

Preoperative Fibrinogen Level and Postcardiac Surgery Morbidity and Mortality Rates

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ABSTRACT

Background: High preoperative fibrinogen levels are associated with reduced bleeding rates after cardiac surgery. Fibrinogen is directly involved in inflammatory processes and is a cardiovascular risk factor. Whether high fibrinogen levels before cardiac surgery are a risk factor for mortality or morbidity remains unclear.

Aims: This study aimed to examine the association between preoperative fibrinogen levels and mortality and morbidity rates after cardiac surgery.

Settings and Design: This is a single-center retrospective study.

Material and Methods: Patients ($n = 1628$) were divided into high (HFGr) and normal (NFGr) fibrinogen level groups, based on the cutoff value of 3.3 g/L, derived from the receiver operating characteristic (ROC) curve analysis. The primary outcome was the 30-day mortality rate. The rates of postoperative complications, including postoperative bleeding and transfusion rates, were examined.

Statistical Analysis: Between-group comparisons were performed with the Mann–Whitney U test and Chi-squared test, as suitable. Model discriminative power was examined with the area under the ROC curve.

Results: The HFGr and NFGr included 1103 and 525 patients, respectively. Mortality rate was higher in the HFGr than in the NFGr (2.7% vs. 1.1%, $P = 0.04$). The 12-h bleeding volume (280 mL [195–400] vs. 305 mL [225–435], $P = 0.0003$) and 24-h bleeding volume values (400 mL [300–550] vs. 450 mL [340–620], $P < 0.0001$) were lower in the HFGr than in the NFGr. However, the rate of red blood cell transfusion during hospitalization was higher in the HFGr than in the NFGr (21.7% vs. 5.9%, $P = 0.0103$). Major complications were more frequent in the HFGr than in the NFGr.

Conclusion: High fibrinogen levels were associated with reduced postoperative bleeding volume and increased mortality and morbidity rates.

Keywords: Cardiac surgery, fibrinogen, morbidity, mortality

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INTRODUCTION

Fibrinogen is essential to coagulation. Cardiac surgery under cardiopulmonary bypass (CPB) is associated with a significant decrease of fibrinogen concentration due to hemodilution and coagulation activation.^[1,2] Previous studies have reported an inverse relationship between

postoperative fibrinogen levels and the amount of bleeding.^[3-5] In addition, high preoperative fibrinogen levels may reduce postsurgical bleeding risk^[6-8] but not the need for postoperative transfusion.^[7] Fibrinogen administration decreases postoperative blood loss after cardiac surgery.^[9] Meanwhile, fibrinogen is directly involved in inflammatory processes,^[10] both of which are major cardiovascular risk

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factors.^[11] Whether high fibrinogen levels before cardiac surgery are beneficial because it reduces postoperative bleeding or a risk factor for mortality or morbidity remains unclear. This study aimed to examine the association between preoperative fibrinogen levels and mortality and morbidity rates after cardiac surgery.

MATERIALS AND METHODS

This single-center retrospective study was based on a prospective database that included all adult patients that underwent elective valve and/or coronary bypass surgery with CPB or thoracic aortic surgery between January 2016 and February 2019. Patients were eligible for this study, if their records included data on preoperative fibrinogen levels. Exclusion criteria were emergency procedures, coronary surgery without bypass, heart transplantation, and left ventricular assist device implantation. Ethical approval for this study was obtained from our institutional ethics committee which waived the requirement for written informed consent due to the retrospective nature of this study.

During the study period, 2182 patients underwent surgery. A total of 338 patients were excluded; specifically, 65, 17, 36, and 220 patients were excluded since they underwent Off-pump coronary artery bypass (OPCAB) surgeries, left ventricular assist device implantation, heart transplantations, or emergent surgeries. Of the remaining 1736 cases, 108 were excluded due to the lack of data on preoperative fibrinogen levels. A total of 1628 patients were included. Plasma fibrinogen levels were analyzed the week before surgery at different laboratories.

All patients received a similar type of anesthesia, surgery, and CPB management. Induction and maintenance of anesthesia were obtained using a target intravenous anesthesia of remifentanyl and propofol. Curarization was used to facilitate intubation. Tranexamic acid was used systematically with a loading dose of 15 mg/kg over 20 min, followed by a continuous infusion of 2 mg/kg/h until the end of the procedure. Cardiac surgery was performed under CPB with a moderate hypothermia of 33°C. Acetate-buffered chloride intravenous infusion (Isolyte S, B. Braun Medical Inc., Bethlehem, PA) was used for priming and perioperative volume expansion. The CPB flow rate was set at 2.2 L/min/m² of body surface area. Myocardial protection was achieved by antegrade and retrograde cold blood cardioplegia composed of arterial blood from CPB at a ratio of 1:4 or mixed with crystalloid (Plegisol®, Abbott Laboratories, North Chicago, IL), antegrade cold cardioplegia.

