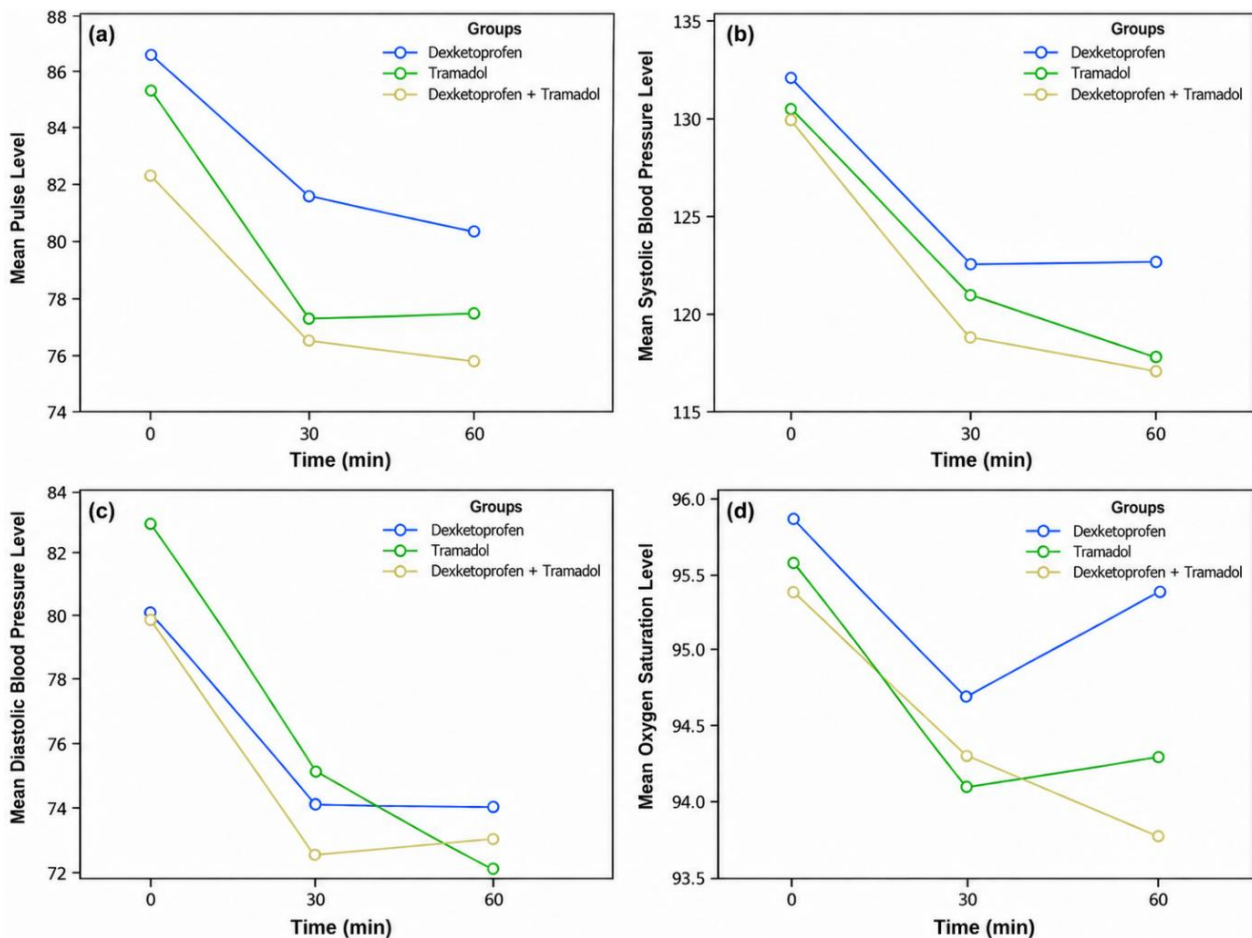


Fig. 2. Changes in vital signs during the observation period: mean values of (a) heart rate; (b) systolic blood pressure; (c) diastolic blood pressure; (d) peripheral oxygen saturation (SpO₂) measured at baseline (T0), 30 minutes (T30), and 60 minutes (T60) following intravenous administration of dexketoprofen trametamol, tramadol, or their combination. Heart rate and blood pressure decreased from T0 to T30 in all groups and remained stable thereafter.

SpO₂ decreased transiently in the dexketoprofen group and remained lower at T60 in the tramadol-containing groups. Because pain scores were not collected, these changes cannot be attributed to analgesic efficacy.

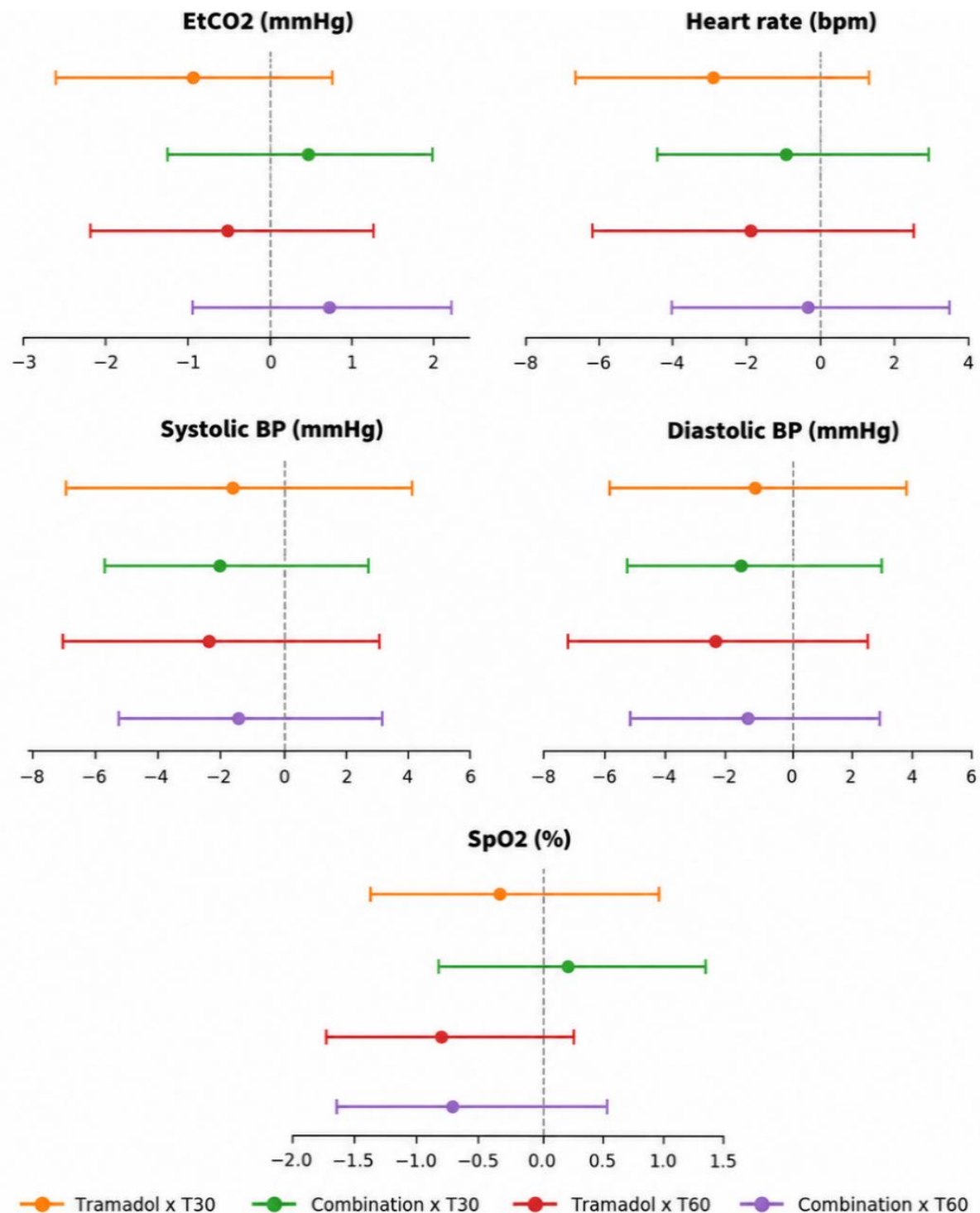


Fig. 3. Linear mixed-effects sensitivity analysis of repeatedly measured parameters. Point estimates and 95% confidence intervals for the group $\times$ time interaction terms (Tramadol $\times$ T30, Combination $\times$ T30, Tramadol $\times$ T60, Combination $\times$ T60, each relative to the dexketoprofen group at T0) are shown for EtCO₂, heart rate, systolic blood pressure, diastolic blood pressure, and SpO₂. All confidence intervals cross zero, indicating no statistically significant interaction between treatment group and time for any parameter.

No significant between-group differences were observed in arterial pH, bicarbonate, PCO₂, lactate, or base deficit at either T0 or T60 (baseline p values: pH 0.227, bicarbonate 0.647, PCO₂ 0.266, lactate 0.722, base deficit 0.472; 60-minute p values: 0.190, 0.099, 0.465, 0.448, and 0.115, respectively). Subsequent within-group analyses revealed a statistically significant decline in lactate levels from T0 to T60 across all three treatment groups (dexketoprofen $p = 0.003$, tramadol $p = 0.008$, combina-

tion $p = 0.001$). Concurrently, base deficit and other blood-gas parameters demonstrated stability (see Table 3 and Fig. 4).

Taken together, these findings indicate that dexketoprofen trometamol, tramadol, and their combination did not adversely affect surrogate markers of global tissue perfusion during the first hour of treatment and were instead associated with a modest, consistent reduction in serum lactate.

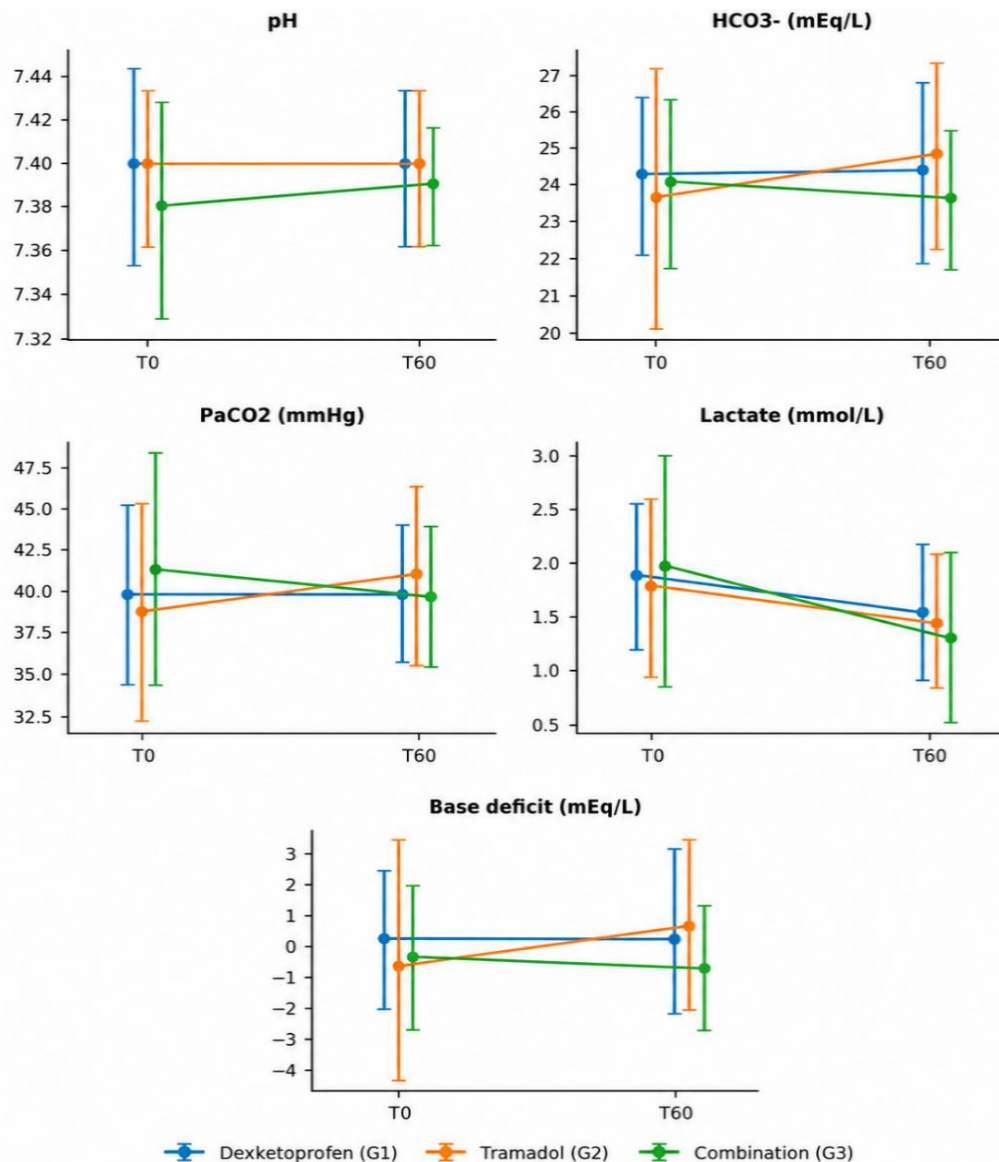
Table 3. Comparison of perfusion-related arterial blood-gas parameters between treatment groups.

Variables		Group 1 (n = 34)		Group 2 (n = 34)		Group 3 (n = 34)	
		T0	T60	T0	T60	T0	T60
pH		7.40 ± 0.05	7.40 ± 0.04	7.40 ± 0.04	7.40 ± 0.04	7.38 ± 0.054	7.39 ± 0.03
	p	0.909		0.831		0.630	
HCO ₃ (mEq/L)		24.18 ± 2.6	24.29 ± 2.62	23.54 ± 3.3	24.81 ± 2.71	23.99 ± 2.48	23.52 ± 2.01
	p	0.795		0.102		0.162	
PCO ₂ (mmHg)		39.59 ± 5.79	39.64 ± 4.31	38.45 ± 7.01	40.82 ± 5.64	41.15 ± 7.56	39.49 ± 4.39
	p	0.950		0.117		0.195	
Lactate (mmol/L)		1.89 ± 0.67	1.55 ± 0.60	1.81 ± 0.79	1.48 ± 0.59	1.97 ± 1.05	1.35 ± 0.74
	p	0.003		0.008		0.001	
Base deficit (mEq/L)		0.18 ± 2.28	0.18 ± 2.78	-0.68 ± 3.8	0.56 ± 2.59	-0.38 ± 2.26	-0.68 ± 1.99
	p	1.0		0.110		0.348	

T0: prior to the initiation of the analgesic infusion.

T30: 30 minutes after the analgesic infusion.

T60: 60 minutes after the analgesic infusion.

**Fig. 4.** Arterial blood-gas parameters before and after analgesic treatment; mean values of arterial blood-gas parameters, including pH, bicarbonate (HCO₃⁻), partial pressure of carbon dioxide (PCO₂), serum lactate, and base deficit, measured at baseline (T0) and 60 minutes (T60) following intravenous administration of dexketoprofen, tramadol, or their combination. Across all treatment groups, arterial blood-gas parameters remained stable over time, with a consistent reduction in serum lactate levels observed at 60 minutes.

4. Discussion

In this prospective randomised study of patients presenting to the emergency department with renal colic, intravenous dexketoprofen trometamol, tramadol, and their combination had comparable short-term effects on EtCO₂, hemodynamic variables, and arterial blood-gas parameters, with no significant group x time interaction for any repeatedly measured parameter. However, SpO₂ exhibited a modest decline that persisted at 60 minutes in the tramadol-containing arms, where all transient desaturations below 90% occurred. Notably, none of these cases necessitated supplemental oxygen or respiratory intervention. It is important to note that the study was not designed or powered to assess comparative safety. Therefore, it is essential that these findings are regarded as physiological observations only.

The clinical relevance of these findings is evidenced by the fact that acute renal colic is characterised not only by severe pain but also by pronounced sympathetic activation. This, in turn, may transiently influence cardiovascular dynamics and metabolic demand. It is therefore reasonable to hypothesise that effective analgesia will attenuate sympathetic tone, which may result in favourable changes in physiological parameters. Conversely, opioid-based analgesia, particularly in higher doses, has the potential to impair ventilation and gas exchange, which raises concerns regarding respiratory safety in spontaneously breathing patients. In the present study, EtCO₂ remained unchanged with all regimens at standard intravenous doses, whereas the modest and sustained SpO₂ decrease in the tramadol-containing arms may reflect a mild opioid-related effect on oxygenation that did not require intervention in this low-risk population.

Numerous studies and meta-analyses have compared the analgesic efficacy and adverse-event profiles of NSAIDs and opioids in renal colic; however, the majority have focused primarily on pain scores, rescue analgesia requirements, and gastrointestinal side effects [6–9,11]. Conversely, data concerning the physiological consequences of analgesic choice, particularly with regard to perfusion-related markers, remain limited. The present study extends the extant literature by demonstrating that commonly used intravenous analgesic regimens for renal colic exert neutral short-term effects on EtCO₂, a parameter increasingly recognised as an indirect marker of cardiac output and tissue perfusion.

Extensive validation of EtCO₂ monitoring has been undertaken in critically ill populations, where low EtCO₂ values are associated with reduced cardiac output, elevated lactate levels, and increased mortality in conditions such as shock, sepsis and cardiac arrest [14,19–22]. In such contexts, EtCO₂ serves as a dynamic, non-invasive indicator of systemic perfusion and response to resuscitative interventions. Nevertheless, the clinical applicability of EtCO₂ for detecting more subtle physiological changes in stable emergency department patients remains to be firmly established. The present findings suggest that, in patients with isolated acute pain and preserved hemodynamic stability, alterations in perfusion induced by analgesia may be too modest to elicit measurable changes in EtCO₂.

It is noteworthy that, despite the stability of EtCO₂ and other vital parameters, a statistically significant reduction in serum lactate levels was observed across all treatment groups. This consistent finding is likely indicative of a reduction in metabolic stress induced by pain, as opposed to a direct effect of the analgesics on systemic perfusion. As serial pain scores and treatment-response data were not collected in this study, it is important to regard this explanation as a hypothesis rather than a demonstrated mechanism linking analgesia to lactate clearance. It is well established that acute pain increases catecholamine release, glycolytic flux, and lactate production, even in the absence of overt hypoperfusion. It may therefore be hypothesized that effective pain control contributes to the normalization of metabolic homeostasis, reflected in modest lactate clearance, although this study cannot establish this mechanism directly. Given that baseline lactate values in this cohort were largely within normal or near-normal ranges, the observed reductions should be interpreted as markers of stress resolution rather than indicators of recovery from pathological hypoperfusion.

Tramadol is frequently regarded as a comparatively safer opioid with respect to respiratory depression due to its weak μ -opioid receptor agonism and additional monoaminergic mechanisms. As demonstrated in previous clinical studies comparing tramadol with morphine by the intravenous and epidural routes and in pharmacovigilance data, clinically significant respiratory depression with tramadol is rare at therapeutic doses [23–25]. Consistent with this, no participant in the present study required respiratory intervention; however, the sustained SpO₂ decrease observed in the tramadol-containing arms indicates that monitoring remains warranted, as discussed below.

While the absence of between-group differences may initially appear to be a null finding, in the context of ED analgesic safety, it carries direct practical value. In clinical practice, tramadol is frequently avoided or underdosed because of concerns about respiratory depression, even at doses well within the recommended limits. In the present study, intravenous tramadol—either as an isolated treatment or in combination with dexketoprofen trometamol—did not alter EtCO₂ during the first hour of treatment in non-intubated, hemodynamically stable renal colic patients. However, SpO₂ decreased modestly and remained lower at 60 minutes in the tramadol-containing arms, in which all seven transient desaturations below 90% occurred. This data therefore provide reassurance regarding hypercapnic ventilatory depression but not regarding oxygenation, and, given the absence of a dedicated safety or non-inferiority design, they cannot be interpreted as a formal demonstration of comparative safety. These findings also suggest that capnography and pulse oximetry provide complementary rather than interchangeable information when tramadol is administered to spontaneously breathing patients.

From a pragmatic standpoint, these findings suggest that, in hemodynamically stable patients with renal colic, the choice between NSAID-based, tramadol-based, or combination analgesic strategies is unlikely to influence short-term global perfusion as assessed by EtCO₂ and arterial blood-gas analysis. Tramadol, at the doses admin-

istered in this study, did not alter EtCO₂; however, given the SpO₂ decrease observed in the tramadol-containing arms, its use should be accompanied by standard monitoring and adherence to dosing limits, particularly in patients with risk factors for respiratory depression [24,25]. Beyond these considerations, the selection of analgesics may be more appropriately guided by contraindications, anticipated side-effect profiles, prior analgesic exposure, and individual patient characteristics, in line with current guideline recommendations [3,10]. It can be hypothesized that lactate may be a more responsive short-term metabolic marker than EtCO₂ in this relatively low-risk population, although its relationship with pain relief could not be assessed in this study.

Nevertheless, caution is warranted when extrapolating these results to patients with hemodynamic instability, significant cardiopulmonary comorbidities, or those requiring repeated or higher-dose opioid administration. In such populations, significant disparities may be observed in both perfusion dynamics and respiratory risk profiles, thus rendering EtCO₂ monitoring a potentially more significant clinical tool.

4.1. Limitations

A significant strength of this study is its prospective, randomized, three-arm design, which facilitates direct comparison of NSAID, opioid, and combination analgesia using objective hemodynamic and metabolic endpoints. Serial EtCO₂ and blood-gas measurements further characterize the immediate physiological response to analgesia in a real-world emergency department setting.

It is imperative to acknowledge the limitations of the present study. Firstly, this was a single-center study with a modest sample size and only 60 minutes of follow-up, so delayed or cumulative effects could not be assessed. Secondly, the distribution of sex differed between groups, with a higher proportion of male subjects in the combination arm. However, there is no clear biological rationale to predict sex-specific differences in short-term EtCO₂ responses to these drugs. Thirdly, the pain scores and clinical outcomes (e.g., the use of rescue analgesia or the time to disposition) were not systematically reported, thus limiting the direct linkage between perfusion markers and analgesic efficacy. It is important to note that EtCO₂ and lactate are global indices that may not detect subtle regional or microcirculatory perfusion abnormalities that do not substantially alter overall CO₂ elimination or lactate production [20–22].

Further research with larger, more heterogeneous populations, longer follow-up, and combined assessment of pain scores, microcirculatory indices, and clinical outcomes could assist in clarifying whether specific analgesic choices offer any nuanced hemodynamic advantages in acute renal colic.

5. Conclusions

In hemodynamically stable adults presenting to the emergency department with renal colic, intravenous dextropropofol, tramadol, and their combination had similar short-term effects on EtCO₂, hemody-

namic variables, and arterial blood-gas parameters. EtCO₂ remained unchanged with all regimens, whereas SpO₂ decreased modestly and remained lower at 60 minutes in the tramadol-containing arms, in which all transient desaturations occurred; capnography and pulse oximetry should therefore be used together when tramadol is administered. The observed reduction in lactate levels across all groups may reflect attenuation of pain-related stress, but this remains hypothetical because pain scores were not collected. Within the limits of a study not designed to assess comparative safety, these findings suggest that the selection of analgesic treatment may be guided by efficacy and patient-specific factors rather than by concerns over short-term perfusion impairment.

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Conflict of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this manuscript.

Data Availability

The datasets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author upon reasonable request.

AI Assistance

During the preparation of this manuscript, DeepL Translate / Write was used exclusively for language editing and stylistic refinement. The authors take full responsibility for the content, interpretation, and conclusions of the published article.

Ethics Approval and Consent to Participate

This study was approved by the Erzincan Binali Yıldırım University Clinical Research Ethics Committee (Approval Number: 2024-16/01; Date: 07 Nov 2024). The first participant was enrolled on 10 November 2024. Written informed consent was obtained from all participants. All procedures were conducted in accordance with relevant guidelines and regulations.

Author Contributions

Gülbahar Demir: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, validation, visualization, writing – original draft, writing – review & editing.

Mevlana Gül: investigation, methodology, writing – original draft, writing – review & editing.

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Challenge Journal of PERIOPERATIVE MEDICINE

Research Article

Ultrasound-guided versus laparoscopic-assisted subcostal transversus abdominis plane block for postoperative analgesia after laparoscopic cholecystectomy: A prospective randomized trial

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ABSTRACT

Objective: To compare the analgesic efficacy of ultrasound-guided and laparoscopic-assisted subcostal transversus abdominis plane (TAP) block after laparoscopic cholecystectomy.

Methods: In this prospective, randomized, double-blind trial, 60 adults undergoing elective laparoscopic cholecystectomy received either ultrasound-guided (US-TAP, $n = 30$) or laparoscopic-assisted (L-TAP, $n = 30$) subcostal TAP block under standardized general anesthesia and multimodal analgesia. The primary outcome was pain intensity on the Numeric Rating Scale (NRS) across the first 24 postoperative hours; comparisons at individual time points were exploratory. Secondary outcomes were analgesic consumption, time to first rescue analgesia, rescue opioid requirement, postoperative nausea and vomiting (PONV), time to ambulation, length of stay, and complications.

Results: Baseline characteristics were comparable; pain scores declined over time in both groups. NRS scores were lower with US-TAP at 1 hour (2.50 ± 1.72 vs 4.03 ± 1.56 ; difference 1.53, 95% CI 0.68 to 2.38; $p = 0.001$) and 6 hours (1.83 ± 1.44 vs 2.70 ± 1.47 ; difference 0.87, 95% CI 0.12 to 1.62; $p = 0.015$), with no differences at the other six time points. No differences were found in time to first analgesic request, rescue analgesic or opioid requirements, PONV, ambulation, hospital stay, complications, or the overall 24-hour reduction in NRS.

Conclusion: Ultrasound guidance was associated with lower early postoperative pain scores, but these differences fell below commonly cited thresholds for clinically important change and were not accompanied by differences in analgesic requirements or recovery outcomes. Without a no-block control group and not being designed to test equivalence, this trial compares the two techniques rather than establishing the efficacy of either.

Trial Registration: The study was registered at ClinicalTrials.gov (ID: NCT07352189). Registration was retrospective.

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1. Introduction

Upper abdominal surgery represents a considerable proportion of surgical procedures performed world-

wide, with laparoscopic cholecystectomy being one of the most common abdominal operations. Compared with open surgery, the laparoscopic approach offers several advantages, including lower postoperative morbid-

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ity, shorter hospital stays, faster recovery, and earlier mobilization. Despite these benefits, postoperative pain remains an important clinical concern. When inadequately controlled, pain can interfere with recovery, delay mobilization and potentially contribute to the development of chronic postsurgical pain [1,2].

For this reason, effective postoperative analgesia is an essential part of perioperative management. Regional anesthesia techniques have increasingly been incorporated into multimodal analgesic strategies because they can provide effective pain relief while reducing opioid requirements and the adverse effects associated with opioid use. Among these techniques, the transversus abdominis plane (TAP) block is widely used in abdominal surgery because it is relatively simple to perform, has a favorable safety profile, and can provide meaningful opioid-sparing analgesia [3].

The TAP block is performed by injecting local anesthetic into the fascial plane between the internal oblique and transversus abdominis muscles. This targets the anterior rami of the lower thoracic and upper lumbar nerves (T6–L1), thereby providing somatic analgesia to the anterolateral abdominal wall. As a result, TAP block has become a well-established component of multimodal analgesia in a range of abdominal surgical procedures [4].

Several techniques have been developed for performing the TAP block. The conventional landmark-based, or “double-pop,” technique depends on the operator’s ability to identify the fascial planes by tactile feedback as the needle is advanced. Ultrasound guidance has largely become the preferred approach because it enables direct visualization of the abdominal wall anatomy and facilitates more precise deposition of local anesthetic. Another option is to perform the block intraoperatively under direct laparoscopic visualization. This laparoscopic-assisted approach does not require additional ultrasound equipment, adds little time to the procedure, and can be easily integrated into the surgical workflow [5].

Although previous studies have compared ultrasound-guided and laparoscopic-assisted TAP block techniques, most investigations have focused on lateral TAP block approaches, heterogeneous abdominal surgery populations, or infraumbilical procedures. Evidence specifically comparing subcostal TAP block techniques in a homogeneous population undergoing laparoscopic cholecystectomy remains limited. In addition, relatively few prospective randomized studies have evaluated these techniques using standardized perioperative protocols together with blinded assessment of postoperative outcomes.

Accordingly, the present prospective randomized trial was designed to compare ultrasound-guided and laparoscopic-assisted subcostal TAP block in patients undergoing laparoscopic cholecystectomy. The primary outcome was postoperative pain intensity across the first 24 postoperative hours. Secondary outcomes were analgesic consumption, time to first rescue analgesia, rescue opioid requirement, postoperative nausea and vomiting, time to ambulation, length of hospital stay, and adverse events.

2. Materials and Methods

2.1. Study design and ethical approval

This prospective, randomized, double-blind trial was conducted in the operating rooms of Maltepe University Faculty of Medicine Hospital in accordance with the Declaration of Helsinki and was designed and reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) recommendations. The study protocol was approved by the Maltepe University Clinical Research Ethics Committee (Decision No. 3; 1 November 2022) and subsequently authorized by the Turkish Medicines and Medical Devices Agency (TİTCK; Reference No. E-66175679-514.13.02-965164; Study No. 22-AKD-156; 26 December 2022). Both approvals were obtained before participant recruitment began in 2023. Written informed consent was obtained from all participants before enrollment. The trial was retrospectively registered at ClinicalTrials.gov (NCT07352189), with the initial registration submitted on 11 January 2026 and the record first posted on 20 January 2026, after enrollment and follow-up had been completed. Retrospective registration is acknowledged as a study limitation.

2.2. Participants

Adult patients aged 18–70 years with American Society of Anesthesiologists (ASA) physical status I–III scheduled for elective laparoscopic cholecystectomy were screened for eligibility. Exclusion criteria were neuropsychiatric disorders potentially affecting pain perception, regular use of antidepressant or antipsychotic medication, chronic opioid use, allergy to any study medication, contraindications to TAP block, bleeding diathesis, ASA physical status IV or higher, and refusal to participate. Following enrolment, patients were randomly assigned in a 1:1 ratio to the ultrasound-guided TAP block group (Group U) or the laparoscopic-assisted TAP block group (Group L) (Fig. 1).

2.3. Randomization and blinding

Eligible patients were allocated in a 1:1 ratio to Group U or Group L. The allocation sequence was generated by drawing lots from a prepared set of 60 slips containing 30 assignments to each group, randomly shuffled before the start of enrolment; this corresponds to restricted randomization within a single block of 60 and ensured equal group sizes. Allocation was concealed using sequentially numbered, opaque, sealed envelopes prepared before the start of enrolment by an independent person who was not otherwise involved in the study and took no part in patient recruitment, block performance, or outcome assessment. Each envelope was opened only after induction of general anesthesia, so that neither the patient nor the investigator assessing postoperative outcomes was aware of the assignment at any point before allocation. Because the two techniques were necessarily performed by different operators, the anesthetist and the surgical team could not be blinded; however, all blocks were performed under general anesthesia and needle entry sites in both groups were covered with

identical adhesive dressings before emergence, so that no external marking distinguished the groups. All post-operative assessments were performed by an independ-

ent investigator who was not present in the operating room and remained blinded to allocation throughout data collection.

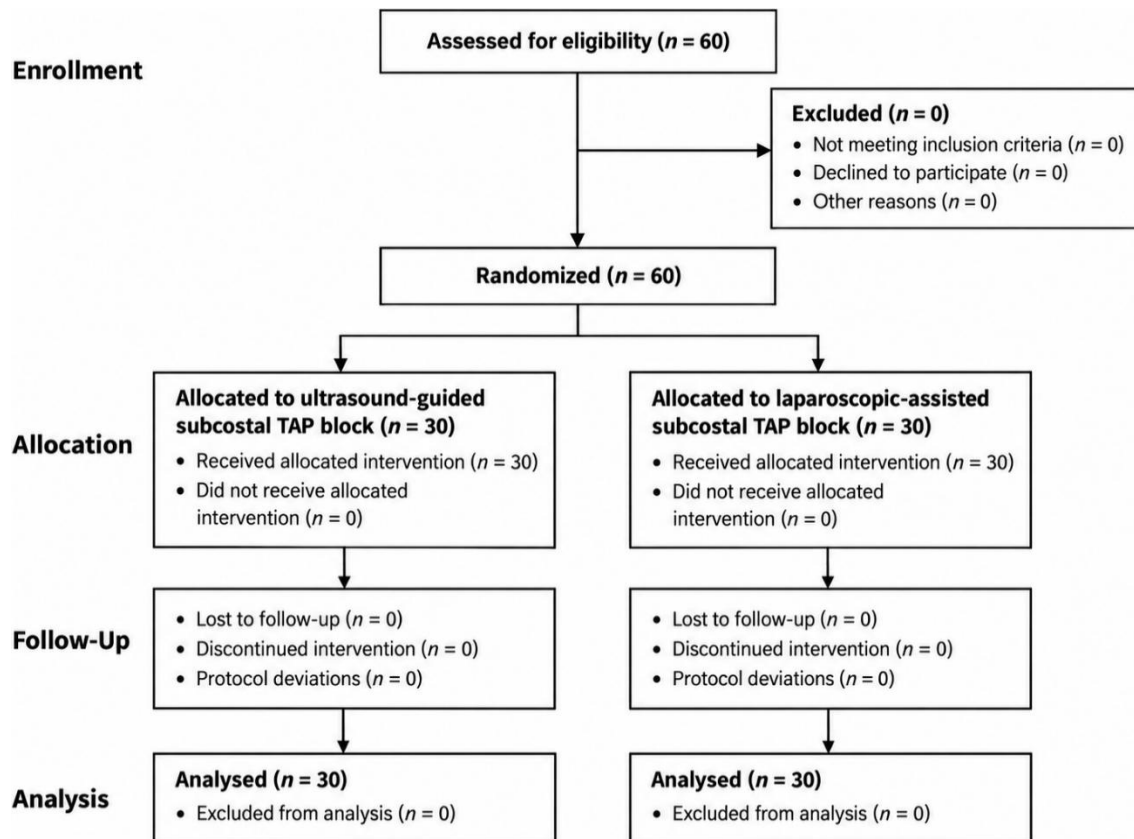


Fig. 1. CONSORT 2010 flow diagram showing patient eligibility assessment, randomization, allocation, follow-up and analysis. No patients were excluded, lost to follow-up or withdrawn, and no protocol deviations occurred.

