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Challenge Journal of PERIOPERATIVE MEDICINE

Research Article

The predictive impact of perioperative hypofibrinogenemia on re-exploration in cardiac surgery: Insights from a single-center analysis

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ABSTRACT

Background: Postoperative bleeding in cardiac surgery is a serious complication associated with increased morbidity, mortality, and healthcare costs. The objective of this study was to identify independent risk factors for re-exploration due to bleeding in patients undergoing cardiac surgery, with a particular emphasis on the predictive role of perioperative hypofibrinogenemia.

Methods: In this single-center retrospective observational cohort study, a total of 593 consecutive adult patients who underwent cardiac surgery between January 1, 2025, and June 30, 2025, were retrospectively reviewed. The primary endpoint was surgical re-exploration for bleeding within 48 hours postoperatively. Demographic characteristics, comorbidities, laboratory parameters, surgical variables, and postoperative complications were recorded. Variables found to be significant in univariate analysis were further analyzed using multivariate logistic regression. The threshold value of postoperative fibrinogen for predicting re-exploration risk was calculated.

Results: The overall re-exploration rate was 15.6%. Approximately 10% of cases were urgent surgeries. Independent risk factors identified in multivariate analysis were female sex (OR=2.7; p=0.001), age ⩾65 years (OR=2.0; p=0.011), body mass index (BMI) outside the normal range (OR=2.7; p=0.002), preoperative fibrinogen <1.5 g/L (OR=3.7; p=0.007), and postoperative fibrinogen <1.5 g/L (OR=2.7; p=0.012). The ROC analysis for postoperative fibrinogen was statistically significant (AUC=0.691; 95% CI 0.629–0.752; p<0.001). The optimal cut-off was 2.06 g/L (Youden index=0.346), with 79.8% sensitivity and 54.8% specificity. Patients undergoing re-exploration had significantly longer ICU stays (p<0.001) and higher mortality rates (p<0.001).

Conclusions: The risk of re-exploration in cardiac surgery is increased in association with female sex, advanced age, abnormal BMI, and particularly perioperative hypofibrinogenemia. A preoperative fibrinogen level <1.5 g/L emerged as the strongest predictor. These findings suggest that close monitoring of fibrinogen and early replacement strategies may play a critical role in reducing re-exploration rates.

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1. Introduction

Cardiac surgical procedures, particularly in complex cases, carry a high risk of perioperative bleeding complications. Postoperative bleeding not only exerts detrimental effects on mortality and morbidity but also significantly increases the need for blood products, intensive care unit (ICU) stay, length of hospitalization, and overall treatment costs [1]. Numerous studies have demonstrated that patients undergoing re-exploration exhibit a markedly higher incidence of complications such as renal failure, prolonged mechanical ventilation, acute respiratory distress syndrome (ARDS), and sepsis [2]. More recent investigations have further reported that re-ex-

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ploration increases mortality threefold, with delayed interventions resulting in even higher mortality rates [3,4]. The decision for re-exploration requires differentiation between insufficient surgical hemostasis, coagulopathy, and microbleeding. However, it remains unclear which patients or which early biomarkers may provide a "warning" signal. In this context, the identification of reliable biomarkers could facilitate optimization of blood and coagulation management strategies, enhance the likelihood of timely intervention, and ultimately contribute to improved outcomes.

In the pathophysiology of postoperative bleeding following cardiac surgery, in addition to surgically related bleeding (e.g., anastomotic leaks, suture lines), coagulopathy, platelet dysfunction, hypofibrinogenemia, and hyperfibrinolytic states play major roles [5]. During cardiopulmonary bypass (CPB), hemodilution, factor consumption, and fibrinogen loss are frequently observed; these processes impair clot stability at the microcirculatory level, potentially leading to diffuse microbleeding [4]. It has been reported that 30–60% of cardiac surgery patients experience factor depletion and coagulation abnormalities after CPB, while the incidence of re-exploration is approximately 2–6% [6]. Among all coagulation factors, fibrinogen is present at the highest plasma concentration and plays a central role in the formation of cross-linked fibrin polymers [7,8]. Several studies have examined the relationship between low perioperative fibrinogen levels and bleeding, and some have specifically linked it to re-exploration.

Nevertheless, many additional risk factors beyond fibrinogen have been described in the literature, including advanced age, small body surface area (BSA), prolonged CPB duration, higher number of distal anastomoses, emergent/urgent surgical status, preoperative antiplatelet use, and preoperative renal dysfunction. For example, Dacey et al. identified advanced age, small BSA, prolonged CPB time, and number of anastomoses as predictors of re-exploration risk in coronary artery bypass grafting (CABG) [9]. Similarly, Elassal et al. reported that higher EuroSCORE, low platelet count, and emergent surgery were associated with re-exploration in their cohort [5]. However, due to the multifactorial nature of re-exploration risk, these studies generally left unresolved whether fibrinogen is an independent predictor. Furthermore, fibrinogen cut-off values, sensitivity and specificity, the optimal time point for measurement, and strategies for translation into clinical practice remain uncertain.

The aim of this study was to identify independent risk factors for re-exploration due to bleeding in patients undergoing cardiac surgery, with a particular focus on determining the predictive role and effect size of perioperative hypofibrinogenemia. By doing so, we sought to enable the identification of high-risk patients in the preoperative or intraprocedural period, facilitate planning of appropriate coagulation management strategies, and promote proactive approaches to prevent re-exploration. The primary outcome of this study was the identification of independent risk factors for re-exploration, while secondary outcomes included postoperative complications, ICU length of stay, and 30-day postoperative mortality.

2. Materials and Methods

This study was approved by the local Clinical Research Ethics Committee (Date: September 24, 2025; Decision No: TABED1-25-1707). All procedures were conducted in accordance with the principles of the Declaration of Helsinki and national regulations. Due to the retrospective design, individual informed consent was not obtained; however, all patient data were anonymized prior to analysis.

2.1. Study design and patient selection

This single-center retrospective observational cohort study included consecutive adult patients who underwent cardiac surgery at our institution between January 1, 2025, and June 30, 2025. Eligible patients were adults aged ≥18 years who underwent open-heart surgery with cardiopulmonary bypass (CPB), either under elective or emergency conditions. Exclusion criteria were as follows: history of known bleeding diathesis or severe coagulopathy in the preoperative period; patients requiring mechanical circulatory support such as intraaortic balloon pump (IABP) or extracorporeal membrane oxygenation (ECMO); cases with major surgical bleeding originating from large arteries or veins identified during re-exploration; and patients who died within the first 24 hours postoperatively. These criteria were designed to isolate patients in whom re-exploration was primarily related to coagulopathic or multifactorial causes rather than to clear surgical bleeding sources. Based on these criteria, of the 609 patients initially screened, 16 were excluded, leaving 593 patients for the final analysis.

Patients were followed for 48 hours postoperatively, focusing on bleeding-related surgical re-exploration as the primary endpoint. Re-exploration was defined as a return to the operating room for hemostasis because of persistent or excessive bleeding or hemodynamic instability that could not be managed by conservative means. The decision for re-exploration was made by the attending cardiac surgeon according to standard institutional criteria: Chest tube drainage exceeding 200 mL/hour for 2 consecutive hours, Hemodynamic instability with evidence of ongoing bleeding, or Tamponade or clot formation confirmed by clinical or echocardiographic evaluation. Secondary outcomes included postoperative complications (acute kidney injury, ARDS, sepsis, stroke, pneumonia), duration of mechanical ventilation, ICU and hospital length of stay, and 30-day mortality. AKI was defined according to the KDIGO criteria as a ≥0.3 mg/dL or ≥50% increase in serum creatinine from baseline within 48 hours postoperatively [10,11]. ARDS, sepsis, and stroke were identified based on standard clinical and laboratory criteria documented by the ICU team. Patients were divided into two groups according to the occurrence of surgical re-exploration due to bleeding within the first 48 postoperative hours: the Re-exploration group (n=93) and the Non–re-exploration group (n=500). This classification was based on operative records and confirmed by surgeon documentation and nursing reports.

Transfusion and coagulation management were performed according to routine clinical practice by the attending anesthesiology and surgical teams. Red blood cell transfusion was generally restrictive in the perioperative/ICU setting. Hemostatic interventions (plasma, platelets, and fibrinogen replacement) were administered in response to clinically relevant bleeding and laboratory results. Fibrinogen concentrate and/or cryoprecipitate may have been used at clinician discretion in actively bleeding patients with low Clauss fibrinogen levels (commonly ≤1.5 g/L), depending on availability and clinical judgement.

2.2. Data collection and measurements

Demographic variables (age, sex, body mass index), comorbidities, ASA and EuroSCORE, as well as the use of antithrombotic agents (e.g., aspirin, clopidogrel) and anticoagulants (e.g., warfarin, DOACs) were recorded. Laboratory values (hemoglobin, hematocrit, platelet count, INR, aPTT, fibrinogen levels) were documented preoperatively, upon admission to the ICU, and at 24 hours postoperatively. Surgical variables included type of procedure, urgency (elective vs. emergency), CPB time, aortic cross-clamp time, autologous blood transfusion, acute normovolemic hemodilution, and ultrafiltration (UF) requirement. Postoperative outcomes included complications, mechanical ventilation (MV) duration, length of ICU and hospital stay, and 30-day mortality. All data were obtained retrospectively from the hospital's electronic medical record system, anesthesia–perfusion charts, intensive care unit (ICU) information system, and surgical reports. Laboratory variables (hemoglobin, platelet count, fibrinogen, INR, aPTT, etc.) were extracted from the institutional laboratory information system (LIS). Re-exploration indications (e.g., excessive drainage, hemodynamic instability, clot accumulation) were verified from surgical and nursing documentation. All patient outcomes, including mortality and discharge data, were confirmed through the institutional database.

The main exposure variables were preoperative and postoperative fibrinogen concentrations (g/L), measured by the Clauss method. Hypofibrinogenemia was defined a priori as fibrinogen <1.5 g/L based on commonly used clinical thresholds in perioperative bleeding management, and this cut-off was not derived from the ROC analysis. Predictor variables potentially associated with re-exploration included demographic and perioperative factors: Age (categorized as <65 or ≥65 years), sex, Body Mass Index (categorized as underweight <18.5, normal 18.5–24.9, overweight ≥25 kg/m^2), EuroSCORE II, Comorbidities (hypertension, diabetes mellitus, chronic kidney disease, COPD, etc.), CPB time (categorized as <120 min or ≥120 min), use of norepinephrine ≥0.1 µg/kg/min, and Type of surgery (CABG, valve, combined). Body mass index was calculated as weight/height^2 (kg/m^2) and categorized according to the WHO adult BMI classification as underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obesity (≥30.0 kg/m^2). For regression analyses, we additionally used a binary variable (abnormal BMI) defined as BMI <18.5 or BMI ≥25 kg/m^2 (i.e., outside the normal range), with 18.5–24.9 kg/m^2 as the reference category. No other laboratory or imaging diagnostic criteria were required beyond those routinely recorded in the institutional protocol.

To minimize bias, all consecutive adult patients undergoing cardiac surgery with cardiopulmonary bypass during the study period were included to reduce selection bias. Information bias was limited by using standardized electronic records and verified data from the institutional laboratory information system. Misclassification was minimized through predefined criteria for re-exploration and consistent laboratory methods (Clauss assay for fibrinogen). Confounding factors such as age, sex, BMI, urgency of surgery, CPB time, and antithrombotic use were adjusted for in multivariable logistic regression. Data extraction was independently verified by two investigators to ensure accuracy.

2.3. Statistical analysis

Statistical analyses were performed using SPSS (IBM SPSS Statistics, version 25). The Kolmogorov–Smirnov test was used to assess the normality of continuous variables. Normally distributed data were presented as mean ± standard deviation, whereas non-normally distributed variables were presented as median (interquartile range). Categorical variables were expressed as frequencies and percentages. For univariate analyses, Student's t-test or Mann–Whitney U test was applied to continuous variables, and the chi-square or Fisher's exact test was applied to categorical variables. Missing data were handled using a complete-case analysis approach. . Variables with $p < 0.05$ in univariate analyses, as well as those deemed clinically relevant, were entered into multivariate logistic regression. Independent risk factors and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using logistic regression modeling. The predictive performance of preoperative and initial postoperative fibrinogen levels for re-exploration was assessed using receiver operating characteristic (ROC) analysis; the area under the curve (AUC) was calculated, and the optimal cut-off point was determined using the Youden index. A p value < 0.05 was considered statistically significant. The overall rate of missing data was low (<5%) and was not expected to affect the study's statistical power or validity. Because this was a retrospective study based on complete electronic hospital records, loss to follow-up did not occur.

No separate sample size calculation was performed, as all eligible adult cardiac surgery patients operated during the study period were included. However, in the available dataset, the incidence of the primary endpoint (re-exploration) was approximately 15%. For the final model with five independent predictors, this corresponds to an Events Per Variable (EPV) of ~18.6, exceeding the threshold recommended in the literature and supporting the stability of the estimated coefficients.

3. Results

Between January 1 and June 30, 2025, we retrospectively screened 609 consecutive adult patients who underwent open cardiac surgery with cardiopulmonary

bypass at our institution. After excluding 16 patients (pre-existing coagulopathy/bleeding diathesis, n=5; requirement for mechanical circulatory support, n=4; major surgical bleeding from identifiable arterial/venous sources at re-exploration, n=3; and death within the first 24 postoperative hours, n=4), 593 patients constituted the final cohort. Patients were followed for 48 hours postoperatively for the primary endpoint of surgical re-exploration for bleeding, defined as return to the operating room for hemostasis due to persistent/excessive bleeding or hemodynamic instability not controlled conservatively, based on standard institutional criteria and operative documentation. Accordingly, patients were categorized into a Re-exploration group (n=93) and a Non–re-exploration group (n=500). Demographic, clinical, and perioperative data were extracted from electronic medical records, anesthesia–perfusion charts, ICU information systems, and surgical reports; laboratory parameters, including fibrinogen measured by the Clauss method, were recorded preoperatively, on ICU admission, and at 24 hours postoperatively. Perioperative hypofibrinogenemia was predefined as a fibrinogen level <1.5 g/L, and analyses were conducted using a complete-case approach with a low overall rate of missing data (<5%).

Approximately 10% of procedures were emergent. Demographic, clinical, and surgical characteristics of the groups are summarized in Table 1. The proportion of female patients was significantly higher in the re-exploration group (p<0.001). The prevalence of diabetes mellitus was lower among those who underwent re-exploration (p=0.026). No significant differences were observed regarding age, body mass index (BMI), EuroSCORE II, ejection fraction, other comorbidities, surgical type, CPB duration, or cross-clamp times. Autologous blood transfusion was more frequent in the re-exploration group (p=0.003). Our cohort included a substantial proportion of complex procedures (Table 1): isolated CABG (n=280), isolated valve surgery (n=96), aortic surgery involving the ascending aorta/arch (n=29) and thoracoabdominal aortic surgery (n=14), and combined procedures (n=174); 60 cases were performed on an emergency basis. The incidence of re-exploration varied by procedural category, with the highest rates observed in aortic surgery (ascending/arch: 7/29, 24.1%) and emergency cases (13/60, 21.7%).

Table 1. Demographic, clinical, and surgical characteristics of the study groups.

	Re-exploration (-) (n=500)	Re-exploration (+) (n=93)	p*
	n (%)/Median (IQR)	n (%)/Median (IQR)	
Female/Male	256/244 (51.2/48.8)	66/27 (71.0/29.0)	<0.001
Age, years	64 (58-70)	66 (59-71)	0.187
Body mass index, kg/m^2	26.16 (23.23-29.24)	27.09 (24.97-29.94)	0.100
EuroSCORE II	2.10 (1.15-3.79)	1.96 (1.10-4.18)	0.978
Ejection fraction, %	55 (50-60)	55 (48-60)	0.600
Comorbidities			
Coronary artery disease	172 (34.4)	35 (37.6)	0.548
Congestive heart failure	20 (4)	6 (6.5)	0.289
Diabetes mellitus	218 (43.6)	29 (31.2)	0.026
Hypertension	310 (62)	61 (65.6)	0.511
COPD	52 (10.4)	16 (17.2)	0.061
Chronic kidney disease	28 (5.6)	4 (4.3)	0.600
Cerebrovascular event	22 (4.4)	6 (6.5)	0.397
ASA II/III/IV	126/348/26 (25.2/69.6/5.2)	19/69/5 (20.4/74.2/5.4)	0.616
Surgical Features			
CABG	238 (47.8)	42 (45.2)	0.585
Valve surgery	78 (15.7)	18 (19.6)	
Aortic surgery (ascending, arch)	22 (4.4)	7 (7.6)	
Thoracoabdominal aortic surgery	12 (2.4)	2 (2.2)	
Combined procedures	150 (30.0)	24 (26.1)	
Emergency surgery	47 (9.4)	13 (14.0)	0.179
Cross-clamp time, min	102 (78-131)	100 (72-133)	0.700
Cardiopulmonary bypass time, min	145 (115-186)	140 (117-183)	0.835
Autologous blood transfusion	94 (18.8)	30 (32.3)	0.003
Acute normovolemic hemodilution	26 (5.2)	7 (7.5)	0.369
Ultrafiltration	60 (12)	12 (12.9)	0.807

ASA: American Society of Anesthesiologists; CABG: coronary artery bypass grafting; COPD: chronic obstructive pulmonary disease; CPB: cardiopulmonary bypass.

*Categorical variables were compared using the chi-square test, and continuous variables were compared using the Mann–Whitney U test.

In preoperative laboratory values, hemoglobin (p<0.001) and hematocrit (p<0.001) levels were significantly higher, while aPTT was longer (p=0.001) in the re-exploration group. Preoperative fibrinogen levels did not differ significantly between groups (p=0.134). In the first ICU laboratory measurements, PT (p<0.001), aPTT (p<0.001), and INR (p<0.001) were significantly higher, while fibrinogen (p<0.001) and platelet counts (p<0.001) were markedly lower in the re-exploration group. Hemoglobin was also lower in this group (p=0.029). At 24 hours postoperatively, PT (p<0.001), aPTT (p<0.001), and INR (p<0.001) remained significantly higher, whereas fibrinogen (p<0.001) and platelet counts (p<0.001) were lower in the re-exploration group. No significant differences were observed in hemoglobin and hematocrit levels at this time point (p>0.05) (Table 2).

Table 2. Preoperative, early postoperative, and 24-hour laboratory data for re-exploration groups.

