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Fibrinogen is an Independent Preoperative Predictor of Hospital Length of Stay among Patients Undergoing Coronary Artery Bypass Grafting

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Abstract

Objective: This study aimed to explore the effects of preoperative fibrinogen concentration on outcomes of patients undergoing Coronary Artery Bypass Grafting (CABG) over a short- term period and hospital Length of Stay (LOS).

Methods: A retrospective study included 936 patients who consecutively underwent isolated, primary off-pump or on-pump CABG between December 2017 and November 2018. Preoperative fibrinogen concentration, baseline index, intraoperative data, duration of Intensive Care Unit (ICU) stay and LOS were recorded. The prime endpoint was LOS. Univariate and multiple linear regressions were used to evaluate the correlation between preoperative fibrinogen concentration and LOS.

Results: Preoperative variables that independently shortened the likelihood of LOS was preoperative fibrinogen concentration (B=0.073, P=0.04); a significant shorten in likelihood was found with High Hemoglobin (HGB) (B= -0.140, P<0.001). Preoperative variables that significantly decreased the likelihood of duration of ICU stay was Male gender (B= -0.092, P=0.02). Like Plateletcrit (PCT) (B= -0.121, P<0.001), preoperative fibrinogen concentration (B= -0.073, P=0.03) was also associated with postoperative bleeding volume.

Conclusion: Fibrinogen is an independent preoperative predictor of LOS and postoperative bleeding volume. Patients with low preoperative fibrinogen concentration lost more blood and had longer LOS. Male gender was association with shorter duration of ICU stay and preoperative higher HBG was association with longer LOS.

Keywords: Fibrinogen; Hospital length of stay; Coronary artery bypass grafting; Bleeding

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Abbreviations

ACEI: Angiotensin-Converting Enzyme Inhibitors; ARB: Angiotensin Receptor Blocker; BMI: Body Mass Index; CABG: Coronary Artery Bypass Grafting; CVD: Cardiovascular Disease; CHD: Coronary Heart Disease; CPB: Cardiopulmonary Bypass; FDP: Fibrinogen Degradation Product; HGB: Hemoglobin; LOS: Length of Stay; LMWH: Low Molecular Weight Heparin; LVEF: Left Ventricular Ejection Fraction; PLT: Platelet; RBC: Red Blood Cell; ICU: Intensive Care Unit; WBC: White Blood Cell

Introduction

Cardiovascular Diseases (CVD) is a global health care concern with rising trends across the world. In 2015, 2712,630 resident deaths were registered in the United States; the leading cause of death was CVD [1]. Similarly in Europe, more than 3.9 million people die of cardiovascular disease per year, or about 45% of all deaths [2].

Coronary Heart Disease (CHD) is one of the CVD and the leading cause of deaths attributable to CVD, accounting for 45% [1]. CABG is a very common and effective treatment for CHD in both developed and developing countries. In 2007, more than 800,000 CABG operations were conducted worldwide [3]. Although CABG usually enhances quality of life, improves health status and increases survival, some outcomes are still unexplained [3-6]. Even a considerable proportion of patients who underwent CABG have poor postoperative recovery [5].

Currently, although a number of researchers have demonstrated that short-term outcomes are important for recovery, most studies focus on long-term outcomes [7,8]. Prior to this, postoperative bleeding, severe perioperative complications and mortality within 30 days are often used as indicators of short-term outcomes after CABG [9,10]. However, a newly investigated study shows that LOS is also considered as an important marker of surgical recovery, a proxy measure of acute physical recovery, and a vital indicator of long-term recovery [11,12]. Patients with complications and poor recovery after CABG are expected to stay in the hospital longer.

Many factors associated with prolonged LOS included the body mass index, cardiopulmonary bypass machine use, packed red blood cells use, non-elective surgery and number of complications [13]. A large sample multicenter study showed that differences in diagnosis and treatment of CHD and wound infections significantly increase LOS [14]. Another clinical respective cohort study indicated that every unit increase in preoperative anxiety increased LOS by 0.381 days [15]. To the best of our knowledge, there are no other identified preoperative predictors to accurately predict LOS among patients undergoing CABG.

