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## 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  $\geq 65$  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  $\geq 18$  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 intra-aortic 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  $\geq 0.3$  mg/dL or  $\geq 50\%$  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  $\leq 1.5$  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  $\geq 65$  years), sex, Body Mass Index (categorized as underweight  $< 18.5$ , normal  $18.5$ – $24.9$ , overweight  $\geq 25$  kg/m<sup>2</sup>), EuroSCORE II, Comorbidities (hypertension, diabetes mellitus, chronic kidney disease, COPD, etc.), CPB time (categorized as  $< 120$  min or  $\geq 120$  min), use of norepinephrine  $\geq 0.1$   $\mu$ g/kg/min, and Type of surgery (CABG, valve, combined). Body mass index was calculated as weight/height<sup>2</sup> (kg/m<sup>2</sup>) and categorized according to the WHO adult BMI classification as underweight ( $< 18.5$  kg/m<sup>2</sup>), normal weight ( $18.5$ – $24.9$  kg/m<sup>2</sup>), overweight ( $25.0$ – $29.9$  kg/m<sup>2</sup>), and obesity ( $\geq 30.0$  kg/m<sup>2</sup>). For regression analyses, we additionally used a binary variable (abnormal BMI) defined as BMI  $< 18.5$  or BMI  $\geq 25$  kg/m<sup>2</sup> (i.e., outside the normal range), with  $18.5$ – $24.9$  kg/m<sup>2</sup> 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  $\pm$  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  $\sim 18.6$ , 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 <sup>2</sup>	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
<b>Comorbidities</b>			
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
<b>Surgical Features</b>			
CABG	238 (47.8)	42 (45.2)	
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)	0.585
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, $10^3/\mu\text{L}$	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, $10^3/\mu\text{L}$	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, $10^3/\mu\text{L}$	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  $\geq 120$  minutes ( $p=0.044$ ), norepinephrine use  $\geq 0.1 \mu\text{g}/\text{kg}/\text{min}$  ( $p=0.018$ ), preoperative fibrinogen  $<1.5 \text{ g}/\text{L}$  ( $p<0.001$ ), and initial postoperative fibrinogen  $<1.5 \text{ g}/\text{L}$  ( $p<0.001$ ) 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  $\geq 65$  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<sup>2</sup>=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.

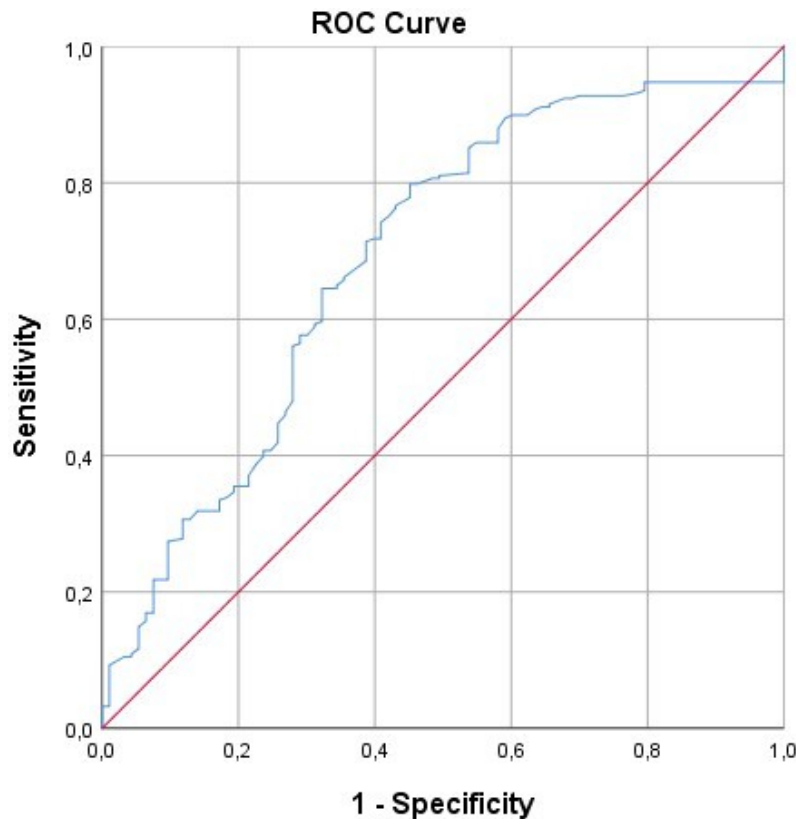
ROC analysis for preoperative fibrinogen was not statistically significant (AUC=0.554; 95% CI 0.479–0.630; p=0.134). Although preoperative fibrinogen showed limited univariable discrimination, very low preoperative fibrinogen (<1.5 g/L) was independently associated with re-exploration in the multivariable 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 im-

portance 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  $\approx 2.0$  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  $\approx 2.0$  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 ( $\geq 65$  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 con-

ditions (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.*

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### 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 Arıran:** conceptualization, data curation, investigation, methodology, resources, validation.

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

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