	Re-exploration (-) (n=500)	Re-exploration (+) (n=93)	p*
Preoperative Period (Baseline)			
PT, sec	12.4 (11.7-13.2)	12.3 (11.7-13.2)	0.571
aPTT, sec	24.30 (22.60-26.40)	25.50 (23.60-27.80)	0.001
INR	1.10 (1.00-1.20)	1.10 (1.00-1.20)	0.974
Fibrinogen, g/L	2.81 (2.20-3.79)	2.51 (2.00-3.59)	0.134
Hemoglobin, g/dL	11.9 (10.5-13.4)	13.1 (11.6-14.3)	<0.001
Hematocrit, %	37.2 (32.9-40.5)	40.6 (37.0-43.2)	<0.001
Platelets, $10^3/\mu L$	240 (200-305)	233 (197-282)	0.258
ICU Admission (0 hour)			
PT, sec	14.2 (13.3-15.8)	15.9 (14.6-17.5)	<0.001
aPTT, sec	27.30 (24.80-31.05)	32.50 (28.30-38.10)	<0.001
INR	1.30 (1.20-1.40)	1.40 (1.30-1.50)	<0.001
Fibrinogen, g/L	2.65 (2.14-3.29)	1.98 (1.52-2.81)	<0.001
Hemoglobin, g/dL	9.4 (8.8-9.9)	9.0 (8.2-9.9)	0.020
Hematocrit, %	28.4 (26.6-30.4)	27.7 (24.9-30.1)	0.070
Platelets, $10^3/\mu L$	159 (117-199)	118 (92-169)	<0.001
Postoperative 24-hour data			
PT, sec	14.20 (13.10-15.60)	15.60 (14.30-18.30)	<0.001
aPTT, sec	28.3 (25.6-32.1)	30.5 (27.6-35.0)	<0.001
INR	1.3 (1.2-1.4)	1.4 (1.3-1.6)	<0.001
Fibrinogen, g/L	4.55 (3.78-5.24)	3.91 (2.81-4.79)	<0.001
Hemoglobin, g/dL	9.0 (8.6-9.4)	9.1 (8.6-9.7)	0.403
Hematocrit, %	27.1 (25.9-28.6)	27.5 (25.7-28.9)	0.674
Platelets, $10^3/\mu L$	148.0 (110.0-184.0)	118.0 (85.0-149.0)	<0.001

aPTT: activated partial thromboplastin time; INR: international normalized ratio; PT: prothrombin time.

*The Mann–Whitney U test was used for intergroup comparisons.

Postoperative complications are presented in Table 3. During the same period, postoperative complications included acute kidney injury in 27.5%, prolonged mechanical ventilation in 31.8%, and 30-day mortality in 6.6% of patients. These data reflect the early postoperative risk pattern and allow for temporal comparison between re-exploration and non–re-exploration groups. Acute kidney injury was more common in the re-exploration group (p<0.001). No significant differences were found between groups regarding ARDS, stroke, pneumonia, or sepsis. Duration of mechanical ventilation and ICU stay were significantly longer in the re-exploration group (p<0.001). Although length of hospital stay was longer in the re-exploration group, the difference did not reach statistical significance (p=0.089). The 30-day mortality rate was significantly higher among patients who underwent re-exploration (p<0.001).

Both unadjusted and adjusted associations between potential risk factors and surgical re-exploration were evaluated. In univariate logistic regression, male sex (p=0.001), abnormal BMI (p=0.015), CPB time ≥120 minutes (p=0.044), norepinephrine use ≥0.1 μg/kg/min (p=0.018), preoperative fibrinogen <1.5 g/L (p<0.001), and initial postoperative fibrinogen <1.5 g/L (p<0.001) were significantly associated with re-exploration. In multivariate analysis, independent predictors of re-exploration were female sex (OR 2.74; 95% CI 1.55–4.86; p<0.001), age ≥65 years (OR 2.05; 95% CI 1.18–3.57;

p=0.011), abnormal BMI (OR 2.69; 95% CI 1.43–5.06; p=0.002), preoperative fibrinogen <1.5 g/L (OR 3.70; 95% CI 1.43–9.57; p=0.007), and initial postoperative fibrinogen <1.5 g/L (OR 2.72; 95% CI 1.25–5.94; p=0.012) (Table 4). The model demonstrated acceptable calibration (Hosmer–Lemeshow p=0.157) and moderate explanatory power (Nagelkerke R^2=0.195).

Table 3. Postoperative data.

	Re-exploration (-) (n=500)	Re-exploration (+) (n=93)	p*
Atrial fibrillation	52 (10.4)	16 (17.2)	0.059
Acute kidney injury	54 (10.8)	24 (25.8)	<0.001
Acute respiratory distress syndrome	70 (14.0)	18 (19.4)	0.182
Cerebrovascular event	34 (6.8)	6 (6.5)	0.902
Pneumonia	44 (8.8)	9 (9.7)	0.785
Sepsis	18 (3.6)	5 (5.4)	0.415
Duration of mechanical ventilation, hours	14.2 (7.0-24.0)	24.0 (19.2-72.0)	<0.001
Duration of intensive care, days	2 (1-4)	3 (2-5)	<0.001
Length of hospital stay, days	9 (7-17)	12 (8-18)	0.089
30-day mortality	36 (7.2)	20 (21.5)	<0.001

*Categorical variables were analyzed using the chi-square test, and continuous variables were analyzed using the Mann–Whitney U test.

Table 4. Univariate and multivariate logistic regression analysis for re-exploration.

	Univariate Logistic Regression			Multivariate Logistic Regression		
	p	OR	95% CI	p	OR	95% CI
Female gender	0.001	2.330	1.440-3.768	0.001	2.742	1.548-4.859
65 years and older	0.076	1.496	0.959-2.334	0.011	2.053	1.180-3.571
BMI 18.5< and >24.9	0.015	1.891	1.134-3.155	0.002	2.686	1.425-5.062
CPR duration>120 min	0.044	1.692	1.014-2.826			
Norepinephrine	0.013					
Norepinephrine <0.1 mcg/kg/min	0.389	0.784	0.450-1.365			
Norepinephrine ≥0.1 mcg/kg/min	0.018	1.917	1.120-3.282			
Dopamine	0.054					
Dopamine ≤5 mcg/kg/min	0.679	1.122	0.650-1.938			
Dopamine >5 mcg/kg/min	0.029	2.023	1.074-3.813			
Preoperative fibrinogen<1.5 g/L	0.001	3.756	1.778-7.932	0.007	3.702	1.432-9.570
Postoperative initial fibrinogen<1.5 g/L	0.000	3.779	2.088-6.841	0.012	2.722	1.248-5.936
Constant				0.000	0.015	

BMI: body mass index; CI: confidence interval; CPB: cardiopulmonary bypass; OR: odds ratio.

ROC analysis for preoperative fibrinogen was not statistically significant (AUC=0.554; 95% CI 0.479–0.630; p=0.134). Although preoperative fibrinogen showed limited univariable discrimination, very low preoperative fibrinogen (<1.5 g/L) was independently associated with re-exploration in the multivariable model. ROC analysis for the initial postoperative fibrinogen level was statistically significant (AUC=0.691; 95% CI 0.629–0.752; p<0.001), indicating moderate discriminatory ability for re-exploration (Fig. 1). The optimal cut-off value, determined by maximizing the Youden index, was 2.06 g/L, with a sensitivity of 79.8% and specificity of 54.8% (Youden index=0.346). However, this threshold showed limited specificity (54.8%), implying a substantial false-positive rate. Therefore, this cut-off should be interpreted as an exploratory discriminator rather than a standalone clinical trigger.

4. Discussion

In this retrospective cohort of adults undergoing open cardiac surgery with cardiopulmonary bypass, we examined the incidence of surgical re-exploration for bleeding and identified perioperative factors associated with this outcome. The overall re-exploration rate in our cohort was 15.7%, and re-exploration was accompanied by a substantially higher postoperative morbidity burden, including increased acute kidney injury, prolonged mechanical ventilation and ICU stay, and higher mortality. In multivariable analyses, perioperative hypofibrinogenemia emerged as the strongest predictor of re-exploration, with the early postoperative fibrinogen level (<1.5 g/L) showing the most clinically informative discrimination compared with preoperative fibrinogen. Beyond fibrinogen, female sex, older age (≥65 years), and

body mass index outside the normal range were independently associated with re-exploration risk, suggesting a multifactorial bleeding phenotype in this population. Collectively, these findings emphasize the importance of early, targeted hemostatic assessment—particularly prompt postoperative fibrinogen evaluation—to identify high-risk patients and potentially reduce the need for re-exploration.

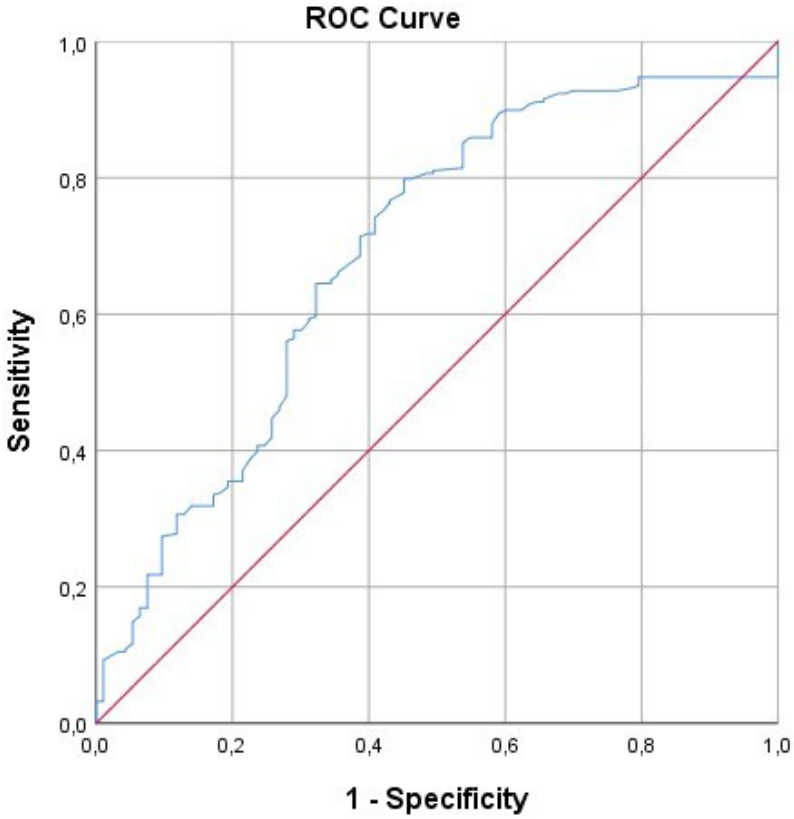


Fig. 1. ROC curve for the first postoperative fibrinogen value (diagonal segments are produced by ties).

The observation that perioperative hypofibrinogenemia (<1.5 g/L) is associated with bleeding and re-exploration is consistent with blood management (PBM) guidelines for adult cardiac surgery patients recommending targeted replacement at low fibrinogen levels [12]. On the other hand, the thresholds proposed in the literature vary across studies, and some have suggested higher cut-off values [13]. While the guideline-based threshold of 1.5 g/L remains clinically safe, our findings suggest that an additional "high-risk" alert threshold around ≈2.0 g/L could be considered. However, given its limited specificity, this value should not be used in isolation but rather interpreted in the context of multivariable risk models and clinical judgment. We acknowledge an apparent discrepancy between the limited univariable discrimination of preoperative fibrinogen (AUC 0.554) and the association observed for a threshold-based definition (<1.5 g/L) in multivariable analysis. These findings are not necessarily contradictory because the AUC reflects overall discrimination across the full distribution, whereas a cut-off may identify a small high-risk tail even when global overlap is substantial. Nevertheless, dichotomizing a continuous variable can reduce information and may exaggerate effect estimates; therefore, the threshold-based result should be interpreted cautiously and primarily as a clinically interpretable risk signal rather than evidence of strong standalone discrimination.

Our results indicate that the initial postoperative measurement is more informative than the preoperative level in predicting re-exploration. The superiority of postoperative fibrinogen derives from its temporal proximity to the etiology: it reflects the cumulative impact of CPB-related hemodilution, intraoperative fibrinogen consumption, blood loss, and transfusions. Thus, it directly measures the "current hemostatic capacity." This is consistent with previous studies showing that immediate postoperative fibrinogen levels strongly correlate with bleeding and transfusion requirements [7,8,14]. By contrast, preoperative values reflect only the baseline reserve. Postoperative values incorporate baseline reserve, intraoperative processes, and administered replacements, thereby providing a closer signal for re-exploration decisions. Hypofibrinogenemia identified postoperatively, particularly in the presence of active bleeding, serves as a pragmatic trigger for targeted replacement. In our dataset, preoperative fibrinogen had limited discriminatory power in ROC analysis, whereas its categorization as <1.5 g/L in multivariate modeling emerged as an independent risk factor, underscoring that threshold-based classification more closely reflects clinical reality. This suggests that while baseline reserve is important, the immediate postoperative balance is more decisive for re-exploration. In high-risk patients, raising fibrinogen above the ≈2.0 g/L threshold identified in our study may be beneficial. Clinically, any deci-

sion threshold should be evaluated in conjunction with the broader bleeding phenotype rather than in isolation.

Female sex remained independently associated with a 2.7-fold increased risk of re-exploration even after adjustment for other covariates. Female sex has frequently been reported as a risk factor for bleeding and transfusion in cardiac surgery [15,16]. This finding may be explained by greater hemodilution due to smaller circulating blood volume, smaller graft and vessel calibers complicating surgical hemostasis, and the higher prevalence of preoperative anemia and iron deficiency in women, which are well-recognized transfusion risk factors. The markedly higher proportion of women in the re-exploration group in our cohort is consistent with these biological and procedural explanations.

Advanced age (≥65 years) increases the likelihood of bleeding and re-exploration due to reduced platelet function, vascular fragility, and greater use of antithrombotic agents. Contemporary PBM guidelines recommend protocolized, targeted coagulation management in elderly patients; our findings support this approach. Re-exploration has been shown in multiple studies to significantly increase morbidity and mortality, an effect even more pronounced with delayed re-exploration [17].

Low BMI (<18.5) predisposes to bleeding through small circulating volume, disproportionate hemodilution, and reductions in hematocrit and coagulation factors [18]. High BMI (>24.9) increases bleeding risk via technical challenges, prolonged CPB, inflammatory response, anticoagulation imbalance due to dilutional dosing, and delayed postoperative mobilization [19]. In our study, the combined effect of abnormal BMI demonstrated by an odds ratio of approximately 2.7 is consistent with this U-shaped biological relationship.

Our findings suggest that patients with the triad of female sex, advanced age, and abnormal BMI warrant stricter perioperative PBM protocols, with prioritization of early fibrinogen replacement at the <1.5 g/L threshold and individualized dosing/priming strategies. This population represents a clinically relevant target group in whom re-exploration risk may be substantially reduced. Such strategies could potentially mitigate the chain of morbidity reflected in increased AKI incidence and ICU resource utilization observed in our study.

Although re-exploration for bleeding is commonly reported in the 2–6% range in unselected adult cardiac surgery cohorts, procedure type and operative urgency materially influence this rate [20]. Published series report higher incidences in more complex settings (e.g., combined procedures approaching ~10% and emergency operations up to ~15%) [21]. Consistent with this, our cohort was enriched for combined and aortic procedures and included a notable proportion of emergency cases, with the highest re-exploration rates observed in aortic and emergency categories. This underscores the influence of patient selection and surgical complexity on re-exploration incidence. Despite the relatively large cohort, the event count for re-exploration may have limited precision for some multivariable and subgroup analyses, and the findings should be interpreted with this uncertainty in mind.

This study has certain limitations. The retrospective design and single-center data limit causal inference. A further limitation is the exclusive reliance on Clauss fibrinogen measurements. Although widely used, Clauss-based fibrinogen may be affected by perioperative conditions (e.g., hemodilution and anticoagulant/heparin effects) and may not fully capture functional fibrinogen contribution to clot firmness, which can be assessed more rapidly using viscoelastic assays (e.g., ROTEM/TEG fibrinogen parameters). The absence of viscoelastic/functional fibrinogen testing may have limited mechanistic interpretation and the transportability of fibrinogen thresholds across institutions. Nevertheless, the inclusion of all consecutive patients and the large sample size represent major strengths. The relatively high re-exploration rate represents a limitation of the study; however, it also provided sufficient event density to robustly evaluate predictors of re-exploration, particularly perioperative hypofibrinogenemia. Decision-making for re-exploration is not uniform across institutions and may reflect center- and surgeon-specific thresholds and local algorithms; therefore, our single-center re-exploration incidence may not be directly generalizable to programs with different practice patterns, which may limit external validity.

5. Conclusions

In conclusion, perioperative hypofibrinogenemia emerged as the strongest and most modifiable predictor of re-exploration, which in turn was associated with increased AKI, mechanical ventilation duration, ICU stay, and mortality. In clinical practice, routine fibrinogen monitoring integrated into risk stratification (age, sex, BMI) and threshold-based replacement guided by PBM protocols may help reduce re-exploration rates and resource burden. Our findings provide a rationale for multicenter, prospective validation studies and fibrinogen-focused randomized protocols incorporating viscoelastic testing and decision-curve analyses to clarify clinical benefit.

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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 Bilkent City Hospital Local Ethics Committee (Approval Number: TABED1-25-1707; Date: September 24, 2025). Due to the retrospective design, individual informed consent was not obtained; however, all patient data were anonymized prior to analysis. All methods were performed in accordance with relevant guidelines and regulations.

Author Contributions

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

Nisan Özsan: *conceptualization, data curation, investigation, methodology, resources, validation, visualization, writing – original draft.*

Fatıma Beyza Artıran: *conceptualization, data curation, investigation, methodology, resources, validation.*

Zeliha Aslı Demir: *project administration, supervision, visualization, writing – original draft, writing – review & editing.*

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Challenge Journal of PERIOPERATIVE MEDICINE

Research Article

The effects of intravenous esmolol on hemodynamic response to endotracheal intubation and rocuronium onset time: A retrospective analysis

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ABSTRACT

Background: Airway instrumentation during induction can elicit acute sympathetic stimulation with transient cardiovascular fluctuations, particularly elevations in arterial blood pressure. Esmolol, an ultra–short-acting β_1-selective antagonist, is often administered peri-induction to blunt these peri-intubation responses. However, its effects on neuromuscular blockade onset in routine clinical practice remain insufficiently explored. This retrospective study evaluated the association between peri-induction intravenous esmolol administration, hemodynamic responses to endotracheal intubation, and the onset time of rocuronium-induced neuromuscular blockade.

Methods: We retrospectively reviewed anesthesia charts of adult patients (18–60 years) with ASA physical status I–II who underwent elective surgery. Patients were classified according to peri-induction esmolol use: an esmolol group receiving a single intravenous bolus of 0.5 mg/kg (500 µg/kg) administered over 1 minute, and a control group without beta-blocker administration (30 patients per group). Anesthesia induction was performed with thiopental, fentanyl, and rocuronium (0.6 mg/kg). Neuromuscular blockade onset time was defined as the time from rocuronium administration to Train-of-Four count 1. Hemodynamic parameters were recorded before and after endotracheal intubation, and intubation conditions were assessed using the Cooper scale.

Results: Demographic characteristics were comparable between groups. The time to Train-of-Four count 1 was significantly longer in the esmolol group compared with controls (129.9 ± 22.8 s vs. 88.5 ± 12.0 s, $p < 0.001$). Between-group differences in systolic and diastolic arterial pressure were observed at specific early peri-intubation time points but were not sustained thereafter. Intubation conditions were significantly better in the esmolol group, with a higher proportion of patients achieving excellent Cooper scale scores ($p < 0.05$).