2.4. Perioperative anesthetic management

Baseline demographic and clinical characteristics, including age, sex, weight, height, body mass index, ASA physical status, smoking status, comorbid conditions and previous abdominal surgery, were recorded. Standard intraoperative monitoring included electrocardiography, non-invasive blood pressure monitoring, pulse oximetry and neuromuscular monitoring using train-of-four stimulation. After three minutes of preoxygenation with 100% oxygen, anesthesia was induced with intravenous propofol (2–3 mg/kg), fentanyl (1–2 µg/kg) and rocuronium (0.6 mg/kg), and orotracheal intubation was performed after adequate neuromuscular blockade. Mechanical ventilation was adjusted to maintain tidal volumes of 6–8 mL/kg and end-tidal carbon dioxide between 30 and 35 mmHg. Anesthesia was maintained with sevoflurane ~2% in 50% O₂/air (flow 2 L/min) and remifentanyl (0.05 µg/kg/min). Thirty minutes before completion of surgery, all patients received intravenous paracetamol (1 g) and tenoxicam (20 mg) as part of a multimodal analgesic regimen.

2.5. Subcostal TAP block procedures

All blocks were performed bilaterally after completion of surgery and before emergence from anesthesia, with patients supine under general anesthesia. In both

groups the target was the subcostal segment of the transversus abdominis plane, and an identical local anesthetic solution and volume were administered. All ultrasound-guided blocks were performed by the same anesthetist and all laparoscopic-assisted blocks by the same surgical team, both experienced in their respective techniques before the start of the study.

2.6. Ultrasound-guided subcostal TAP block (Group U)

After sterile skin preparation and draping, a high-frequency linear transducer (8–12 MHz) (LOGIQ e, GE Medical Systems, Jiangsu, China) enclosed in a sterile sheath was positioned obliquely along and parallel to the costal margin, with its medial end adjacent to the xiphoid process. The rectus abdominis muscle was identified medially, and the internal oblique and transversus abdominis muscles laterally. A 22-G, 80-mm short-bevel block needle (Stimuplex D plus 0.71 × 80 mm; B. Braun, Melsungen, Germany) was advanced in plane along the subcostal line toward the fascial plane separating the rectus abdominis and internal oblique muscles from the transversus abdominis muscle. Needle-tip position was confirmed by hydrodissection with 0.5–1 mL of the local anesthetic solution to confirm the correct needle tip position. Subsequently, the remaining volume of the solution was administered, ensuring a total injection volume of 20 mL per side.

The identical sequence was repeated on the contralateral side, and needle entry sites were covered with adhesive dressings. This oblique subcostal approach targets the T6–T9 dermatomes relevant to upper abdominal incisions [6].

2.7. Laparoscopic-assisted subcostal TAP block (Group L)

In Group L the block was performed by the operating surgeon under direct laparoscopic vision before trocar removal, targeting the same subcostal plane. The needle was introduced immediately below the costal margin close to the midline, superficial to the rectus abdominis,

and directed along the subcostal line. Correct deposition was confirmed by two criteria applied together: the tactile perception of two distinct fascial “pops” corresponding to passage through the anterior and posterior layers of the rectus sheath, and direct laparoscopic visualisation of a smooth extraperitoneal bulge of the abdominal wall developing as the local anesthetic was injected, without intraperitoneal spill of the injectate. The needle tip is deliberately not advanced into the peritoneal cavity and is therefore not visualised laparoscopically; the developing bulge is the endpoint that confirms correct extraperitoneal deposition. Twenty millilitres were administered on each side, and the procedure was repeated bilaterally (Fig. 2).

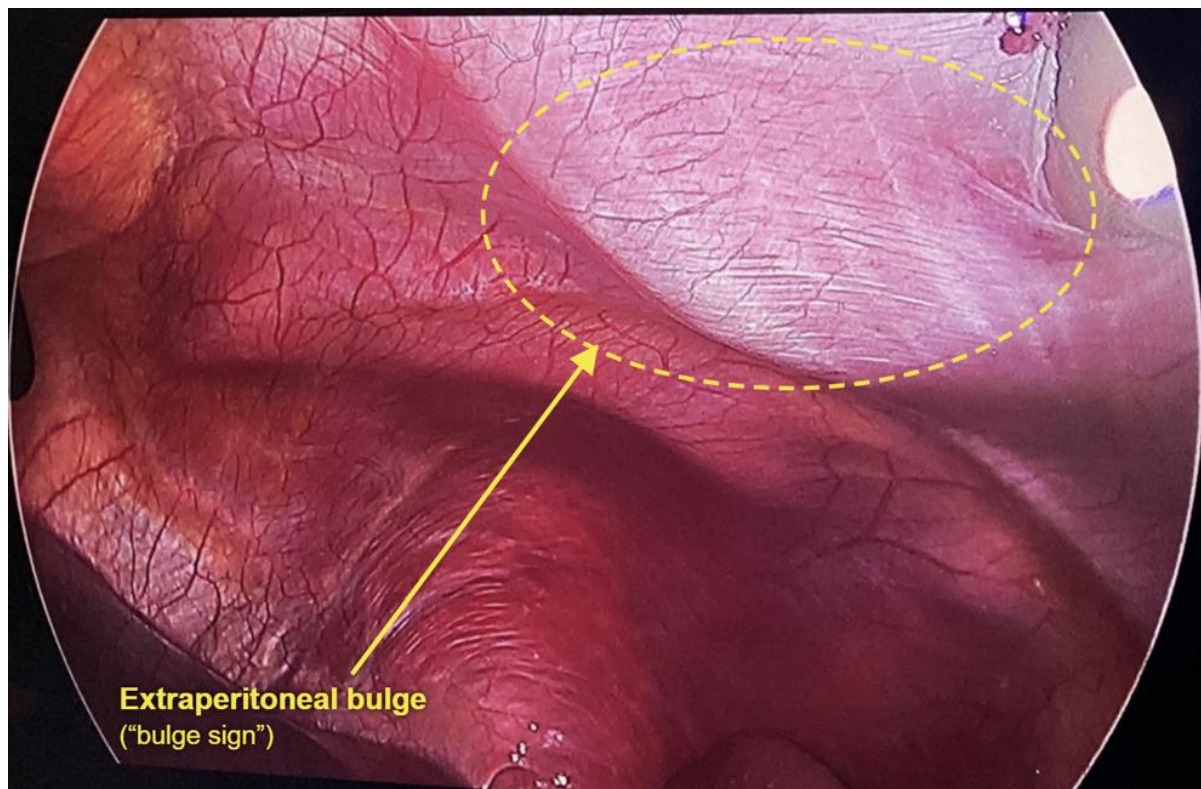


Fig. 2. Representative intraoperative laparoscopic view during laparoscopic-assisted subcostal transversus abdominis plane block. The dashed ellipse indicates the extraperitoneal bulge (“bulge sign”) that develops as local anesthetic is deposited in the subcostal transversus abdominis plane.

2.8. Local anesthetic solution

In both groups, the block was performed using 40 mL of a solution containing 30 mL of 0.25% bupivacaine and 10 mL of 1% lidocaine, divided equally as 20 mL per side, as specified in the approved study protocol. The final concentrations were 0.1875% bupivacaine and 0.25% lidocaine, corresponding to total doses of 75 mg and 100 mg, respectively. Given the potential for systemic absorption following abdominal wall blocks [7,8] and the additive toxicity of concurrently administered local anesthetics [9], the combined dose fraction was calculated using reference maximum doses of 2 mg/kg for bupivacaine and 4.5 mg/kg for lidocaine. At the cohort's mean body weight of 78.47 kg, the combined dose fraction was approximately 76.1%. However, this calculation based on mean body weight does not establish that the reference threshold was met for every individual participant.

2.9. Postoperative analgesia and outcome assessment

After block administration, neuromuscular blockade was reversed with intravenous atropine (0.02 mg/kg) and neostigmine (0.04 mg/kg), and patients were extubated after adequate spontaneous ventilation and recovery of neuromuscular function. Postoperative analgesia was standardized: intravenous paracetamol 1 g was administered every 8 hours during the first 24 postoperative hours. Pain intensity was assessed using an 11-point Numeric Rating Scale (NRS), where 0 represented no pain and 10 the worst imaginable pain, at 20 minutes, 40 minutes, 1, 3, 6, 12, 18 and 24 hours postoperatively by the blinded investigator. Patients with an NRS score of 4 or above received intramuscular diclofenac sodium 75 mg as rescue analgesia; if pain remained at 4 or above after 30 minutes, intravenous tramadol 1 mg/kg was administered.

All NRS assessments were performed with the patient at rest. Pain on movement or during coughing was not assessed.

Postoperative nausea and vomiting was recorded as a single composite outcome (presence of nausea, vomiting, or both) during the first 24 postoperative hours. No antiemetic prophylaxis was administered to either group; antiemetic treatment was given on demand.

2.10. Outcome measures

The primary outcome was postoperative pain intensity, assessed by serial NRS measurements across the first 24 postoperative hours. No single time point was prespecified as the primary endpoint. Secondary outcomes were paracetamol consumption, time to first rescue analgesia, requirement for rescue analgesia and for rescue opioid, postoperative nausea and vomiting, time to first ambulation, time to first flatus, length of hospital stay, and adverse events including pruritus, pneumothorax and local anesthetic systemic toxicity.

2.11. Sample size calculation

An a priori power analysis was performed using G*Power (version 3.1.9.2; Heinrich-Heine University, Düsseldorf, Germany) for the primary outcome of postoperative pain intensity. A between-group difference of approximately 1 NRS point was regarded as the smallest difference of clinical interest, and a large effect size (Cohen's $d = 0.80$) was used in the calculation on that basis. The standard deviation assumed at the planning stage was not recorded in the study documentation. With a two-sided alpha of 0.05 and 80% power, the minimum required sample size was 26 patients per group; 30 patients were recruited into each group to allow for losses to follow-up or protocol deviations.

With the standard deviations subsequently observed in this cohort (1.07 to 2.01), an effect size of $d = 0.80$ corresponds to detectable between-group differences of approximately 0.86 to 1.61 NRS points, depending on the assessment time point, that is, below the median minimum clinically important difference of approximately 1.7 points reported for acute pain [10]. This is a translation of the prespecified effect size into clinical units using the observed variability, and not a post hoc power calculation based on the observed effect.

2.12. Statistical analysis

Statistical analyses were performed using NCSS software (Number Cruncher Statistical System, version 2007; Kaysville, UT, USA). Normality was assessed using the Shapiro–Wilk test together with histograms and Q–Q plots. Normally distributed continuous variables are presented as mean $\pm$ standard deviation and non-normally distributed variables as median (range). Categorical variables are summarized as frequencies and percentages. Between-group comparisons used the independent-samples t test or the Mann–Whitney U test as appropriate, and the Pearson chi-square test, Fisher's exact test or the Fisher–Freeman–Halton test for categorical variables.

The primary analysis was the comparison of the postoperative pain trajectory over the first 24 hours. Within-group changes over time were assessed using the Friedman test, with Bonferroni–Dunn post hoc tests for pairwise comparisons. The change in NRS score from the first to the final postoperative assessment was compared between groups using the Mann–Whitney U test. Between-group comparisons of NRS scores at each postoperative time point were also performed using the Mann–Whitney U test; because no single primary time point was prespecified, these comparisons were considered exploratory and were not adjusted for multiple testing. To provide an estimate of the magnitude and precision of the between-group differences, mean differences with 95% confidence intervals were additionally calculated from the group means, standard deviations, and sample sizes using the t distribution; these estimates were considered descriptive and are reported alongside the rank-based hypothesis tests. All statistical tests were two-tailed, and a p value below 0.05 was considered statistically significant.

An additional longitudinal analysis of postoperative NRS scores was performed using generalized estimating equations (GEE), with treatment group, assessment time, and their interaction included as predictors. Assessment time was treated as a categorical variable, and an exchangeable working correlation structure was used to account for repeated measurements within participants. A Gaussian model with robust standard errors was fitted. The group-by-time interaction was evaluated using a joint Wald test. The overall between-group difference was estimated using a separate GEE model without the interaction term. This analysis was conducted after the initial statistical analysis and is reported as exploratory.

3. Results

Between January and June 2023, 60 patients undergoing elective laparoscopic cholecystectomy were enrolled and randomly assigned to laparoscopic-assisted (L-TAP, $n = 30$) or ultrasound-guided (US-TAP, $n = 30$) subcostal TAP block. All 60 patients received the allocated intervention, completed the 24-hour follow-up and were included in the analysis; there were no exclusions, losses to follow-up or protocol deviations (Fig. 1).

Baseline demographic and clinical characteristics are presented in Table 1. The mean age of the study population was 48.45 ± 14.96 years and 40 patients (66.7%) were female. The mean body mass index was 28.72 ± 5.94 kg/m², most participants were ASA physical status II (61.7%), and approximately half had at least one comorbid condition. No statistically significant differences were observed between groups with respect to demographic characteristics, anthropometric measurements, ASA classification, smoking status, comorbidities or previous abdominal surgery (all $p > 0.05$). Previous abdominal surgery was present in 24 patients (40.0%) and was similarly distributed between the groups (11 [36.7%] vs 13 [43.3%], $p = 0.598$). In every case the previous procedure was an appendectomy; no patient had undergone previous upper abdominal surgery, and no patient therefore had a previous incision within the subcostal region in which the block was performed.

Table 1. Baseline demographic and clinical characteristics.

Variable	Overall (<i>n</i> = 60)	L-TAP (<i>n</i> = 30)	US-TAP (<i>n</i> = 30)	<i>p</i>
Age (years)	48.45 ± 14.96	48.03 ± 16.25	48.87 ± 13.81	0.831
Female, <i>n</i> (%)	40 (66.7)	21 (70.0)	19 (63.3)	0.584
Weight (kg)	78.47 ± 16.82	75.13 ± 15.06	81.80 ± 18.04	0.126
Height (cm)	165.40 ± 9.25	165.23 ± 9.88	165.57 ± 8.74	0.890
BMI (kg/m ²)	28.72 ± 5.94	27.48 ± 4.56	29.97 ± 6.90	0.106
ASA I, <i>n</i> (%)	20 (33.3)	11 (36.7)	9 (30.0)	0.833
ASA II, <i>n</i> (%)	37 (61.7)	18 (60.0)	19 (63.3)	—
ASA III, <i>n</i> (%)	3 (5.0)	1 (3.3)	2 (6.7)	—
Any comorbidity, <i>n</i> (%)	31 (51.7)	16 (53.3)	15 (50.0)	0.796
Hypertension, <i>n</i> (%)	15 (25.0)	10 (33.3)	5 (16.7)	0.104
Diabetes mellitus, <i>n</i> (%)	11 (18.3)	7 (23.3)	4 (13.3)	0.320
Current smoker, <i>n</i> (%)	14 (23.3)	9 (30.0)	5 (16.7)	0.511
Previous abdominal surgery, <i>n</i> (%)	24 (40.0)	11 (36.7)	13 (43.3)	0.598

Data are mean ± standard deviation or *n* (%). ASA, American Society of Anesthesiologists; BMI, body mass index.

Perioperative and postoperative recovery outcomes are summarized in Table 2. All patients underwent elective laparoscopic cholecystectomy. Mean operative duration was comparable between the L-TAP and US-TAP groups (104.83 ± 30.10 vs 109.00 ± 36.09 minutes, *p* = 0.629), and no significant between-group differences were observed in time to first ambulation, time to first flatus or length of hospital stay. No postoperative complications occurred in either group.

Postoperative analgesic consumption is presented in Table 3. Mean intravenous paracetamol consumption during the first 24 postoperative hours did not differ between groups (3.67 ± 0.71 vs 3.73 ± 0.69 g, *p* = 0.553; median 4 g, range 1–4 g in both groups). This total includes the 1 g administered intraoperatively; the range reflects variation in the number of scheduled postoperative doses received before discharge. Time to first analgesic request was comparable (2.93 ± 2.29 vs 3.23 ± 2.24 hours, *p* = 0.403). Additional analgesia was required by 24 patients (80.0%) in the L-TAP group and 19 (63.3%) in the US-TAP group (*p* = 0.152), and rescue opioid was required by 7 (23.3%) and 6 (20.0%) patients respectively (*p* = 0.754). Postoperative nausea and vomiting occurred in 23 patients (76.7%) and 21 patients (70.0%) respectively (*p* = 0.559).

Within-group analysis demonstrated a significant reduction in postoperative pain over time in both groups (Friedman test, both *p* < 0.001), as shown in Table 5. The mean reduction in NRS from the first to the final postoperative assessment was 2.90 ± 1.54 points in the L-TAP group and 3.17 ± 1.82 points in the US-TAP group, and the magnitude of reduction did not differ between groups (*p* = 0.830).

The additional exploratory longitudinal analysis demonstrated a statistically significant group-by-time interaction in postoperative NRS scores (Wald $\chi^2(7)$ = 22.56, *p* = 0.002), indicating different postoperative pain trajectories between the groups. However, the overall between-group difference was not statistically significant (mean difference: 0.44, 95% CI –0.09 to 0.97; *p* = 0.10).

No block-related complications occurred in either group. One patient in the US-TAP group developed an urticarial rash intraoperatively, before performance of the block. The reaction was confined to the skin, with no haemodynamic or respiratory involvement, and resolved after intravenous corticosteroid administration without sequelae; it was therefore not attributable to the block technique. No patient in either group developed pruritus, pneumothorax, signs of local anesthetic systemic toxicity, or any postoperative complication.

Table 2. Operative and postoperative recovery outcomes.

Variable	L-TAP (<i>n</i> = 30)	US-TAP (<i>n</i> = 30)	<i>p</i>
Operative duration (min)	104.83 ± 30.10	109.00 ± 36.09	0.629
Time to ambulation (h), mean ± SD	5.23 ± 2.14	5.03 ± 1.07	0.658
Time to ambulation (h), median (range)	5 (2–12)	5 (3–8)	—
Time to first flatus (h)	9.37 ± 2.08	8.90 ± 1.77	0.352
Hospital stay (days)	1.20 ± 0.41	1.13 ± 0.35	0.488
Postoperative complications, <i>n</i> (%)	0 (0)	0 (0)	—

Table 3. Analgesic consumption and adverse events.

Variable	L-TAP (<i>n</i> = 30)	US-TAP (<i>n</i> = 30)	<i>p</i>
IV paracetamol (g), mean ± SD	3.67 ± 0.71	3.73 ± 0.69	0.553
IV paracetamol (g), median (range)	4 (1–4)	4 (1–4)	—
Time to first analgesic (h), mean ± SD	2.93 ± 2.29	3.23 ± 2.24	0.403
Time to first analgesic (h), median (range)	1.5 (1–6)	2.5 (1–6)	—
Additional analgesia required, <i>n</i> (%)	24 (80.0)	19 (63.3)	0.152
Rescue opioid required, <i>n</i> (%)	7 (23.3)	6 (20.0)	0.754
Postoperative nausea/vomiting, <i>n</i> (%)	23 (76.7)	21 (70.0)	0.559
Urticarial rash (intraoperative), <i>n</i> (%)	0 (0)	1 (3.3)	—
Pruritus, <i>n</i> (%)	0 (0)	0 (0)	—
Pneumothorax, <i>n</i> (%)	0 (0)	0 (0)	—
Local anaesthetic systemic toxicity, <i>n</i> (%)	0 (0)	0 (0)	—

Paracetamol consumption includes the 1 g administered intraoperatively; the range reflects variation in the number of scheduled postoperative doses received before discharge. The urticarial rash developed before the block was performed and was not attributable to the block technique.

Table 4. Postoperative pain scores (Numeric Rating Scale).

Time	L-TAP mean ± SD	L-TAP median (range)	US-TAP mean ± SD	US-TAP median (range)	Difference (95% CI)	<i>p</i>
20 min	3.50 ± 1.43	3 (0–7)	3.50 ± 2.01	3 (0–9)	0.00 (–0.90 to 0.90)	0.474
40 min	3.50 ± 1.07	4 (1–5)	3.37 ± 1.90	3 (0–8)	0.13 (–0.67 to 0.93)	0.233
1 h	4.03 ± 1.56	4 (1–7)	2.50 ± 1.72	2.5 (0–6)	1.53 (0.68 to 2.38)	0.001
3 h	3.00 ± 1.49	3 (0–6)	2.47 ± 1.68	2 (0–6)	0.53 (–0.29 to 1.35)	0.151
6 h	2.70 ± 1.47	3 (0–6)	1.83 ± 1.44	2 (0–6)	0.87 (0.12 to 1.62)	0.015
12 h	1.93 ± 1.23	2 (0–4)	1.57 ± 1.55	1 (0–6)	0.36 (–0.36 to 1.08)	0.165
18 h	1.30 ± 1.26	1 (0–6)	1.47 ± 1.55	1 (0–6)	–0.17 (–0.90 to 0.56)	0.871
24 h	0.60 ± 0.77	0 (0–3)	0.33 ± 0.66	0 (0–2)	0.27 (–0.10 to 0.64)	0.092

Between-group hypothesis testing by Mann–Whitney *U* test. Differences are between-group differences in means (L-TAP minus US-TAP) with 95% confidence intervals derived from the *t* distribution and reported as descriptive effect estimates; positive values indicate higher pain scores in the L-TAP group. Time-point comparisons were exploratory and were not adjusted for multiplicity.

Table 5. Longitudinal pain analysis.

Variable	L-TAP (<i>n</i> = 30)	US-TAP (<i>n</i> = 30)	<i>p</i>
Baseline NRS (20 min)	3.50 ± 1.43	3.50 ± 2.01	0.474
Final NRS (24 h)	0.60 ± 0.77	0.33 ± 0.66	0.092
Change in NRS (final minus first), mean ± SD	–2.90 ± 1.54	–3.17 ± 1.82	0.830
Change in NRS (final minus first), median (range)	–3 (–7 to 1)	–3 (–8 to 0)	—
Within-group change over time	Friedman <i>p</i> < 0.001	Friedman <i>p</i> < 0.001	—

NRS, Numeric Rating Scale. Within-group change over time assessed by Friedman test; between-group comparisons by Mann–Whitney *U* test.

4. Discussion

In this randomized trial comparing ultrasound-guided and laparoscopic-assisted subcostal TAP block after laparoscopic cholecystectomy, patients in the ultrasound-guided group reported lower NRS scores at the

first and sixth postoperative hours. Across the remaining six assessment points, no significant between-group differences were detected. However, the additional exploratory longitudinal analysis demonstrated a significant group-by-time interaction over the first 24 hours (*p* = 0.002), indicating different postoperative pain trajectory

ries, although the overall between-group difference in NRS scores was not statistically significant ($p = 0.10$). No significant differences were detected in time to first analgesic request, rescue analgesic or opioid requirements, postoperative nausea and vomiting, time to ambulation, length of hospital stay, or complication rates.

Real-time sonographic guidance allows the operator to identify the fascial plane, to follow the needle tip during advancement and to observe the distribution of the injectate, so that deposition can be adjusted before the full volume is delivered [11]. Laparoscopic-assisted placement instead relies on tactile fascial endpoints combined with the intra-abdominal appearance of the abdominal wall, which confirms that injection is extra-peritoneal but does not display the fascial plane itself [12,13]. More consistently positioned injectate could plausibly produce a more reliable sensory block during the hours when local anesthetic concentrations at the target nerves are highest, which would be compatible with an early separation between groups that had resolved by the twelfth hour. Ultrasound-guided TAP block was first described in this surgical population by El-Dawlatly et al. and has since become the reference approach against which alternative delivery techniques are compared [14].

The magnitude of the observed differences deserves emphasis. At 1 hour the between-group difference was 1.53 NRS points (95% CI 0.68 to 2.38) and at 6 hours 0.87 points (95% CI 0.12 to 1.62). A systematic review of empirical studies of the minimum clinically important difference in acute pain reported a median absolute difference of approximately 1.7 points on an 11-point scale [10]. Both point estimates in the present study fall below that threshold, and at 6 hours the entire confidence interval lies below it; the lower confidence limits are compatible with differences of no practical relevance to patients. Considered together with the absence of any detectable difference in analgesic consumption or recovery endpoints, the early statistical separation should not be interpreted as evidence of a clinically important analgesic advantage.

Previous comparisons of the two guidance modalities have produced mixed results. Elamin et al., in a double-blind randomized trial in which a laparoscopically delivered TAP block was compared with wound infiltration, reported significantly lower pain scores at 1, 3 and 6 hours both at rest and on coughing, although postoperative analgesic requirements did not differ [15]. Ravichandran et al. compared the two guidance modalities directly in 60 patients undergoing laparoscopic cholecystectomy and found comparable pain relief and opioid consumption, with the laparoscopic block faster to administer [16]. Diyaolu et al. similarly found comparable recovery-room pain scores and opioid consumption in 50 children undergoing laparoscopic procedures (1.2 ± 1.3 vs 1.6 ± 1.6 , $p = 0.24$), again with a shorter block performance time in the laparoscopic arm (2.1 vs 7.9 minutes) [17], and the meta-analysis of Hamid et al. found no difference in analgesic efficacy across the first 24 hours [18]. In a non-randomized three-arm comparison that also included a no-block control, Reyna-Sepulveda et al. found lower pain scores and less postoperative analgesic requirement with both blocks than with

intravenous analgesia alone, without a significant difference between the two guidance techniques [19]. The present results fall within this range: a small early advantage for ultrasound guidance, not sustained over time and not accompanied by differences in any patient-centred endpoint.

Recent evidence syntheses point in the same direction. Wang et al. found that TAP block reduces early postoperative pain after laparoscopic cholecystectomy but confers limited additional benefit over alternative local techniques such as port-site infiltration [20], while Park et al. reported lower opioid consumption and pain scores with subcostal TAP block compared with wound infiltration, with comparable rates of nausea and vomiting [21]. A systematic review comparing ultrasound-guided with laparoscopic-assisted placement specifically reported lower pain scores with ultrasound guidance at 6 hours, but no differences at later time points, in opioid consumption, or in postoperative nausea and vomiting [22]. The present trial contributes data from a single procedure managed under a standardized perioperative protocol and is consistent with the view that the principal difference between the modalities lies in early pain scores rather than in recovery outcomes.

Time to first analgesic request did not differ between groups despite lower early pain scores with ultrasound guidance. Pain intensity in both groups generally remained below the NRS threshold of 4 that triggered rescue analgesia, so a modest downward shift in scores would not necessarily translate into fewer rescue doses; Saliminia et al. similarly showed that the effect of TAP block on this interval is most apparent when the comparison is with no block at all [23]. Postoperative nausea and vomiting occurred in 70–77% of patients, higher than is commonly reported after laparoscopic cholecystectomy. No antiemetic prophylaxis was administered in either group and the cohort carried several established risk factors — female predominance, a high proportion of non-smokers, laparoscopic surgery, volatile anaesthesia and perioperative opioid exposure — that together predict a high baseline risk. The absence of prophylaxis is the most probable explanation for the observed incidence and represents a departure from current guideline-based practice.

The present study was not designed to compare resource utilization, equipment requirements, cost or training burden and none of these variables was measured. Procedural time, however, has been measured in three of the comparative studies cited above and each found laparoscopic-assisted placement to be quicker: block performance took 2.1 versus 7.9 minutes in the paediatric trial of Diyaolu et al. [17], the laparoscopic block was significantly faster to administer in the trial of Ravichandran et al. [16], and Reyna-Sepulveda et al. reported a shorter total operative time with the laparoscopic technique (74 versus 92 minutes) in a non-randomized comparison [19]. In the present randomized trial, total operative duration did not differ between groups (109.0 versus 104.8 minutes, $p = 0.629$), which suggests that time saved in performing the block does not necessarily translate into a shorter operation. Laparoscopic-assisted placement uses equipment already present in the operative field and can be performed by

the operating surgeon, which may be relevant where ultrasound machines or regional anesthesia expertise are limited; this consideration is offered as clinical context rather than as a finding of this trial.

This study has several strengths: a randomized design with allocation concealment, a single homogeneous surgical procedure, standardized anesthetic and analgesic management, blinded outcome assessment, and a subcostal approach matched to the dermatomes relevant to upper abdominal surgery [6]. Several limitations should be acknowledged. The study was conducted at a single center with a modest sample. The sample size calculation was based on a clinically defined target difference of approximately 1 NRS point; power to detect smaller differences and differences in the secondary outcomes was limited. Because the primary outcome was pain intensity across the first 24 postoperative hours rather than at any single prespecified time point, comparisons at individual time points were considered complementary analyses. Crucially, the trial included no no-block control group and was not designed as an equivalence or non-inferiority study, so the absence of detectable differences cannot be interpreted as demonstrated equivalence, and the absolute efficacy of either technique cannot be established from these data. Block success was not verified objectively, either by sensory dermatome testing or by imaging. Pain was assessed only at rest; dynamic pain on movement or coughing, which may differ substantially after laparoscopic abdominal surgery, was not evaluated. Patient-controlled analgesia was not used and cumulative rescue opioid dose was recorded as a requirement rather than in milligrams, so analgesic consumption was captured less precisely. The earliest assessments were performed shortly after emergence and may have been influenced by residual anesthetic effects. A mixture of two local anesthetics was used rather than a single agent, which may limit comparability with other studies. Finally, the trial was registered retrospectively, after completion of enrolment and follow-up.

5. Conclusions

In patients undergoing laparoscopic cholecystectomy within a standardized multimodal analgesic regimen, ultrasound-guided subcostal TAP block was associated with lower pain scores at the first and sixth postoperative hours than laparoscopic-assisted placement. These differences were smaller than commonly cited thresholds for clinically important change, were not sustained beyond the sixth hour, and were not accompanied by differences in rescue analgesic or opioid requirements, postoperative nausea and vomiting, time to ambulation, length of stay, or complication rates. Because no no-block control group was included and the trial was not designed to test equivalence, these findings support a comparison between the two guidance modalities rather than a conclusion about the absolute efficacy of either. Adequately powered trials with a prespecified primary time point and a longitudinal analysis are needed to determine whether the early difference observed here has any clinical consequence.

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Presentation at a Meeting

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Conflict of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this manuscript.

Data Availability

The datasets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author upon reasonable request.

AI Assistance

An AI assistant (Claude, Anthropic) was used specifically for refining figure-caption wording and light language polishing. The model did not generate or interpret clinical data, and no identifiable patient information was provided. All study design, analyses and clinical interpretation were produced and critically verified by the authors, who take full responsibility for the content.

Ethics Approval and Consent to Participate

This study was approved by the Maltepe University Clinical Research Ethics Committee (Decision No. 3, November 1, 2022) and authorized by the Turkish Medicines and Medical Devices Agency (TİTCK; Study Code 22-AKD-156, Reference No. E-66175679-514.13.02-965164, December 26, 2022). All procedures were conducted in accordance with the Declaration of Helsinki and relevant regulations. Written informed consent was obtained from all participants prior to enrollment.

Author Contributions

Berfin Gizem Özelsel: data curation, formal analysis, investigation, methodology, resources, validation, visualization, writing – original draft.

Talat Ercan Şerifsoy: conceptualization, methodology, supervision, data curation, investigation, writing – review and editing.

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Research Article

Clinical characteristics and outcomes of patients hospitalized with electrical burns: A retrospective cohort study

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ABSTRACT

Objective: This study evaluated the demographic and clinical characteristics of patients hospitalized for electrical burns and examined factors associated with voltage level, burn depth, and clinical outcomes.

Methods: This retrospective descriptive study included 51 patients hospitalized for electrical burns from January 1, 2020, to August 1, 2024. We analyzed demographic data, injury mechanism, voltage level, burn depth, total body surface area (TBSA), Abbreviated Burn Severity Index (ABSI) score, hospital and intensive care unit (ICU) lengths of stay, surgical intervention, amputation, complications, and in-hospital mortality.

Results: The median age was 36 years (interquartile range [IQR], 20–44), and 90.2% of patients were male. High-voltage injuries comprised 58.8% of cases. The median TBSA was 18% (IQR, 10–30), and the median ABSI score was 5 (IQR, 4–6). Surgical intervention was performed in 84.3% of patients. Amputation, complications, and in-hospital mortality occurred in 29.4%, 64.7%, and 3.9% of patients, respectively. Compared to the low-voltage group, high-voltage injuries were associated with significantly longer hospital and ICU stays, greater TBSA involvement, higher ABSI scores, and increased rates of fourth-degree burns, amputation, and complications (all $p < 0.05$).

Conclusion: High-voltage electrical burns were associated with greater burn extent, higher ABSI scores, longer hospital and ICU stays, and higher rates of surgical intervention, amputation, and complications. These findings indicate greater clinical severity in high-voltage electrical injuries.

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1. Introduction

The widespread use of electricity in daily life and industry has made electrical burns a significant public health concern [1]. Although they account for less than 5% of burn center admissions worldwide, electrical burns are among the most severe due to high morbidity

and mortality rates [2]. Understanding their epidemiological features is essential for prevention and improved outcomes. Electrical burns most often result from faulty installations, contact with electrical cables or high-voltage power lines, and lightning strikes [1,2]. Injuries may occur through direct current passage, exposure to heat from an electrical arc (arc flash), or flame burns from ig-

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nited clothing [3]. As a result, electrical burns range from superficial skin injuries to limb loss, permanent neurological damage, cardiac arrhythmias, and multiple organ failure [4–6].