Before aortic cannulation, 300 IU/kg of unfractionated heparin (UFH) was administered. Activated clotting time (ACT) (ACTII monitor; Medtronic BV, Kerkrade, the Netherlands) was used to guide UFH administration and to maintain a target ACT of >400 s. ACT assessments were repeated during CPB every 30 min, and a heparin bolus was administered, if required. At the end of CPB, a dose of protamine, identical to the initial UFH dose, was administered, regardless of surgery duration and the delay since the last UFH injection. The ACT was measured after 10 min, and a further dose of protamine was administered, if required. During CPB, pericardial blood was collected in the reservoir through cardiotomy suction and after weaning from bypass; the residual blood was routinely processed by cell-saver (Sorin Xtra® Autotransfusion System) and re-administered to the patient at the end of surgery.

During and after the surgery, red blood cells were transfused to maintain a hemoglobin level of >70 g/L. Transfusion of concentrated clotting factors, fresh frozen plasma, and platelet concentrates was performed in cases of nonsurgical bleeding guided by thromboelastogram TEG® (Model 5000, Hemoscope Corporation, Niles, IL) parameters, according to our usual protocols. Aspirin was administered until the day before surgery, and clopidogrel was stopped 5 days before surgery. Antivitamin K and oral anticoagulants were also stopped 5 days before surgery, and replaced by UFH, as required. Postoperative bleeding was evaluated by the total amount of chest tube drainage during the first 12 and 24 h after admission to the intensive care unit; massive bleeding was defined according to the universal definition of perioperative bleeding in cardiac surgery.^[12] The incidence of the main postoperative complications was recorded.

Quantitative data were presented as the median and inter-quartile; qualitative data were presented as counts and percentages. Quantitative variables were compared using the Mann–Whitney *U* test. Qualitative variables were compared with the Chi-squared test. *P* values of <0.05 were considered significant. We drew the receiver operating characteristic (ROC) curve for preoperative fibrinogen levels to predict 30-day mortality rates; the Youden Index was used to determine the cutoff value.^[13] This value was used to divide patients into normal (NFG_r) and high (HFG_r) fibrinogen level groups.

The relationship between preoperative fibrinogen levels and 30-day mortality rates was investigated using three models: EuroSCORE 2^[14] alone, EuroSCORE 2 and NFG_r and HFG_r, and EuroSCORE 2 and preoperative

fibrinogen level in g/L. The discriminative power of the different models was quantified with the area under the ROC curve (AUC) and also studied in patients undergoing isolated valve surgery or coronary artery surgery. Statistical analyses were conducted with Medcalc software (MedCalc for Windows, version 12.5, Ostend, Belgium).

RESULTS

Plasma fibrinogen concentration of 3.3 g/L corresponded to the best Youden Index with sensitivity and specificity of 83% and 33%, respectively. Accordingly, 1103 and 525 patients were included in the HFGr and NFGGr, respectively. Patients in the HFGr had more comorbidities than the patients in the NFGGr [Table 1]. The 30-day mortality rate was significantly higher in the HFGr than in the NFGGr (2.7% vs. 1.1%, $P = 0.04$). The AUC of fibrinogen was low. EuroSCORE 2 AUC was high but it did not increase when EuroSCORE 2 was combined with fibrinogen group or fibrinogen levels (g/L) in the logistic regression model [Table 2 and Figure 1].

Postoperative blood loss volume was significantly lower in the HFGr than in the NFGGr at 12 (280 mL [195–400] vs. 305 mL [225–435], $P = 0.0003$) and 24 h (400 mL [300–550] vs. 450 mL [340–620] $P < 0.0001$) after surgery. The frequency of reoperation due to bleeding or cardiac tamponade was similar in both groups (3.1% vs. 2.5%, $P = 0.49$). The rates of massive bleeding^[12] were similar in both groups (5.9% in HFGr vs. 5.5 in NFGGr, $P = 0.76$).

Red blood cell transfusion was more common in the HFGr than in the NFGGr during both surgery and hospitalization (6.6% vs. 3.4% $P = 0.009$; 21.7% vs. 5.9% $P = 0.0103$, respectively). A total of 2% of the patients received a pre- or postoperative fibrinogen transfusion, including 1.4% and 3.4% of the patients in the HFGr and in the NFGGr, respectively ($P = 0.006$). The rates of other blood product transfusions were similar in both groups. The rate of postoperative complications was higher in the HFGr than in the NFGGr [Table 3].