Conclusions: Peri-induction intravenous esmolol was associated with modulation of early hemodynamic responses to endotracheal intubation and a delayed onset of rocuronium-induced neuromuscular blockade. These findings suggest that esmolol may influence both cardiovascular responses and neuromuscular block onset during anesthesia induction. Future prospective investigations are needed to better delineate the clinical significance and mechanistic basis of this observed association.

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1. Introduction

Endotracheal intubation is an essential component of general anesthesia, providing airway protection and controlled ventilation during surgery. Airway manipulation during induction of general anesthesia commonly triggers sympathetic activation, which may manifest as transient cardiovascular instability, particularly elevations in arterial blood pressure [1,2]. This response is typically characterized by transient increases in arterial blood pressure and other signs of cardiovascular stimulation and may occasionally be exaggerated despite adequate anesthetic depth [3]. Opioids and intravenous local anesthetics such as lidocaine are commonly administered during induction to attenuate this response [3–5]. Nevertheless, excessive hemodynamic reactions to intubation continue to be encountered in clinical practice, particularly in patients with limited cardiovascular reserve.

Esmolol is an ultra–short-acting β1-selective adrenergic antagonist that is frequently administered during anesthetic induction to modulate peri-intubation cardiovascular responses. In addition to its routine use for rhythm regulation, several studies have reported its effectiveness in suppressing the hemodynamic response associated with laryngoscopy and endotracheal intubation, similar to other beta-adrenergic antagonists [6,7]. However, data regarding its peri-induction effects in routine clinical settings remain limited.

Therefore, in this retrospective analysis, we aimed to evaluate the effects of a peri-induction intravenous esmolol bolus administered during induction of general anesthesia on the hemodynamic response to endotracheal intubation and on rocuronium onset time.

2. Materials and Methods

We performed a retrospective record-based study using routinely collected anesthesia data based on data derived from a specialty thesis performed between January 1, 2007, and January 1, 2008. At the time of data collection, formal ethics committee approval was not mandatory under national regulations. The data were obtained during routine clinical practice, with no additional interventions performed. Approval for the retrospective analysis and publication of anonymized patient data was subsequently obtained from the local Ethics Committee (Koşuyolu KAEK approval date: 20.05.2025; decision no: 2025/08/1112). Informed consent was waived by the Ethics Committee because of the retrospective nature of the study.

We extracted peri-induction variables from anesthesia charts of adult patients (18–60 years, ASA I–II) undergoing elective surgery. Patients with incomplete records were excluded, as were those with chronic medication use, anticipated difficult airway, morbid obesity, cardiovascular or central nervous system disease, neuromuscular disorders, diabetes mellitus, or hypovolemia

Patients were retrospectively classified according to the administration of esmolol during anesthesia induction as part of routine clinical practice. In the esmolol group, esmolol was administered according to the institutional protocol as a single intravenous bolus of 500 μg/kg delivered over 1 minute during anesthetic induction. No continuous esmolol infusion was used. The decision to administer esmolol was at the discretion of the attending anesthesiologist. Anesthesia induction in both groups was performed using thiopental (4–7 mg/kg) and fentanyl (1 μg/kg), followed by rocuronium (0.6 mg/kg) for neuromuscular blockade. Train-of-Four stimulation was applied at the ulnar nerve, with neuromuscular response measured at the adductor pollicis muscle.

The depth and onset of neuromuscular blockade were evaluated using peripheral nerve stimulation with Train-of-Four methodology. Arterial pressures (SAP, DAP, and MAP) were recorded at predefined time points before and after endotracheal intubation. Routine monitoring included pulse oximetry (SpO_2). Intubation conditions were evaluated using the Cooper scale.

2.1. Statistical analysis

Statistical evaluation was undertaken with NCSS 2007 (Kaysville, UT, USA). The distributional characteristics of continuous variables were examined using the Shapiro–Wilk test. When normality was supported, results were reported as mean ± SD and between-group comparisons were made with a two-sample t test. For variables deviating from normality, data were summarized as median (IQR) and assessed using the Mann–Whitney U test. Proportions were compared with the chi-square test, with Fisher's exact test applied when expected cell counts were small. Serial hemodynamic measurements obtained at predefined peri-intubation time points were analyzed using repeated-measures ANOVA. All tests were two-sided, and statistical significance was set at $p < 0.05$.

3. Results

A total of 60 patients were included in the analysis, with 30 patients in the esmolol group and 30 in the control group. Demographic characteristics and ASA physical status were comparable between groups, and no statistically significant differences were observed (Table 1).

The time to Train-of-Four count 1 was significantly longer in the esmolol group than in the control group (129.9 ± 22.8 s vs. 88.5 ± 12.0 s, $p < 0.001$) (Fig. 1).

To address potential selection bias related to clinician-directed esmolol administration, we compared pre-induction arterial blood pressure between groups. Baseline systolic and diastolic arterial pressures were comparable between the esmolol and control groups (Table 2), suggesting no evidence of higher baseline blood pressure–related risk in patients who received esmolol.

Baseline hemodynamic variables were comparable between groups. In between-group comparisons at each predefined time point, systolic arterial pressure differed significantly at post-induction, post-rocuronium, 1 min, and 3 min (all $p < 0.05$), whereas no significant difference was observed at baseline, immediately after intubation, or at 5 min. Diastolic arterial pressure differed significantly at post-rocuronium and 1 min ($p < 0.05$),

while other time points were not significantly different (Table 2). Intubation conditions assessed by the Cooper scale were significantly better in the esmolol group, with a higher proportion of patients rated as having excellent intubation conditions compared with the control group ($p < 0.05$).

Table 1. Demographic characteristics and ASA physical status of the study groups.

	Esmolol group (n = 30)	Control group (n = 30)	p value
Age (years)	33.2 ± 10.1	33.7 ± 11.7	0.869
Body weight (kg)	72.7 ± 10.5	69.9 ± 8.3	0.257
Height (cm)	169.3 ± 7.7	167.1 ± 9.1	0.301
Body mass index (kg/m^2)	25.3 ± 2.6	25.0 ± 1.2	0.555
Sex (male/female)	17 / 13	15 / 15	0.605
ASA physical status (I / II)	22 / 8	22 / 8	0.872

Note: Data are presented as mean ± standard deviation or number of patients.

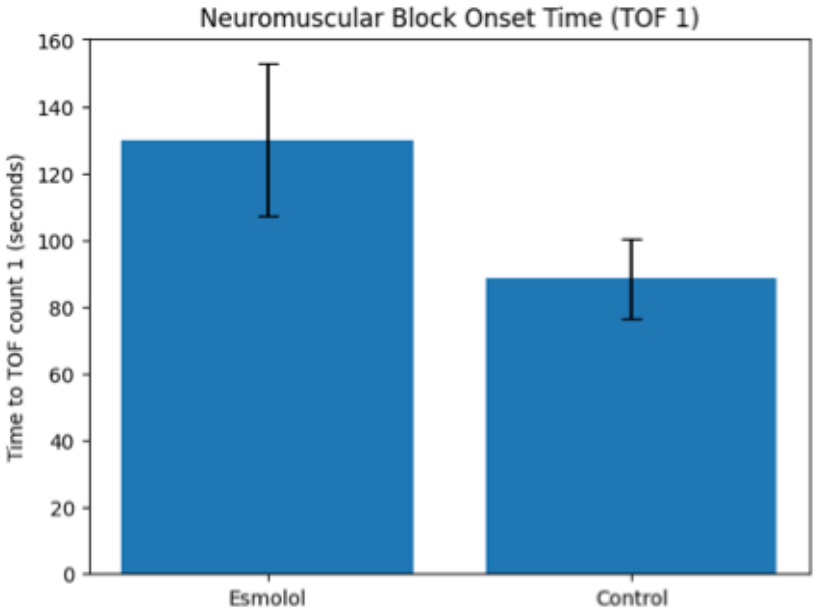


Fig. 1. Neuromuscular block onset time (TOF count 1) in the esmolol and control groups (bars represent mean values, and error bars indicate standard deviation).

Table 2. Hemodynamic parameters at predefined time points.

Time point	SAP (mmHg) esmolol	SAP control	p value	DAP (mmHg) esmolol	DAP control	p value
Baseline	126 ± 11	127 ± 12	0.737	78.8 ± 11.0	76.7 ± 10.0	0.442
Post-induction	112 ± 10	106 ± 11	0.031	75.3 ± 12.2	70.2 ± 13.4	0.128
Post-rocuronium	105 ± 11	116 ± 12	<0.001	69.3 ± 11.5	75.7 ± 10.8	0.030
Post-intubation	132 ± 13	138 ± 14	0.090	92.5 ± 14.1	85.3 ± 15.9	0.068
1 min	126 ± 12	112 ± 11	<0.001	92.7 ± 12.8	85.1 ± 12.1	0.021
3 min	130 ± 13	121 ± 12	0.007	78.0 ± 12.3	76.0 ± 16.5	0.596
5 min	112 ± 11	117 ± 12	0.097	75.4 ± 12.2	74.6 ± 13.2	0.808

Note: Values are presented as mean ± SD.

p-values represent between-group comparisons (Esmolol vs Control) at each predefined time point (two-sided independent-samples t-test).

4. Discussion

In this retrospective study, peri-induction administration of intravenous esmolol was associated with selective changes in early peri-intubation hemodynamics and neuromuscular block onset. Between-group differences in systolic and diastolic arterial pressure were confined to specific early time points around intubation and were not sustained later. Importantly, the time to Train-of-Four (TOF) count 1 after rocuronium administration was significantly longer in the esmolol group, indicating a delayed onset of neuromuscular blockade. While a 41-second delay in neuromuscular block onset is unlikely to be clinically relevant in elective cases, it may become more meaningful in rapid sequence induction scenarios, where rapid airway control is prioritized; nevertheless, this consideration remains theoretical, as our study was conducted under elective conditions. In addition, intubation conditions assessed by the Cooper scale were more favorable in patients receiving esmolol. A plausible explanation is that intubation conditions (e.g., coughing and laryngeal movement) may be influenced not only by the degree of neuromuscular block but also by the intensity of the sympathetic response to laryngoscopy; thus, β1-mediated attenuation of sympathetic activation and stress-related airway reactivity with esmolol might improve Cooper scores even when the onset of rocuronium is slower. However, because we did not measure anesthetic depth, airway reflex markers, or catecholamine levels, this mechanistic interpretation remains speculative. Together, these findings suggest that esmolol influences both early cardiovascular responses to intubation and the onset characteristics of rocuronium-induced neuromuscular blockade.

Several clinical studies have examined peri-induction esmolol in the context of airway instrumentation on the hemodynamic response to laryngoscopy and endotracheal intubation, and most have reported that esmolol effectively and most have reported that esmolol attenuates the magnitude of peri-intubation cardiovascular stimulation, particularly early surges in arterial blood pressure [4,6,7]. This effect is generally attributed to its rapid onset, short duration of action, and β1-selective blockade, making it suitable for use during the induction period. Similar hemodynamic attenuation has also been described with other agents commonly used during induction, such as opioids and intravenous lidocaine; however, these drugs may be associated with limitations related to respiratory depression, delayed recovery, or inconsistent efficacy. In line with the existing literature, our findings demonstrate that peri-induction esmolol administration is associated with modulation of the early hemodynamic response to endotracheal intubation, supporting its role as an effective adjunct for controlling intubation-related sympathetic activation [8,9].

An interesting finding of the present study was the prolongation of the time to TOF count 1 in patients receiving esmolol. To our knowledge, the effect of esmolol on the onset of nondepolarizing neuromuscular blockade has not been specifically investigated in previous studies, and available literature primarily focuses on its cardiovascular effects during induction [10,11]. Esmolol itself does not possess intrinsic muscle-relaxant properties, and the observed delay in neuromuscular block onset cannot be directly attributed to a neuromuscular mechanism. It is possible that alterations in early hemodynamics, such as reduced cardiac output or changes in muscle perfusion, may have influenced the distribution kinetics of rocuronium during the onset phase. Alternatively, a pharmacodynamic interaction cannot be excluded. However, given the retrospective design of this study and the absence of dedicated pharmacological or mechanistic data, these explanations remain speculative. Further prospective and experimental studies are required to clarify the relationship between beta-blockade and neuromuscular block onset [12,13].

This study has several limitations that should be acknowledged. First, its retrospective design limits causal interpretation of the observed associations and may be subject to selection bias. Pre-induction and peri-intubation heart rate measurements were not systematically recorded in this retrospective dataset; therefore, we could not evaluate the effect of esmolol on heart rate control or analyze heart rate variability. Second, the decision to administer esmolol was left to the discretion of the attending anesthesiologist, which may have introduced variability in patient selection and dosing. Third, neuromuscular blockade was evaluated using time to TOF count 1 only; therefore, conclusions regarding block depth, duration, or recovery cannot be drawn. In addition, detailed pharmacokinetic or pharmacodynamic data were not available, precluding mechanistic interpretation of the prolonged onset of neuromuscular blockade. Finally, the study was based on data derived from a single center and a limited sample size, which may restrict the generalizability of the findings.

5. Conclusions

In this retrospective analysis, peri-induction intravenous esmolol was associated with modulation of early hemodynamic responses to endotracheal intubation and a delayed onset of rocuronium-induced neuromuscular blockade. These effects were confined to the early peri-intubation period and were not sustained over time. Further prospective studies are needed to clarify the clinical significance and underlying mechanisms of these findings.

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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 conducted as a retrospective observational analysis based on data derived from a specialty thesis performed between 01.01.2007, and 01.01.2008. At the time of data collection, formal ethics committee approval was not mandatory under national regulations. The data were obtained during routine clinical practice, with no additional interventions performed. Approval for the retrospective analysis and publication of anonymized patient data was subsequently obtained from the local Ethics Committee (Koşuyolu KAEK Approval Date: 20.05.2025; Decision No: 2025/08/1112).

Author Contributions

Mustafa Simsek: *conceptualization, data curation, formal analysis, investigation, methodology, validation, visualization, supervision, writing – original draft, writing – review & editing.*

Elif Bombaci: *data curation, formal analysis, investigation, visualization, writing – original draft.*

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Challenge Journal of PERIOPERATIVE MEDICINE

Research Article

Perioperative factors associated with severe early postoperative pain after single-level lumbar discectomy: A retrospective cohort study

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ABSTRACT

Background: Lumbar disc herniation is a frequent cause of radicular low back pain, and lumbar discectomy remains one of the most commonly performed spinal procedures when conservative treatment fails. Despite advances in surgical technique and perioperative management, postoperative pain—particularly during the early postoperative period—remains clinically relevant. Severe pain within the first 24 hours after surgery may delay mobilization, increase opioid requirements, and complicate recovery. However, perioperative factors associated with severe early postoperative pain following elective single-level lumbar discectomy remain incompletely understood.

Methods: This retrospective cohort study included adult patients undergoing elective single-level lumbar discectomy under general anesthesia. Postoperative pain intensity was assessed using the maximum numeric rating scale score recorded within the first 24 hours. Severe pain was defined as a score $\geqslant$7. Demographic, operative, and analgesic variables, including operative duration, intraoperative opioid exposure (fentanyl equivalents), multimodal analgesia, and rescue opioid use, were analyzed. Univariable and multivariable logistic regression analyses identified factors independently associated with severe early postoperative pain.

Results: Among 322 patients, 78 (24.2%) experienced severe early postoperative pain. Longer operative duration (adjusted odds ratio 1.38 per 10-minute increase), higher intraoperative opioid exposure (adjusted odds ratio 1.29 per 50 microgram increase), absence of multimodal analgesia (adjusted odds ratio 0.46), and post-anesthesia care unit rescue opioid administration (adjusted odds ratio 3.12) were independently associated with severe pain within the first 24 hours.

Conclusions: Severe early postoperative pain after single-level lumbar discectomy is common and is influenced by perioperative factors. Optimizing multimodal analgesia and limiting intraoperative opioid exposure may improve outcomes.

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1. Introduction

Lumbar disc herniation is a common cause of radicular low back pain, and lumbar discectomy remains one of the most frequently performed surgical procedures when conservative treatment fails [1]. Despite advances in surgical technique and perioperative management, postoperative pain continues to be a clinically relevant problem, particularly during the early postoperative period [2].

Pain intensity during the first 24 hours after lumbar discectomy varies substantially among patients. Even

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after technically uncomplicated single-level procedures, postoperative pain may range from minimal discomfort to severe pain requiring additional analgesic interventions [2]. Early postoperative pain is clinically important, as it may delay mobilization, increase opioid requirements, and complicate early postoperative care. Moreover, recent studies have suggested that higher pain intensity in the immediate postoperative period may be associated with poorer functional outcomes after lumbar disc surgery [3].

A number of perioperative factors have been investigated as potential contributors to postoperative pain following spine surgery. Operative duration is often considered a surrogate marker for surgical complexity and tissue trauma and has been included among predictors of postoperative pain intensity in lumbar disc surgery populations [2]. In addition, perioperative analgesic strategy represents a potentially modifiable determinant of postoperative pain. In spine surgery, multimodal analgesia has been widely recommended, with systematic reviews and umbrella reviews consistently reporting improved early pain control and opioid-sparing effects when non-opioid adjuncts are incorporated into perioperative care [4–6]. Studies focusing specifically on lumbar disc surgery frequently assess pain at 24 hours as a key outcome, underscoring the clinical relevance of the immediate postoperative period [7].

The role of intraoperative opioid exposure in postoperative pain control has also been increasingly examined. Experimental and clinical evidence indicates that higher intraoperative opioid requirements do not necessarily result in superior postoperative analgesia and may, in some settings, be associated with opioid-induced hyperalgesia or increased pain sensitivity during early recovery [8–10]. These findings suggest that the relationship between intraoperative opioid administration and postoperative pain is complex and may not be linear.

Despite the growing body of literature on postoperative pain after spine surgery, important gaps remain. Many previous studies have evaluated heterogeneous surgical populations, including multilevel procedures or instrumented operations, limiting procedure-specific interpretation [2,6]. Furthermore, much of the existing literature has focused on mid- or long-term outcomes, while determinants of severe pain within the first 24 hours have received comparatively less attention. Data specifically addressing early severe postoperative pain in patients undergoing elective single-level lumbar discectomy therefore remain limited.

Accordingly, the present study was designed to evaluate perioperative factors associated with severe early postoperative pain following elective single-level lumbar discectomy.

2. Materials and Methods

2.1. Study design and ethical approval

This retrospective cohort study was conducted at a tertiary care center after approval was obtained from the İstinye University Human Research Ethics Committee (Approval Number: 2026/11; Date: 09.01.2026). Due to the retrospective nature of the study and the use of anonymized patient data, the requirement for written informed consent was waived.

2.2. Study population

Adult patients ($\geqslant$18 years) who underwent elective single-level lumbar microdiscectomy under general anesthesia were eligible for inclusion. All procedures were performed using a standard open midline posterior approach.Patients were identified through the hospital electronic medical record system. Only primary procedures were included.

Patients were excluded if they underwent multilevel surgery, procedures involving fusion or instrumentation, emergency operations, revision surgery, postoperative intensive care unit admission, early reoperation, or had missing postoperative pain documentation within the first 24 hours.