Several prognostic scoring systems have been developed to predict outcomes, guide treatment decisions, and estimate mortality risk in patients with burn injuries. Among these, the Abbreviated Burn Severity Index (ABSI) is one of the most widely used. It incorporates five parameters: age, sex, presence of inhalation injury, full-thickness burns, and total body surface area (TBSA) burned [6]. Higher ABSI scores have consistently been associated with increased mortality risk and reduced survival probability [7].

Electrical burns differ significantly from other burn injuries in mechanisms, clinical presentation, and outcomes. Epidemiological and clinical outcomes vary by region, patient population, and healthcare system, underscoring the need for current, center-specific data. However, contemporary regional data on the clinical characteristics and outcomes of hospitalized patients with electrical burns, particularly comparisons between high- and low-voltage injuries, remain limited. Comprehensive evaluation of burn depth, TBSA, ABSI score, surgical intervention, amputation, complications, and mortality may provide a clearer characterization of injury severity and clinical course in this population. The present study aimed to evaluate the demographic, clinical, and injury characteristics, as well as treatment outcomes, of patients hospitalized with electrical burns at a tertiary burn center, and to compare the clinical characteristics and outcomes of high- and low-voltage electrical injuries.

2. Materials and Methods

2.1. Study design and patient population

This retrospective study was conducted at the burn center of a tertiary care teaching and research hospital. Ethical approval was obtained from the Samsun University Clinical Research Ethics Committee (Approval No. GOKAEK 2024/14/14; Date: August 14, 2024). Pediatric and adult patients hospitalized for the treatment of electrical burns between January 1, 2020, and August 1, 2024, were eligible for inclusion.

2.2. Inclusion criteria

Patients were included if they met all of the following criteria:

- Hospitalization at the burn center with a diagnosis of electrical burn during the study period;
- Availability of complete demographic and clinical data in the medical records; and
- Completion of treatment and follow-up at our institution.

2.3. Exclusion criteria

Patients were excluded if they:

- Were managed on an outpatient basis;

- Had incomplete medical records; or
- Had multiple hospital admissions related to the same injury, in which case only the first admission was included in the analysis.

A total of 51 patients met the eligibility criteria and were included in the study.

2.4. Data collection

Potentially eligible patients were identified through the electronic hospital information system by screening the records of patients hospitalized and treated at our burn center using the International Classification of Diseases, 10th Revision (ICD-10) codes W85 (exposure to electric transmission lines), W86 (exposure to other specified electric current), and W87 (exposure to unspecified electric current) during the study period. Eligibility was subsequently confirmed by reviewing electronic medical records in accordance with the predefined inclusion and exclusion criteria. A total of 57 hospitalized patients were initially identified. Of these, six patients were excluded: one patient was transferred to another center before completion of treatment, and five patients had insufficient medical records. Thus, the final study cohort consisted of 51 patients. Patient data were retrospectively retrieved from the electronic hospital information system and medical records. The following variables were recorded: age, sex, occupational injury status, mechanism of injury, location of exposure, voltage category, burn depth, total body surface area (TBSA), Abbreviated Burn Severity Index (ABSI) score, length of hospital stay, length of intensive care unit (ICU) stay, requirement for surgical intervention, amputation status, occurrence of complications, burn severity, and in-hospital mortality. Recorded complications included psychiatric complications, neurological or nerve injury, musculoskeletal injury, renal injury, compartment syndrome, cardiac injury, shock, fractures, pulmonary injury, and other organ injuries. The single patient with a lightning injury was excluded from subgroup comparisons according to burn etiology because this category contained only one patient.

Electrical injuries were classified according to voltage level as low-voltage (<1,000 V) or high-voltage ($\geq$ 1,000 V), in accordance with previous reports [5]. Burn depth was categorized as second-, third-, or fourth-degree burns. TBSA and ABSI scores were obtained from the patients' medical records, and ABSI mortality risk categories were subsequently determined for all patients.

2.5. Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA) and Microsoft Excel 2024. Categorical variables are presented as frequencies (n) and percentages (%), whereas continuous variables are expressed as the median and interquartile range (IQR). The distribution of continuous variables was assessed both graphically and using the Shapiro–Wilk test. Categorical variables were compared using Pearson's chi-square test when the assumptions of the test were satisfied. Fisher's exact test was used for 2×2 contingency tables with

small expected cell counts, whereas the Fisher–Freeman–Halton exact test was used for larger contingency tables with sparse expected frequencies. Categorical data were presented as frequencies (n) and percentages (%). Continuous variables, including age, length of hospital stay, length of ICU stay, TBSA, and ABSI score, were compared between low- and high-voltage groups using the Mann–Whitney U test. Comparisons of continuous variables across three or more groups, including burn depth, amputation status, and burn etiology, were performed using the Kruskal–Wallis test. When statistically significant differences were identified among three or more groups, Bonferroni-adjusted post hoc analyses were conducted to determine pairwise group differences. A two-sided p -value < 0.05 was considered statistically significant.

3. Results

The median age of the 51 patients included in the study was 36 years (IQR, 20–44), and 90.2% were male. The median length of hospital stay was 29 days (IQR, 14–44), and the median length of intensive care unit (ICU) stay was 2 days (IQR, 0–8). Occupational injuries accounted for 29.4% of all cases. The most common cause of injury was indoor electrical accidents (43.1%), followed by occupational accidents (29.4%) and outdoor electrical accidents (25.5%). Injuries occurred outdoors in 51.0% of patients, and fourth-degree burns were identified in 45.1%. The median total body surface area (TBSA) burned was 18% (IQR, 10–30), and the median Abbreviated Burn Severity Index (ABSI) score was 5 (IQR, 4–6). Surgical intervention was performed in 84.3% of patients, whereas amputation, complications, and in-hospital mortality occurred in 29.4%, 64.7%, and 3.9% of patients, respectively (Table 1). Among the 43 patients who underwent surgical intervention, the most common procedures were debridement ($n = 43$), skin grafting ($n = 38$), amputation ($n = 15$), escharotomy/eschar excision ($n = 11$), and fasciotomy ($n = 10$). Some patients underwent multiple procedures during hospitalization. The most frequent complications were psychiatric complications and neurological or nerve injuries ($n = 10$ each), followed by musculoskeletal injury, renal injury, and compartment syndrome ($n = 4$ each). Some patients had more than one complication.

When patients were stratified according to voltage category, the high-voltage group demonstrated significantly longer hospital stays [41.5 (30–61) vs. 14 (5–26) days; $p < 0.001$], longer ICU stays [6 (2–9) vs. 0 (0–0) days; $p < 0.001$], greater TBSA involvement [22.5 (15–35) vs. 10 (5–20); $p = 0.001$], and higher ABSI scores [6 (5–7) vs. 4 (4–4); $p < 0.001$]. Occupational injuries, outdoor exposure, fourth-degree burns, the need for surgical intervention, amputation, and complications were all significantly more frequent in the high-voltage group (43.3% vs. 9.5%, $p = 0.009$; 76.7% vs. 14.3%, $p < 0.001$; 63.3% vs. 19.0%, $p < 0.001$; 100% vs. 61.9%, $p < 0.001$; 46.6% vs. 4.8%, $p = 0.004$; and 76.7% vs. 47.6%, $p = 0.033$, respectively) (Table 2, Fig. 1).

Table 1. Demographic and clinical characteristics of the patients.

	Total ($n = 51$)
Age (years) *	36.0 (20–44)
Sex **	
Female	5 (9.8)
Male	46 (90.2)
Length of hospital stay (days) *	29.0 (14–44)
ICU length of stay (days) *	2.0 (0–8)
Occupational injury **	
No	36 (70.6)
Yes	15 (29.4)
Cause of burn **	
Outdoor electrical accident	13 (25.5)
Indoor electrical accident	22 (43.1)
Occupational accident	15 (29.4)
Lightning	1 (2.0)
Location of injury **	
Outdoor	26 (51.0)
Indoor	25 (49.0)
Burn depth **	
Second-degree	7 (13.7)
Third-degree	21 (41.2)
Fourth-degree	23 (45.1)
TBSA (%) *	18.0 (10–30)
ABSI score *	5.0 (4–6)
ABSI mortality risk **	
Very low	4 (7.8)
Low	29 (56.9)
Moderate	11 (21.6)
High	6 (11.8)
Very high	1 (2.0)
Surgery **	
No	8 (15.7)
Yes	43 (84.3)
Major/minor amputation **	
No	36 (70.6)
Minor	10 (19.6)
Major	4 (7.8)
Minor+major	1 (2.0)
Mortality **	
Survive	49 (96.1)
Exitus	2 (3.9)
Complications **	
No	18 (35.3)
Yes	33 (64.7)
Voltage level **	
Low voltage	21 (41.2)
High voltage	30 (58.8)
Burn severity **	
Moderate	8 (15.7)
Major	43 (84.3)

* Median (IQR), ** n (%). TBSA, total body surface area; ABSI, Abbreviated Burn Severity Index; ICU, intensive care unit.

Table 2. Comparison of demographic and clinical characteristics according to voltage category.

	Low voltage (n = 21)	High voltage (n = 30)	p
Age (years) *	35 (20-41)	38 (20-45)	0.247
Length of hospital stay (days) *	14 (5-26)	41.5 (30-61)	< 0.001
ICU length of stay (days) *	0 (0-0)	6 (2-9)	< 0.001
Sex **			
Female	4 (19.0)	1 (3.3)	0.085
Male	17 (81.0)	29 (96.7)	
Occupational injury (yes) **	2 (9.5)	13 (43.3)	0.009
Cause of burn **			
Outdoor electrical accident	2 (9.5)	11 (36.7)	< 0.001
Indoor electrical accident	17 (81.0)	5 (16.7)	
Occupational accident	2 (9.5)	13 (43.3)	
Lightning	0 (0.0)	1 (3.3)	
Location of injury **			
Outdoor	3 (14.3)	23 (76.7)	< 0.001
Indoor	18 (85.7)	7 (23.3)	
TBSA (%) *	10 (5-20)	22.5 (15-35)	0.001
ABSI score *	4 (4-4)	6 (5-7)	< 0.001
Burn depth **			
Second-degree	7 (33.3)	0 (0.0)	< 0.001
Third-degree	10 (47.6)	11 (36.7)	
Fourth-degree	4 (19.0)	19 (63.3)	
Surgery (yes) **	13 (61.9)	30 (100.0)	< 0.001
ABSI mortality risk **			
Very low	4 (19.0)	0 (0.0)	< 0.001
Low	15 (71.4)	14 (46.7)	
Moderate	2 (9.5)	9 (30.0)	
High	0 (0.0)	6 (20.0)	
Very high	0 (0.0)	1 (3.3)	
Amputation **			
No	20 (95.2)	16 (53.3)	0.004
Minor	1 (4.8)	9 (30.0)	
Major	0 (0.0)	4 (13.3)	
Minor+major	0 (0.0)	1 (3.3)	
Complications (yes) **	10 (47.6)	23 (76.7)	0.033
Mortality (ex) **	0 (0.0)	2 (6.7)	0.341
Burn severity **			
Moderate	8 (38.1)	0 (0.0)	< 0.001
Major	13 (61.9)	30 (100.0)	

* Median (IQR), ** n (%). TBSA, total body surface area; ABSI, Abbreviated Burn Severity Index; ICU, intensive care unit.

When patients were compared according to burn depth, significant overall differences were observed among the groups in age ($p = 0.013$), length of hospital stay ($p < 0.001$), ICU length of stay ($p = 0.001$), TBSA ($p = 0.007$), and ABSI score ($p = 0.012$). Bonferroni-adjusted post hoc comparisons showed that patients with second-degree burns were significantly older than those with

third-degree burns. Length of hospital stay was significantly longer in both the third- and fourth-degree burn groups than in the second-degree burn group. ICU length of stay, TBSA, and ABSI score were significantly higher in the fourth-degree burn group than in the second-degree burn group. No other pairwise differences were statistically significant for these continuous variables (Table 3).

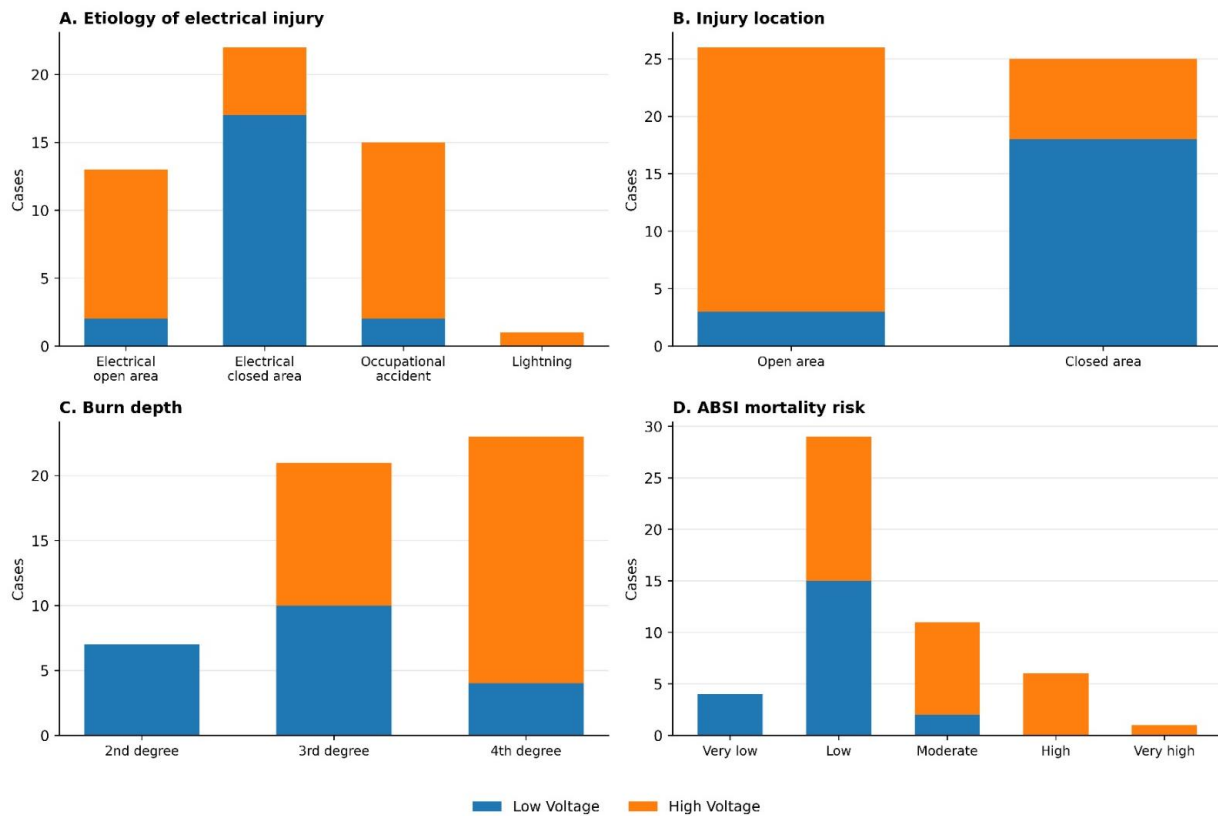


Fig. 1. Distribution of injury etiology, injury location, burn depth, and ABSI mortality risk categories among patients with low-voltage and high-voltage electrical injuries: (a) Etiology of electrical injury; (b) Injury location; (c) Burn depth; (d) ABSI mortality risk categories.

Table 3. Comparison of demographic and clinical characteristics by burn depth.

	2nd-degree (n = 7)	3rd-degree (n = 21)	4th-degree (n = 23)	p
Age (years) *	44 (36-48) ^a	27 (15-39) ^b	38 (28-49) ^{a,b}	0.013
Length of hospital stay (days) *	5 (3-7) ^a	29 (22-38) ^b	42 (20-63) ^b	< 0.001
ICU length of stay (days) *	0 (0-0) ^a	2 (0-5) ^{a,b}	6 (1-10) ^b	0.001
Sex **				
Female	0 (0.0)	4 (19.0)	1 (4.3)	0.133
Male	7 (100.0)	17 (81.0)	22 (95.7)	
Occupational injury (yes) **	1 (14.3)	6 (28.6)	8 (34.8)	0.548
Cause of burn **				
Outdoor electrical accident	0 (0.0)	4 (19.0)	9 (39.1)	0.049
Indoor electrical accident	6 (85.7)	11 (52.4)	5 (21.7)	
Occupational accident	1 (14.3)	6 (28.6)	8 (34.8)	
Lightning	0 (0.0)	0 (0.0)	1 (4.3)	
Location of injury **				
Outdoor	1 (14.3)	9 (42.9)	16 (69.6)	0.018
Indoor	6 (85.7)	12 (57.1)	7 (30.4)	
TBSA (%) *	5 (2-15) ^a	20 (15-25) ^{a,b}	25 (15-32) ^b	0.007
ABSI score *	4 (4-4) ^a	5 (4-5) ^{a,b}	6 (4-7) ^b	0.012
Surgery (yes) **	0 (0.0)	20 (95.2)	23 (100.0)	< 0.001
ABSI mortality risk **				
Very low	1 (14.3)	3 (14.3)	0 (0.0)	0.045
Low	5 (71.4)	14 (66.6)	10 (43.5)	
Moderate	1 (14.3)	1 (4.8)	9 (39.2)	
High	0 (0.0)	3 (14.3)	3 (13.0)	
Very high	0 (0.0)	0 (0.0)	1 (4.3)	

	2nd-degree (n = 7)	3rd-degree (n = 21)	4th-degree (n = 23)	p
Amputation **				
No	7 (100.0)	19 (90.5)	10 (43.5)	0.008
Minor	0 (0.0)	2 (9.5)	8 (34.8)	
Major	0 (0.0)	0 (0.0)	4 (17.4)	
Minor+major	0 (0.0)	0 (0.0)	1 (4.3)	
Complications (yes) **	4 (57.1)	11 (52.4)	18 (78.3)	0.173
Mortality (ex) **	0 (0.0)	0 (0.0)	2 (8.7)	0.193
Burn severity **				
Moderate	6 (85.7)	2 (9.5)	0 (0.0)	< 0.001
Major	1 (14.3)	19 (90.5)	23 (100.0)	

Superscript letters (^a, ^b) indicate the results of Bonferroni-adjusted post hoc pairwise comparisons. Groups without a common superscript letter differ significantly ($p < 0.05$), whereas groups sharing at least one letter do not differ significantly. * Median (IQR), ** n (%). TBSA, total body surface area; ABSI, Abbreviated Burn Severity Index; ICU, intensive care unit.

When patients were compared by amputation status, significant differences were observed among groups in length of hospital stay ($p = 0.021$), TBSA ($p = 0.042$), and ABSI score ($p = 0.035$). In Bonferroni-adjusted post hoc comparisons, the ABSI score was significantly higher in the major amputation group than in the no-amputation group.

In contrast, no significant pairwise differences were observed for length of hospital stay or TBSA. Cause of burn ($p = 0.002$) and location of injury ($p = 0.018$) also differed significantly among the amputation groups. No significant differences were observed in age, ICU length of stay, complication rates, or mortality (all $p > 0.05$) (Table 4).

Table 4. Comparison of the demographic and clinical characteristics of the patients according to amputation status.

	No (n = 36)	Minor amputation (n = 10)	Major amputation (n = 5)	p
Age (years) *	33 (17-39.3)	41 (29-53.3)	49 (38-49)	0.071
Length of hospital stay (days) *	26.5 (8.8-37.8)	39.5 (23.5-59.5)	44 (42-63)	0.021
ICU length of stay (days) *	1 (0-5)	3 (2-8.3)	7 (6-12)	0.060
Sex **				
Female	5 (13.9)	0 (0.0)	0 (0.0)	0.749
Male	31 (86.1)	10 (100.0)	5 (100.0)	
Occupational injury (yes) **	9 (25.0)	3 (30.0)	3 (60.0)	0.243
Cause of burn **				
Outdoor electrical accident	5 (13.9)	6 (60.0)	2 (40.0)	0.002
Indoor electrical accident	21 (58.3)	1 (10.0)	0 (0.0)	
Occupational accident	9 (25.0)	3 (30.0)	3 (60.0)	
Lightning	1 (2.8)	0 (0.0)	0 (0.0)	
Location of injury **				
Outdoor	14 (38.9)	7 (70.0)	5 (100.0)	0.018
Indoor	22 (61.1)	3 (30.0)	0 (0.0)	
TBSA (%) *	16.5 (10-25.8)	15 (12.8-18.8)	35 (30-38)	0.042
ABSI score *	4 (4-6) ^a	5 (4-6) ^{a, b}	7 (6-7) ^b	0.035
Surgery (yes) **	28 (77.8)	10 (100.0)	5 (100.0)	0.194
ABSI mortality risk **				
Very low	4 (11.1)	0 (0.0)	0 (0.0)	0.051
Low	22 (61.1)	7 (70.0)	0 (0.0)	
Moderate	5 (13.9)	2 (20.0)	4 (80.0)	
High	4 (11.1)	1 (10.0)	1 (20.0)	
Very high	1 (2.8)	0 (0.0)	0 (0.0)	
Complications (yes) **	21 (58.3)	7 (70.0)	5 (100.0)	0.249
Mortality (ex) **	2 (5.6)	0 (0.0)	0 (0.0)	1.000
Burn severity **				
Moderate	8 (22.2)	0 (0.0)	0 (0.0)	0.195
Major	28 (77.8)	10 (100.0)	5 (100.0)	

Superscript letters (^a, ^b) indicate the results of Bonferroni-adjusted post hoc pairwise comparisons. Groups without a common superscript letter differ significantly ($p < 0.05$), whereas groups sharing at least one letter do not differ significantly.

* Median (IQR), ** n (%). TBSA, total body surface area; ABSI, Abbreviated Burn Severity Index; ICU, intensive care unit.

In the subgroup analysis according to burn etiology ($n = 50$), patients with occupational electrical injuries had the longest hospital stay [41 (26–59.5) days; $p = 0.009$], whereas those injured in outdoor electrical accidents had the highest median age [40 (38–56) years; $p = 0.009$] and ABSI score [6 (4–7); $p = 0.023$]. Outdoor exposure was observed in 100% of the outdoor electrical accident

group and 80.0% of the occupational injury group, but in none of the indoor electrical accident group ($p < 0.001$). Furthermore, the proportion of major burns was 100%, 93.3%, and 68.2% in the outdoor electrical accident, occupational injury, and indoor electrical accident groups, respectively ($p = 0.026$) (Table 5).

Table 5. Comparison of demographic and clinical characteristics according to the cause of burn.

	Outdoor electrical accident ($n = 13$)	Indoor electrical accident ($n = 22$)	Occupational injury ($n = 15$)	p
Age (years) *	40 (38–56) ^a	27.5 (14–41) ^b	36 (23.5–41.5) ^{a,b}	0.009
Length of hospital stay (days) *	34 (20–49) ^{a,b}	22.5 (5–32) ^a	41 (26–59.5) ^b	0.009
ICU length of stay (days) *	6 (0–8)	0 (0–5)	4 (1.5–10)	0.075
Sex **				
Female	0 (0.0)	4 (18.2)	0 (0.0)	0.112
Male	13 (100.0)	18 (81.8)	15 (100.0)	
TBSA (%) *	15 (12–30)	15 (8–25)	20 (15–41)	0.182
ABSI score *	6 (4–7) ^b	4 (4–5) ^a	5 (4–7.5) ^b	0.023
Mortality (ex) **	0 (0.0)	0 (0.0)	1 (6.7)	0.560
Location of injury **				
Outdoor	13 (100.0)	0 (0.0)	12 (80.0)	< 0.001
Indoor	0 (0.0)	22 (100.0)	3 (20.0)	
Burn severity **				
Moderate	0 (0.0)	7 (31.8)	1 (6.7)	0.026
Major	13 (100.0)	15 (68.2)	14 (93.3)	
ABSI mortality risk **				
Very low	0 (0.0)	3 (13.6)	1 (6.7)	0.222
Low	7 (53.8)	15 (68.2)	7 (46.7)	
Moderate	4 (30.8)	4 (18.2)	3 (20.0)	
High	2 (15.4)	0 (0.0)	3 (20.0)	
Very high	0 (0.0)	0 (0.0)	1 (6.7)	

Superscript letters (^a, ^b) indicate the results of Bonferroni-adjusted post hoc pairwise comparisons. Groups without a common superscript letter differ significantly ($p < 0.05$), whereas groups sharing at least one letter do not differ significantly. * Median (IQR), ** n (%). TBSA, total body surface area; ABSI, Abbreviated Burn Severity Index; ICU, intensive care unit. The single patient with a lightning injury was not included in the subgroup analysis because this category contained only one patient and was not suitable for meaningful statistical comparison; therefore, the analysis included 50 patients.

4. Discussion

Electrical burns are among the most devastating traumatic injuries because of the extensive deep tissue damage, multisystem involvement, and high risk of complications that contribute substantially to morbidity and mortality [1–3,8]. Therefore, a comprehensive evaluation of the epidemiological and demographic characteristics of this patient population, together with the underlying mechanisms of injury, may improve our understanding of the factors influencing clinical course and treatment outcomes. Although several epidemiological studies on electrical burns have been published, contemporary data from the Black Sea region remain limited. Kurt et al. previously evaluated 94 patients hospitalized for electrical burn injuries in Samsun between 2008 and 2012 [9]. Building on this earlier regional research, our study evaluates a more recent cohort of patients hospitalized at a tertiary burn center, providing updated information on the epidemiological and clinical characteristics, complications, and treatment outcomes of electrical burn injuries.

Furthermore, as our tertiary burn center serves the Black Sea region and accepts referrals from neighboring provinces, our findings provide contemporary regional epidemiological and clinical data, contributing to both regional knowledge and the national literature.

Chen and Wang reported that 89.2% of patients with electrical burn injuries were male, with a median age of 28 years, based on data from the World Health Organization Global Burn Registry [10]. Similarly, Kurt et al. found that 89% of patients in their regional cohort were male [9]. Sun et al. likewise reported that 90.3% of patients were male and that 20% of the study population consisted of pediatric patients [11]. Our findings are consistent with these previous reports, with males accounting for 90.2% of the study population and a median patient age of 36 years (IQR, 20–44). These findings further support the observation that electrical burn injuries predominantly affect men of working age.

In the present study, eight of the 51 patients were children, and a lightning strike caused one case. Electrical burns remain an important cause of morbidity in chil-

dren because their ability to recognize environmental hazards and protect themselves is not yet fully developed. In a recent pediatric study, Hu et al. demonstrated that most electrical burn injuries occurred in younger children and predominantly in the home environment, emphasizing that improved parental supervision and strengthened household electrical safety measures play a crucial role in preventing these injuries [12]. Accordingly, increasing public awareness, promoting home electrical safety, and educating families should be considered essential preventive strategies to reduce the incidence of pediatric electrical burn injuries.

Karadaş et al. reported that 54.5% of electrical injury cases resulted from high-voltage exposure, whereas 45.5% resulted from low-voltage exposure [13]. Similarly, Al et al. found that 41.8% of cases were caused by high-voltage injuries and 58.2% by low-voltage injuries [14]. Consistent with these findings, high-voltage electrical burns were more common than low-voltage burns in our cohort, accounting for 58.8% of all cases. The relatively higher amputation rate observed in our study may be attributable to the inclusion of only hospitalized patients treated at a tertiary burn center, who generally presented with more severe injuries. Reported mortality rates following electrical burns range from 2.35% to 26.7% in the literature [9,10,13]. The in-hospital mortality rate in our study was 3.9%, which is within the reported range.

Our findings demonstrate that high-voltage electrical burns were associated with a more severe clinical course than low-voltage injuries, characterized by greater burn extent and severity, longer hospital and ICU stays, and higher frequencies of deep burns, surgical intervention, amputation, and complications. This pattern is consistent with the greater energy transfer and deep tissue involvement characteristic of high-voltage electrical injuries.

Cutaneous lesions do not always reflect the true extent of tissue injury following electrical burns. Particularly in high-voltage injuries, damage to muscles, blood vessels, and nerves along the path of the electrical current may result in extensive tissue necrosis disproportionate to the apparent skin lesions. Our findings are consistent with previous studies demonstrating that high-voltage electrical burns are associated with larger burn size, more extensive deep tissue injury, and a more severe clinical course [9,11,13–15]. In addition, the higher frequency of occupational accidents and outdoor exposure among patients with high-voltage burns observed in our study further supports that these injuries are predominantly related to occupational exposure.

Although mortality occurred exclusively in the high-voltage group, the difference between the voltage groups was not statistically significant. The small sample size and limited number of deaths may have reduced the statistical power to detect a difference in mortality. Başaran et al. [16] reported a positive correlation between TBSA and both hospital and ICU length of stay in patients with electrical burns. Still, they concluded that TBSA alone was insufficient to predict the development of complications. Similarly, the higher TBSA, elevated ABSI scores, increased complication and amputation rates, and prolonged hospitalization observed in patients with high-voltage injuries in our cohort indicate an association be-

tween high-voltage exposure and greater overall injury severity.

In the present study, greater burn depth was associated with greater TBSA involvement, higher ABSI scores, increased burn severity, and a higher frequency of amputation. In particular, fourth-degree burns were associated with greater TBSA and higher ABSI scores compared with second-degree burns. These findings are consistent with previous studies reporting associations between deep electrical burns and a more severe clinical course and poorer treatment outcomes [6–9,15]. Overall, the observed associations suggest that greater burn depth may reflect greater injury severity; however, the present analysis does not establish burn depth as an independent prognostic determinant.

In the present study, length of hospital stay, TBSA, and ABSI score differed significantly among the amputation groups. However, after Bonferroni adjustment, pairwise differences in length of hospital stay and TBSA were not statistically significant. Previous studies have reported prolonged hospitalization among patients with electrical burns requiring amputation [5,8,17]. In contrast, the ABSI score was significantly higher in patients undergoing major amputation than in those without amputation in our cohort, suggesting greater overall injury severity in patients requiring major amputation. Previous studies have suggested that amputation following electrical burns is related not only to the extent of burns but also to deep muscle necrosis, vascular injury, and the anatomical pathway of the electrical current through the body [4,5]. However, given the small number of patients in the major amputation group, these findings should be interpreted with caution.

Patients with occupational electrical injuries had significantly longer hospital stays, whereas those injured in outdoor electrical accidents exhibited higher ABSI scores and a greater proportion of major burns. These findings suggest that injury mechanism and location are associated with differences in clinical severity. Previous studies have likewise demonstrated that electrical burns sustained outdoors or during occupational activities are predominantly associated with high-voltage exposure and consequently result in a more severe clinical course and prolonged treatment [2,3,9,11]. Our findings are in agreement with these observations.

5. Limitations

This study has several limitations. First, the retrospective, single-center design limits the generalizability of the findings. The small sample size and limited number of deaths and major amputations may have reduced the statistical power of the analyses. The inclusion of hospitalized patients only and the exclusion of patients with incomplete medical records may have introduced selection bias. Moreover, the small number of patients in some subgroup analyses may limit the reliability of these comparisons. Given these limitations, multivariable analysis was not considered appropriate; therefore, the observed associations should not be interpreted as independent predictors of clinical outcomes. Finally, the retrospective assessment of variables such as burn depth,

TBSA, voltage category, and complications relied on existing medical records and may therefore be subject to documentation or misclassification bias. Therefore, our findings should be interpreted with caution and validated in larger, multicenter, prospective studies.

6. Conclusions

This study provides contemporary epidemiological and clinical data on patients hospitalized with electrical burns at a tertiary burn center. High-voltage electrical injuries were associated with greater burn extent, higher ABSI scores, longer hospital and ICU stays, and higher rates of surgical intervention, amputation, and complications. Greater burn depth was also associated with increased injury severity. Given the retrospective, single-center design and small sample size, the findings should be interpreted with caution and confirmed in larger, multicenter studies.

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Conflict of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this manuscript.

Data Availability

The datasets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author upon reasonable request.

AI Assistance

During the preparation of this manuscript, ChatGPT (GPT-5.5, OpenAI) was used exclusively for language editing and stylistic refinement. The authors take full responsibility for the content, interpretation, and conclusions of the published article.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Samsun University Clinical Research Ethics Committee (Approval No. GOKAEK 2024/14/14; Date: August 14, 2024). Due to the study's retrospective design, the ethics committee waived the requirement for informed consent.

Author Contributions

Serap Samut Bülbül: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, validation, visualization, writing – original draft, writing – review and editing.

Ayhan Sönmez: data curation, formal analysis, investigation, resources, supervision, visualization, writing – original draft.

Doğukan Can Öztürk: conceptualization, data curation, investigation, supervision, visualization.

Selim Görgün: visualization, writing – original draft.

Alper Ceylan: resources, supervision.

Metin Ocak: conceptualization, formal analysis, supervision, validation, visualization, writing – review and editing.

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Research Article

Temporal changes in pediatric respiratory syncytial virus and adenovirus positivity across COVID-19-related periods: A six-year retrospective cohort study

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ABSTRACT

Objective: To describe temporal changes in respiratory syncytial virus (RSV) and adenovirus positivity among children tested across three COVID-19-related periods.

Methods: This single-center retrospective cohort study included 8,253 children aged 0–18 years who underwent concurrent RSV and adenovirus antigen testing for suspected acute respiratory infection from January 2018 through June 2023. Periods were defined as pre-pandemic (January 2018–February 2020), restrictive pandemic (March 2020–May 2021), and post-restriction (June 2021–June 2023). Positivity proportions were compared by period. Unadjusted odds ratios (ORs) were calculated from period-specific counts using the pre-pandemic period as reference.