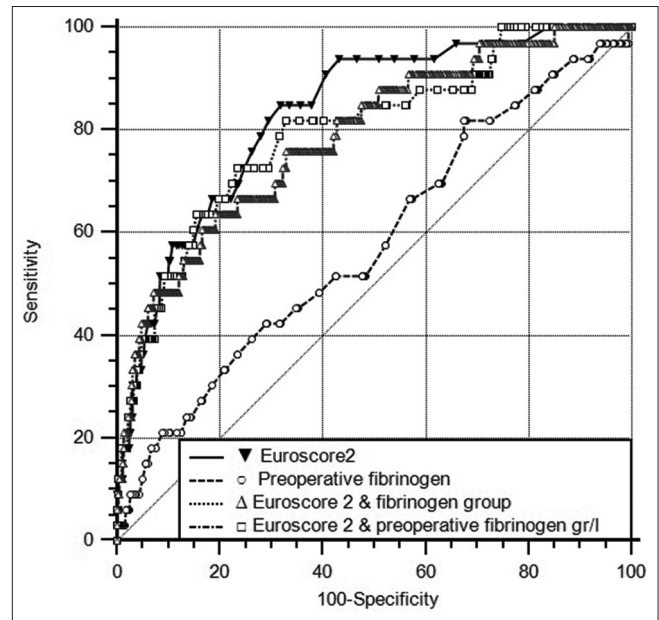


Figure 1: Receiver operating characteristic curve for mortality rates associated with Euroscore 2, preoperative fibrinogen level, Euroscore 2 and high fibrinogen group (HFGr) and normal fibrinogen group (NFGGr), Euroscore 2 and preoperative fibrinogen (g/L)

Table 1: Participant characteristics and between comparisons of high fibrinogen group (HFGr) and normal fibrinogen group (NFGGr)

	Total (n=1628)	HFGr (n=1103)	NFGGr (n=524)	P
Age (years)	71 (63-76)	72 (64-77)	69 (60-75)	<0.0001
Euroscore 2 (%)	1.6 (1.0-2.7)	1.7 (1.1-3.0)	1.3 (0.9-2.1)	<0.0001
Weight (kg)	75 (67-86)	76 (68-87)	75 (66-85)	0.01
Height (cm)	170 (164-176)	171 (164-175)	170 (164-176)	0.01
Gender (M)	73%	72%	77%	0.031
Creatinine (µmol/L)	84 (71-98)	84 (71-95)	83 (71-101)	0.25
Hemoglobin (g/L)	14.0 (12.9-15)	13.8 (12.7-14.8)	14.4 (13.4-15.3)	<0.0001
Fibrinogen (g/L)	3.7 (3.2-4.4)	4.1 (3.7-4.7)	3.0 (2.7-3.2)	<0.0001
LVEF (%)	61 (55-68)	60 (55-67)	65 (60-70)	<0.0001
Smokers	13%	14%	10%	0.03
Extracardiac arteriopathy	14%	15.8%	11.4%	0.019
COPD	7%	8%	5%	0.034
Hypertension	64%	33%	42%	0.0002
Diabetes	27%	30%	22%	0.001
Surgery: CABG	643	471 (42.7%)	172 (32.8%)	$P=0.0003$
Valve surgery	616	398 (36.1%)	218 (41.5%)	
Combined surgery	165	116 (10.5%)	49 (9.3%)	
Surgery on thoracic aorta	186	107 (9.7%)	79 (15.0%)	
Other	18	11 (1.0%)	7 (1.3%)	
Aortic clamp time	66 (53-86)	65 (52-85)	68 (65-70)	0.15
Duration of CPB (min)	99 (79-129)	100 (79-128)	98 (79-128)	0.98

CABG=Coronary artery bypass grafting; LVEF: left ventricular ejection fraction; COPD: chronic obstructive pulmonary disease

Table 2: Area under the curve (AUC) for models, including preoperative fibrinogen levels or Euroscore 2 alone, Euroscore 2 and preoperative fibrinogen levels, and Euroscore 2 and the preoperative fibrinogen group