2.3. Data collection

Demographic and perioperative data were retrospectively extracted from electronic medical records. Collected variables included age, sex, body mass index, ASA physical status, operated disc level, and operative duration.

Perioperative analgesic variables included intraoperative opioid administration (expressed as fentanyl equivalents), use of multimodal analgesia, requirement for rescue opioid analgesia in the post-anesthesia care unit (PACU), and postoperative patient-controlled analgesia use. Intraoperative analgesia was provided using fentanyl and remifentanil, with cumulative opioid exposure standardized by conversion to fentanyl equivalents. Multimodal analgesia was based on the routine postoperative analgesic protocol of the neurosurgery clinic and consisted of scheduled paracetamol administered every 8 hours during the first 24 hours after surgery. Intravenous tramadol was administered as rescue analgesia when clinically indicated based on postoperative pain assessment.

Postoperative pain intensity was routinely assessed and documented by nursing staff using a standard numeric rating scale (NRS; 0–10) as part of usual postoperative care. All pain scores recorded within the first 24 hours after surgery were reviewed, and the maximum NRS value during this period was used for analysis.

2.4. Outcome measures

Postoperative pain severity was categorized based on the maximum NRS score within the first 24 hours as follows:

- Mild pain: NRS 0–3
- Moderate pain: NRS 4–6
- Severe pain: NRS $\geqslant$7

For regression analyses, pain severity was dichotomized into non-severe pain (NRS 0 – 6) and severe pain (NRS $\geqslant$7).

The primary outcome of interest was the occurrence of severe early postoperative pain within the first 24 hours after surgery.

2.5. Statistical analysis

Continuous variables were assessed for normality and are presented as mean ± standard deviation or median with interquartile range, as appropriate. Categorical variables are presented as number and percentage.

Comparisons between patients with severe and non-severe postoperative pain were performed using the independent samples t-test or Mann–Whitney U test for continuous variables and the chi-square or Fisher's exact test for categorical variables, as appropriate.

Variables showing clinical relevance or a univariable association with severe postoperative pain were entered into a multivariable logistic regression model to identify factors independently associated with severe early postoperative pain. Results are reported as odds ratios with 95% confidence intervals. A two-sided p value <0.05 was considered statistically significant. Statistical analyses were performed using standard statistical software.

3. Results

During the study period, 327 adult patients underwent elective single-level lumbar discectomy. Five patients were excluded due to incomplete postoperative pain data within the first 24 hours. Accordingly, a total of 322 patients were included in the final analysis. Flowchart in Fig. 1 depicts the patient eligibility assessment, exclusions, and formation of the final study cohort. Postoperative pain severity was determined using the maximum numeric rating scale (NRS) score recorded within the first 24 hours after surgery and classified as mild (NRS 0 – 3), moderate (NRS 4 – 6), or severe (NRS ⩾7).

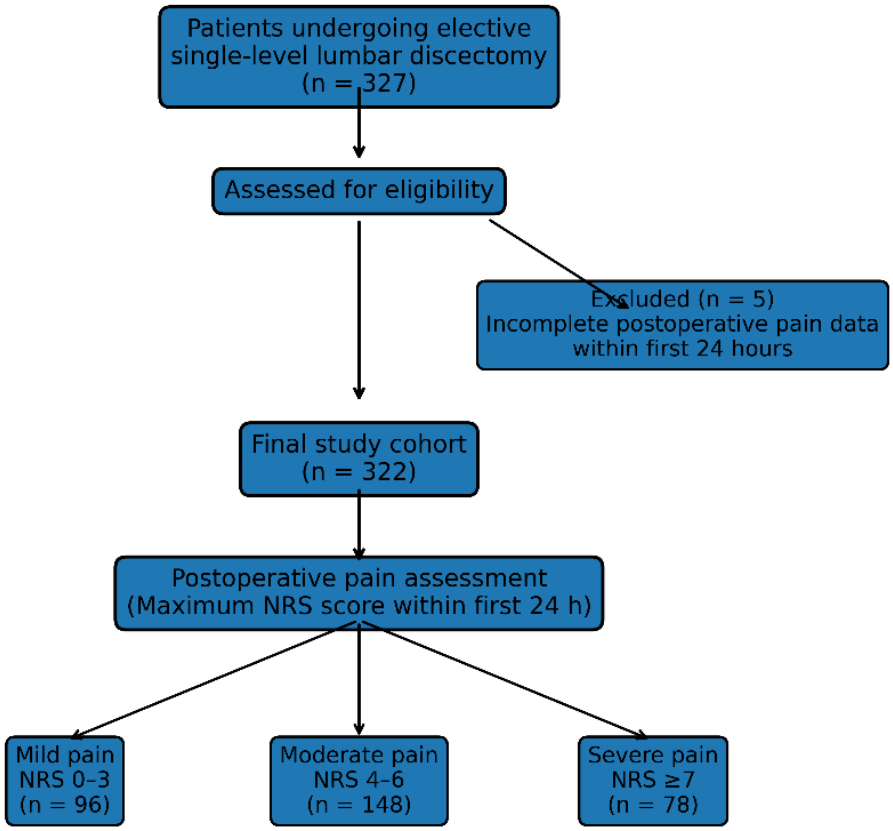


Fig. 1. Flowchart of patient selection and postoperative pain classification.

Postoperative pain severity was assessed using the maximum numeric rating scale (NRS) score recorded within the first 24 hours after surgery. Based on this value, pain severity was categorized as mild (NRS 0–3), moderate (NRS 4–6), or severe (NRS ≥7). Mild pain was observed in 96 patients (29.8%), moderate pain in 148 patients (46.0%), and severe pain in 78 patients (24.2%) (Table 1). Postoperative pain severity was classified according to the maximum numeric rating scale (NRS) score recorded within the first 24 hours after surgery. Values are presented in percentage.

Table 1. Distribution of postoperative pain severity within the first 24 hours.

Postoperative pain severity (NRS)	n	%
Mild (0–3)	96	29.8
Moderate (4–6)	148	46.0
Severe (≥7)	78	24.2

In contrast, several perioperative variables showed significant differences. Patients with severe postoperative pain had longer operative durations and received

higher amounts of intraoperative opioids. The use of multimodal analgesia was less frequent in the severe pain group. In addition, rescue opioid administration in the post-anesthesia care unit and postoperative patient-controlled analgesia use were both more common among patients with severe postoperative pain (Table 2). Values are presented as mean ± standard deviation, median [interquartile range], or percentage, as appropriate.

Table 2. Baseline and perioperative characteristics according to postoperative pain severity.

Variable	Non-severe pain (NRS 0–6) (n = 244)	Severe pain (NRS ≥7) (n = 78)	p value
Age, years	47.6 ± 11.8	49.1 ± 12.3	0.31
Male sex, n (%)	146 (59.8)	49 (62.8)	0.64
Body mass index, kg/m^2	27.1 ± 3.9	27.8 ± 4.2	0.18
ASA physical status I–II / III, n	198 / 46	58 / 20	0.07
Operated disc level (L4–5 / L5–S1), n	140 / 104	46 / 32	0.88
Operative duration, min	52 [45–62]	67 [58–78]	<0.001
Intraoperative opioid dose (fentanyl equivalents), µg	180 [140–220]	250 [210–310]	<0.001
Multimodal analgesia, n (%)	188 (77.0)	42 (53.8)	<0.001
PACU rescue opioid administration, n (%)	64 (26.2)	52 (66.7)	<0.001

ASA: American Society of Anesthesiologists; PACU: post-anesthesia care unit; PCA: patient-controlled analgesia.

In univariable logistic regression analysis, longer operative duration, higher intraoperative opioid exposure, absence of multimodal analgesia, and requirement for rescue opioid administration in the post-anesthesia care unit were significantly associated with severe early postoperative pain (Table 3). Age, sex, and body mass index were not significantly associated with pain severity.

Odds ratios (ORs) with 95% confidence intervals (CIs) are shown in Table 3. Continuous variables were scaled as indicated: operative duration per 10-minute increase and intraoperative opioid dose per 50-µg fentanyl equivalent increase. PACU denotes post-anesthesia care unit.

In the multivariable logistic regression model, longer operative duration (adjusted OR 1.38 per 10-minute increase), higher intraoperative opioid exposure (adjusted OR 1.29 per 50 µg fentanyl equivalents), absence of multimodal analgesia (adjusted OR 0.46), and requirement for rescue opioid administration in the post-anesthesia care unit (adjusted OR 3.12) remained independently associated with severe early postoperative pain. Age and body mass index were not independently associated with the outcome.

Table 3. Univariable and multivariable logistic regression analyses for severe early postoperative pain (NRS ⩾7).

Variable	Univariable OR (95% CI)	p value	Multivariable OR (95% CI)	p value
Operative duration (per 10 min)	1.42 (1.25–1.61)	<0.001	1.38 (1.18–1.62)	<0.001
Intraoperative opioid dose (per 50 µg fentanyl eq.)	1.35 (1.20–1.52)	<0.001	1.29 (1.14–1.47)	<0.001
Multimodal analgesia (yes vs no)	0.39 (0.23–0.65)	<0.001	0.46 (0.26–0.79)	0.005
PACU rescue opioid (yes vs no)	5.46 (3.18–9.37)	<0.001	3.12 (1.78–5.46)	<0.001
Age (per year)	1.02 (0.99–1.04)	0.18	1.01 (0.99–1.03)	0.34
Body mass index (per kg/m^2)	1.06 (1.00–1.12)	0.07	1.04 (0.98–1.10)	0.19
Sex (male vs female)	1.13 (0.68–1.87)	0.64	—	—

4. Discussion

In this retrospective cohort of patients undergoing elective single-level lumbar discectomy, severe postoperative pain within the first 24 hours was observed in approximately one-quarter of cases. Severe pain was associated with longer operative duration, higher intraoperative opioid exposure, lower use of multimodal analgesia, and an increased requirement for rescue opioid administration in the post-anesthesia care unit, while demographic variables were not significantly different between pain groups.

Operative duration showed a clear association with early postoperative pain severity. In spine surgery cohorts, operative time has been discussed as a proxy for tissue trauma and procedural complexity, and longer operations have been linked to increased postoperative pain and analgesic consumption [11,12]. Our findings indicate that this relationship persists even in relatively homogeneous populations undergoing single-level, non-instrumented lumbar discectomy.

Higher intraoperative opioid exposure was independently associated with severe early postoperative

pain. This observation aligns with recent perioperative literature indicating that increasing intraoperative opioid dosing does not always improve postoperative analgesia. Contemporary reviews describe opioid-induced hyperalgesia and acute opioid tolerance as clinically relevant phenomena that may contribute to increased pain during early recovery, particularly with higher opioid exposure [13–15]. Although mechanistic conclusions cannot be drawn from the present study, the observed association supports a cautious approach to escalating intraoperative opioid administration.

In contrast, multimodal analgesia was less frequently used among patients who experienced severe postoperative pain. Recent spine-specific reviews and enhanced recovery protocols emphasize the role of multimodal analgesic strategies in improving early pain control and reducing opioid consumption [16–19]. The present findings reinforce the importance of multimodal analgesia even in procedures that are often perceived as minimally invasive, such as single-level lumbar discectomy.

The requirement for rescue opioid administration in the post-anesthesia care unit was strongly associated with severe early postoperative pain. Early postoperative opioid rescue has been proposed as a marker of insufficient baseline analgesia rather than a direct cause of worse outcomes [20]. Identification of such patients in the immediate postoperative period may allow earlier optimization of analgesic strategies. However, this finding should not be interpreted as a causal relationship. The requirement for opioid rescue analgesia in the post-anesthesia care unit more likely represents a consequence and clinical marker of severe early postoperative pain, reflecting insufficient baseline analgesia rather than a contributing factor, thereby addressing the issue of potential reverse causality.

Several limitations should be acknowledged. First, preoperative pain intensity measured by numeric rating scale (NRS) and a detailed history of chronic opioid use were not consistently available in the retrospective records and therefore could not be included in the analysis. Both factors are well-established predictors of postoperative pain and their omission may have resulted in residual confounding. Consequently, the adjusted odds ratios reported in this study may partially reflect unmeasured baseline pain severity or opioid tolerance, potentially influencing the observed associations. These findings should therefore be interpreted with caution.

5. Conclusions

Severe postoperative pain within the first 24 hours remains common after elective single-level lumbar discectomy and appears to be driven mainly by perioperative factors rather than baseline patient characteristics. Longer operative duration, higher intraoperative opioid exposure, limited use of multimodal analgesia, and early requirement for rescue opioids were associated with an increased risk of severe pain. These findings highlight the importance of optimizing perioperative analgesic strategies, with an emphasis on multimodal and opioid-sparing approaches, to improve early postoperative pain control after lumbar discectomy.

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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 İstinye University Human Research Ethics Committee (Approval Number: 2026/11; Date: 09.01.2026). Due to the retrospective design, individual informed consent was not obtained; however, all patient data were anonymized prior to analysis. All methods were performed in accordance with relevant guidelines and regulations.

Author Contributions

Erkan Bayram: *conceptualization, data curation, formal analysis, investigation, methodology, supervision, validation, visualization, writing – original draft, writing – review & editing.*
Şükrü Çiftçi: *data curation, visualization, writing – original draft.*

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Challenge Journal of PERIOPERATIVE MEDICINE

Research Article

Prediction of postoperative acute kidney injury after cardiopulmonary bypass cardiac surgery: The role of preoperative inflammatory indices and intraoperative perfusion stress

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ABSTRACT

Background: Postoperative acute kidney injury is a frequent complication after cardiac surgery performed with cardiopulmonary bypass and is closely associated with increased mortality. This study aimed to evaluate the predictive value of preoperative renal function, routinely available inflammatory indices, and intraoperative perfusion stress–related parameters for the development of postoperative acute kidney injury in adult cardiac surgery.

Methods: This single-center retrospective cohort study included 455 adult patients aged 18 years or older who underwent elective or urgent coronary artery bypass grafting, valve surgery, or combined procedures with cardiopulmonary bypass between January 1, 2025 and January 1, 2026. Postoperative acute kidney injury was defined according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria by comparing the highest serum creatinine value measured within the first 72 postoperative hours with the preoperative creatinine level obtained within 48 hours before surgery. Preoperative inflammatory indices derived from routine blood tests and intraoperative perfusion-related variables were recorded. Independent predictors of acute kidney injury were identified using parsimonious multivariable logistic regression analysis, and discriminative performance was assessed by receiver operating characteristic analysis.

Results: Postoperative acute kidney injury occurred in 216 patients (47.5%), and 12.7% developed stage two or higher acute kidney injury. In-hospital mortality was significantly higher in patients with acute kidney injury compared with those without acute kidney injury (25.5% versus 6.7%), increasing progressively with advancing severity. Advanced age, higher preoperative serum creatinine, and longer cardiopulmonary bypass duration were independently associated with postoperative acute kidney injury. For stage two or higher acute kidney injury, age and cardiopulmonary bypass duration remained independent predictors. Although inflammatory indices were associated with acute kidney injury, they did not retain independent predictive value in adjusted models. Cardiopulmonary bypass duration demonstrated the strongest discriminative performance for KDIGO stage $\geqslant$2 acute kidney injury.

Conclusions: Postoperative acute kidney injury is common after cardiac surgery with cardiopulmonary bypass and is strongly associated with increased in-hospital mortality. Age, baseline renal function, and cardiopulmonary bypass duration are key determinants of postoperative acute kidney injury, highlighting intraoperative perfusion stress as a clinically relevant and potentially modifiable risk factor.

Trial Registration: The study was registered at ClinicalTrials.gov (ID: NCT05405049).

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1. Introduction

Acute kidney injury (AKI) is a common complication after cardiac surgery performed with cardiopulmonary bypass (CPB) and represents a major clinical problem that substantially influences both early postoperative morbidity and long-term prognosis. The occurrence of AKI after cardiac surgery is closely associated with increased mortality and morbidity, prolonged intensive care unit and hospital length of stay, and higher healthcare costs. In the literature, the incidence of AKI after CPB-assisted cardiac surgery has been reported to be approximately 20–30%, and both short- and long-term mortality increase significantly, particularly among patients who develop severe AKI [1, 2].

During CPB, several mechanisms—including non-pulsatile flow, hemodilution, hypothermia, systemic inflammatory response, and ischemia–reperfusion injury—may adversely affect renal blood flow and oxygen delivery, thereby triggering kidney injury [3]. However, the observation that AKI does not develop in all patients despite similar surgical and perfusion conditions suggests that individual risk profiles, preoperative renal reserve, inflammatory status, and intraoperative perfusion stress may be decisive determinants of AKI development [4]. Therefore, early identification of high-risk patients using readily available preoperative and intraoperative parameters is clinically important to guide targeted preventive strategies.

In recent years, accessible and low-cost inflammatory indices derived from routine complete blood count and basic biochemistry tests have emerged as potential biomarkers for AKI. In particular, parameters such as the neutrophil-to-lymphocyte ratio (NLR), the systemic immune-inflammation index (SII), and the C-reactive protein-to-albumin ratio have been reported to be associated with AKI after cardiac surgery, with cohort studies and systematic reviews indicating that higher values correlate with an increased risk of AKI [5, 6]. Nevertheless, much of the existing evidence evaluates these indices in isolation, whereas studies that integrate them—within the same patient cohort and within the same multivariable modeling framework—together with intraoperative markers of perfusion stress, such as CPB duration, lactate levels, and metabolic acidosis, remain limited. Yet, AKI is a multifactorial outcome arising from the interaction between preoperative susceptibility (renal reserve and an inflammatory milieu) and intraoperative triggers (perfusion stress); simultaneous assessment of these axes may strengthen clinical risk stratification.

The aim of this retrospective cohort study was to investigate the independent predictive value of preoperative indicators of renal function and inflammatory biomarkers, together with intraoperative perfusion stress–related parameters, for postoperative AKI after cardiac surgery performed with CPB. We hypothesized that incorporating preoperative inflammatory indices and renal reserve in conjunction with intraoperative markers of perfusion stress would improve the accuracy of AKI risk prediction. A key strength of the present study is the concurrent evaluation of routinely available preoperative inflammatory indices and intraoperative perfusion stress–related markers within the same cohort and within the same multivariable modeling framework. By integrating "preoperative susceptibility" and "intraoperative exposure" axes—often examined separately in prior reports—we sought to provide a more holistic and clinically applicable framework for AKI risk stratification. This approach enables a structured evaluation of interacting risk domains within a single multivariable model.

Unlike previous studies that have primarily examined inflammatory indices or intraoperative variables in isolation, the present study integrates preoperative inflammatory biomarkers, baseline renal reserve, and intraoperative perfusion stress parameters within the same multivariable framework. By simultaneously evaluating these interacting domains, this study provides a structured risk model that reflects the multifactorial pathophysiology of AKI after CPB. Moreover, the identification of CPB duration and baseline creatinine as dominant determinants, despite the presence of inflammatory signals, refines the relative weight of modifiable versus non-modifiable risk components in perioperative risk stratification.