Results: RSV was detected in 266 children (3.2%) and adenovirus in 612 (7.4%). RSV positivity was 1.5% (55/3,785) pre-pandemic, 1.2% (13/1,055) during restrictions, and 5.8% (198/3,413) post-restriction. Relative to the pre-pandemic period, the odds of RSV positivity did not differ during restrictions (OR 0.85, 95% CI 0.46–1.55) but were higher post-restriction (OR 4.18, 95% CI 3.09–5.65). Adenovirus positivity was 8.8%, 10.2%, and 5.0%, respectively; corresponding ORs were 1.18 (95% CI 0.94–1.48) and 0.54 (95% CI 0.45–0.66).

Conclusion: Among clinically selected children who were tested, RSV and adenovirus positivity followed different temporal patterns. These unadjusted associations should not be interpreted as causal effects of specific public-health measures because seasonality, testing practices, and healthcare-seeking behavior may have differed across periods.

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1. Introduction

Respiratory viruses are an important source of illness and healthcare use in childhood. Respiratory syncytial virus (RSV) and human adenovirus can cause disease ranging from uncomplicated upper respiratory symptoms to lower respiratory tract infection requiring hospital care. Infants and preschool children carry a particularly high burden because immune defenses are still developing and contact within households and community settings is frequent. Despite marked differences in virol-

ogy and transmission, both pathogens contribute to pediatric respiratory morbidity and seasonal healthcare demand [1,2].

In infants and young children, RSV is a major cause of bronchiolitis and pneumonia. Its circulation in temperate climates was generally seasonal and predictable before 2020. Adenovirus differs in being a non-enveloped DNA virus that may be detected throughout the year, with geographic and type-related variation in seasonality. Clinical manifestations include febrile respiratory illness, pharyngoconjunctival fever, bronchiolitis, and

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pneumonia; severe presentations occur more often in younger or immunocompromised patients [2–5].

The public-health response to COVID-19 changed opportunities for transmission of many respiratory pathogens. During the most restrictive phases, surveillance systems in multiple countries recorded marked reductions in RSV, influenza, and other seasonal infections [6–8]. When mitigation policies were eased, respiratory-virus activity returned, but not uniformly across pathogens. RSV outbreaks were often delayed or displaced from their customary seasons, whereas adenovirus trends were less consistent between regions [9–11].

Most post-pandemic reports have emphasized RSV, and fewer have followed RSV and adenovirus concurrently over an extended interval in one pediatric testing population. We therefore compared positivity for both viruses across pre-pandemic, restrictive pandemic, and post-restriction periods. The analysis was designed to describe temporal associations, not to estimate the causal effect of individual public-health measures.

2. Materials and Methods

This single-center retrospective cohort study examined consecutive pediatric test encounters at an anonymized tertiary hospital in Istanbul, Türkiye. Electronic records were searched for children who underwent concurrent RSV and adenovirus antigen testing from January 2018 through June 2023. This study was approved by the Hisar Hospital Intercontinental Clinical Research Ethics Committee (Approval Number: 23-57; Date: December 1, 2023). The study followed the Declaration of Helsinki. Because anonymized routine-care data were analyzed retrospectively, the requirement for individual informed consent was waived.

Eligible children were aged 0–18 years and were tested during evaluation for suspected acute respiratory infection. When multiple tests occurred within the same illness episode, only the earliest was retained. Invalid assays were excluded. The periods were defined from the verified dataset as pre-pandemic (January 2018–February 2020), restrictive pandemic (March 2020–May 2021), and post-restriction (June 2021–June 2023). The three periods differed in duration and calendar-month composition. All eligible records were included; therefore, no *a priori* sample-size calculation was performed.

Nasopharyngeal samples were obtained during routine clinical assessment. RSV and adenovirus antigens were tested simultaneously using a commercial rapid immunochromatographic assay according to the manufacturer's protocol. Each pathogen was reported separately as detected or not detected.

Age, sex, specimen date, RSV result, and adenovirus result were retrieved from the electronic record. Obvious spelling variants in the laboratory export (for example, 'Pozitif' and 'pozitif*') were harmonized with the positive category before analysis. Three children with missing sex were retained in overall and period-specific analyses but excluded from sex-specific comparisons; no imputation was performed. The analytical dataset was de-identified.

Primary outcomes were RSV and adenovirus positivity proportions within each epidemiological period. All denominators comprised children tested because of suspected respiratory infection and do not represent the general pediatric population.

2.1. Statistical analyses

Continuous data are summarized as medians with interquartile ranges and categorical data as counts and percentages. Period comparisons used the Kruskal–Wallis test for age and Pearson's chi-square test for categorical variables. Because the previously reported adjusted model could not be reconciled with the observed counts and its coding could not be independently verified, it was not retained. Instead, period-specific unadjusted ORs and 95% confidence intervals were calculated directly from 2×2 tables, with the pre-pandemic period as reference. These analyses included all 8,253 children because period and virus results were complete. The models did not adjust for age, sex, calendar month, season, or year and are interpreted as descriptive temporal associations. Tests were two-sided; $p < 0.05$ indicated statistical significance. Analyses were conducted using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA).

3. Results

The analysis included 8,253 children tested concurrently for RSV and adenovirus from January 2018 through June 2023 (Fig. 1).

The pre-pandemic, restrictive pandemic, and post-restriction periods included 3,785 (45.9%), 1,055 (12.8%), and 3,413 (41.4%) children, respectively. Three children in the restrictive period had missing sex data (Table 1). Median age differed across periods ($p < 0.001$).

RSV was detected in 266 children (3.2%): 55/3,785 (1.5%) pre-pandemic, 13/1,055 (1.2%) during restrictions, and 198/3,413 (5.8%) post-restriction ($p < 0.001$; Table 2). Adenovirus was detected in 612 children (7.4%): 334/3,785 (8.8%), 108/1,055 (10.2%), and 170/3,413 (5.0%), respectively ($p < 0.001$; Table 3).

Relative to the pre-pandemic period, RSV odds were not significantly different during the restrictive period (OR 0.85, 95% CI 0.46–1.55; $p = 0.590$) but were higher post-restriction (OR 4.18, 95% CI 3.09–5.65; $p < 0.001$). Adenovirus odds were not significantly different during restrictions (OR 1.18, 95% CI 0.94–1.48; $p = 0.159$) and were lower post-restriction (OR 0.54, 95% CI 0.45–0.66; $p < 0.001$; Table 4).

4. Discussion

In this tested pediatric population, RSV and adenovirus positivity followed different patterns across the three COVID-19-related periods. RSV positivity remained low during the first two periods and increased post-restriction. Adenovirus positivity was numerically higher during restrictions but declined post-restriction. The count-derived ORs were consistent with these descriptive proportions.

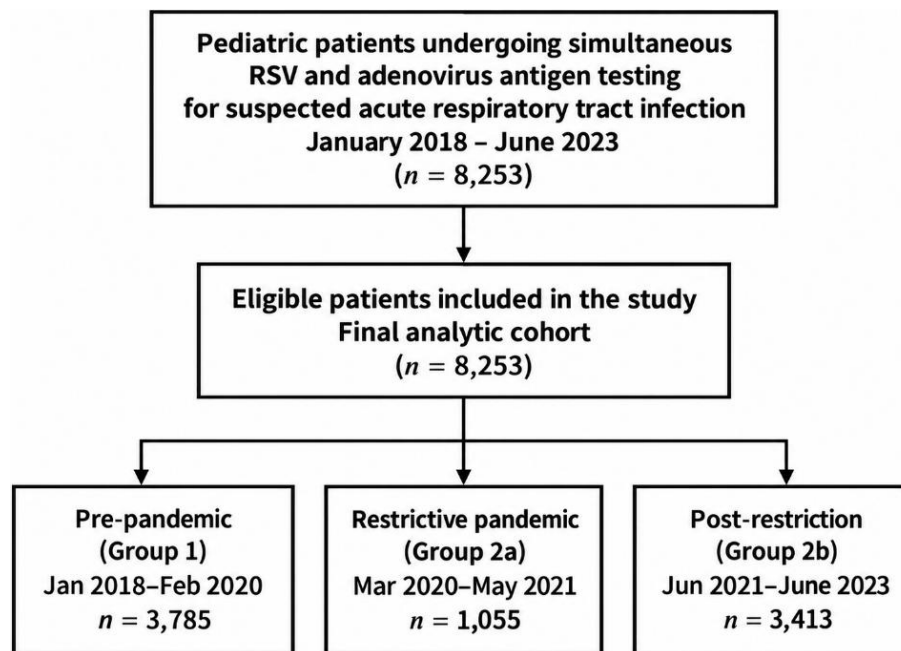


Fig. 1. Flow diagram of patient selection and classification. A total of 8,253 children underwent concurrent RSV and adenovirus antigen testing from January 2018 through June 2023 and were classified as pre-pandemic (January 2018–February 2020; $n = 3,785$), restrictive pandemic (March 2020–May 2021; $n = 1,055$), or post-restriction (June 2021–June 2023; $n = 3,413$).

Table 1. Baseline characteristics according to epidemiological period.

Characteristic	Pre-pandemic ($n = 3,785$)	Restrictive pandemic ($n = 1,055$)	Post-restriction ($n = 3,413$)	p value
Number of children, n (%)	3,785 (45.9)	1,055 (12.8)	3,413 (41.4)	—
Age (years), median (IQR)	2.8 (1.2–5.0)	2.2 (1.0–4.3)	4.0 (1.7–6.4)	< 0.001
Male sex, n (%)	2,078 (54.9)	611 (57.9)	1,902 (55.7)	0.208
Female sex, n (%)	1,707 (45.1)	441 (41.8)	1,511 (44.3)	—
Missing sex, n (%)	0	3 (0.3)	0	—

IQR, interquartile range. Age was compared with the Kruskal–Wallis test; sex with Pearson’s chi-square test. Percentages may not sum to 100 because of rounding.

Table 2. Respiratory syncytial virus positivity according to epidemiological period.

Period	Tested, n	RSV positive, n (%)	RSV negative, n (%)	p value
Pre-pandemic	3,785	55 (1.5)	3,730 (98.5)	—
Restrictive pandemic	1,055	13 (1.2)	1,042 (98.8)	—
Post-restriction	3,413	198 (5.8)	3,215 (94.2)	—
Total	8,253	266 (3.2)	7,987 (96.8)	< 0.001

RSV, respiratory syncytial virus. p value from Pearson’s chi-square test.

Table 3. Adenovirus positivity according to epidemiological period.

Period	Tested, n	Adenovirus positive, n (%)	Adenovirus negative, n (%)	p value
Pre-pandemic	3,785	334 (8.8)	3,451 (91.2)	—
Restrictive pandemic	1,055	108 (10.2)	947 (89.8)	—
Post-restriction	3,413	170 (5.0)	3,243 (95.0)	—
Total	8,253	612 (7.4)	7,641 (92.6)	< 0.001

p value from Pearson’s chi-square test.

Table 4. Unadjusted period-specific odds ratios for virus positivity.

Outcome and period	OR	95% CI	p value
RSV: pre-pandemic	Reference	—	—
RSV: restrictive pandemic	0.85	0.46–1.55	0.590
RSV: post-restriction	4.18	3.09–5.65	< 0.001
Adenovirus: pre-pandemic	Reference	—	—
Adenovirus: restrictive pandemic	1.18	0.94–1.48	0.159
Adenovirus: post-restriction	0.54	0.45–0.66	< 0.001

CI, confidence interval; OR, odds ratio; RSV, respiratory syncytial virus. Estimates were calculated directly from period-specific 2×2 tables and were not adjusted for age, sex, month, season, or year.

The post-restriction increase in RSV is consistent with reports of delayed or off-season RSV activity after relaxation of COVID-19-related restrictions [5–7]. Reduced exposure during periods of limited social contact may have increased the number of susceptible children, while resumption of school and childcare contacts may have facilitated transmission [7,8]. These mechanisms are plausible but were not measured directly in this study.

Adenovirus showed a different pattern. Environmental durability, prolonged shedding, and multiple routes of transmission may contribute to its heterogeneous temporal behavior [11,12]. Nevertheless, because the analysis did not account for calendar month or season, differences in seasonal composition between periods could partly or substantially explain the observed associations.

The denominator requires particular caution. Participants were children selected for testing because of suspected acute respiratory infection, not a population-based sample. Pandemic-related changes in referral patterns, healthcare-seeking behavior, test availability, or clinicians' thresholds for requesting antigen testing may have changed both the composition and number of children tested. Consequently, positivity proportions cannot be interpreted directly as population incidence or virus circulation.

Strengths include the large dataset and concurrent evaluation of both viruses within one center. Limitations include the retrospective single-center design, use of antigen rather than molecular assays, unequal period duration and month composition, lack of adjustment for season or calendar year, and absence of information on symptoms, severity, comorbidity, admission, viral genotype, and changing testing practices. Residual seasonal and secular confounding is therefore likely. The findings indicate temporal associations only and should not be interpreted as causal effects of specific public-health measures.

5. Conclusions

Among children selected for concurrent antigen testing, RSV positivity increased and adenovirus positivity decreased in the post-restriction period relative to the pre-pandemic period. Because the periods differed in seasonality, duration, testing context, and healthcare-seeking conditions, these findings are descriptive tem-

poral associations rather than evidence that particular public-health measures caused the changes. Multicenter analyses incorporating calendar month, season, year, and testing indications are needed.

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Conflict of Interest

The author declares no potential conflicts of interest with respect to the research, authorship, and/or publication of this manuscript.

Data Availability

The datasets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author upon reasonable request.

AI Assistance

During the preparation of this manuscript, ChatGPT was used exclusively for language editing and stylistic refinement. It was not used for statistical analyses or scientific interpretation. The author reviewed and approved the final manuscript and takes full responsibility for its content, accuracy, and conclusions.

Ethics Approval and Consent to Participate

This study was approved by the Hisar Hospital Intercontinental Clinical Research Ethics Committee (Approval Number: 23-57; Date: December 1, 2023). The study followed the Declaration of Helsinki. Because anonymized routine-care data were analyzed retrospectively, the requirement for individual informed consent was waived.

Author Contributions

Yunus Nas: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, validation, visualization, writing – original draft, writing – review and editing.

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Research Article

Association of preoperative anxiety with acute postoperative pain after total knee arthroplasty

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ABSTRACT

Objective: Preoperative anxiety may influence postoperative pain perception and analgesic requirements. This study aimed to investigate the association between preoperative anxiety and acute postoperative pain during the first 24 hours following primary total knee arthroplasty.

Methods: This prospective observational cohort study included 100 adults undergoing elective primary total knee arthroplasty under spinal anesthesia. Preoperative anxiety was assessed using the Amsterdam Preoperative Anxiety and Information Scale (APAIS). Postoperative pain intensity was evaluated using the Numerical Rating Scale (NRS) at 1, 6, 12 and 24 hours. All patients received a standardized multimodal analgesic regimen and intravenous tramadol was administered as rescue analgesia when NRS scores were ≥ 4 . Associations between preoperative anxiety and postoperative pain were evaluated using correlation and multivariable regression analyses.

Results: The median APAIS anxiety score was 10.0 (IQR 5.0–15.0). Higher preoperative anxiety was significantly associated with higher postoperative pain scores at all evaluated time points during the first 24 hours (all adjusted $p < 0.001$). In multivariable analysis, preoperative anxiety remained independently associated with higher pain intensity at 24 hours after adjustment for age, sex and preoperative pain. Higher preoperative anxiety was also associated with greater cumulative rescue tramadol consumption during the first 24 postoperative hours.

Conclusion: Higher preoperative anxiety was associated with greater acute postoperative pain and greater cumulative rescue tramadol consumption after total knee arthroplasty. Preoperative anxiety screening may help identify patients at risk of more intense early postoperative pain and support individualized perioperative pain management strategies.

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1. Introduction

Total knee arthroplasty (TKA) is a widely performed and effective surgical treatment for pain and functional impairment caused by advanced knee osteoarthritis. Despite advances in surgical techniques, regional anesthesia and multimodal analgesic strategies, acute postoperative pain remains a major clinical challenge after TKA.

Moderate-to-severe pain in the early postoperative period can delay mobilization and participation in rehabilitation, reduce patient satisfaction and increase the need for rescue analgesia [1]. The marked interindividual variability in pain and functional recovery after TKA also suggests that outcomes are influenced not only by surgical and analgesic factors but also by patient-specific characteristics.

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Postoperative pain is a complex, multidimensional experience that cannot be explained solely by the extent of surgical tissue injury. Preoperative pain intensity, age, sex, previous surgical experiences, expectations and psychological status may all influence how pain is perceived and reported. Among these psychological factors, preoperative anxiety is one of the most frequently investigated in relation to acute postoperative pain. Anxiety may heighten attention to painful stimuli, reinforce negative expectations and reduce perceived coping capacity. In addition, anxiety and acute pain share neurobiological and behavioral pathways that may interact bidirectionally [2].

The role of preoperative psychological status in outcomes after TKA has received increasing attention. Previous studies have shown that patients with greater preoperative anxiety, more severe pain and poorer functional status may report less favorable outcomes after surgery [3]. Similarly, preoperative anxiety has been associated with higher pain intensity, greater analgesic use and poorer early functional outcomes after TKA [4]. More recent prospective data also suggest that patients with symptoms of anxiety or depression may experience greater pain and worse patient-reported functional outcomes both before and after TKA [5]. However, much of the existing literature has focused on long-term functional outcomes, chronic pain or combined psychiatric diagnoses rather than acute postoperative pain.

Assessing preoperative anxiety with a standardized and practical instrument may help identify patients at greater risk before surgery. The Amsterdam Preoperative Anxiety and Information Scale (APAIS) is a brief, patient-reported measure developed to assess anxiety related to surgery and anesthesia, as well as the patient's need for information [6]. The Turkish version has demonstrated acceptable validity and reliability, supporting its use in perioperative clinical research in Türkiye [7]. Because the APAIS can be readily incorporated into routine preoperative assessment, it may be useful not only for research purposes but also for identifying patients who could benefit from additional psychological support or more individualized perioperative care. Although preoperative anxiety has previously been associated with outcomes after TKA, prospective evidence focusing specifically on acute pain during the first postoperative day remains limited. In this prospective cohort, preoperative anxiety was assessed using the APAIS and examined in relation to serial pain scores over the first 24 hours within a standardized spinal anesthesia and postoperative analgesia protocol. Cumulative rescue tramadol consumption was also evaluated as a complementary measure of early postoperative analgesic requirements.

The aim of this prospective observational cohort study was to investigate the association between preoperative anxiety, assessed using the APAIS, and acute postoperative pain intensity during the first 24 hours after elective primary TKA. We hypothesized that higher preoperative anxiety scores would remain independently associated with higher postoperative Numerical Rating Scale (NRS) pain scores after adjustment for relevant demographic and clinical variables.

2. Materials and Methods

2.1. Study design and ethical approval

This prospective observational cohort study was designed to evaluate the association between preoperative anxiety and acute postoperative pain intensity in patients undergoing elective primary TKA. The study was conducted in the operating rooms and relevant surgical wards of Tuzla State Hospital between May 2026 and August 2026. The study protocol was approved by the Koşuyolu High Specialization Training and Research Hospital Scientific Research Ethics Committee (decision date: April 21, 2026; decision no.: 2026/08/1449). The study was conducted in accordance with the principles of the Declaration of Helsinki. Before enrollment, all patients were informed about the purpose and procedures of the study and written informed consent was obtained from all participants.

2.2. Study population

Patients undergoing elective unilateral primary total knee arthroplasty (TKA) were assessed for eligibility according to the following criteria.

2.2.1. Inclusion criteria

- Age ≥ 18 years
- Scheduled for elective unilateral primary TKA
- American Society of Anesthesiologists (ASA) physical status I–III
- Planned spinal anesthesia

2.2.2. Exclusion criteria

- Previous total knee arthroplasty or revision surgery involving either the ipsilateral or contralateral knee
- Severe cognitive impairment
- Neurological or psychiatric disorders that could interfere with communication or reliable completion of the study questionnaires
- Chronic pain syndrome requiring regular opioid or neuropathic pain medication use
- Requirement for general anesthesia or sedation
- Known allergy or contraindication to paracetamol, diclofenac or tramadol

2.3. Preoperative assessment

Age, sex, height, body weight, body mass index, ASA physical status, comorbidities and history of previous surgery were recorded for all participants.

Preoperative anxiety was assessed using the Amsterdam Preoperative Anxiety and Information Scale. The APAIS consists of six items evaluating anxiety related to surgery and anesthesia and the patient's need for perioperative information. Each item was rated from 1 to 5. The four-item anxiety subscale has a total score ranging from 4 to 20, whereas the two-item information requirement subscale ranges from 2 to 10. Higher scores indicate greater anxiety or a greater need for information.

The APAIS was administered face to face by a trained investigator in the preoperative holding area before transfer to the operating room and before the administration of any sedative medication. Intravenous cannulation had already been performed in the surgical ward as part of routine preoperative care. The assessment was performed at a standardized preoperative time point under comparable conditions for all participants. The total APAIS anxiety subscale score was used as the primary independent variable in this study.

2.4. Anesthetic management

All patients underwent standard intraoperative monitoring, including electrocardiography, noninvasive arterial blood pressure monitoring and peripheral oxygen saturation. After intravenous access was established, spinal anesthesia was performed under aseptic conditions according to the institutional protocol. With the patient in the sitting position, the subarachnoid space was accessed at the L3–L4 or L4–L5 intervertebral level and 10–15 mg (2.0–3.0 mL) of 0.5% hyperbaric bupivacaine was administered intrathecally. No intrathecal opioid or other adjuvant was used. Adequacy of the spinal block was confirmed by bilateral pinprick assessment before the start of surgery. Surgery was initiated only after an adequate sensory block had been achieved. None of the patients included in the study received intraoperative sedation. Three patients required conversion from spinal to general anesthesia because of inadequate spinal blockade and were excluded from the final analysis.

Duration of surgery was recorded in minutes from skin incision to completion of skin closure.

2.5. Postoperative analgesia protocol

All patients received a standardized multimodal analgesic regimen consisting of intravenous paracetamol 1 g every 8 hours and intramuscular diclofenac sodium 75 mg every 12 hours. The first doses of intravenous paracetamol 1 g and intramuscular diclofenac sodium 75 mg were administered at the end of surgery. The pharmacological components of this standardized regimen were aligned with the PROSPECT recommendations for TKA, which recommend paracetamol and a nonsteroidal anti-inflammatory drug as basic analgesics, with opioids reserved for rescue analgesia [1]. No peripheral nerve block or periarticular local anesthetic infiltration was performed.

Postoperative pain intensity at rest was assessed using an 11-point Numerical Rating Scale ranging from 0 to 10, where 0 indicated no pain and 10 represented the worst pain imaginable. Pain assessments were performed at 1, 6, 12 and 24 hours after the end of surgery. Postoperative pain assessments were performed by an investigator who was blinded to the patients' preoperative APAIS scores. At each predefined assessment time point (1, 6, 12 and 24 hours after the end of surgery), the NRS score was recorded before the administration of rescue analgesia. Patients with an NRS score of 4 or higher received 100 mg intravenous tramadol as rescue analgesia, with a maximum total daily dose of 400 mg.

Rescue tramadol was administered only at these predefined assessment time points and the administered dose was recorded at each assessment.

2.6. Outcome measures

The primary outcome was the association between the preoperative APAIS anxiety score and the NRS pain score at 24 hours postoperatively. Secondary outcomes included the associations between the APAIS anxiety score and NRS scores at 1, 6 and 12 hours postoperatively, changes in postoperative NRS scores during the first 24 hours, the association between preoperative anxiety level and rescue tramadol requirements at different postoperative time points and the potential effects of demographic and clinical variables on postoperative pain intensity.

2.7. Sample size calculation

The sample size calculation was based on the primary hypothesis of an association between preoperative anxiety and postoperative pain, both analyzed as continuous variables. At the planning stage, reliable effect-size estimates for an adjusted multivariable regression model were not available; therefore, the calculation was based on detecting a moderate correlation between these two continuous measures. The minimum required sample size was determined using an a priori power analysis with G*Power 3.1. Assuming a moderate correlation coefficient ($r = 0.30$), a two-sided alpha level of 0.05 and 80% statistical power, a minimum sample size of 84 patients was required. To account for potential data loss or incomplete assessments, the target sample size was increased to 100 patients. The final multivariable model included four predictors and was kept parsimonious relative to the available sample size.

2.8. Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 29.0 (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was assessed using the Shapiro–Wilk test together with graphical methods. Normally distributed variables are presented as mean $\pm$ standard deviation, non-normally distributed variables as median and interquartile range and categorical variables as counts and percentages.

The internal consistency of the APAIS anxiety and information requirement subscales was evaluated using Cronbach's alpha. Associations between preoperative APAIS anxiety scores and postoperative NRS scores were examined using Spearman rank correlation analysis. Holm–Bonferroni correction was applied to related multiple comparisons.

Changes in NRS scores at 1, 6, 12 and 24 hours postoperatively were analyzed using the Friedman test. When a significant overall difference was identified, pairwise comparisons were performed using the Wilcoxon signed-rank test with Holm–Bonferroni adjustment.

Covariates for the multivariable model were selected based on their clinical relevance to postoperative pain

while maintaining a parsimonious model. Preoperative NRS score, age, and sex were included as potential confounding variables. Previous surgical history and duration of surgery differed between the exploratory high- and low-anxiety groups; however, these post hoc group differences were not used to determine covariate inclusion in the primary model, in which APAIS anxiety score was analyzed as a continuous variable.

Multiple linear regression analysis was used to evaluate whether preoperative anxiety was independently associated with pain intensity at 24 hours. The 24-hour NRS score was entered as the dependent variable, while the APAIS anxiety score, preoperative NRS score, age and sex were entered simultaneously as independent variables. Regression results are presented as unstandardized regression coefficients, 95% confidence intervals and *p* values.

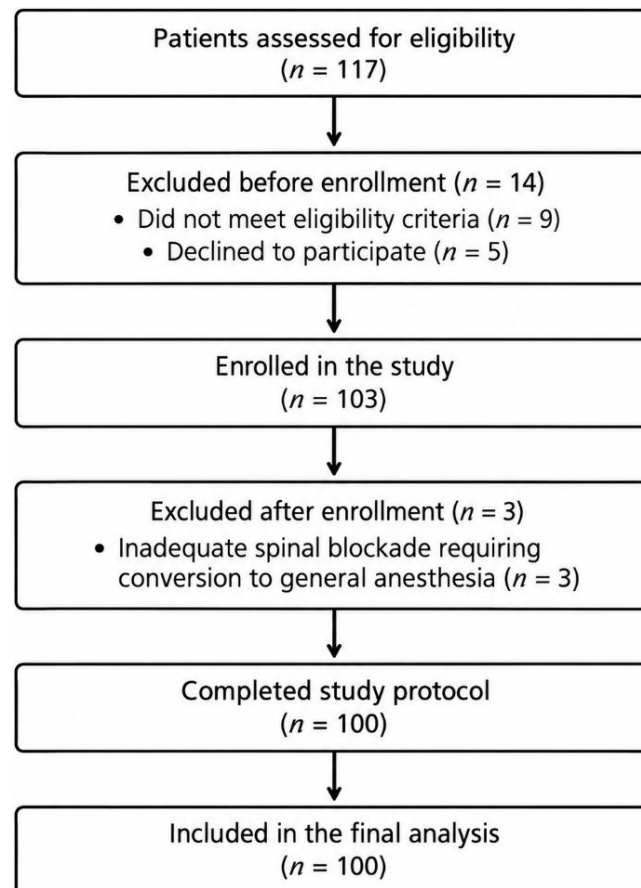
For exploratory analyses, patients were categorized into high- and low-anxiety groups using an APAIS anxiety subscale cut-off of ≥ 11 , as originally proposed by Moerman et al. [6]. Continuous variables were compared between groups using the independent-samples *t* test or

Mann–Whitney *U* test, as appropriate, and categorical variables were compared using the chi-square test or Fisher's exact test. Total tramadol consumption during the first 24 postoperative hours was calculated as the sum of the 100-mg rescue doses administered.

All statistical tests were two-sided and a *p* value < 0.05 was considered statistically significant.

3. Results

A total of 117 patients were assessed for eligibility. Fourteen patients were excluded before enrollment: nine did not meet the eligibility criteria and five declined participation. The remaining 103 patients were enrolled in the study. Three patients required conversion from spinal to general anesthesia because of inadequate spinal blockade and were excluded from the final analysis. None of the enrolled patients required intraoperative sedation. The remaining 100 patients completed the study protocol and were included in the final analysis. The participant flow is shown in Fig. 1.



No enrolled patient required intraoperative sedation.

Fig. 1. Participant flow diagram of the study.

The mean age was 67.34 ± 6.86 years, the mean body mass index was 32.26 ± 4.64 kg/m² and 64% of the cohort were women. Sixty-two patients (62%) were classified as ASA II and 38 (38%) as ASA III. The median preoperative NRS score was 7.0 (IQR, 6.0–7.0) and the median duration of surgery was 122.5 minutes (IQR, 110.0–

140.0). The median APAIS anxiety subscale score was 10.0 (IQR, 5.0–15.0) and the median information requirement subscale score was 4.0 (IQR, 2.0–6.0). Internal consistency was high for both subscales, with Cronbach's alpha values of 0.951 for anxiety and 0.948 for information requirement (Table 1).

Table 1. Demographic and clinical characteristics of the study population.

Variable	All patients (<i>n</i> = 100)	High anxiety (<i>n</i> = 48)	Low anxiety (<i>n</i> = 52)	<i>p</i>
Age (years)	67.34 ± 6.86	67.65 ± 7.34	67.06 ± 6.45	0.672
Female sex, <i>n</i> (%)	64 (64.0)	39 (81.3)	25 (48.1)	< 0.001
Body mass index (kg/m ²)	32.26 ± 4.64	32.77 ± 4.69	31.79 ± 4.58	0.292
ASA II/III, <i>n</i>	62/38	30/18	32/20	0.921
History of previous surgery, <i>n</i> (%)	50 (50.0)	17 (35.4)	33 (63.5)	0.005
Duration of surgery (min)	122.5 (110.0–140.0)	120.0 (103.8–126.3)	137.5 (120.0–150.0)	< 0.001
Preoperative NRS score	7.0 (6.0–7.0)	7.0 (6.0–7.0)	7.0 (6.0–7.0)	0.443
AP AIS anxiety subscale (4–20)	10.0 (5.0–15.0)	—	—	—
AP AIS information requirement subscale (2–10)	4.0 (2.0–6.0)	—	—	—

Data are presented as mean ± standard deviation, median (interquartile range) or *n* (%). High anxiety was defined as an AP AIS anxiety subscale score ≥ 11. Continuous variables were compared using the independent-samples *t* test or Mann-Whitney *U* test, as appropriate, and categorical variables were compared using the chi-square test. AP AIS, Amsterdam Preoperative Anxiety and Information Scale; ASA, American Society of Anesthesiologists; NRS, Numerical Rating Scale. High- and low-anxiety group comparisons were exploratory.

Preoperative AP AIS anxiety scores were positively and significantly correlated with NRS scores at all postoperative assessment points. Spearman correlation coefficients at 1, 6, 12 and 24 hours were 0.649, 0.680, 0.590

and 0.570, respectively (all adjusted *p* < 0.001). The strongest association was observed with pain intensity at 6 hours postoperatively (Table 2).

Table 2. Association between preoperative anxiety and postoperative pain scores.

Postoperative assessment	Spearman <i>ρ</i>	95% CI	Adjusted <i>p</i>
NRS at 1 hour	0.649	0.510–0.755	< 0.001
NRS at 6 hours	0.680	0.550–0.778	< 0.001
NRS at 12 hours	0.590	0.436–0.711	< 0.001
NRS at 24 hours	0.570	0.411–0.695	< 0.001

The explanatory variable was the AP AIS anxiety subscale score (4–20). Holm–Bonferroni correction was applied for multiple comparisons. AP AIS, Amsterdam Preoperative Anxiety and Information Scale; CI, confidence interval; NRS, Numerical Rating Scale.

In the multivariable linear regression model with the 24-hour NRS score as the dependent variable, the AP AIS anxiety score remained independently associated with greater pain intensity after adjustment for preoperative NRS score, age and sex (*B* = 0.144; 95% CI, 0.088–0.201;

p < 0.001). The model explained 37.1% of the variance in 24-hour pain scores. Male sex was associated with lower 24-hour NRS scores, whereas age and preoperative NRS score were not significantly associated with the outcome (Table 3).

Table 3. Multiple linear regression analysis of factors associated with pain intensity at 24 hours.

Variable	<i>B</i>	95% CI	<i>p</i>
AP AIS anxiety score	0.144	0.088–0.201	< 0.001
Preoperative NRS score	–0.178	–0.545–0.188	0.336
Age	0.007	–0.027–0.042	0.675
Male sex	–0.587	–1.141–0.032	0.039

The dependent variable was the NRS score at 24 hours postoperatively. All variables were entered simultaneously into the model. Model: *F*(4,95) = 13.99; *p* < 0.001; *R*² = 0.371; adjusted *R*² = 0.344. *B*, unstandardized regression coefficient; AP AIS, Amsterdam Preoperative Anxiety and Information Scale; CI, confidence interval; NRS, Numerical Rating Scale.

Postoperative pain intensity changed significantly over the first 24 hours (Friedman χ^2 [3] = 78.94; *p* < 0.001). Median NRS scores were 2.0 at 1 hour, 5.0 at 6 hours, 4.0 at 12 hours and 4.0 at 24 hours. Pain peaked at 6 hours, whereas the difference between the 12- and 24-hour scores was not statistically significant.