Plasma fibrinogen as precursor of fibrin plays an essential role in hemostasis by promoting clot formation and platelet aggregation by binding platelet glycoprotein IIb/IIIa receptors [16]. A meta-analysis has explored that the plasma fibrinogen level was correlated with CHD, and may be a risk factor and predictor of CHD [17]. The relationship between preoperative fibrinogen concentration and bleeding volume after CABG remains unclear. Karlsson et al. [18] reported that preoperative fibrinogen concentration (even within the normal range) is a limiting factor for postoperative hemostasis. Solomon et al. [19] showed that fibrinogen concentrate administration increased the fibrin clot quality and helped achieve hemostasis in the patients with bleeding after Cardiopulmonary Bypass (CPB). However, Jalali et al. [20] indicated that Preoperative assessment of plasma fibrinogen levels failed to predict bleeding after CABG. To our knowledge, there is no study on fibrinogen and LOS. We hypothesized that fibrinogen is related to LOS. So, we further explored whether higher fibrinogen can increase LOS with the goal of our current study being to utilize a large cohort and multivariable analyses. These new methods allowed us to ascertain the significance of fibrinogen as an independent preoperative indicator of LOS.

Materials and Methods

Study population

This single center retrospective study was approval by Ethical Committee of Fuwai Hospital, Beijing, China and the written informed consent was waived. Data were collected from consecutive patients who received isolated primary CABG (on- or off-pump), performed by a single surgeon at State Key Laboratory of Cardiovascular Disease, National Clinical Research Center of Cardiovascular Diseases, Fuwai Hospital between December 2017 and November 2018. Isolated primary CABG was defined as coronary artery bypass graft surgery alone for the first time with or without CPB. All anesthesiologists involved in the study had extensive experience with cardiac anesthesia. Blood transfusion and fluid input were controlled by anesthesiologists according to an accepted fluid management guideline [21]. Patients of emergency CABG, concomitant surgical procedures and patients of liver and kidney dysfunction were excluded. A total of 936 patients met our inclusion criteria.

Data collection

Date was collected *via* hospital medical records. We obtained preoperative medical therapy, laboratory coagulation parameters [Platelet (PLT) count, Plateletcrit (PCT), Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), D-dimers, fibrinogen (Fibrinogen and Fibrinogen Degradation Product (FDP)], intraoperative data, postoperative bleeding volume within 24 h after surgery, Blood transfusion, fluid input, ICU stay, mechanical ventilation time and LOS.

Postoperative bleeding volume was defined as the total amount of chest tube drainage within 24 h postoperatively, which was recorded by a nurse who had been trained in accurate record in the ICU. Blood transfusion, fluid input, ICU stay, and mechanical ventilation time also were recorded.

High fibrinogen and normal fibrinogen were defined as follows: fibrinogen <3.5 g/L (normal fibrinogen), fibrinogen ≥ 3.5 g/L (high fibrinogen).

Statistical analysis

There were no data losses for categorical variables. Continuous variables were lost less than 5%, so mean values were used to replace missing values. Categorical variables were expressed as number and percentage, and continuous variables were expressed in the form of mean ±standard deviation (for normally distributed continuous variable comparisons between groups) or the median (IQR) (for non-normally distributed continuous variable comparisons between groups).

SPSS version 23.0 software (SPSS Inc., Chicago, IL, USA) was used for all statistical analysis. All test results were considered as statistically significant at P<0.05. Patients were divided into two groups based on preoperative fibrinogen levels by comparing baseline levels. We used Analysis of Variance (ANOVA) or the Wilcoxon ranked sum test, and c2 test or Fisher exact tests were used for group comparisons, as appropriate. Simple linear regression analysis was used to analyze the relationship between demographic data and postoperative bleeding volume, ICU stay and LOS. A multiple linear regression model was used to identify the independent variable associated with postoperative bleeding volume, ICU stay and LOS. For both models, covariates were selected into the multiple linear regression models if the P value of any independent variable was less than 0.05 after univariate regression analysis.