2. Materials and Methods

2.1. Study design, setting, and ethical approval

This single-center retrospective cohort study was conducted at a tertiary-care university hospital between January 1, 2025 and January 1, 2026. Institutional Ethics Committee approval was obtained (approval number: B.30.2.ATA.0.01.00/932). The study was registered at ClinicalTrials.gov (ID: NCT05405049) for transparency purposes in the context of a retrospective observational design. The study was performed in accordance with the principles of the Declaration of Helsinki. Due to the retrospective nature of the study and the use of anonymized data, informed consent was waived. The study period was defined a priori as January 1, 2025 to January 1, 2026, and the cohort was assembled by consecutive case identification from the institutional electronic records.

2.2. Patient population and eligibility criteria

Adult patients (≥18 years) who underwent elective or urgent cardiac surgery with cardiopulmonary bypass (CPB) between January 1, 2025 and January 1, 2026 at Atatürk University Research Hospital were screened for eligibility. Eligible procedures included coronary artery bypass grafting, valve surgery, or combined coronary and valve operations performed under CPB. Both elective and emergency surgical cases performed under CPB during the study period were included in order to reflect routine clinical practice.

Patients were consecutively identified from institutional electronic surgical records to minimize selection bias.

The following exclusion criteria were applied a priori:

1. Preoperative end-stage renal disease requiring chronic dialysis,
2. Preoperative serum creatinine >4.0 mg/dL (to avoid inclusion of advanced renal failure cases that may confound AKI adjudication),
3. Off-pump cardiac surgery,

4. Congenital or non-standard cardiac procedures (e.g., atrial septal defect repair, surgery for intracardiac mass or thrombus),
5. Emergency cardiac trauma surgery,
6. Missing preoperative or postoperative serum creatinine measurements.

2.3. Data sources and data collection

Data were retrospectively obtained from the hospital information management system, anesthesia records, and the laboratory information system. Detailed intraoperative ultrafiltration practices and perioperative diuretic administration (including dose and duration), as well as renal replacement therapy parameters, were not uniformly accessible through the electronic database and were therefore not incorporated into the analysis. Detailed intraoperative hemodynamic variables (e.g., continuous mean arterial pressure, cardiac output, pump flow targets) and vasoactive/inotropic drug doses and duration were not uniformly accessible in the electronic database and were therefore not included in the analysis. The following variables were recorded for each patient:

Demographic and clinical data: age, sex, body mass index, type of surgery (coronary artery bypass grafting, valve surgery, or combined procedures), and surgical status (elective or urgent).

Preoperative laboratory parameters: renal function indices (serum creatinine and blood urea nitrogen), metabolic parameters (fasting glucose and glycated hemoglobin), inflammatory and nutritional markers (C-reactive protein and albumin), complete blood count variables (white blood cell count, neutrophil, lymphocyte, monocyte counts, hemoglobin, hematocrit, red cell distribution width, and platelet count), and coagulation profile (international normalized ratio). The preoperative serum creatinine value was defined as the measurement obtained within the last 48 hours before surgery. Derived inflammatory indices were calculated as follows: neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, systemic immune-inflammation index (neutrophil × platelet / lymphocyte), and the C-reactive protein-to-albumin ratio.

Preoperative echocardiography: left ventricular ejection fraction was recorded.

Intraoperative perfusion and cardiopulmonary bypass variables: During CPB, temperature management followed a standardized institutional protocol. Mild systemic hypothermia (target core temperature approximately 32–34°C) was routinely applied. Deep hypothermia and circulatory arrest techniques were not performed in any patient during the study period; therefore, no circulatory arrest cases were included in this cohort. Rewarming was performed in a controlled manner before separation from CPB. All cardiopulmonary bypass procedures were performed using a standardized institutional protocol. A conventional roller pump system was used in all cases, and non-pulsatile flow was applied throughout CPB. Membrane oxygenators without direct blood–gas interface were used uniformly. During the study period, two identical CPB machines with the same technical specifications were available in the operating rooms, and no variation in pump technology or flow mode occurred across cases. Cardiopulmonary bypass duration, aortic cross-clamp time, highest intraoperative lactate level, lowest intraoperative pH value, and minimum intraoperative hemoglobin and hematocrit values were recorded. To summarize the degree of hemodilution, the changes in hemoglobin (Δhemoglobin = preoperative hemoglobin − minimum intraoperative hemoglobin) and hematocrit (Δhematocrit = preoperative hematocrit − minimum intraoperative hematocrit) were calculated. In this study, the concept of "perfusion stress" was used as a conceptual framework and was represented by parameters including cardiopulmonary bypass duration, lactate levels, pH, and minimum intraoperative hemoglobin and hematocrit values.

2.4. Outcomes and definitions

Primary outcome: Postoperative AKI was diagnosed according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria based on changes in serum creatinine [7]. Urine output criteria were not evaluated due to limitations inherent to retrospective data collection. Baseline creatinine was defined as the last measurement obtained within 48 hours prior to surgery.

In our institution, serum creatinine is routinely measured at 12-hour intervals during the first 72 postoperative hours (six measurements in total). For AKI assessment, the highest value recorded within this 72-hour window was defined as the "postoperative peak creatinine," and KDIGO staging was determined by comparison with the preoperative baseline value.

In cases where one of the scheduled postoperative measurements was missing, patients were not excluded; AKI classification was based on the highest available creatinine value within the 72-hour period. No patient was excluded due to incomplete postoperative creatinine surveillance.

All preoperative laboratory variables required for inflammatory index calculation were available for the entire cohort.

KDIGO staging (serum creatinine criteria):

- Stage 1: increase in serum creatinine ≥0.3 mg/dL or 1.5–1.9 times baseline
- Stage 2: increase in serum creatinine 2.0–2.9 times baseline
- Stage 3: increase in serum creatinine ≥3 times baseline or ≥4.0 mg/dL

Secondary outcomes: Secondary outcomes were AKI stage and in-hospital mortality.

2.5. Statistical analysis

All analyses were performed using SPSS (IBM Corp., Armonk, NY) statistical software. The distribution of continuous variables was assessed using the Kolmogorov–Smirnov test and visual inspection methods. Normally distributed variables are presented as mean ± standard deviation, whereas non-normally distributed variables are reported as median with interquartile range. Comparisons between two groups were conducted using the Student's t-test or the Mann–Whitney

U test, as appropriate. Categorical variables were compared using the chi-square test or Fisher's exact test when expected cell counts were low.

To identify independent predictors associated with the development of postoperative AKI, multivariable logistic regression analysis was performed. A purposeful selection strategy was applied to obtain parsimonious models: clinically relevant variables and those associated with the outcome at $p < 0.10$ in univariable analyses were considered, and variables that did not materially improve model fit or that showed instability due to collinearity were not retained. Model calibration was evaluated using the Hosmer–Lemeshow test, and discrimination was quantified by the area under the ROC curve. Type of surgery (isolated CABG, isolated valve surgery, or combined procedures) was evaluated as a potential confounder in exploratory multivariable analyses to account for procedural heterogeneity. Surgical status (elective vs. emergency) was also evaluated as a potential confounder in exploratory analyses to assess its independent association with postoperative AKI. To reduce the risk of overfitting, model construction accounted for an events-per-variable ratio of at least 10. The potential for multicollinearity was assessed based on clinical judgment and statistical considerations, and results are reported as odds ratios with 95% confidence intervals. Discriminative performance was evaluated using receiver operating characteristic curve analysis; the area under the curve, sensitivity, specificity, and optimal cutoff value (based on the Youden index) were calculated. A two-sided p value <0.05 was considered statistically significant.

2.6. Sample size

Sample size planning was based on the expected incidence of AKI (20–30%) and the number of variables to be evaluated in logistic regression models. Given the observed AKI incidence and the number of events in the final cohort, the events-per-variable ratio remained ≥10, supporting model stability.

3. Results

During 2025, a total of 1187 patients underwent cardiac surgery at our institution. Of these, 701 patients were excluded because cardiopulmonary bypass was not used, and 486 patients who underwent surgery with cardiopulmonary bypass were initially evaluated. After excluding patients with a preoperative requirement for dialysis (n = 21), those operated on for intracardiac mass or thrombus (n = 3), patients who underwent atrial septal defect repair (n = 5), and those who underwent surgery for emergency cardiac trauma (n = 2), the final analytical cohort consisted of 455 patients (Fig. 1). According to the Kidney Disease Improving Global Outcomes criteria, postoperative acute kidney injury developed in 216 patients (47.5%), whereas 239 patients (52.5%) did not develop acute kidney injury.

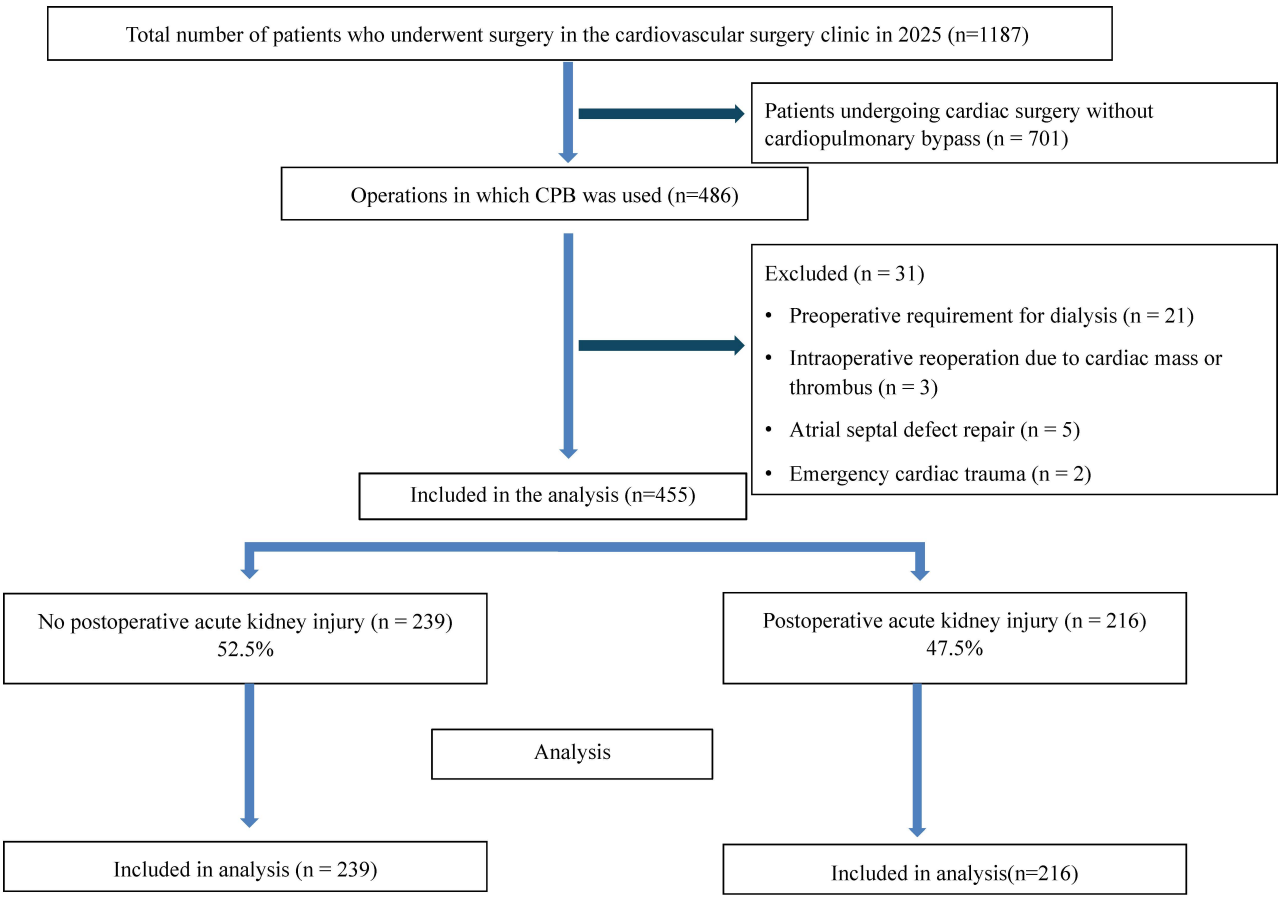


Fig. 1. Flowchart illustrating patient selection and distribution of the study cohort according to postoperative acute kidney injury status (CPB, cardiopulmonary bypass; ASD, atrial septal defect; AKI, acute kidney injury).

Postoperative AKI developed in 216 of 455 patients (47.5%). Patients who developed AKI were older than those without AKI [62.5 (55–70) vs. 59.0 (50–65), p < 0.001]. No significant differences were observed between the groups with respect to sex distribution, body mass index, or preoperative ejection fraction (p = 0.906, p = 0.430, and p = 0.095, respectively). The distribution of surgical type and surgical status was also similar between patients with and without AKI (p = 0.210 and p = 0.117, respectively) (Table 1). When surgical status (elective vs. emergency) was entered into exploratory multivariable models, it was not independently associated with postoperative AKI and did not materially alter the effect estimates of age, baseline creatinine, or CPB duration.

Table 1. Demographic and surgical characteristics of the patients according to acute kidney injury status.

Variable	No AKI (n = 239)	AKI (n = 216)	p value
Age (years)	59.0 (50–65)	62.5 (55–70)	<0.001
Sex, n (%)			0.906
• Male	176 (73.6)	158 (73.1)	
• Female	63 (26.4)	58 (26.9)	
BMI (kg/m^2)	27.4 (24.7–30.1)	27.8 (24.8–31.1)	0.430
Type of surgery, n (%)			0.210
• Isolated CABG	159 (66.5)	131 (60.6)	
• Isolated valve	46 (19.2)	41 (19.0)	
• Combined group surgery	34 (14.2)	44 (20.4)	
Surgical status, n (%)			0.117
• Elective surgery	226 (94.6)	196 (90.7)	
• Emergency surgery	13 (5.4)	20 (9.3)	
Preoperative EF (%)	55 (50–55)	55 (50–55)	0.095

Data are presented as median (interquartile range) or number (percentage). Continuous variables were compared using the Mann–Whitney U test, and categorical variables were compared using the Pearson chi-square test. A p value < 0.05 was considered statistically significant.

Abbreviations: AKI, acute kidney injury; BMI, body mass index; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; EF, ejection fraction. Isolated CABG refers to coronary artery bypass grafting performed with cardiopulmonary bypass without concomitant valve replacement or repair. Isolated valve surgery includes cases undergoing aortic or mitral valve replacement or repair. The combined group includes patients who underwent CABG together with valve replacement or repair during the same operative session.

Preoperative lymphocyte count was lower in patients who developed AKI [1.80 (1.33–2.46) vs. 2.03 (1.50–2.51) ×10^3/μL; p = 0.016]. With respect to inflammatory markers, the AKI group had higher RDW [13.5 (13.0–14.2) vs. 13.1 (12.7–14.0)%; p = 0.009], NLR [2.58 (1.82–4.66) vs. 2.44 (1.72–3.59); p = 0.037], CRP [5.0 (2.4–18.1) vs. 3.7 (2.0–10.9) mg/L; p = 0.018], and CRP/albumin ratio [1.25 (0.59–5.00) vs. 0.88 (0.50–2.81); p = 0.012], whereas albumin levels were lower [4.0 (3.6–4.2) vs. 4.0 (3.8–4.3) g/dL; p = 0.005]. As indicators of renal reserve, serum creatinine [0.93 (0.75–1.13) vs. 0.83 (0.69–1.02) mg/dL; p < 0.001] and BUN [19.0 (15.0–24.5) vs. 16.8 (13.6–22.1) mg/dL; p = 0.002] were significantly higher in the AKI group. No significant differences were observed between groups for other hematological parameters, glucose, HbA1c, or INR (Table 2).

Patients who developed AKI had significantly longer intraoperative perfusion times; CPB duration [112 (89–152) vs. 101 (80–128) min; p < 0.001] and aortic cross-clamp time [60 (45–88) vs. 55 (39–79) min; p = 0.016] were higher compared with patients without AKI. With respect to hemodilution parameters, the AKI group had lower minimum intraoperative hemoglobin [7.3 (6.3–8.1) vs. 7.6 (6.8–8.4) g/dL; p = 0.002] and minimum hematocrit values [22.5 (19.9–24.9) vs. 23.8 (21.0–26.0)%; p = 0.003]. Maximum intraoperative lactate levels showed a trend toward higher values in the AKI group [2.6 (1.8–3.6) vs. 2.4 (1.7–3.0) mmol/L; p = 0.054], whereas no significant differences were observed between groups with respect to minimum intraoperative pH or ΔHb and ΔHct values (Table 3).

Postoperative AKI occurred in 216 of 455 patients (47.5%), of whom 58 (12.7%) were classified as KDIGO stage ≥2 (stages 2–3) (Table 4). Among patients with AKI, the distribution of KDIGO stages was as follows: stage 1, 158/216 (73.1%); stage 2, 43/216 (19.9%); and stage 3, 15/216 (6.9%). In-hospital mortality was significantly higher in patients who developed AKI compared with those who did not (55/216, 25.5% vs. 16/239, 6.7%; p < 0.001). Moreover, mortality increased markedly with increasing AKI severity; in-hospital mortality was 12.7% (20/158) in stage 1, 51.2% (22/43) in stage 2, and 86.7% (13/15) in stage 3 (Table 4).

In the parsimonious multivariable logistic regression model, age, preoperative serum creatinine, and CPB duration were independently associated with postoperative AKI. Each 1-year increase in age was associated with an approximately 3% increase in the odds of AKI (OR 1.03; 95% CI 1.01–1.05; p < 0.001). Each 0.1 mg/dL increase in preoperative creatinine was associated with a 6% higher odds of AKI (OR 1.06; 95% CI 1.01–1.11; p =

0.011). Each 10-minute increase in CPB duration was associated with an approximately 4% increase in the odds of AKI (OR 1.04; 95% CI 1.00–1.08; p = 0.048). Although NLR and minimum intraoperative hemoglobin showed an association with AKI in univariable analyses, neither remained an independent predictor in the multivariable model (p = 0.703 and p = 0.102, respectively). The model demonstrated moderate discriminative performance (AUC = 0.672) with acceptable calibration (Hosmer–Lemeshow p = 0.101) (Table 5). When type of surgery was entered into exploratory multivariable models, it was not independently associated with postoperative AKI and did not materially alter the effect estimates of CPB duration or baseline creatinine.

Table 2. Preoperative laboratory parameters and inflammatory indices according to acute kidney injury status.