In exploratory analyses, 48 patients were classified as having high anxiety and 52 as having low anxiety. Pa-

tients in the high-anxiety group reported higher pain scores at every postoperative assessment point (all *p* < 0.001). Median cumulative tramadol consumption during the first 24 hours was also higher in the high-anxiety group [300 mg (IQR, 300–325) vs 200 mg (IQR, 100–200); *p* < 0.001]. The median cumulative tramadol dose during the first 24 hours was 200 mg (IQR, 175–300). Rescue tramadol was administered at least once to 98%

of patients and was most frequently required at the 6-hour assessment. No patient exceeded the maximum

daily dose of 400 mg. No intraoperative complications were observed (Table 4).

Table 4. Rescue tramadol consumption during the first 24 postoperative hours.

Variable	All patients (<i>n</i> = 100)	High anxiety (<i>n</i> = 48)	Low anxiety (<i>n</i> = 52)	<i>p</i>
Cumulative tramadol (mg)	200 (175–300)	300 (300–325)	200 (100–200)	< 0.001
Cumulative tramadol (mg/kg)	2.59 (1.88–3.75)	3.37 (3.06–4.30)	2.00 (1.16–2.52)	< 0.001
Patients requiring ≥ 1 rescue dose, <i>n</i> (%)	98 (98.0)	—	—	—

Data are presented as median (interquartile range) or *n* (%). Cumulative tramadol dose was calculated as the sum of the 100-mg doses administered according to the standardized rescue analgesia protocol. High anxiety was defined as an APAIS anxiety subscale score ≥ 11. High- and low-anxiety groups were compared using the Mann-Whitney *U* test. Group comparisons were exploratory. APAIS, Amsterdam Preoperative Anxiety and Information Scale.

4. Discussion

In this prospective observational study, higher preoperative anxiety was significantly associated with greater acute postoperative pain during the first 24 hours after elective primary TKA. As APAIS anxiety scores increased, NRS pain scores also increased across the postoperative assessment points and the association persisted after adjustment for relevant demographic and clinical variables. In the adjusted model, each one-point increase in the APAIS anxiety score was associated with a 0.144-point increase in the 24-hour NRS score, indicating a modest effect magnitude despite the statistically robust association. Accordingly, the continuous APAIS analyses and the adjusted regression model provide the stronger evidence for the association between preoperative anxiety and postoperative pain, whereas the high- versus low-anxiety group comparisons should be regarded as exploratory. Higher preoperative anxiety was also associated with greater cumulative rescue tramadol consumption. Together, these findings suggest that preoperative psychological status may have a clinically meaningful role in the early pain experience after TKA.

Our findings are broadly consistent with previous studies examining the relationship between preoperative anxiety and postoperative pain in patients undergoing TKA. Alattas et al. reported that greater preoperative anxiety, higher pain intensity and poorer functional status were associated with worse patient-reported outcomes after TKA [3]. Pan et al. similarly showed in a large patient cohort that anxiety and depression were associated with pain-related symptoms and postoperative complications following TKA [8]. More recent prospective data have also indicated that patients with symptoms of anxiety or depression may experience greater pain and worse subjective functional outcomes both before and after TKA [5]. In another orthopedic population, Nixon et al. found that patients with high preoperative anxiety undergoing foot and ankle surgery reported more residual pain and greater functional limitation after surgery [9].

Several neurobiological and behavioral mechanisms may help explain the relationship between preoperative anxiety and postoperative pain. Patients with greater anxiety may focus more strongly on painful stimuli, anticipate worse outcomes and experience a greater sense

of uncertainty or loss of control, all of which can amplify the pain experience. Anxiety and acute pain also share pathways related to stress responses, autonomic activation and central pain modulation [2]. In a descriptive correlational study of 138 patients undergoing elective general surgery, Gezer and Şişman reported positive associations between preoperative surgical fear and anxiety and postoperative pain intensity throughout the first 24 hours, with the relationship appearing most pronounced in the early postoperative period [10]. This supports our observation that anxiety was associated with pain at multiple postoperative time points across different types of surgery. However, that study found no significant association between anxiety or fear and total analgesic consumption. Differences in patient populations, surgical procedures, anxiety measures, and analgesic protocols may account for this discrepancy. The use of standardized spinal anesthesia and a uniform multimodal postoperative analgesic regimen in our study may have reduced variability attributable to anesthetic and routine analgesic management. Nevertheless, because of the observational design, a causal relationship between anxiety and postoperative pain cannot be established.

Because 98% of patients received at least one rescue tramadol dose, the more informative finding was the difference in cumulative tramadol consumption rather than whether rescue analgesia was required. This finding is also broadly consistent with previous literature. Ardon et al. reported higher opioid consumption on the day of surgery and the first postoperative day among patients using anxiolytic or antidepressant medications before TKA [11]. Although medication use is not a direct measure of anxiety severity, these findings support a possible relationship between psychological burden and early postoperative opioid requirements. Similarly, Rajamäki et al. found that patients using antidepressants or benzodiazepines before total hip or knee arthroplasty had more prolonged postoperative use of opioids and other analgesics [12].

The influence of psychological status on arthroplasty outcomes may extend beyond early pain and analgesic consumption. Harmer et al. reported higher risks of infection, revision and reoperation among patients with depression or anxiety undergoing total hip or knee arthroplasty [13]. Zalikha et al. likewise found that anxiety and depression may be associated with in-hospital com-

plications and healthcare outcomes after total joint arthroplasty [14]. Preoperative anxiety and depression have also been associated with higher direct costs and a greater burden of complications [15].

Not all studies, however, have reported consistent findings. In a multicenter analysis by Seagrave et al., some outcomes appeared less favorable in unadjusted analyses among patients receiving treatment for anxiety or depression, but these differences were no longer significant for one-year arthroplasty outcomes after adjustment for confounding variables [16]. This finding emphasizes that associations between psychological status and surgical outcomes may be influenced by factors such as age, sex, comorbidity, preoperative pain, and baseline function. In addition, a chronic psychiatric condition defined by diagnosis or medication use is not equivalent to short-term, surgery-specific anxiety. Differences in patient selection, assessment instruments, follow-up duration and outcome definitions are therefore likely contributors to the heterogeneity of the literature.

The higher anxiety levels and greater postoperative pain observed among women in our study are also consistent with previous findings. In a study using the APAIS, Celik and Edipoglu found significantly higher anxiety subscale scores in women and reported postoperative pain as one of the most common anesthesia-related concerns [17]. Their findings also support the practicality of the APAIS for identifying surgery and anesthesia-related anxiety during the preoperative visit. Nevertheless, the relationship between sex and pain should not be interpreted solely in biological terms. Pain perception and expression are shaped by a combination of hormonal, psychological, social and cultural influences. Moreover, the higher proportion of women in our high-anxiety group introduces potential confounding between sex and anxiety. Accordingly, even though sex was included in the multivariable analysis, these findings should not be interpreted as evidence of a direct biological causal effect.

The association between preoperative anxiety and acute postoperative pain has practical clinical implications because anxiety can be assessed easily before surgery and may be modifiable. The APAIS is brief, simple to administer and specifically addresses concerns related to anesthesia and surgery. Identifying patients with high anxiety before surgery could help target interventions such as more detailed counseling, realistic expectation setting, patient education, psychological support and individualized analgesic planning. However, our study does not demonstrate that reducing anxiety will necessarily reduce postoperative pain or opioid requirements. Randomized controlled trials comparing targeted preoperative education, cognitive-behavioral strategies or other anxiety-reducing interventions with standard care are needed to determine whether such approaches improve postoperative outcomes.

Preoperative psychological factors may also be relevant to longer-term pain outcomes. Croppi et al. identified anxiety and pain catastrophizing as risk factors for chronic pain after TKA [18]. Similarly, systematic reviews and meta-analyses evaluating the relationship between preoperative anxiety and chronic postsurgical pain suggest that anxiety may be an important marker of

longer-term pain vulnerability [19]. Because our study evaluated only the first 24 postoperative hours, we could not determine whether patients with greater anxiety and more intense early pain are also at increased risk of persistent pain in the months after surgery.

This study has several strengths. Its prospective design, inclusion of a relatively homogeneous primary TKA population, use of spinal anesthesia in all patients and standardized postoperative analgesic protocol reduced variability in perioperative management. Anxiety was assessed using a surgery-specific instrument with established validity in Turkish and pain was measured at multiple time points during the first 24 postoperative hours. In addition, adjustment for preoperative pain and key demographic variables allowed us to examine whether anxiety remained independently associated with postoperative pain.

Several limitations should also be considered. First, the single-center observational design precludes causal inference and may limit the generalizability of the findings to other patient populations or perioperative protocols. In addition, the exploratory high- and low-anxiety group comparisons may have been influenced by residual confounding because the groups differed in sex distribution, previous surgical history and duration of surgery; therefore, these subgroup findings should be interpreted cautiously. Second, the sample size was determined using a correlation-based calculation rather than specifically for the multivariable regression model; therefore, the study may have had limited power to detect smaller adjusted associations. Third, regression of the spinal sensory block was not systematically recorded; therefore, residual spinal anesthesia may have influenced the early postoperative NRS assessment, particularly at 1 hour. Fourth, other psychological factors that may influence postoperative pain, including depression, sleep disturbance, social support, expectations and pain-related self-efficacy, were not assessed. Fifth, pain is a subjective, patient-reported outcome and anxiety may influence both the perception and expression of pain. Sixth, because rescue tramadol was administered according to a standardized threshold of NRS ≥ 4 , the association between anxiety and tramadol requirement is not fully independent of pain intensity itself. Finally, only the first 24 postoperative hours were evaluated; longer-term outcomes such as length of hospital stay, mobilization, functional recovery, patient satisfaction and chronic postsurgical pain were not assessed.

5. Conclusions

Higher preoperative anxiety was associated with greater acute postoperative pain intensity and greater cumulative rescue tramadol consumption during the first 24 hours after elective primary TKA. These findings suggest that preoperative anxiety assessment may provide useful additional information when identifying patients who may experience greater early postoperative pain. Further multicenter and controlled studies are needed to determine whether interventions targeting preoperative anxiety can improve postoperative pain outcomes.

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Conflict of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this manuscript.

Data Availability

The datasets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author upon reasonable request.

AI Assistance

ChatGPT (OpenAI) was used for language refinement. The authors reviewed and verified the scientific content, statistical analyses, interpretations, and references and take full responsibility for the final manuscript.

Ethics Approval and Consent to Participate

This study was approved by the Koşuyolu High Specialization Training and Research Hospital Scientific Research Ethics Committee (Approval Number: 2026/08/1449; Date: April 21, 2026). Written informed consent was obtained from all participants. All procedures were conducted in accordance with the Declaration of Helsinki and relevant guidelines and regulations.

Author Contributions

İrem Durmuş: conceptualization, methodology, supervision, formal analysis, writing – original draft, writing – review & editing.

Merve Bulun Yediyıldız: conceptualization, methodology, supervision, data curation, investigation, writing – review & editing.

Irmak Çimenoglu: methodology, data curation, investigation, writing – review & editing.

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Research Article

Post-heparinization autologous donation with autologous circuit priming versus acute normovolemic hemodilution in cardiac surgery: A retrospective cohort study

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ABSTRACT

Objective: To compare postoperative chest-tube drainage and cumulative allogeneic red blood cell (RBC) exposure between two integrated autologous blood-conservation strategies: post-heparinization pre-bypass acute autologous donation (PAAD), which incorporated autologous circuit priming, and pre-heparinization acute normovolemic hemodilution (ANH).

Methods: This single-center retrospective cohort included 220 adults undergoing first-time elective on-pump cardiac surgery with preoperative hemoglobin ≥ 12 g/dL; 117 received PAAD and 103 ANH as routine care. The primary outcome was cumulative chest-tube drainage during the first 24 hours after intensive care unit admission. The key secondary outcome was allogeneic RBC exposure from cardiopulmonary bypass-flow start through discharge or death. Crude and covariate-adjusted estimates were calculated.

Results: Mean (standard deviation) 24-hour drainage was 876.2 (692.2) mL with PAAD and 855.0 (657.8) mL with ANH. The crude PAAD-minus-ANH mean difference was 21.2 mL (95% confidence interval [CI], -159.1 to 201.6), and the adjusted difference was 44.3 mL (95% CI, -146.3 to 234.9). Cumulative RBC exposure occurred in 38/117 (32.5%) PAAD and 29/103 (28.2%) ANH patients (risk difference, 4.3 percentage points; 95% CI, -7.9 to 16.2; risk ratio, 1.15; 95% CI, 0.77 to 1.73).

Conclusion: In this selected elective cohort, neither outcome clearly differed between the integrated strategies, but the wide intervals were compatible with clinically relevant associations in either direction. These observational data do not establish equivalence, causation, or a preferred strategy.

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1. Introduction

Bleeding and allogeneic transfusion remain interrelated complications of cardiac surgery with cardiopulmonary bypass (CPB). Patient blood-management guidance emphasizes correction of preoperative anemia, antifibrinolytic therapy, careful anticoagulation and reversal, restrictive red blood cell (RBC) transfusion, and con-

servation of autologous blood [1–3]. Postoperative chest-tube drainage reflects surgical bleeding, CPB-associated coagulopathy, and hemostatic management and is therefore clinically relevant when comparing autologous whole-blood strategies.

Acute normovolemic hemodilution (ANH) withdraws whole blood before systemic heparinization, replaces intravascular volume, and returns the blood after CPB.

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Several studies suggested that larger withdrawal volumes could reduce allogeneic transfusion [4–6], but a 2010-patient multicenter randomized trial found no clinically important reduction in in-hospital RBC exposure compared with usual care [7].

Post-heparinization pre-bypass acute autologous donation (PAAD) withdraws blood after systemic heparinization but before CPB flow and before the venous reservoir and oxygenator. Venous-line collection after full heparinization and immediately before CPB has been described [8]. However, PAAD and ANH represent multi-component practices that differ not only in heparinization timing but also in collection route and speed, autologous circuit priming, collection-bag anticoagulant exposure, storage, and reinfusion relative to protamine. The direct comparative and related descriptive literature is small, old, and heterogeneous [9–13].

We evaluated the hypothesis that 24-hour postoperative chest-tube drainage would differ between these two integrated clinical strategies. Our primary aim was to estimate the PAAD-minus-ANH mean difference in 24-hour drainage; cumulative allogeneic RBC exposure was the key secondary outcome.

2. Methods

2.1. Study design, setting, and ethics

This single-center retrospective cohort included operations performed from February 1 through October 1, 2025, at a tertiary cardiac surgery center in Türkiye. Both PAAD and ANH were established routine clinical practices during this period, and no aspect of patient management was modified for research purposes. The study was approved by the institutional ethics committee after the clinical study period and before record review began. The study and its statistical analysis were not registered in advance. Reporting follows the STROBE statement; the RECORD extension informed the description of routinely collected clinical data [14,15].

2.2. Participants and strategy selection

All 624 adult cardiac surgical procedures in the fixed study period specified in the approved ethics protocol were screened. Eligibility required elective, first-time, on-pump surgery, a last preoperative hemoglobin of at least 12 g/dL, clinical suitability for autologous collection, and accessible records. Hierarchical exclusions were emergency surgery ($n = 77$), redo surgery ($n = 32$), off-pump surgery ($n = 11$), last preoperative hemoglobin below 12 g/dL ($n = 237$), another clinical contraindication to collection ($n = 45$), and inaccessible records ($n = 2$). The 45 other contraindications were classified by primary reason as marked cardiac functional limitation, hemodynamic instability, or a fixed-output condition such as severe aortic stenosis ($n = 35$); pulmonary disease or hypoxemia ($n = 8$); and marked renal dysfunction or oliguria ($n = 2$). Each patient was counted once, although multiple contraindications could coexist. The resulting unmatched cohort comprised 220 adults (Fig. 1).

The attending anesthesiologist selected PAAD or ANH

in routine care according to preoperative hemoglobin, body habitus, ventricular function, hemodynamic stability, overall clinical condition, and usual clinician practice. PAAD tended to be favored in patients with lower left ventricular ejection fraction. Five anonymized attending-anesthesiologist identifiers were available, and every anesthesiologist used both strategies. All eligible patients were included; there was no outcome-based sampling or matching.

2.3. Autologous blood collection and reinfusion

The strategies were evaluated as integrated clinical practices because they differed in heparinization timing, collection route and speed, autologous circuit priming, and collection-bag anticoagulant exposure. Because these components co-occurred, the comparison is best interpreted as one between the strategies as implemented and not as isolating the effect of heparinization timing.

For ANH, whole blood was collected by gravity from a central venous catheter before systemic heparinization, with concurrent crystalloid according to hemodynamic response. For PAAD, after the initial intravenous unfractionated-heparin bolus, confirmation of an activated clotting time (ACT) of at least 480 seconds, and cannulation, crystalloid in the arterial and venous limbs of the CPB circuit was displaced by the patient's own blood to complete autologous circuit priming. Immediately before full CPB flow, heparinized autologous whole blood was collected by gravity from a side arm of the venous drainage line, upstream of the venous reservoir and oxygenator, into sterile collection bags. PAAD did not include reservoir blood or collection during ongoing bypass. Concurrent crystalloid replacement was administered according to hemodynamic response, as in the ANH group.

Both strategies had an approximate center-level target of 650–700 mL of blood in total. Anesthesia records documented collection into two bags for all completed procedures (117 PAAD and 100 ANH); however, bag weights and calibrated fill volumes were not recorded. Because the degree of filling could vary, bag count could not be converted reliably into an achieved patient-level blood volume. Collection-replacement volumes and postcollection/pre-CPB hematocrit values were not systematically retained. Nominal 450-mL bags containing 63 mL of citrate-phosphate-dextrose-adenine solution 1 (CPDA-1) were used. For ANH, each bag retained its CPDA-1; for PAAD, the CPDA-1 solution was drained before collection because the blood was already systemically heparinized. Bags were stored at approximately 4°C in a medical blood-storage refrigerator, warmed, and reinfused through a peripheral intravenous line. Reinfusion began before protamine and usually ended afterward. No PAAD collection was clinically interrupted. Three ANH collections were interrupted after hypotension developed at approximate collected volumes of 250, 200, and 300 mL; crystalloid and ephedrine were administered, and the partially collected blood was returned. These patients remained in the primary cohort (Supplementary Fig. S1). The partial volumes do not estimate achieved volumes in completed collections.

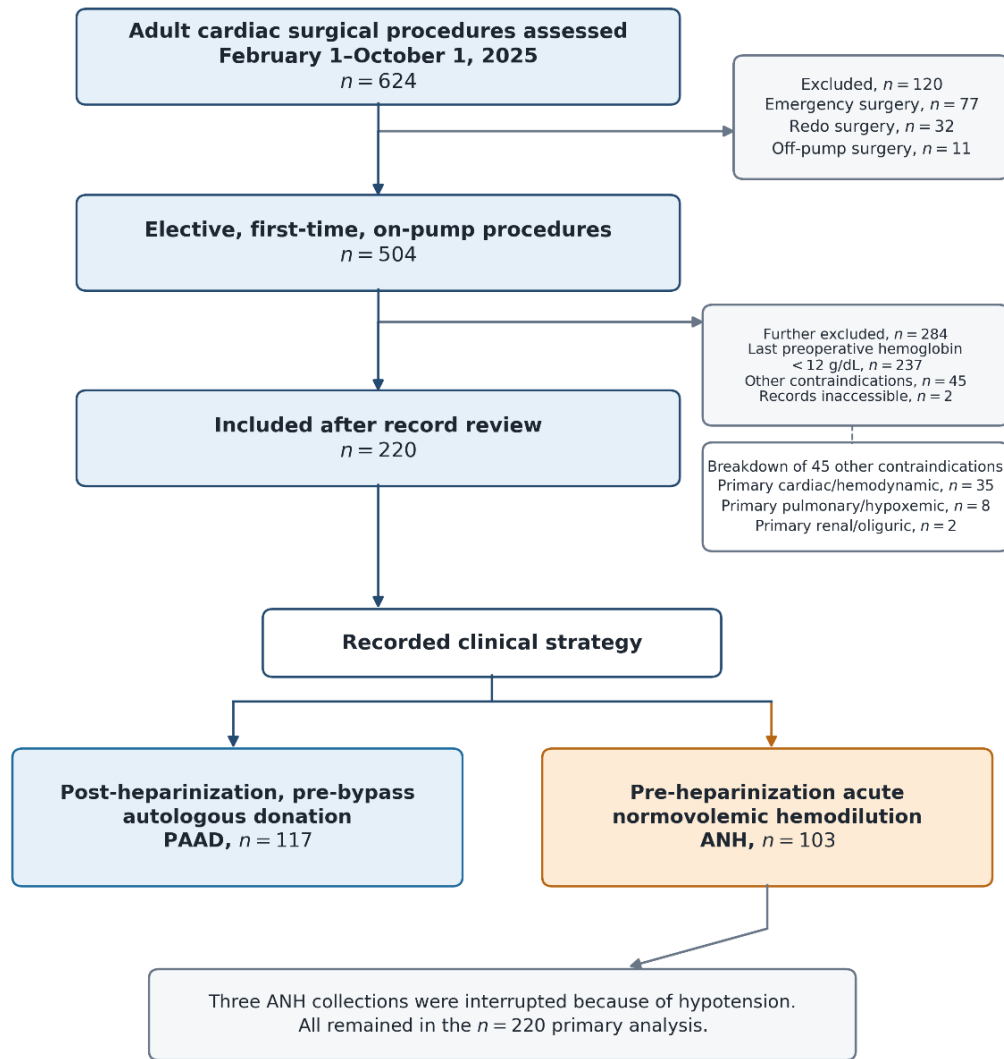


Fig. 1. Cohort assembly and collection strategies. Flow diagram showing all 624 adult cardiac surgical procedures screened during the fixed study period, hierarchical exclusions, and 220 analyzed patients divided into PAAD ($n = 117$) and ANH ($n = 103$). The three interrupted ANH collections remained in the primary cohort. ANH, acute normovolemic hemodilution; PAAD, post-heparinization pre-bypass acute autologous donation.

2.4. Anesthesia, CPB, and transfusion practice

General anesthesia and monitoring followed routine cardiac surgery practice and included invasive arterial and central venous pressure, bispectral index, and bilateral cerebral oximetry. Anesthesia was induced with midazolam, thiopental, fentanyl, and rocuronium and maintained with sevoflurane plus intermittent fentanyl and rocuronium; volatile anesthesia continued during CPB.

The CPB circuit was started with a crystalloid prime containing 1,000 mL calcium-free ISOLYTE-S pH 7.4 (Koçak Farma, Tekirdağ, Türkiye), 60 mEq sodium bicarbonate, and 10,000 IU unfractionated heparin. The initial systemic heparin bolus was 300–350 IU/kg. ACT was maintained at 480 seconds or longer with additional 5,000-IU boluses when needed. Nonpulsatile pump flow was targeted to a cardiac index of 2.2–2.4 L/min/m², mean arterial pressure to 65–80 mm Hg, and hematocrit to 24%–32%; alpha-stat management was used. Conventional ultrafiltration was selective, and cell-salvaged blood was not used.

Protamine was administered over approximately 10 minutes after separation from CPB. ACT was rechecked

after completion of both protamine administration and autologous blood reinfusion. RBC guidance comprised hematocrit below 22% during CPB and hemoglobin below 8 g/dL afterward, interpreted with bleeding, hemodynamics, and oxygen delivery. Rapid bleeding could prompt transfusion before a new blood-gas result. Tranexamic acid administration was not assigned by study protocol; the attending anesthesiologist and surgeon made the decision jointly according to clinical judgment. When used, approximately 10 mg/kg was given as a single 500-, 750-, or 1000-mg intravenous bolus at the end of CPB. Fresh-frozen plasma was administered routinely to all study patients at CPB separation, with the dose individualized according to the patient's clinical condition. Postoperative fresh-frozen plasma was administered according to ongoing bleeding and clinical assessment. Platelets, cryoprecipitate, and fibrinogen concentrate were administered according to ongoing bleeding and clinical assessment. Neither rotational thromboelastometry (ROTEM) nor thromboelastography (TEG) was available at the hospital during the study period. No patient received aspirin on the morning of surgery.

2.5. Data sources, quality control, and outcomes

Data were collected retrospectively from operating-room, anesthesia, perfusion, ICU, ward, laboratory, and medication records. Patient records were divided among three members of the study team and abstracted using a standardized data-collection form. Records with missing or internally inconsistent information were reviewed jointly before finalization of the study dataset. General quality-control checks assessed completeness, plausible ranges, coding, and internal consistency. Exposure, primary and key secondary outcomes, and all primary-model covariates were complete. The additive European System for Cardiac Operative Risk Evaluation I (EuroSCORE I) value recorded in the preoperative clinical record was used as a baseline descriptor; EuroSCORE II was not retrospectively reconstructed. Outcome definitions and data sources are detailed in Supplementary Tables S1 and S2.

The primary outcome was the sum of recorded hourly chest-tube drainage during ICU hours 1–24 (Supplementary Fig. S2). In patients undergoing re-exploration, this remained the ICU-chart total over the same window; unavailable surgical-field blood loss was not included. The key secondary outcome was receipt of at least one allogeneic RBC unit from CPB-flow start through hospital discharge or in-hospital death. Exploratory windows were CPB-flow start to operating-room exit, operating-room exit through 24 hours afterward, and operating-room exit through discharge or death. No patient received RBCs before CPB flow.

Other exploratory outcomes included drainage above 1500 mL in 24 hours, re-exploration, RBC-unit burden, ICU and hospital length of stay, in-hospital death, and a post hoc 7-day acute kidney injury outcome based on Kidney Disease: Improving Global Outcomes (KDIGO) creatinine, urine-output, and renal replacement therapy (RRT) criteria [16]. Postoperative hemoglobin, hematocrit, platelet count, and creatinine were from the first postoperative-morning sample; lactate was from the ICU-admission blood gas.

2.6. Statistical analysis

The ethics protocol identified 24-hour drainage as the primary outcome and recorded a requirement of at least 85 patients per group. On rechecking, G*Power for a two-sided comparison of two independent means with equal allocation, an alpha of 0.05, 90% power, an anticipated between-group mean difference of 200 mL, and a standard deviation of 400 mL indicated an exact target of 172 patients (86 per group). The protocol's recorded target was therefore one patient per group below the exact integer requirement. All 220 eligible patients in the fixed period were analyzed. The protocol did not specify the final statistical estimands, covariate sets, sensitivity analyses, or analysis software; these were selected after record review and were not preregistered. Continuous variables are reported as mean (standard deviation) or median [interquartile range], and categorical variables as n/N (%). Absolute standardized mean differences describe baseline balance without significance testing.

The lead primary analysis estimated the crude PAAD-minus-ANH mean drainage difference by ordinary least squares with HC3 heteroskedasticity-consistent standard errors and Student t 95% confidence intervals (CIs). A supportive adjusted model included age, sex, body mass index, preoperative hemoglobin, platelets, fibrinogen, creatinine, ejection fraction below 40%, complex procedure, four indicators for the five anesthesiologists, continued aspirin, any P2Y12 inhibitor, and any oral anticoagulant. The adjusted model contained 18 parameters for 220 observations (residual degrees of freedom, 202). Complex procedures were aortic or ascending-aortic procedures, including Bentall surgery, coronary artery bypass grafting (CABG) plus valve, or CABG plus carotid surgery. Postexposure covariates and stepwise selection were not used. Sensitivity analyses used a 20,000-resample patient-level bootstrap and evaluated completed collections, exclusion of re-explorations, linear calendar time, and continuous ejection fraction. The completed-collection and re-exploration restrictions were post hoc, postexposure descriptive analyses.

For binary RBC outcomes, unadjusted risk differences used Newcombe hybrid-score intervals derived from separate Wilson score intervals, and risk ratios used log-scale intervals. Cumulative RBC receipt was supported by logistic standardization for age, sex, body mass index, preoperative hemoglobin, ejection fraction below 40%, procedure complexity, four indicators for the five anesthesiologists, continued aspirin, any P2Y12 inhibitor, and any oral anticoagulant. This model included 67 events and 15 parameters and was treated as supportive and exploratory. Percentile intervals came from 2,978 successful fits among 3,000 patient-level bootstrap resamples. The 22 unsuccessful unpenalized fits reached the 200-iteration limit in sparse resamples with complete or near-complete prediction and were omitted. As a sparse-data sensitivity analysis, the same model was refitted using Firth penalized logistic regression; all 3,000 Firth bootstrap fits converged. Secondary and sensitivity analyses were exploratory; no multiplicity adjustment or imputation was used. No subgroup or interaction analyses were conducted. All analyses were performed in Python 3.12.13 (Python Software Foundation, Wilmington, DE, USA) using NumPy 2.3.5 and pandas 3.0.1. HC3 regression, logistic standardization, Newcombe intervals, bootstrap analyses, and Firth regression were implemented directly in Python with NumPy; full computational details are provided in Supplementary Methods S5 and Table S15.

3. Results

3.1. Cohort and baseline characteristics

The cohort included 117 PAAD and 103 ANH patients (Fig. 1). Mean age was 59.8 versus 58.6 years, and women comprised 12.0% versus 11.7%, respectively. PAAD patients had lower preoperative hemoglobin (14.21 vs 14.46 g/dL; standardized mean difference [SMD], 0.20), and ejection fraction below 40% was more frequent (20/117 [17.1%] vs 7/103 [6.8%]; SMD, 0.32). Oral anticoagulant use was also more frequent with

PAAD (12.8% vs 6.8%; SMD, 0.20). All five anesthesiologists used both strategies; PAAD/ANH counts were 25/23, 22/24, 31/13, 27/16, and 12/27, showing

within-clinician overlap but differing preferences (Supplementary Table S3). Baseline and operative characteristics appear in Tables 1 and 2.

Table 1. Baseline characteristics by autologous collection strategy.

Characteristic	PAAD (<i>n</i> = 117)	ANH (<i>n</i> = 103)	Absolute SMD
Age (years)	59.76 (10.19)	58.55 (9.42)	0.12
Women	14 (12.0%)	12 (11.7%)	0.01
Body mass index (kg/m ²)	27.51 (3.97)	28.21 (4.34)	0.17
Hemoglobin (g/dL)	14.21 (1.24)	14.46 (1.21)	0.20
Platelet count (10 ⁹ /L)	259.4 (81.5)	249.9 (78.6)	0.12
Fibrinogen (mg/dL)	341.4 (66.5)	343.7 (70.5)	0.03
Creatinine (mg/dL)	0.89 (0.20)	0.88 (0.17)	0.08
Ejection fraction <40%	20 (17.1%)	7 (6.8%)	0.32
ASA physical status IV	8 (6.8%)	8 (7.8%)	0.04
Additive EuroSCORE I (points)	3 [2-4]	3 [2-4]	0.07
Hypertension	61 (52.1%)	48 (46.6%)	0.11
Diabetes mellitus	49 (41.9%)	39 (37.9%)	0.08
Coronary artery disease	97 (82.9%)	86 (83.5%)	0.02
Chronic obstructive pulmonary disease	6 (5.1%)	5 (4.9%)	0.01
Complex procedure	15 (12.8%)	15 (14.6%)	0.05
Aspirin continued to surgery	87 (74.4%)	83 (80.6%)	0.15
Any P2Y12 inhibitor use	20 (17.1%)	20 (19.4%)	0.06
Any oral anticoagulant use	15 (12.8%)	7 (6.8%)	0.20

Values are mean (standard deviation), median [interquartile range], or *n* (%). No listed variable was missing. Values were rounded for presentation; all calculations used unrounded data, and percentages may not total 100% because of rounding. SMDs for continuous variables were calculated from unrounded means and standard deviations, including variables presented as median (interquartile range). Complex procedure comprised aortic or ascending-aortic procedures, including Bentall surgery, coronary artery bypass grafting plus valve, and coronary artery bypass grafting plus carotid surgery. ANH, acute normovolemic hemodilution; ASA, American Society of Anesthesiologists; PAAD, post-heparinization pre-bypass acute autologous donation; SMD, standardized mean difference.

Values are *n* (%), mean (standard deviation), or median [interquartile range]. Plasma means and medians were calculated across all patients in each strategy group; postoperative ranges were 0-6 units with PAAD and 0-9 units with ANH, and intraoperative ranges were 1-3 units in both groups. The two-bag entry applies to all completed procedures (117 PAAD and 100 ANH); bag weights and calibrated fill volumes were not recorded. Values were rounded for presentation; all calculations used unrounded data, and percentages may not total 100% because of rounding. *Center-level clinical target for blood volume; actual patient-level volume was not systematically measured. ACT, activated clotting time; ANH, acute normovolemic hemodilution; CABG, coronary artery bypass grafting; CPB, cardiopulmonary by-

pass; CPDA-1, citrate-phosphate-dextrose-adenine-1; PAAD, post-heparinization pre-bypass acute autologous donation.

Median CPB duration was 97 minutes in both groups. Lowest core temperature was 32 [30-32]°C with PAAD and 30 [30-32]°C with ANH. Additional CPB heparin was given to 66/117 (56.4%) and 54/103 (52.4%) patients. Tranexamic acid was given to 81/117 (69.2%; 62,500 mg total) and 72/103 (69.9%; 54,000 mg total), respectively. All patients received intraoperative fresh-frozen plasma: PAAD patients received 218 units in total (mean, 1.86 [standard deviation, 0.37]; median, 2 [range, 1-3]) and ANH patients received 186 units (mean, 1.81 [0.42]; median, 2 [range, 1-3]). Postoperative plasma was administered to 115/117 PAAD patients (269 units; mean per cohort patient, 2.30 [1.09]; median, 2 [range, 0-6]) and 101/103 ANH patients (228 units; mean, 2.21 [1.20]; median, 2 [range, 0-9]) (Supplementary Table S8).