Results

Table 1 describes the preoperative characteristics of the participants. The mean age was around 62 years, and approximately three-quarters of participants were males. There was an imbalance of gender, hypertension, hyperlipidemia, diabetes and other parameters of which the p value is smaller than 0.05 among the two groups. We eliminated this bias in a further multivariate linear regression analysis.

The postoperative bleeding volume in the normal fibrinogen group were markedly higher than in the high fibrinogen group (Table 2, P=0.05). ICU stay (P=0.04) and LOS (P=0.04) in the normal fibrinogen group were substantially less than the high fibrinogen group (Table 2).

Table 1: Baseline characteristics of the patients (n=936).

Variable	Fibrinogen		P
Fibrinogen (g/L)	<3.5	≥ 3.5	
	(n=530)	(n=406)	
Age (years)	61.1 ± 8.26	62.0 ± 7.92	0.08
Men (%)	444 (83.8)	286 (70.4)	<0.001
Smoking (%)	294 (55.5)	204 (50.2)	0.11
Family history of CHD (%)	65 (12.3)	57 (14.0)	0.42
Hypertension (%)	328 (61.5)	280 (69.0)	0.02
Hyperlipidemia (%)	410 (77.4)	338 (83.3)	0.03
Diabetes (%)	163 (30.8)	166 (40.9)	<0.001
Myocardial infarction (%)	47 (8.9)	47 (11.6)	0.17
Interventional stent (%)	11 (2.1)	13 (3.2)	0.28
Heart failure (%)	7 (1.3)	11 (2.7)	0.13
Surgery history (%)	110 (20.8)	105 (25.9)	0.07
Medical therapy			
LMWH (%)	449 (84.7)	349 (86.0)	0.6
Aspirin (%)	183 (34.5)	157 (38.7)	0.19
Ticagrelor (%)	28 (5.3)	27 (6.7)	0.47
ACEI (%)	104 (19.6)	88 (21.7)	0.44
β-blocker (%)	64 (12.1)	64 (15.8)	0.1
LVEF (%)	58.3 ± 12.3	58.13 ± 11.3	0.79
BMI (kg /m^2)	25.69 ± 2.98	26.08 ± 3.51	0.14
HGB (g L^{-1})	136.4 ± 16.3	132.0 ± 15.7	<0.001
WBC (× 10^9/L)	6.41 ± 1.55	6.81 ± 1.62	<0.001
Neutrophil count (× 10^9/L)	3.90 ± 1.24	4.23 ± 1.28	<0.001
Lymphocyte count (× 10^9/L)	1.89 ± 0.59	1.94 ± 0.65	0.27
Monocyte's count (× 10^9/L)	0.43 ± 0.25	0.45 ± 0.15	0.28
PLT count (× 10^9/L)	204.4 ± 51.5	227.4 ± 65.7	<0.001
PCT (%)	0.22 ± 0.05	0.24 ± 0.06	<0.001
PT (sec)	13.13 ± 0.74	13.00 ± 0.88	<0.001
APTT (sec)	36.79 ± 5.26	37.54 ± 6.51	0.06
D-dimers (μg/mL)	0.36 ± 0.40	2.32 ± 20.01	0.1
FDP (μg/mL)	6.69 ± 3.87	8.77 ± 30.07	0.16
CPB (%)	358 (58.1)	258 (41.9)	0.2
Number of anastomoses	3.41 ± 0.86	3.40 ± 0.84	0.94

CHD: Coronary Heart Disease; LMWH: Low Molecular Weight Heparin; ACEI: Angiotensin-Converting Enzyme Inhibitors; LVEF: Left Ventricular Ejection Fraction; BMI: Body Mass Index; HGB: Hemoglobin; WBC: White Blood Cell; PLT: Platelet; PCT: Plateletcrit; PT: Prothrombin Time; APTT: Activated Partial Thromboplastin Time; FDP: Fibrinogen Degradation Product; CPB: Cardiopulmonary Bypass

After further multiple linear regression analysis, as presented in the Table 3-5. It is obvious that preoperative fibrinogen independently predicted postoperative bleeding (Table 3, B= -0.073, P=0.03) and LOS (Table 5, B=0.073, P=0.04). Preoperative PCT was associated closely with postoperative bleeding (Table 3, B= -0.121, P<0.001), whereas male gender decreased ICU stay (Table 4, B= -0.092, P=0.02) and preoperative higher HBG decreased LOS (Table 5, B =-0.140, P<0.001).