Variable	No AKI (n = 239)	AKI (n = 216)	p value
WBC (×10³/μL)	8.10 (6.49–9.88)	8.20 (6.65–10.00)	0.737
Neutrophil (×10³/μL)	5.14 (3.79–6.69)	5.37 (4.00–6.97)	0.300
Lymphocyte (×10³/μL)	2.03 (1.50–2.51)	1.80 (1.33–2.46)	0.016
Monocyte (×10³/μL)	0.59 (0.45–0.72)	0.58 (0.44–0.75)	0.899
Hemoglobin (g/dL)	13.9 (12.2–15.0)	13.3 (12.0–15.0)	0.341
Hematocrit (%)	41.2 (37.0–45.0)	40.1 (36.1–44.0)	0.278
RDW (%)	13.1 (12.7–14.0)	13.5 (13.0–14.2)	0.009
Platelet (×10³/μL)	229 (192–287)	230 (186–276)	0.593
NLR	2.44 (1.72–3.59)	2.58 (1.82–4.66)	0.037
PLR	115.4 (87.0–162.5)	125.6 (87.4–173.4)	0.096
LMR	3.70 (2.58–4.78)	3.26 (2.11–4.40)	0.024
SII	556 (380–904)	622 (402–1167)	0.108
CRP (mg/L)	3.7 (2.0–10.9)	5.0 (2.4–18.1)	0.018
Albumin (g/dL)	4.0 (3.8–4.3)	4.0 (3.6–4.2)	0.005
CRP/Albumin ratio	0.88 (0.50–2.81)	1.25 (0.59–5.00)	0.012
Creatinine (mg/dL)	0.83 (0.69–1.02)	0.93 (0.75–1.13)	<0.001
BUN (mg/dL)	16.8 (13.6–22.1)	19.0 (15.0–24.5)	0.002
Glucose (mg/dL)	106 (91–144)	112 (90–150)	0.446
HbA1c (%)	5.8 (5.5–6.7)	6.0 (5.6–7.2)	0.125
INR	1.04 (0.96–1.15)	1.04 (0.97–1.15)	0.572

Data are presented as median (interquartile range). Groups were compared using the Mann–Whitney U test (two-sided). A p value < 0.05 was considered statistically significant. SII = neutrophil × platelet / lymphocyte; NLR = neutrophil/lymphocyte; PLR = platelet/lymphocyte; LMR = lymphocyte/monocyte.

Abbreviations: AKI, acute kidney injury; WBC, white blood cell count; RDW, red cell distribution width; CRP, C-reactive protein; INR, international normalized ratio; BUN, blood urea nitrogen.

Table 3. Intraoperative perfusion and hemodilution parameters according to AKI status.

Variable	No AKI (n = 239)	AKI (n = 216)	p value
CPB duration (min)	101 (80–128)	112 (89–152)	<0.001
Aortic cross-clamp time (min)	55 (39–79)	60 (45–88)	0.016
Minimum intraoperative pH	7.34 (7.30–7.37)	7.34 (7.29–7.37)	0.903
Maximum intraoperative lactate (mmol/L)	2.4 (1.7–3.0)	2.6 (1.8–3.6)	0.054
Minimum intraoperative Hb (g/dL)	7.6 (6.8–8.4)	7.3 (6.3–8.1)	0.002
Minimum intraoperative Hct (%)	23.8 (21.0–26.0)	22.5 (19.9–24.9)	0.003
ΔHb (g/dL)	6.0 (4.9–7.1)	6.2 (5.0–7.2)	0.328
ΔHct (%)	17.0 (13.4–20.4)	17.9 (13.7–20.8)	0.253

Data are presented as median (interquartile range). Groups were compared using the Mann–Whitney U test (two-sided). A p value < 0.05 was considered statistically significant. ΔHb = preoperative Hb − minimum intraoperative Hb; ΔHct = preoperative Hct − minimum intraoperative Hct.

Abbreviations: AKI, acute kidney injury; CPB, cardiopulmonary bypass; Hb, hemoglobin; Hct, hematocrit.

Table 4. Incidence of postoperative AKI, KDIGO stages, and in-hospital mortality.

Outcome	Total (N = 455)	No AKI (n = 239)	AKI (n = 216)	p value
AKI, n (%)	216 (47.5)	0 (0)	216 (100)	NA
AKI stage ≥2, n (%)	58 (12.7)	0 (0)	58 (26.9)	NA
AKI stage (among AKI patients only), n (%)				NA
• Stage 1	—	—	158 (73.1)	
• Stage 2	—	—	43 (19.9)	
• Stage 3	—	—	15 (6.9)	
In-hospital mortality, n (%)	71 (15.6)	16 (6.7)	55 (25.5)	<0.001
In-hospital mortality by AKI stage (among AKI patients only)				NA
• Stage 1	—	—	20/158 (12.7)	
• Stage 2	—	—	22/43 (51.2)	
• Stage 3	—	—	13/15 (86.7)	

Data are presented as n (%). In-hospital mortality was compared between the AKI and no AKI groups using the Pearson chi-square test (Fisher's exact test was used when expected cell counts were <5). A p value < 0.05 was considered statistically significant. AKI stages were classified according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria.

Abbreviations: AKI, acute kidney injury; KDIGO, Kidney Disease: Improving Global Outcomes; NA: Not applicable.

Table 5. Parsimonious logistic regression model for postoperative acute kidney injury (KDIGO) (N = 455).

Variable (scale)	Univariable OR (95% CI)	p value	Multivariable OR (95% CI)	p value
Age (per 1 year)	1.03 (1.02–1.05)	<0.001	1.03 (1.01–1.05)	<0.001
Preoperative creatinine (per 0.1 mg/dL)	1.07 (1.02–1.12)	0.004	1.06 (1.01–1.11)	0.011
CPB duration (per 10 min)	1.05 (1.02–1.09)	0.004	1.04 (1.00–1.08)	0.048
NLR (per 1 unit)	1.05 (1.00–1.10)	0.070	1.01 (0.96–1.06)	0.703
Intraoperative minimum hemoglobin (per 1 g/dL)	0.83 (0.72–0.95)	0.006	0.89 (0.77–1.02)	0.102

Odds ratios (ORs) with 95% confidence intervals (CIs) are reported. Continuous variables were scaled for clinical interpretability (creatinine per 0.1 mg/dL; CPB duration per 10 min). The multivariable model was constructed in a parsimonious manner based on clinical relevance and univariable screening. Model discrimination was moderate (AUC = 0.672), and calibration was acceptable (Hosmer–Lemeshow $\chi^2 = 13.34$, df = 8; p = 0.101).

Abbreviations: AKI, acute kidney injury; KDIGO, Kidney Disease: Improving Global Outcomes; CPB, cardiopulmonary bypass; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; CI, confidence interval; AUC, area under the curve.

In ROC analysis for the prediction of KDIGO stage ≥2 AKI, CPB duration demonstrated the highest discriminative ability (AUC 0.672; 95% CI 0.599–0.746; p < 0.001). Using the Youden index, an optimal cut-off of ≥123 minutes yielded a sensitivity of 60.3% and a specificity of 68.8% (Table 6). NLR (AUC 0.587; p = 0.045) and preoperative creatinine (AUC 0.584; p = 0.046) showed more limited discriminative performance; however, for NLR, a cut-off of ≥5.28 was characterized by low sensitivity but high specificity (86.9%), suggesting a predominantly "rule-in" rather than screening utility.

In the multivariable parsimonious logistic regression analysis for the KDIGO stage ≥2 AKI (stages 2–3) outcome, age (OR 1.03 per year; 95% CI 1.00–1.06; p = 0.039) and CPB duration (OR 1.07 per 10 minutes; 95% CI 1.02–1.12; p = 0.002) were identified as independent predictors (Table 7). Although NLR and minimum intraoperative hemoglobin were associated with the outcome in univariable analyses, neither retained independent significance in the multivariable model. The model demonstrated moderate discriminative performance (AUC = 0.698) and good calibration (Hosmer–Lemeshow p = 0.681).

Table 6. Receiver operating characteristic (ROC) analysis for prediction of KDIGO stage ⩾2 acute kidney injury (stages 2–3) (N = 455).

Parameter	AUC (95% CI)	p value	Optimal cut-off (Youden)	Sensitivity (%)	Specificity (%)
NLR	0.587 (0.502–0.672)	0.045	≥ 5.28	34.5	86.9
Preoperative creatinine (mg/dL)	0.584 (0.501–0.667)	0.046	≥ 0.94	58.6	60.5
CPB duration (min)	0.672 (0.599–0.746)	<0.001	≥ 123	60.3	68.8

The 95% confidence intervals for AUC were calculated using the DeLong method. Optimal cut-off values were determined by the Youden index (sensitivity + specificity − 1). For all ROC analyses, higher values were assumed to be associated with a higher risk of the outcome.

Abbreviations: AUC, area under the curve; CI, confidence interval; AKI, acute kidney injury; KDIGO, Kidney Disease: Improving Global Outcomes; NLR, neutrophil-to-lymphocyte ratio; CPB, cardiopulmonary bypass.

Table 7. Parsimonious logistic regression model for prediction of KDIGO stage ⩾2 acute kidney injury (stages 2–3) (N = 455).

Variable (scale)	Univariable OR (95% CI)	p value	Multivariable OR (95% CI)	p value
Age (per 1 year)	1.03 (1.01–1.06)	0.012	1.03 (1.00–1.06)	0.039
Preoperative creatinine (per 0.1 mg/dL)	1.02 (0.97–1.08)	0.438	0.99 (0.93–1.06)	0.802
CPB duration (per 10 min)	1.08 (1.04–1.13)	<0.001	1.07 (1.02–1.12)	0.002
NLR (per 1 unit)	1.07 (1.01–1.13)	0.027	1.03 (0.97–1.10)	0.276
Intraoperative minimum hb (per 1 g/dL)	0.80 (0.65–0.98)	0.035	0.91 (0.73–1.12)	0.370

Odds ratios (ORs) with 95% confidence intervals (CIs) are reported. Continuous variables were scaled for clinical interpretability (creatinine per 0.1 mg/dL; CPB duration per 10 min). The parsimonious multivariable model was constructed from clinically relevant variables and/or those with $p < 0.10$ in univariable analyses. Model performance showed good discrimination (AUC = 0.698) and excellent calibration (Hosmer–Lemeshow $\chi^2 = 5.70$, df = 8; p = 0.681).

Abbreviations: AKI, acute kidney injury; KDIGO, Kidney Disease: Improving Global Outcomes; CPB, cardiopulmonary bypass; Hb, hemoglobin; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; CI, confidence interval; AUC, area under the curve.

4. Discussion

In this single-center retrospective cohort study, the incidence of postoperative AKI after adult cardiac surgery performed with CPB was 47.5%, and in-hospital mortality increased markedly with increasing AKI severity. The reported incidence of AKI after cardiac surgery varies widely in the literature (approximately 5%–40%, depending on the definition used, patient case-mix, surgical procedure, and surveillance strategy), and the AKI definition and the frequency of creatinine measurements are among the primary drivers of this variability [8, 9]. In this context, the routine measurement of postoperative creatinine every 12 hours in our institution and the use of the highest creatinine value within the first 72 postoperative hours as the "peak creatinine" may have increased the sensitivity for AKI detection. Accordingly, comparisons of AKI incidence across studies should account for both the operational definition and surveillance intensity, as higher-frequency creatinine sampling tends to preferentially increase detection of KDIGO stage 1 events. This methodological nuance may partly explain why our observed AKI rate appears higher than rates reported in cohorts with less frequent postoperative creatinine monitoring. The KDIGO criteria are based on changes in serum creatinine (an increase of ≥0.3 mg/dL within 48 hours or ≥1.5-fold within 7 days), and more frequent measurement strategies may particularly increase the detection of stage 1 AKI [10]. Consistent with this, the predominance of stage 1 AKI in our cohort (73.1%) aligns with the hypothesis that our surveillance strategy enhanced the likelihood of capturing early or mild creatinine changes. The relatively high incidence of AKI observed in our cohort further underscores the clinical relevance of systematic surveillance and risk stratification in CPB-assisted cardiac surgery.

In our study, the mortality rate was approximately fourfold higher in patients who developed AKI compared with those without AKI (25.5% vs. 6.7%), and mortality increased dramatically with advancing KDIGO stage (stage 1: 12.7%, stage 2: 51.2%, stage 3: 86.7%). These findings support the concept that AKI is not merely a biochemical abnormality, but rather a clinically meaningful outcome that strongly determines prognosis within the spectrum of perioperative multiorgan dysfunction. A graded association between increasing KDIGO stage and mortality has been consistently demonstrated in previous cardiac surgery cohorts, with stage 2–3 AKI showing a particularly strong relationship with short-term mortality [11]. Accordingly, the observed incidence of clinically relevant KDIGO stage ≥2 AKI of 12.7% in our cohort indicates a substantial burden of severe AKI and underscores the need for targeted risk mitigation strategies.

In parsimonious multivariable models, age, preoperative serum creatinine, and CPB duration were independently associated with postoperative AKI. This triad reflects the fundamental components of AKI pathophysiology in cardiac surgery, namely a "susceptible substrate plus intraoperative triggers/exposure": advanced age and elevated baseline creatinine indicate limited renal reserve, whereas prolonged CPB duration increases the exposure dose to injurious mechanisms such as nonpulsatile flow, hemodilution, systemic inflammatory response, and ischemia–reperfusion injury [9]. From a clinical perspective, the modifiable nature of CPB duration is of particular importance. The association between prolonged CPB duration and increased AKI risk has been consistently reported in large-scale analyses and meta-analyses, with longer CPB times conferring a higher risk of AKI across different types of cardiac surgery [12]. In our study, the persistence of age and CPB duration as independent predictors in the model for KDIGO stage ≥2 AKI further supports the concept of a cumulative "exposure dose" effect. Nevertheless, the moderate AUC values observed in ROC analyses (AUC = 0.672 for any AKI and AUC = 0.698 for stage ≥2 AKI) indicate that risk stratification based on a single parameter is inherently limited and highlight the need for multidimensional, externally validated risk models, ideally incorporating biomarker data. Accordingly, CPB duration should not be regarded as a standalone decision-making threshold, but rather as a variable that meaningfully contributes to perioperative risk stratification when interpreted in conjunction with other clinical factors. Although procedural heterogeneity may theoretically influence AKI risk, type of surgery per se was not independently associated with AKI in our cohort, suggesting that perfusion-related exposure variables may be more

influential than surgical category. Similarly, although emergency surgical status may theoretically confer additional risk due to recent contrast exposure or hemodynamic instability, surgical status was not independently associated with AKI in adjusted analyses in our cohort. Importantly, CPB flow mode and pump technology were standardized across the cohort (non-pulsatile roller pump with membrane oxygenator), thereby minimizing potential confounding related to perfusion modality. Importantly, temperature management was standardized (mild hypothermia protocol without circulatory arrest), thereby reducing potential variability related to intraoperative thermal strategies.

With respect to preoperative inflammatory indices, higher NLR, CRP, CRP-to-albumin ratio, and RDW values, together with lower albumin and lymphocyte levels in patients who developed AKI, support an association between AKI development and an underlying state of inflammatory–metabolic vulnerability. These findings are consistent with the existing literature: systematic reviews and meta-analyses evaluating perioperative NLR have reported that elevated NLR may be associated with an increased risk of AKI after cardiac surgery [5,13]. Similarly, RDW—reflecting inflammation, oxidative stress, and disturbed erythrocyte homeostasis—has been linked to adverse renal outcomes in cardiac surgical populations [14]. In addition, the CRP-to-albumin ratio has gained increasing attention as a composite index capturing both inflammatory burden and nutritional/catabolic status, with studies suggesting its potential value in predicting postoperative complications and AKI after coronary artery bypass grafting [15]. However, the loss of independent significance of NLR and RDW in our multivariable models suggests that these inflammatory indices may partly reflect AKI risk through their association with baseline renal reserve and intraoperative exposure, particularly CPB duration. This pattern is biologically plausible: preoperative inflammatory indices may capture a systemic vulnerability phenotype, whereas the development of AKI after CPB is ultimately driven by the interaction between susceptibility and intraoperative exposure dose (e.g., duration and intensity of perfusion-related stress). Therefore, once dominant exposure variables such as CPB duration and baseline renal function are incorporated into the same model, the incremental independent contribution of inflammatory indices may attenuate, despite their clear unadjusted associations. In other words, while inflammatory indices may identify a "high-risk phenotype," their incremental contribution to clinical decision-making in this cohort was limited once dominant clinical determinants were included in the model. Notably, in ROC analysis for KDIGO stage ≥2 AKI, NLR demonstrated low sensitivity but high specificity, indicating that NLR may serve as a potential rule-in signal in selected subgroups, rather than as a standalone screening tool [5]. This finding is particularly relevant in light of previous studies that have reported independent associations between inflammatory indices and AKI after CPB; our results suggest that when baseline renal reserve and intraoperative exposure intensity are simultaneously accounted for, the incremental predictive value of isolated inflammatory markers may diminish.

The association between intraoperative hemodilution/anemia-related parameters and AKI is also noteworthy. In our study, minimum intraoperative Hb and Hct values were lower in the AKI group; however, these variables lost borderline significance in the multivariable model. The potentially deleterious renal effects of hemodilution have been extensively discussed in the literature: low hematocrit/hemoglobin during CPB may reduce renal oxygen delivery, exacerbate medullary hypoxia, and thereby increase the risk of AKI [16, 17]. Accordingly, the impact of hemodilution may be best interpreted as a component of the broader "perfusion stress" axis, which is closely intertwined with CPB duration and perfusion dynamics. Indeed, pathophysiological studies examining the relationship between renal oxygenation and flow targets during CPB suggest that perfusion strategies may exert meaningful effects on renal oxygenation [9]. Therefore, kidney-protective perioperative management in clinical practice likely requires a multifaceted approach, including minimizing CPB duration in high-risk patients, limiting hemodilution, individualizing perfusion pressure and flow targets, closely monitoring global perfusion markers such as lactate and pH, and avoiding nephrotoxic exposures when feasible. It should be acknowledged, however, that lactate represents a downstream metabolic consequence of global hypoperfusion and does not allow precise differentiation of the underlying hemodynamic mechanism (e.g., hypotension, reduced oxygen delivery, microcirculatory dysfunction). Therefore, the concept of "perfusion stress" in this study should be interpreted as a composite surrogate framework rather than a direct measurement of intraoperative hemodynamic instability. It should also be noted that intraoperative ultrafiltration strategies and perioperative diuretic administration may influence fluid balance and renal function. Because these variables were not systematically available in the electronic dataset, their potential contribution to AKI risk could not be evaluated in this study.

An important contribution of this study is the simultaneous integration of routinely available preoperative inflammatory indices with intraoperative perfusion stress markers in a single multivariable framework. This design reflects the multifactorial nature of AKI after CPB and provides a practical structure for perioperative risk phenotyping using variables readily accessible in routine care.

4.1. Clinical implications

The present findings have several practical implications. First, the integration of baseline renal function and intraoperative perfusion-related variables into a unified predictive framework supports the importance of combined preoperative risk assessment and intraoperative optimization strategies in reducing postoperative AKI risk. Patients identified as high-risk based on elevated baseline creatinine or anticipated prolonged CPB duration may benefit from intensified renal-protective strategies, including strict hemodynamic optimization, avoidance of nephrotoxic agents, careful fluid balance management, and closer postoperative surveillance.

Second, although preoperative inflammatory indices did not retain independent significance in multivariable models, their univariable association with AKI suggests that they may serve as early markers of systemic vulnerability. In routine practice, these inexpensive and readily available laboratory parameters may assist in preliminary risk stratification before surgery.

Finally, the findings emphasize that AKI after CPB is driven by the interaction between patient susceptibility and intraoperative exposure. Therefore, perioperative teams should adopt a multimodal prevention strategy rather than focusing on a single risk domain.