3.2. Primary outcome

Mean (standard deviation) 24-hour drainage was 876.2 (692.2) mL after PAAD and 855.0 (657.8) mL after ANH; medians were 650 [550-860] and 680 [550-807.5] mL. The crude PAAD-minus-ANH mean difference was 21.2 mL (95% CI, -159.1 to 201.6; *p* = 0.817), and the adjusted difference was 44.3 mL (95% CI, -146.3 to 234.9; *p* = 0.647) (Table 3; Fig. 2). The adjusted bootstrap interval was -138.6 to 223.7 mL.

Table 2. Operative, anticoagulation, and collection characteristics.

Characteristic	PAAD (n = 117)	ANH (n = 103)
Isolated CABG	82 (70.1%)	77 (74.8%)
Valve only	16 (13.7%)	9 (8.7%)
CABG plus valve	5 (4.3%)	7 (6.8%)
CABG plus carotid	3 (2.6%)	2 (1.9%)
Aortic or ascending-aortic procedure, including Bentall surgery	7 (6.0%)	6 (5.8%)
Atrial septal defect	2 (1.7%)	0
Tumor/myxoma	2 (1.7%)	2 (1.9%)
Operation duration (min)	285 [255-325]	280 [247.5-325]
CPB duration (min)	97 [79-120]	97 [79.5-123.5]
Cross-clamp duration (min)	66 [54-85]	64 [49.5-87]
Lowest core temperature (°C)	32 [30-32]	30 [30-32]
Initial systemic heparin (IU)	25,000 [25,000-30,000]	25,000 [25,000-30,000]
Post-heparin, pre-CPB ACT (s)	577 [524-623]	572 [514.5-624]
Additional heparin during CPB	66 (56.4%)	54 (52.4%)
Total protamine (anti-heparin IU)	25,000 [25,000-25,000]	25,000 [25,000-25,000]
Post-protamine ACT (s)	136 [130-145]	136 [129-143]
Tranexamic acid, recipients/total dose (mg)	81/62,500	72/54,000
Intraoperative fresh-frozen plasma (units)	218 total; mean 1.86 (0.37); median 2 [2-2]	186 total; mean 1.81 (0.42); median 2 [2-2]
Postoperative fresh-frozen plasma (units)	115 recipients/269 total; mean 2.30 (1.09); median 2 [2-3]	101 recipients/228 total; mean 2.21 (1.20); median 2 [2-3]
Collection interrupted	0	3 (2.9%)
Documented bags in completed collections	2	2
Approximate collection target*	650-700 mL	650-700 mL
Concurrent crystalloid replacement	Used according to hemodynamics	Used according to hemodynamics
CPDA-1 in collection bags	Removed before collection	Retained

Table 3. Primary, transfusion, bleeding, and clinical outcomes.

Outcome	PAAD	ANH	PAAD-minus-ANH estimate (95% CI)	Analysis role
Chest-tube drainage, first 24 h (mL)	Mean 876.2 (SD 692.2); median 650 [550-860]	Mean 855.0 (SD 657.8); median 680 [550-807.5]	Crude mean difference 21.2 mL (-159.1 to 201.6); $p = 0.817$	Primary
Chest-tube drainage, adjusted	–	–	Mean difference 44.3 mL (-146.3 to 234.9); $p = 0.647$	Supportive primary model
Cumulative RBC recipient, CPB start to discharge/death	38/117 (32.5%)	29/103 (28.2%)	RD 4.3 pp (-7.9 to 16.2); RR 1.15 (0.77 to 1.73)	Key secondary
Cumulative RBC recipient, standardized	33.2%	27.4%	RD 5.7 pp (-5.9 to 17.7); RR 1.21 (0.82 to 1.82)	Supportive secondary
Intraoperative RBC recipient, CPB start to OR exit	26/117 (22.2%)	14/103 (13.6%)	RD 8.6 pp (-1.7 to 18.5); RR 1.63 (0.90 to 2.96)	Exploratory
Early postoperative RBC recipient, OR exit through 24 h after OR exit	18/117 (15.4%)	15/103 (14.6%)	RD 0.8 pp (-8.9 to 10.2); RR 1.06 (0.56 to 1.99)	Exploratory
Any postoperative RBC recipient, OR exit to discharge/death	24/117 (20.5%)	21/103 (20.4%)	RD 0.1 pp (-10.7 to 10.7); RR 1.01 (0.60 to 1.70)	Exploratory
Drainage >1500 mL in first 24 h	13/117 (11.1%)	12/103 (11.7%)	RD -0.5 pp (-9.4 to 8.0)	Exploratory
Re-exploration for bleeding	11/117 (9.4%)	5/103 (4.9%)	RD 4.5 pp (-2.7 to 11.8)	Exploratory
KDIGO acute kidney injury within 7 d	16/117 (13.7%)	14/103 (13.6%)	RD 0.1 pp (-9.3 to 9.2)	Post hoc exploratory
KDIGO stage 2 or 3 within 7 d	7/117 (6.0%)	3/103 (2.9%)	Descriptive	Post hoc exploratory
Renal replacement therapy within 7 d	3/117 (2.6%)	2/103 (1.9%)	RD 0.6 pp (-4.5 to 5.5)	Post hoc exploratory
ICU length of stay (d)	3 [3-4]	3 [3-4]	Descriptive	Exploratory
Hospital length of stay (d)	8 [7-10]	8 [7-10]	Descriptive	Exploratory
In-hospital death	3/117 (2.6%)	2/103 (1.9%)	RD 0.6 pp (-4.5 to 5.5)	Exploratory

Values were rounded for presentation; all calculations used unrounded data, and percentages may not total 100% because of rounding. Unadjusted binary-outcome confidence intervals are Newcombe score intervals for risk differences and log intervals for risk ratios. Adjusted primary estimates use ordinary least squares with HC3 standard errors and Student *t* confidence intervals. Adjusted cumulative red blood cell estimates use logistic standardization with a bootstrap confidence interval. ANH, acute normovolemic hemodilution; CI, confidence interval; CPB, cardiopulmonary bypass; ICU, intensive care unit; KDIGO, Kidney Disease: Improving Global Outcomes; OR, operating room; PAAD, post-hepa-

rinization pre-bypass acute autologous donation; pp, percentage points; RBC, red blood cell; RD, risk difference; RR, risk ratio; SD, standard deviation.

The completed-collection analysis included 217 patients and gave an adjusted difference of 25.4 mL (95% CI, -168.3 to 219.1; $p = 0.796$). Estimates were similar after adding calendar time (44.4 mL; 95% CI, -147.5 to 236.3) and modeling ejection fraction continuously (43.5 mL; 95% CI, -149.7 to 236.8). Excluding the 16 patients who underwent re-exploration gave a descriptive adjusted difference of -73.6 mL (95% CI, -202.0 to 54.7). Detailed drainage summaries and sensitivity analyses are provided in Supplementary Tables S4 and S5.

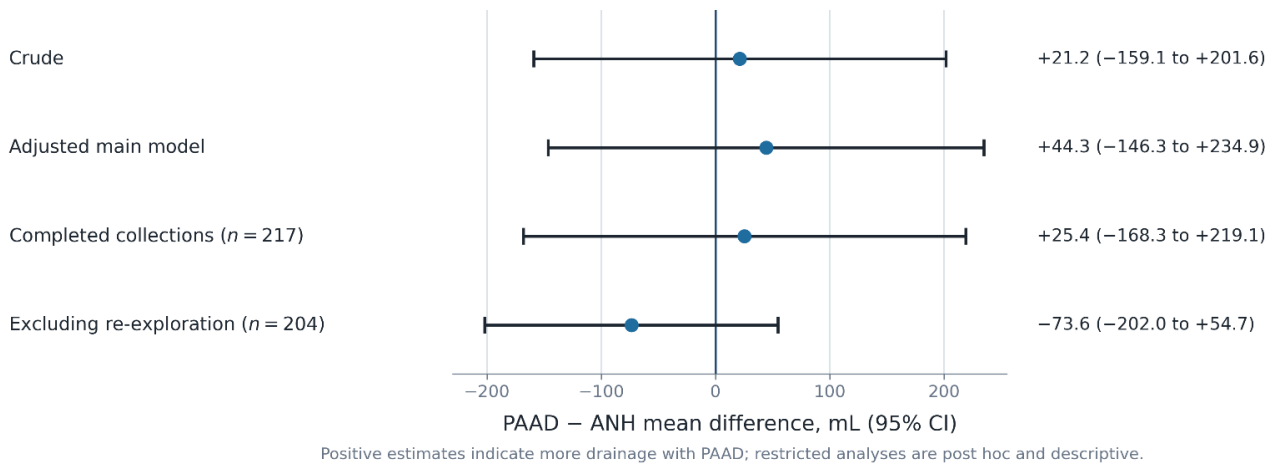


Fig. 2. Estimates for 24-hour chest-tube drainage. PAAD-minus-ANH mean differences with 95% confidence intervals for the crude and adjusted primary analyses and the post hoc completed-collection and re-exploration restrictions. Positive values indicate greater drainage with PAAD. Adjusted estimates are observational associations. ANH, acute normovolemic hemodilution; CI, confidence interval; PAAD, post-heparinization pre-bypass acute autologous donation.

3.3. Red blood cell transfusion outcomes

Cumulative RBC exposure occurred in 38/117 (32.5%) PAAD and 29/103 (28.2%) ANH patients. The crude risk difference was 4.3 percentage points (95% CI, -7.9 to 16.2), and the risk ratio was 1.15 (95% CI, 0.77 to

1.73). Standardized risks were 33.2% and 27.4%, giving an adjusted risk difference of 5.7 percentage points (95% bootstrap CI, -5.9 to 17.7) and risk ratio of 1.21 (95% bootstrap CI, 0.82 to 1.82) (Table 3; Fig. 3). Firth-penalized estimates were similar to the primary adjusted analysis (Supplementary Table S6).

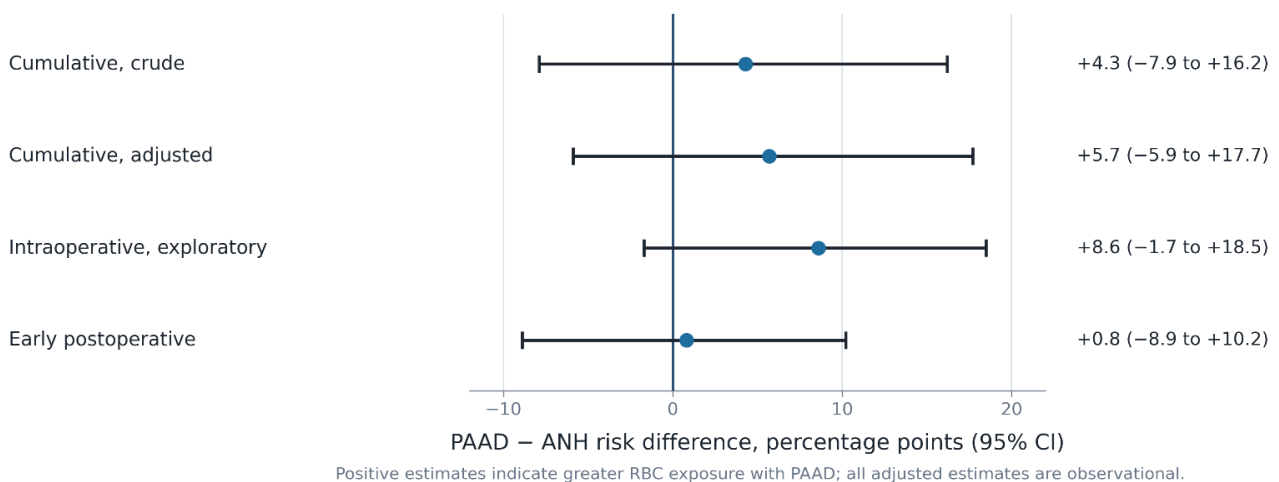


Fig. 3. Estimates for red blood cell exposure. PAAD-minus-ANH risk differences with 95% confidence intervals for cumulative, intraoperative, and early postoperative RBC exposure. Positive values indicate greater risk with PAAD. Crude intervals use Newcombe score methods; the adjusted cumulative-RBC interval is a percentile-bootstrap interval. Adjusted estimates are observational associations. ANH, acute normovolemic hemodilution; CI, confidence interval; PAAD, post-heparinization pre-bypass acute autologous donation; RBC, red blood cell.

Intraoperative RBC exposure occurred in 26/117 (22.2%) and 14/103 (13.6%) patients (risk difference, 8.6 percentage points; 95% CI, -1.7 to 18.5; risk ratio, 1.63; 95% CI, 0.90 to 2.96). Early postoperative exposure occurred in 18/117 (15.4%) and 15/103 (14.6%), while any postoperative exposure occurred in 24/117 (20.5%) and 21/103 (20.4%). Cumulative RBC-unit totals were 109 and 85. Two patients, one in each strategy group, had cumulative totals of 17 RBC units. Complete recipient-window and unit-distribution results are provided in Supplementary Tables S6 and S7.

3.4. Other clinical outcomes

Drainage above 1500 mL occurred in 13/117 (11.1%) PAAD and 12/103 (11.7%) ANH patients. Re-exploration occurred in 11/117 (9.4%) and 5/103 (4.9%). Post hoc 7-day acute kidney injury occurred in 16/117 (13.7%) and 14/103 (13.6%), and RRT was initiated within seven days in 3/117 (2.6%) and 2/103 (1.9%) patients, respectively. Median ICU stay was 3 [3–4] days and hospital stay 8 [7–10] days in both groups. In-hospital death occurred in three and two patients, respectively; all five deaths were associated with low cardiac output or cardiogenic shock (Supplementary Tables S8–S10). General data-quality checks, anticoagulation, antithrombotic treatment, and postoperative laboratory details are provided in Supplementary Tables S11–S14. Hourly urine-output trajectories are shown in Supplementary Fig. S3.

4. Discussion

In this comparison of two integrated clinical strategies, the estimated difference in 24-hour chest-tube drainage was small relative to its uncertainty. The crude PAAD-minus-ANH difference was 21 mL and the adjusted difference 44 mL; both confidence intervals included lower and higher drainage with PAAD. The drainage distribution was markedly right-skewed, and medians differed in the opposite direction from means (650 vs 680 mL). Excluding the 16 patients who underwent re-exploration changed the adjusted point estimate from +44.3 mL to -73.6 mL, although both confidence intervals included no difference. This finding indicates sensitivity of the mean-based estimate to extreme bleeding events without changing the overall conclusion of uncertainty.

Cumulative in-hospital RBC exposure was also imprecisely estimated. The crude absolute difference was 4.3 percentage points and the adjusted difference 5.7 percentage points, with both intervals spanning no difference. The larger intraoperative point estimate was exploratory, and postoperative RBC exposure was nearly identical. The findings should not be interpreted as evidence that either strategy reduces bleeding or transfusion.

Most evidence compares ANH with usual care rather than another autologous collection strategy. Several studies associated larger ANH volumes with lower transfusion [4–6], whereas a multicenter trial found no clinically important reduction in its primary in-hospital RBC outcome [7]. One 2026 meta-analysis found no reduction in in-hospital RBC exposure [17], whereas another re-

ported lower transfusion and total blood loss but no significant difference in chest-tube drainage [18]. Neither directly compared ANH with PAAD.

A 2026 administrative-database cohort associated ANH with lower 7-day RRT use than no ANH, but defined acute kidney injury by RRT alone and remained vulnerable to residual confounding [19]. The KDIGO analysis used here was post hoc and contained few severe events. A separate propensity-score-matched cohort using low-volume ANH (median withdrawal, 450 mL) found no significant reduction in allogeneic RBC transfusion, reinforcing the likely importance of collection volume and clinical context [20].

In this cohort, the PAAD strategy combined autologous priming of the arterial and venous circuit limbs with venous-line whole-blood collection after full heparinization and immediately before CPB; the latter technique has been described [8]. It remained distinct from reservoir sequestration and collection during ongoing bypass. Older studies of pre- and post-heparinization collection, including direct comparisons, differed in anticoagulants, storage, volume, and reinfusion and reported inconsistent platelet, bleeding, and transfusion findings [9–13].

ANH may protect platelets and coagulation factors from heparin and CPB but produces pre-bypass hemodilution through crystalloid replacement. The PAAD strategy combined autologous circuit priming and concurrent crystalloid replacement with venous-line collection; its product was heparinized and was not exposed to CPDA-1. ANH blood retained CPDA-1, whereas CPDA-1 was removed from PAAD collection bags. Because actual blood volume and bag-specific filling were not measured, the precise anticoagulant-to-blood ratio for ANH was unavailable. Cold storage and reinfusion spanning protamine provide additional mechanisms, but platelet function, peri-reinfusion ionized calcium, and actual collected volume were unavailable.

Although anesthesia records documented two bags for every completed procedure, bag weights and calibrated fill volumes were unavailable. Because the degree of filling could vary, we could not determine whether individual patients received comparable collection volumes or evaluate a volume-response relation. Collection-replacement volume and postcollection/pre-CPB hematocrit were also unavailable. The three interrupted ANH volumes document partial collections but do not inform achieved volumes in completed procedures. Differences in achieved collection volume could therefore have influenced the observed comparison in either direction.

Clinician-dependent strategy selection is another plausible explanation. Lower preoperative hemoglobin and ejection fraction below 40% were more common with PAAD. All five anesthesiologists used both strategies, but the proportion managed with PAAD ranged from 30.8% to 70.5%. This overlap allowed within-clinician comparisons, but adjustment for measured differences and anesthesiologist indicators cannot eliminate residual confounding or confounding by indication. Procedural factors occurring after strategy selection were not treated as baseline confounders.

Tranexamic acid and plasma were post-selection co-interventions that could affect drainage and transfusion. Tranexamic acid use was similar by group, but treatment

was based on clinical judgment rather than study assignment. Routine plasma at CPB separation and postoperative plasma in 216/220 patients may have reduced the ability to observe between-strategy differences. These center-specific practices also limit generalizability to contemporary algorithm-guided patient blood-management pathways.

The study has several strengths. Every procedure in the period specified in the approved retrospective ethics protocol was screened, the complete eligible cohort was retained, and the primary outcome stated in that protocol was used. Drainage was reconstructed from hourly ICU records, a common CPB-flow landmark was applied to RBC outcomes, and general data-quality checks were performed. Primary and key secondary outcomes and all primary-model fields were complete.

This study has important limitations. It was retrospective, single-center, nonrandomized, and vulnerable to unmeasured confounding; surgeon or team identity and operative hemostatic technique were unavailable. Statistical methods were selected after record review and were not registered in advance, creating potential analysis-selection bias. The observed drainage standard deviations of 692.2 mL with PAAD and 657.8 mL with ANH were substantially greater than the 400-mL value assumed during sample-size planning, resulting in less precise estimates than anticipated. Accordingly, interpretation is based on the effect estimates and their confidence intervals; no post hoc power calculation was performed. Drainage was strongly right-skewed, and excluding re-explorations changed the direction of the point estimate. The ICU-based outcome omitted unrecorded operating-room and re-exploration surgical-field blood loss and may therefore incompletely characterize total bleeding in the most severe cases. Actual collected volume, bag-specific fill, replacement volume, platelet function, ionized calcium, and systematically timed postoperative coagulation tests were unavailable. Transfusion thresholds guided but did not determine care, and neither ROTEM nor TEG was available. The absence of cell salvage and the center-specific use of plasma limit transportability. The groups also differed descriptively in lowest core temperature; because temperature was a postexposure intraoperative variable, its contribution could not be separated from other procedural factors. Only 220 of 624 screened procedures (35.3%) entered the cohort, which therefore represents elective, first-time, on-pump cardiac surgical patients with preoperative hemoglobin ≥ 12 g/dL who were considered clinically suitable for autologous blood collection. Generalization to patients with anemia, hemodynamic vulnerability, emergency or redo surgery, or off-pump procedures should therefore be made cautiously. Because PAAD and ANH differed in several procedural components in addition to the timing of heparinization, the findings are best interpreted as a comparison of the two clinical strategies as implemented at our center, rather than as an isolated comparison of pre- versus post-heparinization blood collection. Few women were included.

5. Conclusions

Among selected adults undergoing elective, first-time, on-pump cardiac surgery with preoperative hemoglobin

of at least 12 g/dL, 24-hour chest-tube drainage and cumulative RBC exposure were imprecisely estimated and did not clearly differ between the two integrated clinical strategies. The confidence intervals remained compatible with clinically relevant associations in either direction and do not establish equivalence, causation, or a preferred strategy. These findings apply to the two strategies as implemented and should not be attributed solely to the timing of blood collection relative to heparinization. Actual collection volume, clinician-dependent selection, and center-specific hemostatic co-interventions limit interpretation and generalizability. Prospective comparisons with measured collection volumes and standardized co-interventions are needed.

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Conflict of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this manuscript.

Data Availability

Deidentified participant-level data, the data dictionary, quality-control documentation, and machine-readable analysis results are available from the corresponding author on reasonable request, subject to institutional ethics and data-governance approval.

AI Assistance

OpenAI Codex (OpenAI) was used for English-language editing and statistical assistance. All outputs were reviewed and verified by the authors, who take full responsibility for the manuscript.

Ethics Approval and Consent to Participate

The study was approved by the Medical Sciences Ethics Committee of the University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, on November 5, 2025 (Approval No. 2024-TBEK 2025/11-15), after the clinical study period and before retrospective record review began. Individual informed consent was not obtained in this retrospective study. The study and its statistical analysis were not registered in advance.

Consent for Publication

Not applicable; no identifiable individual participant information is reported.

Trial Registration

Not applicable; this retrospective observational study was not registered.

Author Contributions

Anıl Onur: conceptualization; methodology; supervision; investigation; data curation; writing – original draft.

Ayşe Neslihan Balkaya: supervision; resources; investigation; data curation.

Tuğba Onur: conceptualization; methodology; investigation; writing – original draft.

Osman Sıla Aydın: resources; formal analysis; investigation.

Eşe Hanım Çaran Karaoğlu: methodology; resources; investigation; data curation.

Gürcan Güler: resources; formal analysis; writing – review and editing.

Şermin Eminoğlu: conceptualization; supervision; writing – review and editing.

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Supplementary Material

Post-heparinization autologous donation with autologous circuit priming versus acute normovolemic hemodilution in cardiac surgery: A retrospective cohort study

This supplement documents cohort assembly, clinical practice, outcome definitions, data sources, quality control, and supporting analyses for the accompanying manuscript. The retrospective record review was approved by the institutional ethics committee. The primary outcome stated in the approved retrospective ethics protocol was first-24-hour postoperative drainage. The statistical methods reported here were selected after retrospective review of the records and are not presented as prospectively specified analyses.

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- Methods S2. Clinical practice and exposure definitions
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Methods S1. Cohort construction and analysis populations

Study period and screening

The source population comprised 624 adult cardiac surgical procedures recorded between February 1 and October 1, 2025. Exclusions were applied hierarchically: emergency surgery (n=77), redo surgery (n=32), off-pump surgery (n=11), last preoperative hemoglobin <12 g/dL (n=237), another contraindication to autologous collection (n=45), and inaccessible records (n=2). The 45 other contraindications were classified by primary reason as marked cardiac functional limitation, hemodynamic instability, or a fixed-output condition such as severe aortic stenosis (n=35); pulmonary disease or hypoxemia (n=8); and marked renal dysfunction or oliguria (n=2). More than one contraindication could be present, but each patient was counted once according to the primary reason. The remaining 220 patients underwent elective, first-time, on-pump cardiac surgery with one of the two autologous blood-collection strategies. This was an unmatched cohort; no matching was performed.

Analysis populations

The all-records population comprised 117 patients managed with post-heparinization pre-bypass acute autologous donation (PAAD) and 103 managed with pre-heparinization acute normovolemic hemodilution (ANH). This population was used for the primary analysis.

No PAAD collection was clinically interrupted. Collection was interrupted because of hypotension in three ANH patients. Their approximate partial collection volumes were 250, 200, and 300 mL. Rapid fluid administration and ephedrine were used, and the partially collected blood was returned. These patients remained in the all-records analysis according to the strategy selected for their care. A completed-collection sensitivity analysis excluded only these three patients (n=217). Because strategy allocation was not randomized, neither population is described as intention-to-treat.

Methods S2. Clinical practice and exposure definitions

The exposure was the multicomponent autologous whole-blood collection strategy used in routine care. The strategies differed in heparinization timing, collection route and speed, autologous circuit priming, and collection-bag anticoagulant exposure and were therefore evaluated as integrated clinical strategies rather than as an isolated contrast in timing.

Strategy selection

The attending anesthesiologist selected the collection strategy according to usual clinical practice, considering preoperative hemoglobin, body habitus, ventricular function, hemodynamic stability, and overall clinical status.

Choice also reflected clinician preference and familiarity. Patients with an ejection fraction <40% tended to be managed with PAAD, but no deterministic allocation rule was used. Five anonymized attending-anesthesiologist identifiers were available, and each clinician used both strategies (Table S3).

ANH

ANH began after central venous catheter placement and before systemic heparinization. Whole blood was collected by gravity from the central venous catheter while crystalloid was administered according to hemodynamic response. Collection generally required approximately 15–20 minutes.

PAAD

PAAD began after the initial systemic unfractionated-heparin bolus, confirmation of an activated clotting time (ACT) of at least 480 seconds, and arterial and venous cannulation, but before cardiopulmonary-bypass (CPB) flow. Crystalloid in the arterial and venous limbs of the CPB circuit was first displaced by the patient's own blood to complete autologous circuit priming. Immediately before full CPB flow, heparinized autologous whole blood was collected by gravity from a side arm of the venous drainage line, upstream of the venous reservoir and oxygenator, directly into sterile collection bags. It therefore had not entered the venous reservoir or oxygenator and was not collected during ongoing CPB flow. Concurrent crystalloid replacement was administered according to hemodynamic response, as in the ANH group. No roller pump was used. Collection was rapid, but patient-level collection duration was not retained.

Collection bags, storage, and reinfusion

Both strategies had an approximate clinical target of 650–700 mL of blood in total. The target was an estimate; completed-collection volumes were not systematically weighed or recorded. Nominal 450-mL collection bags prefilled with 63 mL citrate-phosphate-dextrose-adenine solution 1 (CPDA-1) were used. For ANH, CPDA-1 was retained in the bags. For PAAD, CPDA-1 was drained before collection because the blood was already systemically heparinized. Bags were kept at approximately 4°C in a medical blood-storage refrigerator, warmed before use, and reinfused through a peripheral intravenous line. Reinfusion began before protamine and usually ended after protamine. Patient-level reinfusion duration, bag order, peri-reinfusion ionized calcium, and ex vivo platelet function were not recorded systematically. The two protocol timelines are summarized in Fig. S1.

Anesthesia, CPB, anticoagulation, and transfusion practice

No premedication was administered. Monitoring included standard monitors, invasive radial arterial pressure, central venous pressure, bispectral index (target 40–60), and bilateral cerebral oximetry. Anesthesia was induced with midazolam 0.02–0.03 mg/kg, thiopental 3–5 mg/kg, fentanyl 2 µg/kg, and rocuronium 0.8 mg/kg, and was maintained with sevoflurane 0.8–1.0 minimum alveolar concentration plus intermittent fentanyl and rocuronium. Volatile anesthesia continued during CPB. Initial ventilation used an inspired oxygen fraction of 0.50, tidal volume 6 mL/kg, positive end-expiratory pressure 5 cmH₂O, and respiratory rate 12/min, with subsequent adjustment to gas exchange.

The CPB circuit was primed with 1,000 mL calcium-free ISOLYTE-S pH 7.4 (Koçak Farma, Tekirdağ, Türkiye), 60 mEq sodium bicarbonate in 60 mL, and 10,000 IU unfractionated heparin. Nonpulsatile flow was targeted to a cardiac index of 2.2–2.4 L/min/m², mean arterial pressure to 65–80 mmHg, and hematocrit to 24%–32%; alpha-stat acid-base management was used. Conventional ultrafiltration was used according to the patient-level judgment of the perfusionist and clinical team.

The initial systemic heparin bolus was 300–350 IU/kg and was separate from heparin in the prime. ACT was measured at approximately 30-minute intervals and maintained at 480 seconds or longer; additional 5,000-IU boluses were administered when required. After CPB, protamine was administered slowly over approximately 10 minutes. The initial protamine dose was calculated from the initial systemic heparin bolus; any additional protamine was included in the recorded total. ACT was rechecked after completion of both protamine administration and autologous blood reinfusion.

During CPB, an RBC transfusion threshold of hematocrit <22% was used. After CPB, a hemoglobin threshold of <8 g/dL was interpreted with active bleeding, hemodynamics, oxygen delivery, and clinician judgment; in rapidly evolving bleeding, transfusion could begin before a new blood-gas result was available. The decision to administer tranexamic acid was made jointly by the attending anesthesiologist and surgeon. When used, approximately 10 mg/kg was given as a single 500-, 750-, or 1000-mg intravenous bolus at the end of CPB. No cell-salvaged blood was used. Fresh-frozen plasma was administered routinely to all study patients as a bolus at separation from CPB; the dose was individualized according to bleeding up to that point and the patient's clinical condition. Postoperative fresh-frozen plasma was administered according to the treating clinician's judgment based on ongoing bleeding and overall clinical assessment; no fixed laboratory or viscoelastic threshold was used. Platelets, cryoprecipitate, and fibrinogen concentrate were administered for ongoing diffuse bleeding after exclusion of a surgical source. Viscoelastic testing was not used. No patient received aspirin on the morning of surgery.

Methods S3. Outcomes and time origins

Primary outcome

The primary outcome was cumulative chest-tube drainage during the first 24 hours after admission to the intensive care unit (ICU), in milliliters. Hourly interval volumes were transcribed from ICU charts, and the primary value was calculated as the sum of hours 1–24. For patients who underwent re-exploration, the primary outcome remained the recorded ICU-chart total over the same 24-hour window; surgical-field blood loss during re-exploration was unavailable and was not included. Cumulative 2-, 4-, 6-, 12-, and 48-hour values were supporting postoperative drainage summaries. The 24- to 48-hour record was available as an interval total. Recorded hourly drainage and urine-output trajectories are shown separately in Figures S2 and S3.

Key secondary outcome

The key secondary outcome was receipt of at least one allogeneic RBC unit from initiation of CPB flow through hospital discharge or in-hospital death. No patient received an allogeneic RBC unit before CPB flow. Recorded RBC units were divided into CPB-flow start to operating-room exit, operating-room exit through 24 hours after operating-room exit, and more than 24 hours after operating-room exit through discharge/death. Cumulative RBC units were the sum of these mutually exclusive intervals.

Other exploratory outcomes

Exploratory RBC recipient outcomes were intraoperative receipt (CPB-flow start to operating-room exit), early postoperative receipt (operating-room exit through 24 hours after operating-room exit), and any postoperative receipt (operating-room exit to discharge/death). Other exploratory outcomes included RBC-unit counts; plasma, platelet, cryoprecipitate, and fibrinogen-concentrate administration; drainage >1500 mL in 24 hours; any first-24-hour interval with drainage >400 mL; a study-defined post hoc exploratory bleeding composite (either drainage criterion or re-exploration); re-exploration; first postoperative-morning laboratory results; ICU and hospital length of stay; recorded complication categories; RRT within seven days (post hoc exploratory); and in-hospital mortality. These bleeding definitions are study operational definitions and are not labeled as BARC, UDPB, or E-CABG bleeding.

Postoperative hemoglobin, hematocrit, platelet count, and creatinine refer to the first postoperative-morning laboratory panel; lactate refers to the ICU-admission value. Preoperative INR, activated partial thromboplastin time, and fibrinogen were recorded. Postoperative INR, activated partial thromboplastin time, and fibrinogen were not analyzed because they were not measured systematically.

Post hoc 7-day KDIGO outcome

A 7-day Kidney Disease: Improving Global Outcomes (KDIGO) acute-kidney-injury analysis was performed after the primary dataset review and was exploratory [16]. Baseline creatinine, the highest postoperative creatinine within seven days, their recorded sampling times relative to ICU admission, hourly urine output for hours 1–24, the 24- to 48-hour urine interval total, recorded body weight, and RRT start time were used.

The creatinine component applied the KDIGO time windows: an increase of at least 0.3 mg/dL within 48 hours or to at least 1.5 times baseline within seven days defined stage 1; at least 2.0 times baseline within seven days defined stage 2; and at least 3.0 times baseline within seven days, or a peak of at least 4.0 mg/dL after the acute-kidney-injury definition had been met, defined stage 3. No patient reached a peak creatinine of 4.0 mg/dL. Urine-output stages used actual recorded body weight: <0.5 mL/kg/h for a rolling 6-hour window defined stage 1; <0.5 mL/kg/h for a rolling 12-hour window defined stage 2; and <0.3 mL/kg/h across a complete 24-hour interval or anuria for a rolling 12-hour interval defined stage 3. Rolling 6- and 12-hour windows were available only during the first 24 hours; the 24- to 48-hour record could support only a complete 24-hour rate. RRT starting within seven days defined stage 3. The combined stage was the maximum of the creatinine, urine-output, and RRT components.

Methods S4. Data sources and quality control

Data sources

Patient-level values were abstracted from anesthesia, perfusion, operating-room, ICU, ward, laboratory, and medication records and reconciled into one study record per patient; no external or probabilistic database linkage was performed. General quality-control checks assessed completeness, plausible ranges, group and procedure coding, and internal consistency among drainage, transfusion, anticoagulation, and kidney-outcome variables. Exposure, primary and key secondary outcomes, and all primary-model fields were complete. A summary of the data-quality checks is provided in Table S11. Reporting was guided by STROBE and the RECORD extension [14,15].