Discussion

As far as we know, our study was firstly demonstrated to explore the correlation between preoperative fibrinogen concentration and LOS so far. The main finding is that preoperative fibrinogen concentration, even within normal range, maybe can inhibit postoperative bleeding volume and increase LOS. Therefore preoperative fibrinogen concentration may be considered as an independent predictor to evaluate postoperative bleeding volume and LOS after CABG.

Table 2: Postoperative outcome parameters of the Patients (n=936).

Variable	Fibrinogen		P
Fibrinogen (g/L)	<3.5	≥ 3.5	
	(n=530)	(n=406)	
Surgery time (h)	3.94 ± 1.21	4.02 ± 1.17	0.32
Fluid input (mL)	2213.11 ± 598.04	2145.15 ± 517.65	0.25
Postoperative bleeding (mL/24 h)	471.50 ± 252.24	440.08 ± 247.00	0.05
RBC transfusion (%)	120 (55.3)	97 (44.7)	0.65
Ventilation time (min)	1050.01 ± 588.65	1129.53 ± 787.46	0.16
Chest drainage tube placement time (days)	4.62 ± 2.34	4.47 ± 1.68	0.24
ICU stay (min)	3607.41 ± 2659.34	4056.64 ± 2741.12	0.04
Reoperation (%)	6 (1.1)	4 (1.0)	0.83
Hospital stays (days)	14.94 ± 6.05	15.73 ± 5.90	0.04

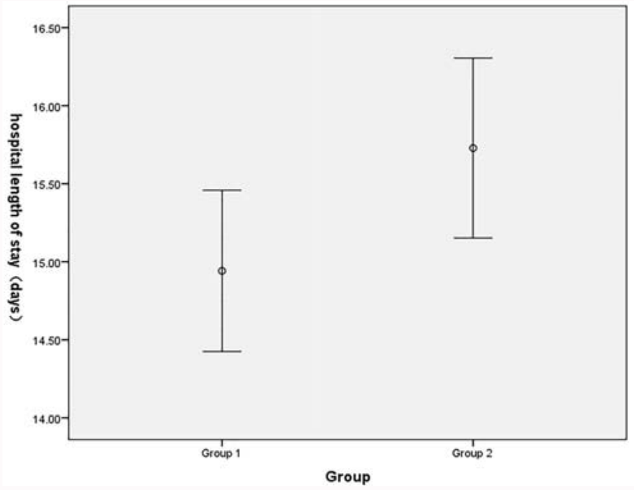
RBC: Red Blood Cell; ICU: Intensive Care Unit

Table 3: Linear regression analysis for Postoperative bleeding.

	Simple linear regression		Multiple linear regression	
Postoperative bleeding	**B**	**P Value**	**B**	**P Value**
Fibrinogen (g/L)	-0.099	<0.01	-0.073	0.03
Men (%)	0.09	0.01	0.063	0.06
Hypertension (%)	-0.011	0.73		
Hyperlipidemia (%)	-0.049	0.14		
Diabetes (%)	-0.071	0.03	-0.059	0.07
Surgery history (%)	-0.019	0.58		
HBG (g /L)	0.005	0.88		
WBC (×10^9/L)	-0.072	0.04	-0.04	0.25
Neutrophil count (× 10^9/L)	-0.041	0.25		
PLT count (× 10^9/L)	-0.134	<0.001	-0.047	0.62
PCT (%)	-0.138	<0.001	-0.121	<0.001
PT (sec)	0.047	0.15		
APTT (sec)	0.026	0.42		