Taken together, these findings clarify the relative contribution of inflammatory burden versus intraoperative exposure in AKI development and position CPB duration within a clinically actionable risk framework.

In conclusion, our findings indicate that postoperative AKI is closely associated not only with preoperative susceptibility but also with intraoperative perfusion stress, and that age, baseline renal function, and CPB duration represent core variables for perioperative risk stratification. Although inflammatory indices may convey a meaningful biological signal, they did not remain independent predictors in this cohort and appeared to function primarily as adjunctive markers for risk phenotyping. Given the moderate model performance and the lack of external validation, the generalizability of this approach requires multicenter prospective validation studies, ideally incorporating biomarker integration.

4.2. Limitations

This study has several important limitations. First, the single-center retrospective design precludes causal inference and carries a risk of residual confounding due to unmeasured or incompletely recorded variables. Second, the definition of AKI was based solely on serum creatinine criteria; urine output criteria could not be incorporated because of the retrospective nature of the study and limitations in available records. Third, routine measurement of serum creatinine every 12 hours in the postoperative period may have contributed to a higher detection rate of early or mild AKI, and the use of the highest creatinine value within the first 72 postoperative hours, while increasing sensitivity, may have affected clinical comparability across studies. Fourth, the lack of detailed characterization of surgical subtypes (e.g., number of bypass grafts, valve pathology, or repair versus replacement) limited a more granular assessment of procedure-specific risk. Furthermore, coronary artery bypass grafting, valve surgery, and combined procedures were analyzed together rather than through separate subgroup-specific multivariable models. Although type of surgery was evaluated as a potential confounder and was not independently associated with AKI, the absence of formal subgroup analyses may limit procedure-specific interpretation. The relatively limited number of KDIGO stage ≥2 AKI events further constrained the feasibility of stable subgroup modeling. In addition, the preoperative comorbidity burden of patients (e.g., diabetes mellitus, hypertension, chronic kidney disease, chronic obstructive pulmonary disease) could not be comprehensively reported, and residual confounding therefore cannot be fully excluded. Furthermore, detailed data regarding the timing and volume of preoperative coronary angiography and contrast exposure—particularly in emergency cases—were not uniformly available in the retrospective records and could not be incorporated into the analyses. Therefore, residual confounding related to potential contrast-associated renal injury cannot be entirely excluded. Fifth, detailed intraoperative hemodynamic data (including continuous mean arterial pressure, cardiac output, pump flow targets, and oxygen delivery indices) as well as vasoactive and inotropic drug doses and duration were not available in the electronic database and therefore could not be incorporated into the analyses. Given that vasoactive agents at certain doses may influence renal perfusion through vasoconstrictive effects, residual confounding related to unmeasured hemodynamic instability cannot be excluded. Accordingly, the "perfusion stress" construct used in this study should be interpreted as a surrogate conceptual model rather than a comprehensive hemodynamic assessment. Additionally, intraoperative ultrafiltration practices and perioperative diuretic use (including type, dose, and duration) were not retrievable from the electronic system and could not be analyzed. Given that both ultrafiltration and diuretic administration may influence renal perfusion, intravascular volume status, and serum creatinine dynamics, residual confounding related to these factors cannot be excluded. Finally, although the regression models were constructed in a parsimonious manner, external validation was not performed and model performance remained moderate; consequently, multicenter prospective validation is required to confirm the generalizability of these findings.

5. Conclusions

Postoperative AKI is common after cardiac surgery performed with CPB, and in-hospital mortality increases dramatically with escalating AKI severity. In this cohort, the independent determinants of postoperative AKI were age, preoperative creatinine, and CPB duration, whereas age and CPB duration emerged as key predictors of KDIGO stage ≥2 AKI. Although preoperative inflammatory indices appeared to be associated with AKI, they did not remain independent predictors in multivariable models. Overall, these findings support the clinical value of a risk stratification framework centered on "preoperative renal reserve plus intraoperative perfusion stress" and underscore the importance of kidney-protective strategies in high-risk patients, including minimizing CPB duration and optimizing perfusion and hemodilution targets. Prospective multicenter studies incorporating biomarker data are warranted to validate this approach. These findings reinforce the conceptual model of "susceptibility plus exposure" in cardiac surgery–associated AKI and support targeted intraoperative optimization strategies in high-risk individuals.

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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 single-center retrospective cohort study was conducted at Atatürk University Faculty of Medicine Hospital between 01.01.2025 and 01.01.2026. Institutional Ethics Committee approval was obtained (Approval Number: B.30.2.ATA.0.01.00/932; Date: 30.01.2026), and the study was registered at ClinicalTrials.gov (ID: NCT05405049). The ClinicalTrials.gov registration was completed to enhance transparency in the context of a retrospective design (at the time the data analysis plan was established); the study represents a non-interventional observational analysis. The study was performed in accordance with the principles of the Declaration of Helsinki. Due to the retrospective nature of the study, informed consent was not obtained from participants.

Author Contributions

Mehmet Akif Yilmaz: *conceptualization, data curation, formal analysis, investigation, methodology, supervision, validation, visualization, writing – original draft, writing – review & editing.*
Mehmet Zubeyir Guney: *data curation, formal analysis, investigation, visualization, writing – original draft.*
Nuray Uzun: *conceptualization, methodology, validation.*
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Ebubekir Sonmez: *conceptualization, methodology, validation.*
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Review

Failed labour epidural analgesia: mechanisms, risk factors and stepwise management: Guideline-based review

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ABSTRACT

Bacgkround: Epidural analgesia is the most widely used neuraxial technique for labour pain management; however, inadequate or failed analgesia remains a frequent and clinically relevant problem. This review aims to summarise the mechanisms and risk factors associated with failed labour epidural analgesia and to present a stepwise management approach aligned with current European Society of Anaesthesiology and Intensive Care (ESAIC) guidance.

Methods: A review of clinical guidelines, observational studies and interventional trials addressing labour epidural failure, breakthrough pain and rescue strategies was performed.

Results: Failed labour epidural analgesia is a multifactorial condition involving catheter-related issues such as suboptimal insertion depth, migration, unilateral or patchy block and unintended catheter placement, in addition to maternal, obstetric and operator-related factors. Effective management requires structured reassessment of pain characteristics, labour progression, sensory block level, catheter position and infusion parameters. Stepwise rescue strategies, including catheter manipulation, patient repositioning and adjustment of local anaesthetic dosing, may restore analgesic efficacy. Persistent inadequacy necessitates timely senior review and early consideration of catheter re-siting or alternative neuraxial techniques.

Conclusions: Early recognition and structured, stepwise management are essential for the effective treatment of failed labour epidural analgesia. Adherence to evidence-based guidelines, optimization of technical practice and appropriate organisational support may reduce failure rates and improve maternal outcomes.

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1. Introduction

Epidural analgesia has been the predominant and most effective neuraxial technique for labour pain management since its widespread adoption in the 1960s and is currently regarded as the gold standard in obstetric anaesthesia [1]. Ideal pain management during childbirth should be integrated with a multidisciplinary care approach that is centred on the mother's requests and rights, and is specifically tailored to both patients (mother and foetus), alongside the competent application of advanced neuroaxial techniques [2]. International organisations, including the World Health Organization, support its use in appropriate clinical settings due to its superior analgesic efficacy and favourable maternal and fetal outcomes [1]. In addition to epidural analgesia, the use of advanced techniques such as combined spinal-epidural (CSE) and dural puncture epidural (DPE) has

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increased analgesic efficacy, enabling more personalised approaches to pain management [3,4]. Despite these advantages, inadequate or failed labour epidural analgesia remains a frequent and clinically relevant problem in daily practice.

Reported failure rates vary widely across the literature, largely due to differences in definitions and outcome measures. Large retrospective analyses have demonstrated that a significant proportion of parturients experience incomplete analgesia, recurrent breakthrough pain or require epidural catheter replacement during labour [5]. Importantly, epidural failure is not confined to the absence of analgesia following initial catheter placement but also includes secondary loss of effect as labour progresses. Breakthrough pain is a key clinical indicator of functional epidural failure and is consistently associated with increased rates of catheter re-siting [6,7].

The mechanisms underlying failed labour epidural analgesia are multifactorial. Catheter migration, suboptimal insertion depth, unilateral or patchy block, sacral sparing and unintended intravascular or subdural placement all contribute to inadequate neuraxial spread [5,8]. In addition, the dynamic physiological changes of labour, evolving pain characteristics and obstetric factors may compromise analgesic effectiveness over time, even when initial catheter placement appears technically satisfactory.

Given this complexity, the European Society of Anaesthesiology and Intensive Care (ESAIC) emphasises the importance of early recognition of inadequate epidural analgesia and the use of structured, stepwise management pathways [9]. The ESAIC focused guidelines advocate systematic reassessment, timely rescue strategies and prompt escalation to catheter re-siting or alternative neuraxial techniques when indicated. Beyond technical considerations, organisational factors such as staffing, supervision, training and interdisciplinary communication play a critical role in ensuring consistent and effective epidural services [9,10].This review aims to synthesise current evidence on the mechanisms and risk factors associated with failed labour epidural analgesia and to present a structured, stepwise management approach aligned with contemporary ESAIC guidance.

2. Materials and Methods

This study was conducted as a guideline-based structured review based on the *ESAIC focused guidelines for the management of the failing epidural during labour epidural analgesia*. The review aimed to synthesise existing guideline recommendations together with recent evidence and to provide a practical, stepwise approach for clinical practice. A literature search was performed in PubMed/MEDLINE and the Cochrane Library to identify studies relevant to the clinical scope addressed in the ESAIC guideline. The search included studies published between January 2017 and February 2025. This time frame was selected to capture contemporary evidence reflecting current clinical practice, as earlier literature had already been comprehensively evaluated during guideline development. Search terms (MeSH and free text) included combinations of: "labour epidural analgesia", "failed epidural", "epidural failure", "inadequate epidural", "breakthrough pain", "epidural troubleshooting", "epidural catheter replacement", "combined spinal epidural", and "dural puncture epidural". Eligible studies included randomized controlled trials, observational studies, systematic reviews, and relevant clinical guidelines published in English and available in full text. Studies not related to obstetric epidural analgesia, case reports without clinically relevant outcome data, and studies with insufficient methodological detail were excluded. Titles and abstracts were screened for relevance, followed by full-text review. Due to clinical and methodological heterogeneity among studies, quantitative meta-analysis was not performed and the evidence was synthesised qualitatively. The findings were integrated with ESAIC guideline recommendations and organised into a clinically oriented stepwise management algorithm (Fig. 1).

3. Definitions and Mechanisms of Failure

Failed epidural analgesia is commonly defined by the inability to achieve adequate pain relief within the first 45 minutes following initiation, the occurrence of dural puncture, the need for catheter repositioning or discontinuation, or maternal dissatisfaction with analgesia [11]. Within this framework, an incomplete epidural block encompasses inadequate sensory blockade (below the T10 dermatome), unilateral or patchy block patterns, or insufficient analgesic intensity despite an apparently adequate sensory level. In contrast, breakthrough pain refers to the recurrence of pain during labour in parturients with previously effective epidural analgesia [9].

Failed epidural analgesia may result from several interacting mechanisms, including:

- Catheter migration or suboptimal insertion depth leading to unilateral or diminishing block [12,13];
- Incomplete neural blockade with patchy and lateralized block patterns [9];
- Intravascular or subdural placement, occasionally presenting with breakthrough pain or systemic symptom [9,11]; and
- Dynamic labour physiology, which may alter drug spread over time [7,9].

Continuous reassessment is therefore essential, as an initially effective block may subsequently deteriorate despite apparently correct placement.

4. Risk Factors

Failed or inadequate epidural analgesia results from the interaction of maternal, obstetric, operator-related and technical factors. Maternal contributors include high BMI, poorly defined anatomical landmarks, nulliparity, increased fetal weight, advanced cervical dilation at the time of insertion, rapidly progressing labour and severe pre-procedural pain. These conditions may hinder optimal drug spread within the epidural space and increase the likelihood of breakthrough pain and secondary loss of efficacy [5,7,12,14–16]. Obstetric

characteristics such as fetal malposition (e.g., occiput posterior), a prolonged second stage and dysfunctional labour patterns have likewise been associated with unilateral block or progressive loss of analgesic effect [10]. The main risk factors associated with epidural failure are summarised in Table 1.

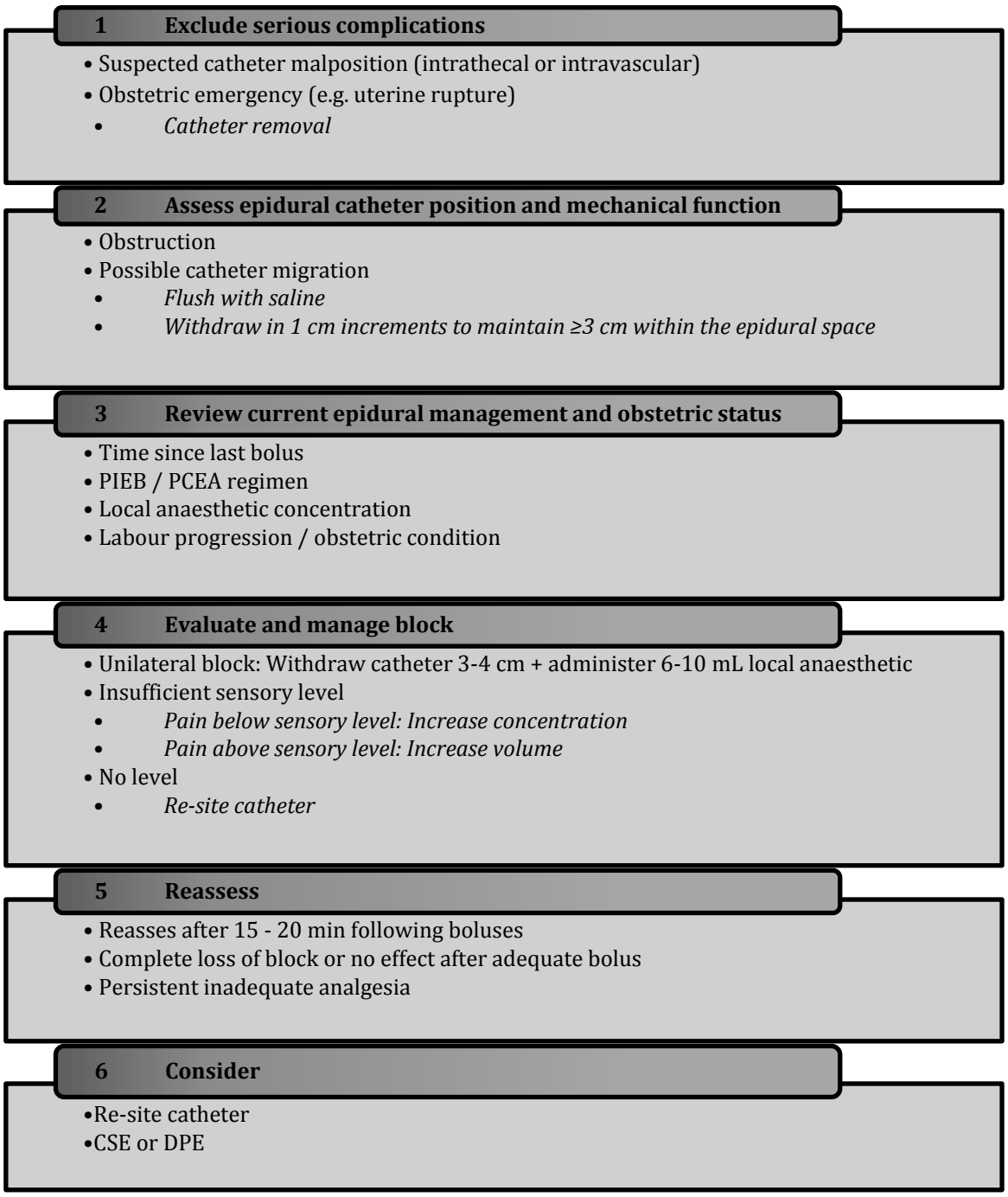


Fig. 1. Stepwise management of failed labour epidural analgesia.

Table 1. Risk factors for epidural failed in labour.

Maternal risk factors	Obstetric risk factors
High Body Mass Index	Nulliparity
Structural back abnormalities	Increased foetal weight
Opioid tolerance	Abnormal foetal presentation
Increasing age	Induction/augmentation of labour
Previous history of failed epidural	Epidural request at cervical dilatation >7 cm
Poor patient cooperation	Prolonged/rapid labour progression

Operator experience represents a major determinant of success. In a cohort of 1,521 labour epidurals, Thangamuthu et al. demonstrated significantly higher rates of failure and catheter re-siting among junior trainees compared with senior anaesthetists, despite similar procedural conditions [11]. Similarly, another study reported that unsuccessful epidural analgesia was associated with a high foetal head level, oxytocin use, and low seniority of the anaesthetist; moreover, unsuccessful epidural analgesia was linked to lower patient satisfaction and increased complication rates, including dural puncture and post-dural puncture headache [17]. These findings are consistent with guideline recommendations emphasising structured supervision, timely escalation of care, and repeated reassessment during labour.

Technical and catheter-related factors have a central role. Optimal catheter insertion depth appears to fall between 5–6 cm; both shallow (<3 cm) and deep (>7 cm) insertions have been associated with increased failure, patchy block and secondary loss of effect [8]. Catheter migration and inadequate fixation remain among the most consistent and modifiable contributors to unilateral or diminishing block, as also demonstrated in fixation trials such as Odor et al., where outward displacement predicted the need for re-placement [8]. Catheter stiffness, multi-orifice catheter design, the choice of loss-of-resistance medium (air vs saline) and insufficient initial dosing have likewise been implicated in incomplete neuraxial spread.

Non-technical and communication-related factors also play a measurable role. Poor patient cooperation, inadequate counselling and suboptimal communication among team members may delay recognition of evolving failure or breakthrough pain, a point emphasised in both ESAIC guidance and contemporary reviews such as Guasch et al., which highlight the multifactorial nature of epidural failure and the importance of early recognition and structured team response [9,10].

5. Assessment and Management

Assessment and management of inadequate labour epidural analgesia should follow a continuous, structured pathway consistent with the ESAIC PICO framework. The first step involves systematic reassessment (PICO 1). The nature, severity and location of pain should be clarified, labour progression reviewed and obstetric causes such as uterine rupture, dystocia or placental abruption excluded [9]. Sensory block levels must be reassessed, confirming adequate catheter depth (≥3 cm) within the epidural space, verifying the absence of migration and ensuring correct drug concentration, infusion rate and pump function prior to administering any rescue bolus [9].