Methods S5. Statistical analysis

Analysis status

The primary outcome stated in the approved retrospective ethics protocol was first-24-hour postoperative drainage. The statistical estimands, covariate sets, and sensitivity analyses below were selected after retrospective review of the records. They are reported as the analyses actually implemented and are not a prospectively registered or prespecified statistical plan. No model was selected by stepwise testing or by choosing the most favorable result.

Descriptive analysis

Continuous variables are summarized as mean (standard deviation) and median [interquartile range] where useful; categorical variables are summarized as n/N (%). Baseline balance is described with standardized mean differences rather than baseline significance tests. All confidence intervals are conventional 95% intervals. P values are two-sided and descriptive.

Primary analysis: 24-hour drainage

The lead estimand was the unadjusted PAAD-minus-ANH difference in mean 24-hour chest-tube drainage. It was estimated by ordinary least squares with an intercept and strategy indicator. Heteroskedasticity-consistent HC3 standard errors were used, and the confidence interval and P value used the Student t reference distribution with residual degrees of freedom.

The supportive adjusted analysis used ordinary least squares with the same HC3 and Student t inference. The fixed, clinically chosen, pre-exposure covariates were age, sex, body mass index, preoperative hemoglobin, platelet count, fibrinogen, creatinine, ejection fraction <40%, complex procedure, four indicators for the five anesthesiologists, aspirin continued to surgery, any P2Y12 inhibitor use, and any oral anticoagulant use. Complex procedures comprised aortic or ascending-aortic procedures, including Bentall surgery, CABG plus valve surgery, and CABG plus carotid surgery. Post-exposure variables were excluded. The model included 220 observations and 18 parameters (residual df=202).

Supporting sensitivity analyses used 20,000 patient-level bootstrap resamples for the adjusted coefficient, excluded the three interrupted ANH collections, excluded 16 patients who underwent re-exploration, added linear calendar time, or replaced ejection fraction <40% with continuous ejection fraction. The completed-collection and re-exploration restrictions were post hoc, postexposure descriptive analyses and were not interpreted as causal estimands.

Key secondary analysis: cumulative RBC receipt

For each RBC window, absolute risks were calculated from integer counts. Risk differences used Newcombe hybrid-score confidence intervals; risk ratios and odds ratios used log-Wald intervals. In this context, “hybrid-score” is the name of the confidence-interval method.

The cumulative-RBC adjusted analysis was supportive and exploratory. An unpenalized logistic model included strategy, age, sex, preoperative hemoglobin, body mass index, ejection fraction <40%, complex procedure, four anesthesiologist indicators, aspirin continued to surgery, any P2Y12 inhibitor use, and any oral anticoagulant use. Risks were marginally standardized by predicting every patient once under PAAD and once under ANH and averaging over the same 220-person covariate distribution. Percentile intervals used 3,000 patient-level bootstrap resamples; 2,978 fits were successful and 22 were excluded because the fit did not converge. Because 67 cumulative events supported a 15-parameter model, this adjusted analysis is not treated as confirmatory. As a post hoc supportive sparse-data sensitivity analysis, the same 15-parameter model was re-estimated with Firth penalized logistic regression. Standardized risks, risk differences, and risk ratios used the same marginal covariate distribution; percentile intervals used 3,000 patient-level bootstrap resamples, all of which converged. The conditional odds-ratio interval used penalized profile likelihood.

Multiplicity, missing data, and software

Secondary and sensitivity analyses are exploratory; no multiplicity adjustment was applied and no confidence interval is a simultaneous interval. The analysis variables used in the reported models were complete, so no imputation was used. Analyses were run in Python 3.12.13 (Python Software Foundation, Wilmington, DE, USA), with NumPy 2.3.5 and pandas 3.0.1. Pseudorandom-number generation was used only for bootstrap resampling.

Supplementary Tables

Values were rounded for presentation; all calculations used unrounded data, and percentages may not total 100% because of rounding.

Tables S1 and S2 define the outcome hierarchy and data sources; Table S3 describes anesthesiologist distribution; Tables S4 and S5 report drainage summaries and analyses; Tables S6 and S7 report RBC outcomes; Table S8 reports hemostatic products; Table S9 reports the post hoc KDIGO analysis; Table S10 reports exploratory clinical outcomes; Table S11 summarizes general data-quality checks; Tables S12 and S13 describe anticoagulation and antithrombotic treatment; and Table S14 reports first postoperative-morning laboratory values and ICU-admission lactate.

Table S1. Outcome hierarchy and operational definitions

Role	Outcome	Window or rule	Data source
Primary	Cumulative chest-tube drainage	Sum of ICU hours 1–24, mL	Derived from 24 recorded hourly intervals
Key secondary	Cumulative allogeneic RBC recipient	At least 1 unit from CPB-flow start to discharge/death	Derived from three recorded unit windows
Exploratory	Intraoperative RBC recipient	At least 1 unit from CPB-flow start to OR exit	Derived from recorded units
Exploratory	Early postoperative RBC recipient	At least 1 unit from OR exit through 24 hours after OR exit	Derived from recorded units
Exploratory	Any postoperative RBC recipient	At least 1 unit from OR exit to discharge/death	Derived from recorded units
Exploratory	High 24-hour drainage	>1500 mL in ICU hours 1–24	Derived
Exploratory	High hourly drainage	Any ICU hour 1–24 >400 mL	Derived
Post hoc exploratory	Study-defined bleeding composite	Either drainage rule or re-exploration	Derived
Post hoc exploratory	7-day KDIGO stage	Maximum creatinine, urine-output, and RRT stage	Derived from recorded values and times

ANH, acute normovolemic hemodilution; CPB, cardiopulmonary bypass; ICU, intensive care unit; OR, operating room; PAAD, post-heparinization pre-bypass acute autologous donation; RBC, red blood cell; RRT, renal-replacement therapy.

Table S2. Key data sources and analysis roles

Domain	Recorded source	Derived use
Exposure	Recorded strategy code; interruption status; approximate volume only for three interrupted collections	PAAD/ANH indicator; collection-completed indicator
Primary drainage	ICU chest-tube intervals for hours 1–24 and interval total for hours 24–48	Cumulative 2-, 4-, 6-, 12-, 24-, and 48-hour drainage; binary drainage rules
RBC transfusion	Units from CPB start to OR exit, during the first 24 hours after OR exit, and >24 hours after OR exit through discharge/death	Recipient indicators; postoperative and cumulative units
Kidney	Baseline and peak creatinine with sample times; hourly urine for 24 hours; 24–48-hour urine total; weight; RRT and start time	Creatinine, urine, and combined 7-day KDIGO stages
Anticoagulation	Initial systemic heparin, baseline/pre-CPB/post-protamine ACT, additional CPB heparin, total protamine	Heparin dose per kilogram; additional-heparin indicators
Antithrombotics	Aspirin, P2Y12 inhibitor, warfarin, and direct oral anticoagulant use and last-dose dates	Aspirin continued, any P2Y12 inhibitor, any oral anticoagulant, stop-day variables
Patient factors	Age, sex, height, weight, hemoglobin, platelets, fibrinogen, creatinine, ejection fraction	Body-mass index, ejection fraction <40%, model covariates

Table S3. Distribution of cases across attending anesthesiologists

Identifier	PAAD	ANH	Total
ANE-01	25	23	48
ANE-02	22	24	46
ANE-03	31	13	44
ANE-04	27	16	43
ANE-05	12	27	39
Total	117	103	220

Table S4. Cumulative postoperative chest-tube drainage

Landmark after ICU admission	PAAD mean (SD), mL	PAAD median [IQR], mL	ANH mean (SD), mL	ANH median [IQR], mL
2 hours	211.2 (167.7)	160 [130–200]	204.0 (141.4)	165 [125–200]
4 hours	378.5 (311.9)	280 [235–365]	363.3 (269.0)	290 [225–360]
6 hours	501.5 (410.2)	365 [310–500]	484.8 (369.4)	380 [307.5–465]
12 hours	727.8 (578.4)	545 [460–715]	708.5 (546.5)	560 [450–670]
24 hours (primary)	876.2 (692.2)	650 [550–860]	855.0 (657.8)	680 [550–807.5]
48 hours	1038.5 (824.7)	780 [645–1055]	1025.3 (803.9)	800 [622.5–940]

n = 117 for PAAD and n = 103 for ANH at every landmark; no drainage value was missing. IQR, interquartile range; SD, standard deviation.

Table S5. Primary 24-hour drainage analyses

Analysis	N	PAAD-minus-ANH estimate, mL	95% CI, mL	P value	Role/method
Crude mean difference	220	21.2	–159.1 to 201.6	.817	Lead; OLS, HC3, Student t
Adjusted mean difference	220	44.3	–146.3 to 234.9	.647	Supportive; OLS, HC3, Student t
Adjusted bootstrap interval	220	44.3	–138.6 to 223.7	—	Sensitivity; 20,000 resamples
Completed-collection analysis	217	25.4	–168.3 to 219.1	.796	Post hoc, postexposure descriptive analysis
Excluding re-exploration	204	–73.6	–202.0 to 54.7	.259	Post hoc, postexposure descriptive analysis
Adding linear calendar time	220	44.4	–147.5 to 236.3	.649	Sensitivity; same adjusted model plus time
Continuous ejection fraction	220	43.5	–149.7 to 236.8	.657	Sensitivity; replaces EF <40%

The adjusted model included age, sex, body mass index, preoperative hemoglobin, platelets, fibrinogen, creatinine, ejection fraction <40%, complex procedure, anesthesiologist fixed effects, aspirin continued, any P2Y12 inhibitor, and any oral anticoagulant. CI, confidence interval; EF, ejection fraction; OLS, ordinary least squares.

Table S6. RBC recipient outcomes

Analysis window	PAAD	ANH	Risk difference, percentage points (95% CI)	Risk ratio (95% CI)	Odds ratio (95% CI)	Role
Cumulative, CPB start to discharge/death	38/117 (32.5%)	29/103 (28.2%)	4.3 (–7.9 to 16.2)	1.15 (0.77–1.73)	1.23 (0.69–2.19)	Key secondary, crude
Cumulative, adjusted standardized risks	33.2%	27.4%	5.7 (–5.9 to 17.7)	1.21 (0.82–1.82)	—	Supportive secondary
Cumulative, Firth standardized risks	34.0%	28.4%	5.6 (–5.6 to 17.2)	1.20 (0.84–1.76)	1.40 (0.71–2.83)	Post hoc supportive sensitivity
Intraoperative, CPB start to OR exit	26/117 (22.2%)	14/103 (13.6%)	8.6 (–1.7 to 18.5)	1.63 (0.90–2.96)	1.82 (0.89–3.70)	Exploratory
Early postoperative, OR exit through 24 hours after OR exit	18/117 (15.4%)	15/103 (14.6%)	0.8 (–8.9 to 10.2)	1.06 (0.56–1.99)	1.07 (0.51–2.24)	Exploratory
Any postoperative, OR exit to discharge/death	24/117 (20.5%)	21/103 (20.4%)	0.1 (–10.7 to 10.7)	1.01 (0.60–1.70)	1.01 (0.52–1.94)	Exploratory

Crude risk-difference intervals are Newcombe hybrid-score intervals. The adjusted cumulative row is based on unpenalized logistic standardization; 2,978 of 3,000 bootstrap fits were successful. The Firth row uses the same covariates and standardization distribution; 3,000 of 3,000 bootstrap fits were successful, and its odds-ratio interval is a penalized profile-likelihood interval. CI, confidence interval.

Table S7. RBC-unit distributions

Window	PAAD recipients/total units	PAAD recipient median [IQR], range	ANH recipients/total units	ANH recipient median [IQR], range
Intraoperative	26/33	1 [1–1.75], 1–2	14/17	1 [1–1], 1–2
Early postoperative, OR exit through 24 hours after OR exit	18/60	2.5 [2–3], 2–12	15/54	3 [2–3.5], 2–12
Late postoperative, >24 hours after OR exit	12/16	1 [1–1], 1–5	9/14	1 [1–1], 1–5
Any postoperative	24/76	2 [1.75–3.25], 1–17	21/68	2 [2–3], 1–17
Cumulative	38/109	1 [1–4], 1–17	29/85	2 [1–3], 1–17

Two patients, one in each strategy group, had cumulative totals of 17 units.

Table S8. Hemostatic products and tranexamic acid

Product/phase	PAAD	ANH
Intraoperative fresh-frozen plasma, recipients/total units	117/218	103/186
Postoperative fresh-frozen plasma, recipients/total units	115/269	101/228
Intraoperative apheresis platelets, recipients/total adult doses	6/6	2/2
Postoperative apheresis platelets, recipients/total adult doses	34/48	24/42
Postoperative cryoprecipitate, recipients/total bags	15/107	12/87
Fibrinogen concentrate, recipients/total grams	11/21	12/22
Tranexamic acid, recipients/total dose, mg	81/62,500	72/54,000

All recipient and total-unit counts represent products actually administered, rather than products ordered or issued. Fresh-frozen plasma at CPB separation was routine center practice in all 220 patients; postoperative plasma was administered in 216/220 patients. The plasma dose and any additional intraoperative or postoperative product administration were individualized according to bleeding and clinical judgment. Product administration is descriptive and was not included as a covariate because it occurred after strategy selection. Platelet units represent adult single-donor apheresis therapeutic doses.

Table S9. Post hoc 7-day KDIGO stage distributions

Component	Stage	PAAD (n=117)	ANH (n=103)	Total (N=220)
Urine output	0	109	97	206
Urine output	1	5	4	9
Urine output	2	1	0	1
Urine output	3	2	2	4
Creatinine	0	101	89	190
Creatinine	1	11	12	23
Creatinine	2	5	2	7
Creatinine	3	0	0	0
Combined	0	101	89	190
Combined	1	9	11	20
Combined	2	4	1	5
Combined	3	3	2	5

The combined stage is the maximum of the creatinine, urine-output, and RRT components. All five RRT episodes began within seven days. The analysis was developed after dataset review and is exploratory.

Table S10. Exploratory clinical outcomes

Outcome	PAAD	ANH	PAAD-minus-ANH risk difference, percentage points (95% CI)
Drainage >1500 mL/24 hours	13/117 (11.1%)	12/103 (11.7%)	-0.5 (-9.4 to 8.0)
Any hourly drainage >400 mL	2/117 (1.7%)	1/103 (1.0%)	0.7 (-3.8 to 5.1)
Study-defined post hoc exploratory bleeding composite	14/117 (12.0%)	12/103 (11.7%)	0.3 (-8.6 to 8.9)
Re-exploration	11/117 (9.4%)	5/103 (4.9%)	4.5 (-2.7 to 11.8)
Any 7-day KDIGO acute kidney injury	16/117 (13.7%)	14/103 (13.6%)	0.1 (-9.3 to 9.2)
RRT within seven days	3/117 (2.6%)	2/103 (1.9%)	0.6 (-4.5 to 5.5)
Cardiac complication	3/117 (2.6%)	2/103 (1.9%)	0.6 (-4.5 to 5.5)
Neurologic complication	3/117 (2.6%)	2/103 (1.9%)	0.6 (-4.5 to 5.5)
Pulmonary complication	17/117 (14.5%)	11/103 (10.7%)	3.9 (-5.3 to 12.7)
Infection complication	19/117 (16.2%)	14/103 (13.6%)	2.6 (-7.1 to 12.0)
In-hospital death	3/117 (2.6%)	2/103 (1.9%)	0.6 (-4.5 to 5.5)

Risk-difference intervals are Newcombe hybrid-score intervals. Complication categories may overlap. Cardiac complications comprised low-cardiac-output syndrome or cardiogenic shock requiring mechanical circulatory support (intra-aortic balloon pump, n=4; extracorporeal membrane oxygenation, n=1). Neurologic complications comprised stroke (n=2), transient ischemic attack (n=1), and CAM-ICU-defined delirium (n=2). Pulmonary complications comprised mechanical ventilation >24 hours (n=16), reintubation (n=5), pleural effusion (n=5), and pneumothorax (n=2); pneumonia was documented in 14 of these patients. Infectious complications comprised surgical-site infection (n=15), pneumonia (n=14), sepsis (n=2), and urinary tract infection (n=2); pneumonia therefore contributed to both pulmonary and infectious categories. All five deaths were attributed in the records to low-cardiac-output syndrome/cardiogenic shock.

ICU length of stay was 3 [3–4] days in each group; hospital length of stay was 8 [7–10] days in each group. Values are medians [IQR].

Table S11. General data-quality summary

Domain	Final result	Status
Analysis records	220	Pass
PAAD/ANH counts	117/103	Pass
Missing primary outcome	0	Pass
Missing key secondary outcome	0	Pass
Missing primary-model fields	0	Pass
Procedure and group coding checks	Completed	Pass
Range, logic, and arithmetic checks	Completed	Pass
Internal outcome-consistency checks	Completed	Pass

Table S12. Recorded anticoagulation and ACT values

Measure	PAAD (n=117)	ANH (n=103)
Initial systemic heparin, IU/kg	322.6 [300.1–350.1]	337.5 [300.1–350.1]
Baseline ACT, seconds	140 [134–145]	139 [132.5–143.5]
Post-heparin, pre-CPB ACT, seconds	577 [524–623]	572 [514.5–624]
Additional heparin during CPB, n (%)	66 (56.4%)	54 (52.4%)
Additional heparin during CPB, IU	5000 [0–10,000]	5000 [0–10,000]
Total protamine, anti-heparin IU	25,000 [25,000–25,000]	25,000 [25,000–25,000]
Post-protamine ACT, seconds	136 [130–145]	136 [129–143]

Values are median [IQR] unless otherwise indicated. Initial systemic heparin excludes heparin in the prime. Additional heparin excludes the initial systemic bolus and heparin in the prime. Total protamine includes any additional dose. ACT, activated clotting time; CPB, cardiopulmonary bypass.

Table S13. Recorded preoperative antithrombotic treatment

Measure	PAAD (n=117)	ANH (n=103)
Aspirin use	96 (82.1%)	89 (86.4%)
Aspirin continued to surgery	87 (74.4%)	83 (80.6%)
Any P2Y12 inhibitor use	20 (17.1%)	20 (19.4%)
Any oral anticoagulant use	15 (12.8%)	7 (6.8%)
No recorded antithrombotic	18 (15.4%)	13 (12.6%)
Aspirin alone	64 (54.7%)	63 (61.2%)
Dual antiplatelet treatment	20 (17.1%)	20 (19.4%)
Oral anticoagulant with or without aspirin	15 (12.8%)	7 (6.8%)
Aspirin stop interval among users, days	1 [1–1]	1 [1–1]
P2Y12 stop interval among users, days	5 [5–6]	5 [5–5]
Warfarin stop interval among users, days	5 [5–5]	5 [4.5–5]
Direct oral anticoagulant stop interval among users, days	2 [2–2]	2 [2–2]

Values are n (%) or median [IQR]. Stop intervals were derived from recorded last-dose and surgery dates. No patient received aspirin on the morning of surgery. Oral anticoagulant use was the union of warfarin and direct oral anticoagulant use.

Table S14. First postoperative-morning laboratory measurements and ICU-admission lactate

Measure	PAAD (n=117)	ANH (n=103)
Hemoglobin, g/dL	9.07 (1.42)	9.19 (1.25)
Hematocrit, %	26.79 (4.39)	27.09 (3.63)
Platelet count, 10 ⁹ /L	203.8 (72.7)	195.1 (65.9)
Creatinine, mg/dL	0.88 [0.74–1.04]	0.85 [0.72–1.04]
Lactate, mmol/L	2.10 [1.90–2.40]	2.10 [1.80–2.55]

Hemoglobin, hematocrit, platelet count, and creatinine were obtained from the first postoperative-morning laboratory panel; lactate was obtained from the ICU-admission blood gas. Values are mean (standard deviation) for hemoglobin, hematocrit, and platelet count and median [interquartile range] for creatinine and lactate. All listed measurements were available for all 220 patients. No between-group hypothesis test was performed. ANH, acute normovolemic hemodilution; ICU, intensive care unit; PAAD, post-heparinization pre-bypass acute autologous donation.

Supplementary Figure Legends

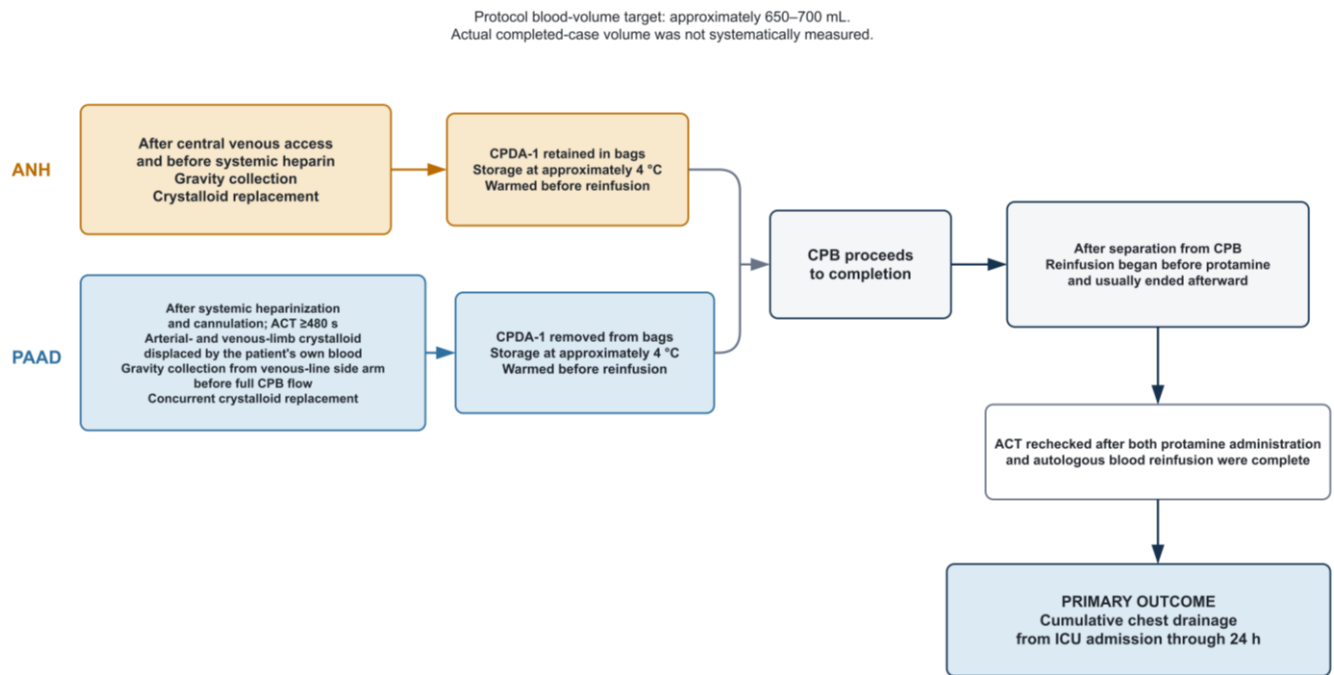
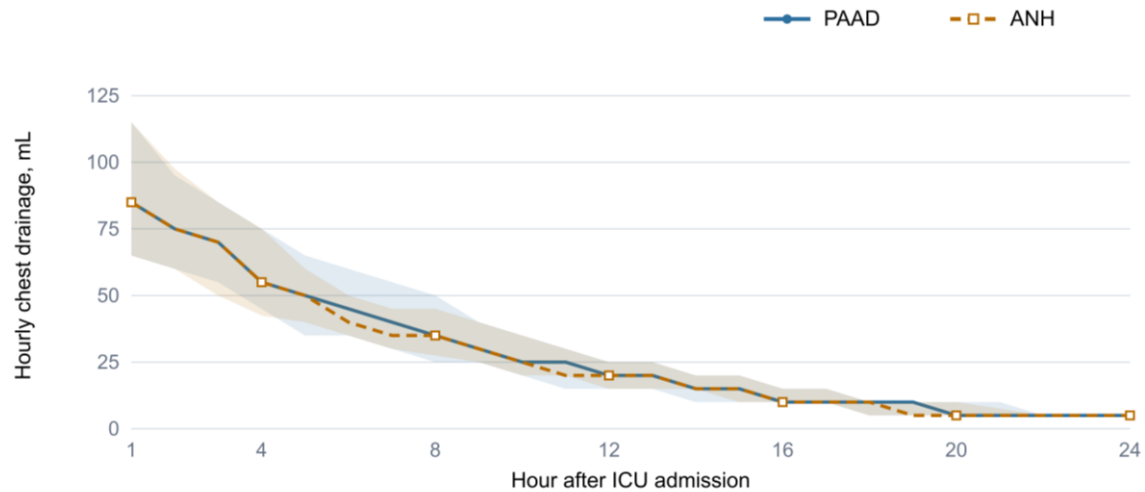


Fig. S1. Protocol timelines and outcome windows

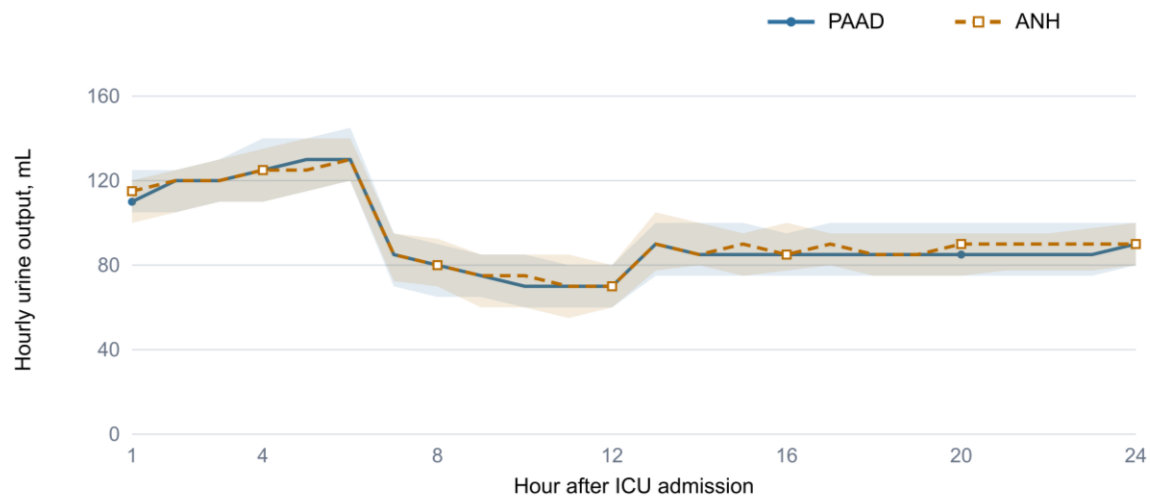
Schematic, not-to-scale comparison of ANH before systemic heparinization and the multicomponent PAAD strategy after systemic heparinization and cannulation but before full CPB flow. In PAAD, autologous circuit priming preceded gravity collection of heparinized whole blood from a side arm of the venous drainage line; CPDA-1 had been removed from the collection bags, and crystalloid replacement was administered concurrently. Both products were stored at approximately 4°C, warmed before reinfusion, and returned after separation from CPB, with reinfusion beginning before protamine and usually ending afterward. ACT was rechecked after both protamine administration and autologous-blood reinfusion were complete. The approximate 650–700-mL collection target and timing annotations summarize clinical practice rather than measured patient-level collection volumes. ANH, acute normovolemic hemodilution; ACT, activated clotting time; CPB, cardiopulmonary bypass; PAAD, post-heparinization pre-bypass acute autologous donation.



Lines show medians; shaded bands show interquartile ranges.

Fig. S2. Hourly postoperative chest-drainage trajectories

Group medians and interquartile ranges for recorded chest-drainage volumes during ICU hours 1-24. PAAD is shown with a solid blue line and filled circles; ANH is shown with a dashed orange line and open squares. The plot is descriptive, and no hour-specific inferential comparison was performed. ANH, acute normovolemic hemodilution; ICU, intensive care unit; PAAD, post-heparinization pre-bypass acute autologous donation.



Lines show medians; shaded bands show interquartile ranges.

Fig. S3. Hourly postoperative urine-output trajectories

Group medians and interquartile ranges for recorded urine-output volumes during ICU hours 1-24. PAAD is shown with a solid blue line and filled circles; ANH is shown with a dashed orange line and open squares. The plot is descriptive, and no hour-specific inferential comparison was performed. ANH, acute normovolemic hemodilution; ICU, intensive care unit; PAAD, post-heparinization pre-bypass acute autologous donation.



Challenge Journal of PERIOPERATIVE MEDICINE

Research Article

Anterior segment angle changes, vault, and intraocular pressure after phakic intraocular lens implantation: An anterior segment optical coherence tomography study

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ABSTRACT

Objective: This study aimed to evaluate 6-month changes in iridocorneal angle morphology, central vault, and intraocular pressure after toric phakic intraocular lens implantation, using anterior segment optical coherence tomography.

Methods: This retrospective single-surgeon cohort included 21 right eyes of 21 patients who completed 1- and 6-month follow-up after toric phakic intraocular lens implantation. Angle opening distance and trabecular–iris space area at 500 and 750 μm , and trabecular–iris angle, were measured nasally and temporally. Anterior chamber depth, anterior chamber width, vault, intraocular pressure, and spherical equivalent were also recorded.

Results: Spherical equivalent improved from -8.06 ± 2.43 D to -0.32 ± 0.32 D at 6 months ($p < 0.001$). Vault was 578 ± 89 μm at 1 month and 559 ± 81 μm at 6 months ($p = 0.006$); all eyes remained within 250–750 μm . Trabecular–iris angle decreased by 42.3%, and angle opening distance and trabecular–iris space area by 52–59% (all $p < 0.001$), with no further narrowing after month 1. Intraocular pressure was 14.5 ± 2.4 , 20.9 ± 3.7 , and 17.8 ± 3.3 mmHg at the three visits. Six-month vault correlated with preoperative anterior chamber width ($r = 0.47$; $p = 0.030$) and axial length ($r = 0.44$; $p = 0.046$).

Conclusion: Toric phakic intraocular lens implantation was associated with early angle narrowing followed by stabilization through month 6. Vault remained within 250–750 μm . Associations between postoperative vault, anterior chamber width, and axial length were exploratory.

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1. Introduction

Myopia is a refractive error whose prevalence is rising rapidly worldwide; by 2050, it is projected to affect approximately half of the global population, with a substantial increase in the prevalence of high myopia [1]. Posterior chamber phakic intraocular lenses (pIOLs) provide a reversible surgical option for correcting myopia, astigmatism, and hyperopia, particularly in patients who are unsuitable for corneal refractive surgery because of thin corneas, irregular corneal topography, dry

eye, or other corneal or refractive considerations [2].

The most widely used platform in this field is the implantable collamer lens (ICL; STAAR Surgical). Nonetheless, a growing body of clinical evidence has accumulated for the Eyecryl Phakic IOL (Biotech Vision Care, Ahmedabad, India), a hydrophilic acrylic, plate-haptic, injectable posterior chamber pIOL. Yaşa and colleagues reported that Eyecryl was effective and safe at 12 months in high myopia, with a mean endothelial cell loss of 3.9% [3]. Kirgiz et al. and Çakır et al. demonstrated refractive stability and acceptable cumulative endothelial loss at 7

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and 5 years, respectively [4,5]. Ürdem and Ağca described successful refractive outcomes and limited endothelial loss at 2 years [6]. In a 2-year comparative study of toric models, Eyecryl yielded efficacy and safety indices similar to those of the Visian toric ICL [7].

Seating of a pIOL in the ciliary sulcus displaces the iris root anteriorly and thereby narrows the iridocorneal angle. Quantitative angle metrics—including angle opening distance (AOD), trabecular–iris space area (TISA), and trabecular–iris angle (TIA)—were first defined on anterior segment OCT by Radhakrishnan and co-workers and validated as a reproducible, non-contact alternative to gonioscopy and ultrasound biomicroscopy [8]. Using Fourier-domain OCT after ICL V4c implantation, Fernández-Vigo et al. documented reductions of approximately 34–42% in TIA and 50–58% in AOD500, with stability from month 1 through 2 years [9,10]; 10-year follow-up from the same group confirmed the absence of progressive long-term narrowing [11]. These observations have been reiterated in a recent review of the clinical role of AS-OCT in the surveillance of phakic and secondary intraocular lenses [12]. Series of IPCL and ICL implants likewise show that AOD and TISA fall at 1 month and remain unchanged thereafter [13–15]; the magnitude of angle narrowing has been related to preoperative anterior chamber depth (ACD) and postoperative vault [14,15].

Vault is defined as the distance between the posterior surface of the pIOL and the anterior surface of the crystalline lens and is a principal marker of postoperative safety. The widely accepted target range is 250–750 μm : values below this interval increase the risk of cataract, whereas higher values may predispose to angle closure and pigment dispersion [16]. Vault height is therefore relevant to anterior segment anatomy and iridocorneal angle morphology after pIOL implantation. Prior Pentacam and AS-OCT studies have examined associations between vault and anterior chamber or angle parameters [17,18], and a relationship between vault and the iridocorneal angle has also been demonstrated [19].

Although long-term vault and endothelial data exist for Eyecryl, nasal–temporal quantification of AOD500/750, TISA500/750, and TIA remains limited for this lens. The present study therefore examined the 6-month course of anterior segment parameters, angle morphology, vault, and IOP after Eyecryl implantation, using a single-surgeon design, a single technician, and only high-quality Optopol REVO FC scans.

2. Methods

2.1. Study design and patients

This was a retrospective observational cohort study. Medical records of patients who underwent toric Biotech Eyecryl posterior chamber phakic intraocular lens implantation between October 1, 2024, and September 1, 2026, were retrospectively reviewed. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Samsun University Non-Interventional Clinical Research Ethics Committee (approval no. 2026/16/24; approval date: September 2,

2026). Because of the retrospective nature of the study, the requirement for informed consent was waived by the ethics committee.