	Odds ratio	95% CI	P	AUC
Fibrinogen	1.33	1.02-1.74	0.038	0.58
Euroscore 2	1.15	1.10-1.22	<0.0001	0.56-0.61
Euroscore 2	1.15	1.10-1.21	<0.0001	0.83
HFGr	2.02	0.79-5.16	0.14	0.81-0.85
Euroscore 2	1.15	1.10-1.21	<0.0001	0.80
Fibrinogen (g/L)	1.18	0.88-1.6	0.274	0.78-0.82
Euroscore 2	1.19	1.02-1.38	0.028	0.79
CABG				0.77-0.81
HFGr	2.49	0.30-20.04	0.39	0.80
CABG				0.77-0.83
Euroscore 2	1.11	1.10-1.21	0.0029	0.72
Valve surgery				0.69-0.76
HFGr	1.64	0.33-58.15	0.54	
Valve surgery				

HFGr= High fibrinogen group, CI=confidence interval

Table 3: Incidence of postoperative complications according to the fibrinogen level group

Complications	HFGr (n=525)	NFGr (n=1103)	P
Atrial fibrillation	16.8%	13%	0.06
Creatinine peak (μmol/L)	88(71-111)	82(68-101)	0.0002
Renal replacement therapy	1.7%	0.6%	0.07
Low cardiac output	14.4%	8.2%	0.0004*
Use of inotrope	18%	10%	0.0003*
Duration of mechanical ventilation (h)	3 (3-4)	3 (3-4)	0.50
Length of stay in intensive care (D)	3 (2-5)	3 (2-4)	0.006

DISCUSSION

To our knowledge, this study was first to examine the relationship between preoperative fibrinogen levels and postoperative mortality and morbidity rates. As expected, elevated preoperative fibrinogen levels were associated with reduced postoperative bleeding volume but an increased postoperative transfusion and morbidity rates. The value of preoperative fibrinogen level in predicting mortality was low.

Postoperative bleeding volume decreases when preoperative fibrinogen levels are high^[8] while the prothrombin time and the activated partial thromboplastin time are not useful.^[15] Fibrinogen contributes to the qualitative formation of a clot. Guidelines suggest its use in cardiac surgery to reduce blood transfusion.^[16]

Despite a small reduction in postoperative blood loss, there was an increase in the red blood cell transfusion rate in patients with high fibrinogen levels; this finding is consistent with that of a previous study.^[7] Patients

with high fibrinogen levels had lower preoperative hemoglobin levels than did their counterparts, which may be associated with inflammatory anemia that could account for this finding. In contrast, a previous study that included only coronary surgery patients reported that preoperative fibrinogen plasma concentration was an independent predictor of postoperative bleeding and that high preoperative fibrinogen plasma levels decreased perioperative transfusion risk;^[17] this difference was significant in univariate and multivariate analyses, but only 29 patients were transfused in a sample of 170 patients.

In addition, high preoperative fibrinogen concentration was associated with significant increase in the rate of postoperative complications, such as low cardiac output, need for inotrope use, and the length of stay in the intensive care unit. Cardiac surgery with CPB is associated with a strong activation of the systemic inflammatory system.^[18,19] This may explain the association between a preoperative inflammatory state and increased morbidity and mortality rates in adult cardiac surgery.^[20] Inflammation leads to the activation of coagulation; fibrinogen has a pro-inflammatory function,^[10] making a link between preoperative fibrinogen plasma concentration and complications risk possible.

Exogenous fibrinogen supply plays a part in the management of hemorrhagic shock; thus, its use may be associated with risk.^[16] This study has shown a statistically significant association between fibrinogen levels and bleeding volume; however, the clinical impact of this association was moderate. Studies on fibrinogen supplementation in cardiac surgery found a decrease in postoperative bleeding, without an increase in postoperative complication rates; however, previous studies focused on thrombotic complications^[9,21] and included a small number of patients.

This study has several limitations. First, it was a single-center retrospective study that involved a relatively large number of patients. Second, patients at high risk of bleeding and those undergoing emergency surgery were excluded from this study; the present findings may not generalize these patients. Third, patients with a high fibrinogen level bleed less, but it is an association and our study did not prove causality; it was the same for postoperative complications, which are multifactorial, and a high fibrinogen level cannot be considered as a causative factor. Fourth, preoperative laboratory test findings were obtained at different laboratories, which used different reference values for fibrinogen plasma concentration.^[22] However, these differences were small. In addition, preoperative laboratory tests were performed at different times, which may have affected test findings and the reported estimates.

In conclusion, preoperative fibrinogen concentration was associated with a small decreased postoperative bleeding volume and increased rates of transfusion and morbidity. Preoperative fibrinogen levels may help predict bleeding and risk of complications such as low cardiac output syndrome or renal failure. Studies including preoperative fibrinogen and other inflammatory markers as C-reactive protein are necessary.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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