Once inadequate analgesia is confirmed, stepwise troubleshooting should be initiated. When a rescue bolus provides no meaningful improvement—or when a potentially hazardous cause such as intrathecal or intravascular catheter placement is suspected—the epidural should be promptly removed and replaced. If partial relief is achieved, additional manual boluses of 6–10 ml of an appropriate local anaesthetic may be used, allowing 20–30 minutes between doses to reassess block development. Higher concentrations than those used for maintenance can be considered when the sensory block appears adequate but pain control remains incomplete. At each stage, analgesic effectiveness must be re-evaluated; persistent pain after a second top-up should trigger consideration of catheter replacement. Unilateral or markedly asymmetrical block warrants targeted catheter manipulation. Withdrawing the catheter until approximately 3–4 cm remain in the epidural space, followed by a 6–10 ml bolus, may enhance drug spread. Positioning the patient laterally on the side of inadequate block during the bolus can further facilitate distribution. As with other troubleshooting measures, reassessment after 20–30 minutes is essential; continued asymmetry or insufficient analgesia despite these interventions strongly supports the need for re-siting [9]. The stepwise management approach is illustrated in Fig. 1.

PICO 2 addresses the most suitable neuroaxial technique to be applied when the decision is made to reposition the epidural catheter. In this context, the Combined Spinal-Epidural technique is recommended for its faster onset of action and more reliable block, while the Dural Puncture Epidural technique is considered an alternative option, particularly for high-risk pregnancies [9]. In this context, the combined spinal-epidural (CSE) technique offers several advantages, including a faster onset of analgesia, reduced local anaesthetic requirements and a lower need for repeated rescue dosing. This reduces the risk of inadequate epidural analgesia and improves maternal satisfaction [18,19]. Within this broader framework, dural puncture epidural (DPE) analgesia may offer faster and satisfactory pain control without an increase in maternal or fetal adverse events compared with conventional epidural analgesia [20]. Combining it with programmed intermittent epidural bolus (PIEB), it may further facilitate a more rapid onset of analgesia and improve sacral block and overall analgesic quality [21].

The use of combined spinal–epidural and patient-controlled analgesia techniques, alignment between antenatal preferences and intrapartum practice, and active involvement of women in informed decision-making improves maternal satisfaction with neuraxial analgesia during labour [22].

Within PICO 3, the evaluation of labour epidural analgesia should not rely solely on reactive responses to reported pain but should incorporate a proactive strategy supported by structured, objective bedside assessments**.** The effectiveness of epidural analgesia should be monitored using parameters such as the Visual Analogue Pain Scale (VAPS)**,** motor block assessment with the Bromage score**,** and sensory block level, assessed in a systematic manner.The guideline highlights that, particularly in high-risk parturients**,** periodic documentation at 1–2-hour intervals may facilitate earlier recognition of epidural deterioration and shorten the time to appropriate intervention. Rising pain scores, inadequate sensory blockade, or discordance between motor block and analgesic effect should be interpreted as early clinical indicators of a potentially failing epidural.When interpreted together, these objective measures allow clinicians to distinguish true epidural failure from insufficient dosing, asymmetric block distribution, or pain escalation related

to rapidly progressing labour, thereby supporting timely and proactive clinical decision-making [9]. Taken together, these steps provide a structured and guideline-aligned framework for the recognition and management of failed epidural analgesia during labour.

6. Organisational and System-Level Factors

Beyond technical and patient-related causes, system-level factors play an increasingly recognized role in the success of labour epidural analgesia. Structured training models, staffing frameworks and decision-support pathways may substantially influence the reliability of epidural services and the timely management of failure. Emerging evidence suggests that competency-based educational approaches, such as Proficiency-Based Progression training, have the potential to improve both technical performance and clinical decision-making. This review therefore examines failed labour epidural analgesia through a system-oriented lens, integrating organisational, educational and clinical perspectives [23].

Within this framework, several organisational factors have been identified as key determinants of clinical outcomes. Adequate staffing models and timely availability of senior anaesthetists are essential to support rapid reassessment and prevent prolonged ineffective troubleshooting, reflecting the intent of the PICO 4 framework. PICO 5 highlights the importance of structured training and skill maintenance: units with defined competency pathways, supervised procedures and simulation-based troubleshooting demonstrate higher block success rates and more consistent decision-making regarding when to escalate or re-site a catheter. Finally, PICO 6 addresses the management of epidural failure in women requiring intrapartum conversion to caesarean delivery. In these situations, clear decision algorithms are needed to determine whether the existing epidural can be safely extended, whether re-siting or switching to a combined spinal-epidural technique is preferable or whether rapid induction of general anaesthesia is warranted. Together, these organisational factors shape the reliability of epidural services and directly affect maternal outcomes, illustrating that the management of failed labour epidural analgesia extends beyond catheter manipulation to encompass system-wide preparedness [9].

7. Prevention

Preventive strategies are essential to minimise secondary failure and reduce the need for catheter re-siting. Evidence consistently supports maintaining an optimal catheter depth of 5–6 cm within the epidural space, as both excessively superficial (<3 cm) and excessively deep placements (>7 cm) are associated with unilateral block, patchy spread and higher failure rates [8]. Secure fixation is equally important to prevent outward migration during labour positioning or maternal movement. The use of structured communication pathways between anaesthesia, obstetrics and midwifery teams has been shown to reduce delays in reporting breakthrough pain and facilitate timely escalation [9].

Modern delivery systems such as PCEA and PIEB may improve block consistency by offering more stable drug distribution and reducing breakthrough episodes, although their superiority remains context dependent. Standardised training programmes, supervision of trainees and institutional protocols for troubleshooting also contribute to preventing failure by ensuring consistent technical performance. Taken together, these preventive measures aim to reduce the incidence of inadequate epidural analgesia and support a more reliable neuraxial service [9].

8. Conclusions

Failed or inadequate labour epidural analgesia remains a multifactorial challenge shaped by maternal, obstetric, technical and organisational determinants. A structured approach grounded in the ESAIC PICO framework provides a coherent pathway for early recognition, standardised troubleshooting and timely re-siting when necessary. Evidence emphasises the importance of optimal catheter placement, secure fixation, consistent training and efficient interdisciplinary communication to minimise block failure and improve maternal satisfaction. Ultimately, effective management of failed epidural analgesia extends beyond catheter manipulation alone and requires system-level preparedness, clinical vigilance and adherence to evidence-based guidelines to ensure safe and reliable neuraxial care throughout labour.

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Author Contributions

Selvinaz Yüksel Tanrıverdi: *conceptualization, data curation, formal analysis, investigation, methodology, supervision, validation, visualization, writing - original draft, writing – review & editing.*
İlknur Hatice Akbudak: *data curation, methodology, validation, visualization, writing – original draft.*

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Case Report

Walking the tightrope: Anaesthesia for fragile hearts and overactive glands in elderly hip surgery

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ABSTRACT

Anesthetic management of elderly patients with ischemic heart disease, dilated cardiomyopathy with severe left ventricular dysfunction, and hyperthyroidism undergoing bipolar hemiarthroplasty presents unique challenges. Hyperthyroidism can exacerbate cardiac conditions, increasing perioperative risks. Preoperative optimization involves achieving euthyroid status using antithyroid medications and beta-blockers to control heart rate. A comprehensive cardiovascular evaluation is essential to manage heart failure and maintain hemodynamic stability. Severe pulmonary arterial hypertension further complicates anesthetic management due to increased perioperative morbidity and mortality. These patients are at higher risk for complications such as myocardial infarction and respiratory failure during anesthesia and surgery. Intraoperatively, regional anesthesia techniques may be preferred to minimize cardiovascular stress. Close monitoring of pulmonary pressures and ventricular function is crucial during the perioperative period. Postoperative care should focus on vigilant monitoring for potential complications, including thyroid storm, cardiac events, and exacerbation of pulmonary arterial hypertension. A multidisciplinary approach involving anesthesiologists, cardiologists, pulmonologists, and surgeons is essential to enhance surgical outcomes in such high-risk patients. In this case report, we present the combination of lumbar and sacral plexus blocks that we applied as the sole anesthesia method in a high-risk patient with multiple comorbidities undergoing bipolar hemiarthroplasty surgery.

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1. Introduction

The anaesthetic management of elderly patients with ischemic heart disease, dilated cardiomyopathy with severe left ventricular dysfunction, and hyperthyroidism undergoing major orthopaedic surgeries like bipolar hemiarthroplasty presents significant challenges. Hyperthyroidism can exacerbate cardiac conditions, increasing perioperative risks. Reduced ejection fraction and left ventricular failure further complicate haemodynamic stability during surgery. Severe pulmonary artery hypertension adds an additional layer of complexity, as it is associated with increased perioperative morbidity and mortality.

A comprehensive preoperative evaluation, meticulous intraoperative management, and vigilant postoperative care are essential to optimise outcomes in such high-risk patients. This case report details the management of a 77-year-old male patient with a right neck of femur fracture, ischemic heart disease, dilated cardiomyopathy with severe left ventricular dysfunction, and hyperthyroidism scheduled for bipolar hemiarthroplasty.

2. Case Report

A 77-year-old male patient with a right neck of femur fracture was scheduled for bipolar hemiarthroplasty. The patient presented with pain in the right hip following a history of fall, with NYHA grade III dyspnea. On physical examination, the patient's general condition

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was weak with HR 68 bpm (irregularly irregular), BP 140/90 mmHg, SpO2 98% on room air, and RR 16 cpm. His past medical history was significant for IHD with LV failure for 4 years, and he was on the following medications preoperatively: T. Ramipril 2.5 mg, T. Sacubitril 24 mg + Valsartan 20 mg, T. Torsemide 10 mg + Spironolactone 50 mg OD, and T. Methimazole 10 mg OD.

The patient's preoperative laboratory investigations were Hb 12.7, TLC 12,300, Plt 212,000/μL, PT 12.6, aPTT 35.6, INR 0.97, creatinine 0.7, serum electrolytes within normal limits, and LFT normal with elevated ALP 236.6 and albumin 3.3. The patient had a history of hyperthyroidism that was well controlled on T. Methimazole, rendering him clinically and biochemically euthyroid at the time of surgery. His chest X-ray showed emphysematous changes and cardiomegaly. ECG revealed left ventricular hypertrophy with ST-T changes in leads II, III, and aVF. A preoperative echocardiography revealed DCM (dilated cardiomyopathy), global hypokinesia of LV, dilated cardiac chambers, sclerotic aortic valve disease, mild-to-moderate mitral regurgitation/tricuspid regurgitation, severe PAH (100 mmHg), reduced LV and RV function, and LVEF 20%. The patient's diagnosis was closed traumatic right neck of femur fracture, belonging to ASA IV, and he was planned for uncemented bipolar hemiarthroplasty.

Grave risk consent was obtained explaining all intraoperative risks pertaining to the cardiac status of the patient. Prior to surgery, the patient fasted for 6 hours and an 18G peripheral IV cannula was secured.

On arrival in the operating room, standard ASA monitors were attached including HR, NIBP, SpO2, and ECG, and baseline hemodynamic parameters were recorded. Under aseptic precautions, left-sided radial artery catheterization was done and invasive blood pressure was noted, and the right IJV was cannulated. Injection ondansetron 4 mg was given. The patient was positioned in a lateral decubitus position, with the dependent limb kept straight while the limb to be blocked was flexed at both the hip and knee.

Using Capdevila's approach [1], the spinous process of L4 was identified. A line was drawn from the centre of the L4 spinous process laterally to intersect with a line passing through the posterior superior iliac spine parallel to the vertebral column on the side to be blocked. At the puncture point, local infiltration with lidocaine 2%, 2 mL, was given at the junction of the lateral one-third and medial two-thirds. The needle was advanced at right angles to the skin until the transverse process of L4 was encountered and then directed caudally, not more than 2 cm. A curvilinear ultrasound (GE) probe was placed in the transverse plane at the level of L3-L4. The transverse process, psoas major muscle, and lumbar plexus, which lies within the posterior part of the psoas major muscle, were visualized. The needle was inserted using an in-plane technique from the posterolateral edge of the probe, aiming anteriorly towards the posterior third of the psoas muscle (Fig. 1). Correct placement of the needle was confirmed using PNS (B Braun) with a current of 1–1.5 mA at 1–2 Hz, and the needle was advanced until twitches of the quadriceps muscle were obtained. The current was then lowered to obtain stimulation between 0.3–0.5 mA. At this point, using a 100 mm Stimuplex needle, 20 mL of 0.375% ropivacaine was given after negative aspiration.

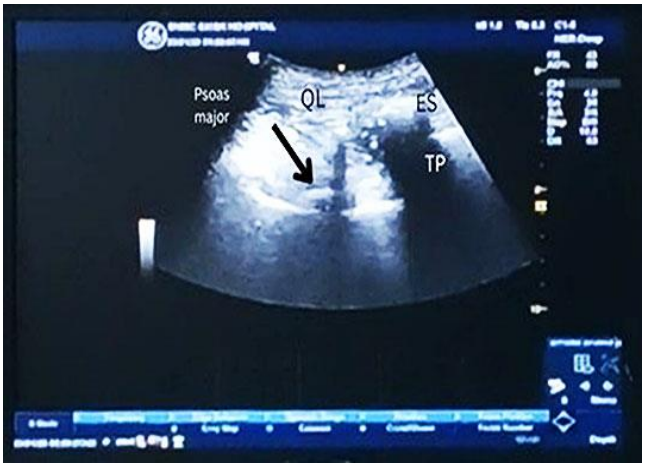


Fig. 1. USG guided lumbar plexus block, black arrow indicates the lumbar plexus (QL: Quadratus lumborum; ES: Erector spinae; TP: Transverse process).

Sacral plexus block was given using Mansour's parasacral approach [2]. A line between the PSIS and the ischial tuberosity was drawn. The needle insertion point lies 6 cm caudad to the PSIS on this line. The needle was inserted perpendicular to the skin and advanced slowly. Motor response of the sciatic plexus was obtained as visible or palpable twitches of the hamstrings, calf muscles, foot, or toes at a current intensity of 0.3–0.5 mA. Here, 15 mL of 0.375% ropivacaine was given after negative aspiration.

Surgical anaesthesia was achieved after 20 min. A low dose of inj norepinephrine infusion was started prophylactically to prevent transient hypotensive episodes, as it maintains systemic vascular resistance and coronary perfusion pressure without causing tachycardia or a significant increase in pulmonary vascular resistance, thereby preserving both left and right ventricular function and preventing acute RV failure. Fluid administration was done with the help of stroke volume variation of IBP. No haemodynamic fluctuations were observed and no pain was reported by the patient. The rest of the operative time was uneventful, and a standard cementless hip hemiarthroplasty was done within an operative time of 40 min.

Postoperatively, the patient was shifted to the ICU for close monitoring where he had AF with a fast ventricular rate, which was well managed with 12.5 mg diltiazem slow IV, and 48 hours later he was shifted to the orthopaedic patient wards.

3. Discussion

The anaesthetic management of elderly patients with significant cardiac comorbidities undergoing non-cardiac surgery presents a formidable challenge. This case highlights the complexities of perioperative care in a 77-year-old male with severely reduced left ventricular ejection fraction (LVEF 20%), dilated cardiomyopathy, and severe pulmonary hypertension (PAH 100 mmHg) undergoing bipolar hemiarthroplasty.

A markedly low ejection fraction is associated with significantly increased perioperative risk. Studies indi-

cate that LVEF <30% is correlated with a 5- to 7-fold increase in perioperative cardiac complications, including myocardial infarction, arrhythmias, and decompensated heart failure [3]. Furthermore, severe PAH (>70 mmHg) is a well-established independent predictor of perioperative mortality, with reported rates ranging from 4% to 24% in non-cardiac surgery [4]. Right ventricular (RV) dysfunction further complicates the clinical picture, as RV failure can rapidly develop under conditions of increased pulmonary vascular resistance, such as those caused by hypoxia, acidosis, or fluid overload [5].

The Revised Cardiac Risk Index (RCRI) categorizes this patient as high risk, with ischemic heart disease and heart failure as major predictors. This implies an estimated >11% risk of major adverse cardiac events (MACE) during the perioperative period [6]. Moreover, due to impaired cardiac reserve, patients with advanced heart failure are unable to mount an adequate increase in cardiac output in response to anaesthetic or surgical stress. In this context, maintaining normovolemia, avoiding afterload surges, and ensuring adequate oxygenation are of paramount importance [7].

This patient was euthyroid, removing the additional anaesthetic risk posed by uncontrolled thyrotoxicosis. This allowed us to focus exclusively on the haemodynamic challenges associated with his cardiac condition.

General anaesthesia (GA) and neuraxial techniques such as spinal or epidural anaesthesia may not be well tolerated in patients with compromised biventricular function. GA carries the risk of myocardial depression, sympathetic stimulation during airway manipulation, and increased susceptibility to arrhythmias [8]. Similarly, central neuraxial blocks can cause profound hypotension due to sympathetic blockade, which these patients may not physiologically compensate for [7].

Given these considerations, a combined ultrasound-guided lumbar plexus and sacral block was selected. This approach provided effective surgical anaesthesia while preserving haemodynamic stability and avoiding the risks of general anaesthesia. Regional techniques allow for stable cardiovascular dynamics, attenuated stress responses, and avoidance of myocardial depressant agents, making them especially suitable in patients with advanced cardiomyopathy and PAH [8,9].

Ultrasound and peripheral nerve stimulator guidance ensured precise local anaesthetic deposition. Ropivacaine 0.375% was preferred due to its lower cardiotoxicity compared to bupivacaine, making it safer in patients with cardiac disease [10]. The intraoperative use of a low-dose norepinephrine infusion provided vasomotor support without increasing heart rate, and fluid administration guided by stroke volume variation (SVV) helped avoid both under- and over-resuscitation [11].

In the early postoperative period, the patient developed atrial fibrillation with rapid ventricular rate, which was effectively managed with intravenous diltiazem. This reflects the high susceptibility of such patients to arrhythmias during perioperative stress and the importance of close cardiac monitoring postoperatively [12].

This case supports the findings of Ravishankar et al. [7], Salami et al. [8], and Gemawan et al. [9], emphasizing that regional anaesthesia, particularly peripheral nerve blocks, can be a safe and effective technique for non-cardiac surgery in patients with severe left ventricular dysfunction. With appropriate planning and vigilance, optimal outcomes can be achieved even in patients with extreme cardiac risk profiles.

4. Conclusions

This case exhibits successful management of a high-risk elderly patient with severe cardiac dysfunction (LVEF 20%, severe PAH, IHD, dilated cardiomyopathy) undergoing bipolar hemiarthroplasty. Regional anaesthesia using combined ultrasound and PNS-guided lumbar and sacral plexus blocks is a safe choice of anaesthesia for a patient having limited cardiac reserve. It reduces afterload, decreases stress response, and avoids airway instrumentation and haemodynamic response to laryngoscopy, thereby reducing morbidity. Careful haemodynamic monitoring with norepinephrine support maintained cardiovascular stability throughout the procedure. The successful result demonstrates that patients with significant heart disease can still safely undergo essential orthopaedic procedures when individualised anaesthetic approaches are employed. This case highlights the importance of adapting clinical management to each patient's unique physiological challenges and demonstrates the growing importance of ultrasound-guided regional anaesthesia techniques for patients with such comorbid conditions.

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Author Contributions
Ranganath Laxman Channappagoudar: *conceptualization, data curation, investigation, methodology, supervision, visualization, writing – original draft, writing – review & editing.*
Shilpa Shivananda: *conceptualization, data curation, methodology, visualization, writing – original draft.*

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