All patients underwent routine preoperative assessment for phakic IOL implantation. In general, phakic IOL implantation was considered in young patients with myopia and/or myopic astigmatism who were not considered suitable candidates for corneal refractive surgery because of corneal thickness, corneal characteristics, or refractive considerations. Patients with conditions precluding phakic IOL implantation, including clinically significant cataract, glaucoma, uveitis, or previous intraocular surgery, were not considered eligible for implantation.

During the study period, 23 consecutive patients who had undergone Eyecryl phakic IOL implantation were screened for eligibility. Two patients were excluded from the analysis because of incomplete postoperative follow-up. The remaining 21 patients fulfilled the study criteria and were included in the final analysis; one eye per patient (the right eye) was analysed.

2.2. Surgery

All procedures were performed by the same surgeon under standard topical anaesthesia through a 2.8-mm clear corneal incision. The lens was placed in the sulcus. The overall lens diameter was selected using the white-to-white (WTW) diameter obtained by optical biometry, while lens power was determined using the manufacturer's calculator based on the preoperative biometric and refractive parameters and the target refraction. Anterior chamber width measured on AS-OCT represented the angle-to-angle distance and was analyzed as an anatomical outcome rather than as an input for lens sizing. Peripheral iridectomy was not performed routinely, because the central 360- μm hole is designed to permit aqueous flow. Postoperatively, a topical moxifloxacin/dexamethasone fixed-combination preparation was administered five times daily during the first postoperative week, followed by topical dexamethasone four times daily for an additional 3 weeks and then discontinued.

2.3. Imaging protocol

All measurements were obtained with the Optopol REVO FC spectral-domain OCT (Optopol Technology, Zawiercie, Poland) by the same experienced technician, without an additional anterior segment adaptor. Examinations were performed with the patient in a seated position under standard clinical room-lighting conditions, without pharmacological pupillary dilation, while the patient fixated on the instrument's internal fixation target. The same acquisition conditions were maintained for all examinations. The device provides built-in software for AOD 500/750, TISA 500/750, angle assessment, and angle-to-angle imaging; definitions follow the method of Radhakrishnan et al. [8]. Only scans with a high signal-to-noise ratio and a clearly identifiable scleral spur were accepted.

Anterior chamber width (AWD) was defined as the angle-to-angle distance measured by AS-OCT and was evaluated as an anatomical parameter; it was not used as

an input for phakic IOL sizing. Central vault was measured in micrometres as the perpendicular distance between the posterior pIOL surface and the anterior capsule of the crystalline lens. ACD was measured from the corneal endothelium. Angle parameters were recorded separately as temporal (T) and nasal (N) measurements in the horizontal meridian:

AOD500 / AOD750: distance from the iris to a line perpendicular to the corneal endothelium 500 and 750

μm anterior to the scleral spur (mm). TISA500 / TISA750: area bounded by the scleral spur, the AOD line, the corneal endothelium, and the anterior iris surface (mm^2). TIA: trabecular meshwork–iris angle (degrees). IOP was measured by Goldmann applanation tonometry and recorded in mmHg. Representative Optopol REVO FC sections illustrating the measurement method are shown in Fig. 1 (vault, ACD, AWD) and Fig. 2 (AOD, TISA, TIA).

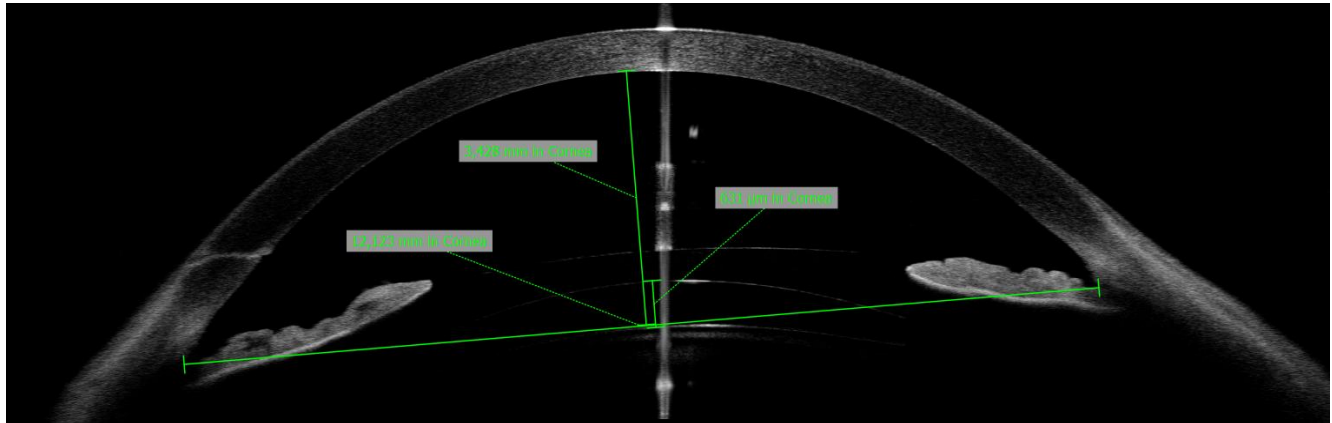


Fig. 1. Postoperative horizontal anterior segment OCT scan showing measurement of central vault, anterior chamber depth, and angle-to-angle distance (Optopol REVO FC). The vertical green caliper measures ACD from the endothelium to the anterior capsule of the crystalline lens (3.428 mm in this section); the short vertical caliper between the posterior lens surface and the anterior capsule indicates central vault (631 μm); the horizontal caliper denotes iridocorneal angle-to-angle distance / AWD (12.123 mm). The pIOL appears as a thin hyper-reflective plate. Patient identity has been concealed.

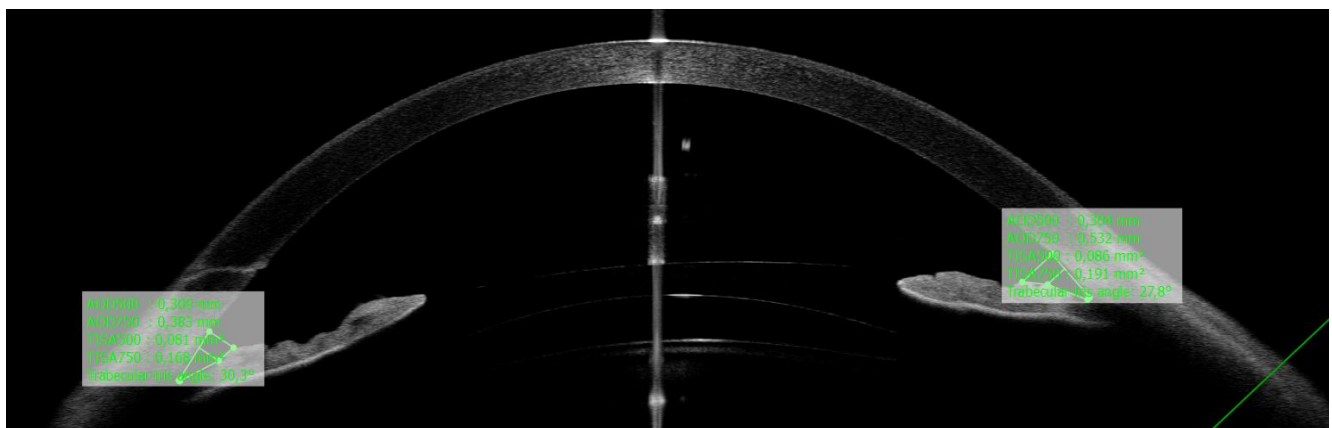


Fig. 2. Postoperative horizontal anterior segment OCT scan (Optopol REVO FC). After the scleral spur is marked, the software automatically calculates AOD500, AOD750, TISA500, TISA750, and trabecular–iris angle (TIA) in the temporal (left box) and nasal (right box) quadrants. In this section, temporal TIA is 30.3° and nasal TIA is 27.8°; AOD500 values are 0.309 mm and 0.304 mm, respectively. Green lines indicate AOD vectors and the TISA polygon. Patient identity has been concealed.

2.4. Statistics

Continuous variables are presented as mean $\pm$ standard deviation (range). The three time points (preoperative, month 1, and month 6) were compared using repeated-measures ANOVA. The Greenhouse–Geisser correction was applied when the assumption of sphericity was violated. The reported overall p value refers to the corrected repeated-measures ANOVA when applicable. When the overall test was significant, three pairwise comparisons were performed with Bonferroni adjust-

ment, with an adjusted significance threshold of $\alpha = 0.017$. The Friedman test was additionally used as a non-parametric, distribution-robust confirmation of the repeated-measures analysis. Because vault was measured only at the two postoperative visits, a single paired t -test was applied. Associations between the 6-month postoperative vault and ACD, AWD, axial length, and angle parameters were assessed using Pearson correlation. Two-sided $p < 0.05$ was considered statistically significant. Because only one eye per patient was included, eyes constituted statistically independent units.

3. Results

3.1. Demographics and refractive outcomes

Twenty-three consecutive patients were screened during the study period. Two patients were excluded because of incomplete postoperative follow-up, leaving 21 patients (21 right eyes) for the final analysis. All 21 included patients completed both the 1- and 6-month follow-up examinations. The patients included 12 women

and 9 men, with a mean age of 25.0 ± 4.2 years (range, 19–35). Preoperative axial length was 26.58 ± 1.35 mm (range, 23.65–28.30). Preoperative sphere was -6.68 ± 2.95 D, cylinder -2.76 ± 1.36 D, and spherical equivalent -8.06 ± 2.43 D (range, -11.63 to -2.63). At 6 months, spherical equivalent was -0.32 ± 0.32 D (RM-ANOVA $p < 0.001$; Bonferroni-adjusted preoperative vs. 6-month $p < 0.001$; month 1 vs. month 6 adjusted $p = 1.00$). At 6 months, 85.7% of eyes were within ± 0.50 D and 100% were within ± 1.00 D (Table 1).

Table 1. Demographic and refractive data ($n = 21$ patients / 21 right eyes).

Parameter	Preoperative	Month 1	Month 6
Sphere (D)	-6.68 ± 2.95	-0.19 ± 0.33	-0.10 ± 0.35
Cylinder (D)	-2.76 ± 1.36	-0.36 ± 0.37	-0.45 ± 0.33
Spherical equivalent (D)	-8.06 ± 2.43	-0.37 ± 0.33	-0.32 ± 0.32
Within ± 0.50 D (%)	—	—	85.7
Within ± 1.00 D (%)	—	—	100
Axial length (mm)	26.58 ± 1.35	—	—

3.2. Vault

Central vault measured 578 ± 89 μ m (416–682) at 1 month and 559 ± 81 μ m (404–700) at 6 months. The difference was statistically significant but clinically small (mean -19 μ m; paired t -test $p = 0.006$; no multiple-comparison correction was required because only two time points were available). At both visits every eye lay within the 250–750 μ m interval; no vault below 250 μ m or above 750 μ m was observed. The 6-month postoperative vault correlated positively with preoperative AWD ($r = 0.47$; $p = 0.030$) and axial length ($r = 0.44$; $p = 0.046$). The association with preoperative ACD was not significant ($r = 0.30$; $p = 0.19$). Vault was not significantly correlated with 6-month TIA, AOD750, or TISA750. A representative 6-month section is shown in Fig. 1.

3.3. Anterior chamber depth and width

ACD was 3.525 ± 0.088 mm preoperatively, 3.449 ± 0.161 mm at 1 month, and 3.449 ± 0.162 mm at 6 months. The overall repeated-measures ANOVA was significant ($p = 0.001$); after Greenhouse–Geisser correction, the overall p value was 0.010. However, the Bonfer-

roni-adjusted preoperative versus 6-month comparison was not statistically significant ($p = 0.030$, adjusted $\alpha = 0.017$), and there was no difference between months 1 and 6 (adjusted $p = 1.00$). The absolute reduction of 0.08 mm was clinically limited.

AWD decreased from 11.855 ± 0.347 mm preoperatively to 11.763 ± 0.378 mm at 1 month and 11.726 ± 0.362 mm at 6 months (Bonferroni-adjusted preoperative vs. 6-month $p < 0.001$).

3.4. Iridocorneal angle parameters

Parallel narrowing was observed in the nasal and temporal quadrants (Tables 2 and 3). Mean $((T+N)/2)$ TIA fell from $52.65 \pm 5.15^\circ$ to $30.61 \pm 3.47^\circ$ at 1 month and $30.38 \pm 3.64^\circ$ at 6 months (-42.3% ; RM-ANOVA $p < 0.001$; Bonferroni preoperative vs 6 months $p < 0.001$). AOD500, AOD750, TISA500, and TISA750 decreased by 52.3%, 52.7%, 59.3%, and 59.0%, respectively (RM-ANOVA and Bonferroni preoperative vs 6 months $p < 0.001$ for all). No angle parameter changed significantly between months 1 and 6 (Bonferroni-adjusted $p = 0.33$ – 1.00). Quadrant asymmetry was not marked. A representative postoperative angle measurement is shown in Fig. 2.

Table 2. Angle opening distance (AOD) and trabecular–iris space area (TISA).

Parameter	Preoperative	Month 1	Month 6	$\Delta\%$ (pre–6 mo)
AOD500-T (mm)	0.835 ± 0.277	0.406 ± 0.111	0.397 ± 0.119	-52.5^*
AOD500-N (mm)	0.850 ± 0.248	0.410 ± 0.110	0.408 ± 0.112	-52.1^*
AOD750-T (mm)	1.540 ± 0.389	0.742 ± 0.255	0.730 ± 0.270	-52.6^*
AOD750-N (mm)	1.591 ± 0.307	0.750 ± 0.266	0.751 ± 0.263	-52.8^*
TISA500-T (mm ²)	0.246 ± 0.080	0.104 ± 0.021	0.102 ± 0.025	-58.3^*
TISA500-N (mm ²)	0.247 ± 0.075	0.102 ± 0.024	0.098 ± 0.022	-60.2^*
TISA750-T (mm ²)	0.531 ± 0.147	0.223 ± 0.052	0.218 ± 0.058	-59.0^*
TISA750-N (mm ²)	0.543 ± 0.129	0.226 ± 0.060	0.223 ± 0.061	-58.9^*

* After RM-ANOVA, Bonferroni-adjusted preoperative vs 6-month $p < 0.001$. Differences between months 1 and 6 were not significant (adjusted $p > 0.05$).

Table 3. Trabecular–iris angle, ACD, AWD, vault, and intraocular pressure.

Parameter	Preoperative	Month 1	Month 6	<i>p</i> *
TIA-T (°)	52.2 ± 5.6	30.7 ± 3.4	30.4 ± 4.2	<0.001
TIA-N (°)	53.1 ± 5.1	30.5 ± 3.8	30.4 ± 3.6	<0.001
Mean TIA (°)	52.7 ± 5.1	30.6 ± 3.5	30.4 ± 3.6	<0.001
ACD (mm)	3.525 ± 0.088	3.449 ± 0.161	3.449 ± 0.162	0.030
AWD (mm)	11.855 ± 0.347	11.763 ± 0.378	11.726 ± 0.362	<0.001
Vault (μm)	—	578 ± 89	559 ± 81	0.006†
IOP (mmHg)	14.5 ± 2.4	20.9 ± 3.7	17.8 ± 3.3	<0.001

* For angle, ACD, AWD, and IOP, the *p* column reports the Bonferroni-adjusted preoperative versus 6-month pairwise *p* value following the repeated-measures ANOVA. The adjusted significance threshold for pairwise comparisons was $\alpha = 0.017$. For ACD, the Greenhouse–Geisser-corrected overall *p* value was 0.010, whereas the Bonferroni-adjusted preoperative versus 6-month pairwise *p* value was 0.030. † Vault was measured only at months 1 and 6 and was compared using a paired *t*-test. IOP, intraocular pressure.

3.5. Intraocular pressure

IOP was 14.5 ± 2.4 mmHg (11–20) preoperatively, 20.9 ± 3.7 mmHg (14–28) at 1 month, and 17.8 ± 3.3 mmHg (12–23) at 6 months. RM-ANOVA for IOP was significant ($F = 49.7$; $p < 0.001$). After Bonferroni correction, the preoperative–month 1, preoperative–month 6, and month 1–month 6 differences all remained significant (adjusted $p \leq 0.001$). The month-1 rise may be related to steroid response, early postoperative inflammation, or angle narrowing; however, these potential mechanisms were not directly investigated in the present study and should therefore be considered speculative. Although IOP increased at month 1, the elevation did not require IOP-lowering treatment in any of the 21 patients. No eye developed persistent glaucoma or an acute angle-closure crisis.

4. Discussion

This series documents the 6-month nasal and temporal quantitative course of AOD, TISA, and TIA after Eyecryl posterior chamber pIOL implantation using Optopol REVO FC imaging. The principal finding is that angle parameters narrow by approximately one-half during the first month and thereafter reach a plateau. This pattern coincides quantitatively with the 34–42% TIA and 50–58% AOD reductions reported by Fernández-Vigo et al. after ICL V4c implantation on Fourier-domain OCT [9–11]. After IPCL implantation, AOD and TISA likewise declined at 1 month and remained stable at 3 and 6 months [13]; a similar early-plateau pattern has been confirmed in eyes with both spacious and shallow anterior chambers [15].

The reduction in TISA (~59%) was slightly greater than that in AOD (~52%). Because TISA incorporates iris configuration and areal geometry, anterior tenting of the iris by the lens may account for this difference. Symmetric nasal and temporal narrowing in the horizontal meridian is consistent with 360° iris displacement by the convex anterior surface of the implant.

Vault was 578 μm at 1 month and 559 μm at 6 months, and all eyes remained within the 250–750 μm range [16]. In the 7-year Eyecryl series of Kirgiz et al., vault declined to a clinically negligible extent over the long term [4]; our 19-μm reduction over 5 months is in the same

direction. In a dynamic vault comparison of ICL and Eyecryl, photopic–scotopic vault change (DVR) was numerically smaller with Eyecryl than with ICL, although the difference approached but did not reach statistical significance (Eyecryl 54.0 ± 36.4 μm vs ICL 86.5 ± 57.9 μm, $p = 0.078$) [18]; distinct mechanical behaviour of the hydrophilic acrylic material may explain this tendency. The positive associations of 6-month vault with preoperative AWD and axial length should be considered exploratory and hypothesis-generating rather than definitive, particularly given the small sample size. These findings may reflect the contribution of preoperative anterior segment anatomy and ocular dimensions to postoperative vault, but they do not establish a direct role for these parameters in lens sizing [19].

Refractive outcomes accord with the published literature: at 6 months, 85.7% of eyes were within ±0.50 D and all were within ±1.00 D. Yaşa et al. reported a mean spherical equivalent of −0.44 D at 12 months [3], and Çakır et al. documented comparable stability at 5 years [5].

IOP rose at 1 month and declined by 6 months, remaining slightly above the preoperative level. In ICL series, early IOP elevation has been attributed to steroid response, residual viscoelastic, or transient angle narrowing; however, these potential mechanisms were not directly investigated in the present study. The 6-month mean IOP was 17.8 mmHg, and no patient required IOP-lowering treatment during the study period. However, given the small sample size and 6-month follow-up, these findings should not be interpreted as evidence of long-term IOP safety.

Strengths of the study include a single surgeon, a single technician, restriction to high-quality OCT, one eye per patient (the right eye), separate nasal and temporal measurements, and paired analysis of months 1 and 6. Limitations are the small sample (21 patients / 21 right eyes), the exclusion of two patients because of incomplete postoperative follow-up, which may have introduced selection bias, the absence of endothelial cell density and logMAR visual acuity from this dataset, lack of superior–inferior quadrant measurements, the absence of a control group, and the 6-month follow-up.

Clinical implication: angle narrowing after Eyecryl implantation was an early and subsequently stable finding in this cohort. The observed 6-month vault values remained within the commonly cited 250–750 μm range,

but this observation should not be interpreted as evidence of long-term safety given the small sample size and 6-month follow-up. The exploratory associations between higher 6-month vault, preoperative AWD, and axial length may help generate hypotheses regarding anatomical determinants of postoperative vault, but they should not be interpreted as definitive guidance for lens sizing.

5. Conclusions

In eyes implanted with the Biotech Eyecryl posterior chamber phakic IOL, AOD, TISA, and TIA measured with Optopol REVO FC narrow by approximately 42–59% during the first postoperative month and remain stable through month 6. Central vault remains within the commonly cited physiological range and declines slightly. Spherical equivalent approaches emmetropia in a predictable manner. An early rise in IOP may occur and partially regress by 6 months. The observed associations between 6-month vault and preoperative AWD and axial length were exploratory and should be interpreted cautiously. Given the small sample size and limited follow-up, these findings do not establish long-term safety or definitive criteria for lens sizing. Larger studies with endothelial data and 360° angle mapping over longer follow-up are warranted.

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Conflict of Interest

The author declares no potential conflicts of interest with respect to the research, authorship, and/or publication of this manuscript.

Data Availability

The datasets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author upon reasonable request.

AI Assistance

No AI-based tools were used in the preparation of this manuscript.

Ethics Approval and Consent to Participate

This study was approved by the Samsun University Non-Interventional Clinical Research Ethics Committee (Approval no. 2026/16/24; Date: September 2, 2026). The requirement for informed consent was waived by the ethics committee due to the retrospective nature of the study. All procedures were conducted in accordance with relevant guidelines and regulations.

Author Contributions

Gökhan Özgür: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, validation, visualization, writing – original draft, writing – review and editing.

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Case Report

Successful awake fibreoptic nasotracheal intubation in a patient with a large thyroid mass undergoing total thyroidectomy

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ABSTRACT

Long-standing large thyroid masses can distort airway anatomy through tracheal deviation and compression and restrict neck mobility. These changes may make conventional tracheal intubation difficult. Awake fibreoptic intubation offers an alternative by maintaining spontaneous ventilation and airway tone during airway instrumentation. We describe the perioperative airway management of a 50-year-old woman with a large papillary thyroid carcinoma scheduled for total thyroidectomy. Airway assessment revealed restricted neck movements, while imaging demonstrated tracheal deviation and narrowing. Awake fibreoptic nasotracheal intubation was planned, with preparation of a difficult airway cart and backup strategies. Following topical airway anaesthesia, the bronchoscope was advanced through the right nostril, and a cuffed endotracheal tube was positioned under direct fibreoptic guidance. General anaesthesia was induced after confirmation of tube placement. Surgery lasted eight hours. Elective postoperative ventilation was continued because of prolonged surgery, laryngeal oedema and anticipated tracheomalacia. The patient underwent ventilator weaning and extubation the following morning. This case illustrates the importance of individualized airway assessment, adequate topical anaesthesia, maintenance of spontaneous ventilation during intubation, and a planned postoperative airway strategy. Clear communication and readiness for alternative techniques remain essential.

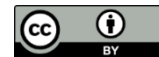
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1. Introduction

Thyroid malignancies can distort the airway leading to difficulty in tracheal intubation. They render conventional intubation techniques difficult due to tracheal compression and difficult Cormack–Lehane grades with non-visualization of the glottic opening. Awake fiberoptic intubation has been reported to be the safest alternative in such cases. We present one such case scenario managed with the help of fiberoptic intubation. This was a thyroid malignancy with significant neck movement restriction with no evidence of retrosternal extension with left IJV thrombosis, unlike other case reports where they had a multinodular goiter with few cases having retrosternal extension with insignificant neck movement restriction.

2. Case Presentation

Informed written consent was obtained from the patient for the procedure, as well as for publication of clinical data and imaging. A 50-year-old female patient, weighing 40 kg with a height of 150 cm, a BMI of 17.78 kg/m², with no known comorbidities presented with complaints of gradually increasing swelling in front of the neck for the past 4 years. She had no compressive symptoms. The swelling was diagnosed to be papillary carcinoma of the thyroid, and the patient was posted for total thyroidectomy.

On pre-anaesthetic evaluation, the patient was conscious, co-operative with a pulse rate of 80 bpm, blood pressure of 110/70 mmHg, room-air saturation of 97%. On airway examination, she had Mallampati grade 2, 3

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finger breadth mouth opening, with an inter-incisor distance of 4 cm, and upper lip bite test grade 1. Neck circumference was 38 cm. The patient had restricted neck movements. Sternomental and thyromental distance could not be estimated. The upper border of thyroid swelling was extending from around 2 cm behind the mentum till the sternal notch. The lateral borders were extending to the posterior border of sternocleidomastoid. The trachea was neither visible nor palpable. There were no compressive symptoms even in the supine position. Neck examination showed remarkably large multiple thyroidal swellings extending from below the jaw to the sternal notch with non-palpation of tracheal position. Pemberton's test was negative, clinically ruling out retrosternal extension of the tumor (Fig. 1). There were no distended veins on the chest. Routine blood investigations and surgical profile were done. Thyroid function tests revealed a euthyroid state. Other blood biochemical reports, electrocardiogram, and echocardiography were within normal limits. Chest x-ray revealed tracheal deviation to the right side. Lateral neck x-ray revealed calcification of the mass (Fig. 2). Ultrasound of the neck revealed multiple cystic swellings, largest measuring $11 \times 9.3 \times 7.1$ cm with adjacent structures and carotid vessels displaced laterally. Computed tomography (CT) scan revealed a soft tissue mass lesion with irregular margins and chunky calcifications arising from the left hemithyroid gland in keeping with neoplastic etiology, projecting into a massive metastatic numerous cystic neck mass predominantly along the deep cervical lymph node chain. There was mild tracheal narrowing in the postcricoid area. Left IJV showed no contrast flow (compressed/thrombosed). Bilateral vocal cords were mobile on indirect laryngoscopy.

Considering anticipated difficult laryngoscopy and tracheal intubation due to the considerable size of the tumor, fiberoptic intubation was planned using topical anaesthetization technique. Safe lidocaine dose was considered as 9 mg/kg (total of 360 mg). The patient was counselled regarding awake intubation technique. The patient was kept nil by mouth for 6 hours for solids and 2 hours for liquids prior to surgery.

In the preoperative room, airway anaesthesia was done with nebulization of lidocaine 4% 2 mL with gargling using lidocaine 2% 2 mL. Xylometazoline nasal drops were administered in bilateral nostrils for vasoconstriction of nasal passage for facilitation of fiberoptic bronchoscope (FOB) without mucosal injury. Intravenous Inj. Ondansetron 0.15 mg/kg and Inj. Glycopyrrolate 0.01 mg/kg were given. ASA standard monitoring - ECG, Pulse oximetry, Non-Invasive Blood Pressure were attached after shifting the patient inside OT. Supplemental oxygen was given using nasal prongs at a rate of 4 L/min in the left nostril - contralateral to the one used for scope. Airway nerve block was deferred due to distorted anatomy of the neck. Topical anaesthesia of the tongue, epiglottis and oropharynx was achieved with 2% lidocaine spray. Lox 2% jelly 2 pinches were applied over the nostrils. Total lidocaine dose administered for airway anaesthesia in all formulations was 330 mg, which was well below the toxic dose. Difficult intubation cart was kept standby as per DAS (Difficult Airway Society) guidelines. The fiberoptic bronchoscope (FOB) was

loaded with a 7.0 mm cuffed armored endotracheal tube. The FOB was negotiated through the right nostril and gradually advanced through the laryngeal inlet. Simultaneous laryngeal, glottic and tracheal mucosal anaesthesia was done with small aliquots of 4% lidocaine (total volume: 4 mL) loaded in a disposable sterile syringe via 18G epidural catheter inserted into the bronchoscope working channel, using Spray-As-You-Go (SAYGO) technique to achieve effective airway anaesthesia while avoiding toxicity. The FOB was inserted through the vocal cords and positioned above the carina. The flexo-metallic tube was advanced over the fiberoptic bronchoscope into position, after which the bronchoscope was carefully withdrawn, and the tube was fixed after confirming equal air entry bilaterally and end-tidal capnography (Figs. 3 and 4). The patient tolerated the awake intubation technique well. Intravenous general anaesthetic induction was done with Inj. Midazolam 0.05 mg/kg, Inj. Propofol 2 mg/kg, Inj. Fentanyl 2 µg/kg and Inj. Vecuronium 0.1 mg/kg as muscle relaxant. Anaesthesia was maintained with 50% Oxygen, 50% Nitrous oxide, Sevoflurane 1 MAC and Inj. Vecuronium boluses. Intraoperative hemodynamic parameters were within normal limits. The surgery lasted for 8 hours (Fig. 5).



Fig. 1. Preoperative image of thyroid swelling.



Fig. 2. Lateral neck x-ray of thyroid swelling showing calcification with mild antero-posterior compression.



Fig. 3. Awake nasotracheal fiberoptic bronchoscope procedure.



Fig. 4. Fiberoptic image of the carina with right and left main bronchus openings.



Fig. 5. Post-excision of the thyroid tumor.

In view of prolonged surgical hours, laryngeal edema, and anticipated tracheomalacia as the surgeon reported a floppy trachea intraoperatively, elective positive pressure ventilation with the Maquet Servo-S Ventilator (Maquet Critical Care AB, Solna, Sweden) was continued postoperatively with ICU sedation using Inj. Fentanyl 0.5 $\mu\text{g/kg/hr}$ and Inj. Dexmedetomidine 0.3 $\mu\text{g/kg/hr}$ and neuromuscular paralysis with intermittent boluses of Inj. Vecuronium 0.05 mg/kg. Overnight, the patient was on Volume Control Ventilation (VCV) mode with FiO_2 50%, tidal volume 350 mL, respiratory rate 12, PEEP of 5 cm of H_2O . VAP care bundle (Ventilator Associated Pneumonia) was followed prophylactically. After stopping sedative hypnotics, at 6 am the next morning, orotracheal suction was done, and a positive cuff leak test was demonstrated on VCV mode. The patient was weaned off to SIMV (VC with PS) for 1 hour. Spontaneous Awakening Trials (SAT) and Spontaneous Breathing Trials (SBT) on CPAP were done for 30 minutes. The patient was weaned to CPAP with PEEP 5 cm H_2O and down setting PS above PEEP to 5 cm H_2O followed by T-piece trial with endotracheal cuff deflated. Inj. Dexamethasone 0.1 mg/kg was given postoperatively and prior to extubation to reduce any laryngeal edema. Under C-MAC video laryngoscope visualization, oral and tracheal suctioning was done followed by cuff deflation and extubation. Inhaled bronchodilator nebulization was given post-extubation with Ipratropium Bromide, Levosalbutamol and Budesonide. Integrity of bilateral vocal cord mobility was tested by 'E' phonation and cough test.

3. Discussion

Large thyroid masses commonly produce tracheal deviation, compression, or both; they can also limit neck extension and distort anatomy, making mask ventilation and direct laryngoscopy unreliable [1]. A focused airway assessment clinically, combined with cross-sectional imaging, is invaluable in such patients. Imaging quantifies tracheal narrowing, length of compression, and mediastinal extension, which help decide whether conventional endotracheal intubation is feasible or alternative strategies such as awake tracheostomy, rigid bronchoscopy, or extracorporeal oxygenation should be kept as standby options [2].

Awake fibreoptic bronchoscopic intubation is often considered one of the safest strategies in such a scenario of anticipated difficult airway [3]. Establishing a secure airway while the patient remains awake and breathing spontaneously helps maintain the airway tone, reducing the risk of tracheal collapse that leads to "Can't intubate, can't oxygenate" scenarios during the induction of anaesthesia [4].

In our patient, the imaging and bedside assessment pointed toward a high likelihood of difficult direct laryngoscopy but a potentially passable endoluminal path suitable for the awake fibreoptic approach. Hence, we proceeded with adequate airway topicalization with avoidance of nerve blocks given the altered anatomy. The procedure was well tolerated by the patient with hemodynamic parameters maintained throughout. Current difficult airway management guidelines emphasize the

importance of preformulated airway strategies, availability of alternative devices, and preparedness for emergency invasive airway access [5]. These principles were strictly followed in our case, with a difficult airway cart and surgical backup readily available.

Tracheomalacia is a predictable but uncommon complication that may be seen post-thyroidectomy, particularly in those with long-standing, large goiters [6]. Chronic external compression from the enlarged thyroid can weaken and soften the tracheal cartilages over time. As a result, once the endotracheal tube is removed, the unsupported tracheal wall may collapse, leading to airway obstruction. In thyroid neck surgeries, evidence of laryngeal edema, laryngomalacia, laryngospasm, post-operative stridor leading to upper airway obstruction with possible negative pressure pulmonary edema have been reported in the literature [7]. In cases where clinical assessment raises strong concerns about such complications, it is prudent to electively maintain the endotracheal tube until airway stability is assured, ensuring the safest means of maintaining a secure airway [8]. Hence, elective ventilation was done overnight postoperatively. Weaning protocol was followed with the pa-

tient maintaining normal arterial blood gases on T-piece trial. Difficult intubation cart was kept standby. Following the demonstration of a leak around the tracheal tube after deflation, it was considered safe to extubate the patient.

4. Conclusions

When dealing with a difficult airway, the choice of intubation technique should be individualized after weighing the risks and benefits of each available option, guided by current evidence and clinical judgment. No single approach fits all patients, especially in cases involving thyroid enlargement where airway anatomy may be significantly distorted. This case highlights the clinical utility of awake fiberoptic intubation in anticipated difficult airway scenarios with anatomical distortion. Meticulous planning and clear communication with both the patient and the surgical team regarding anticipated challenges and backup plans are essential to ensure a safe and successful outcome while minimizing morbidity and mortality.

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Data Availability

The datasets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author upon reasonable request.

AI Assistance

No AI-based tools were used in the preparation of this manuscript.

Ethics Approval and Consent to Participate

Informed written consent was obtained from the patient, for the procedure, as well as for publication of clinical data and imaging.

Author Contributions

Sunil H. Mokashi: conceptualization, data curation, formal analysis, validation, visualization, writing – original draft, writing – review and editing.

Jennifer Daniel: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, validation, visualization, writing – original draft, writing – review and editing.