HGB: Hemoglobin; WBC: White Blood Cell; PLT: Platelet; PCT: Plateletcrit; PT: Prothrombin Time; APTT: Activated Partial Thromboplastin Time

The role of fibrinogen as a predictor of LOS has not been reported before. Previous studies mainly focus on the association of fibrinogen and outcomes after CABG. Fibrinogen is one of the strong predictors of CHD, which is related to the incidence of CHD [22]. Decreasing fibrinogen level may be a potential method to reduce the risk of CHD [23]. In addition, fibrinogen, as a marker of inflammation and coagulation, may also play a part in increasing all-cause mortality of CHD [24]. After CABG, there is a marked and protracted activation of several molecular pathways indicating increased inflammatory status, hemostasis activation, as well as increased oxidative stress [25]. In terms of regards inflammatory pathways, even non-specific inflammatory markers such as preoperative leukocyte count and C-Reactive Protein (CRP) can predict in-hospital mortality after CABG [26]. Besides mortality, increasing baseline CRP levels can



Central figure: Comparison of hospital length of stay between the two groups (Group 1 = normal fibrinogen group, Group 2 = high fibrinogen group).

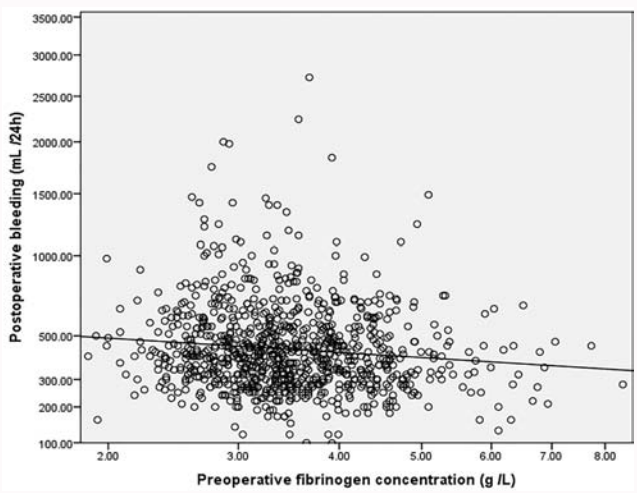


Figure 1: Correlation between fibrinogen and postoperative bleeding.

also be an independent predictor both of early major post-operative complications and CRP levels may also play a role in early graft occlusion [27]. What's even more surprising is that levels of fibrinogen were correlated with CRP, with a one unit increase in CRP associated with a 1.9% increase in fibrinogen after adjustment for potential confounders [28]. The effect of fibrinogen on postoperative recovery was not only such, but the higher the level of circulating fibrinogen, the greater the decrease of pulmonary function after CABG [29]. While inflammation is essential for clearing infection and debris after surgery, it can cause tissue damage if it lasts too long [30]. This can lead to increased scarring or chronic wounds that prolong LOS. This can lead to increased scarring or chronic wounds, which, like wound infection, can prolong LOS [14].

Our results demonstrating preoperative fibrinogen is a significant preoperative indicator of decreased postoperative bleeding correlates well with other similar studies. PLT consumption and hemodilution have been considered to be two important factors in the pathogenesis of bleeding after cardiac surgery [31]. However, Fibrinogen counteracts dilutional coagulopathy and impaired hemostasis caused by thrombocytopenia [18]. As mentioned above, fibrinogen as an inflammatory factor was associated with pro-coagulant activity of platelets, which can lead to complement activation and thereby increase the available pro-coagulant membrane surface [32]. All these mechanisms may explain our results regarding the association of preoperative higher fibrinogen levels and less postoperative bleeding.

Table 4: Linear regression analysis for ICU stay.

	Simple linear regression		Multiple linear regression	
ICU stay	**B**	**P Value**	**B**	**P Value**
Fibrinogen (g /L)	0.027	0.49		
Men (%)	-0.086	0.03	-0.092	0.02
Hypertension (%)	-0.088	0.03	-0.078	0.06
Hyperlipidemia (%)	-0.051	0.19		
Diabetes (%)	-0.068	0.08	-0.061	0.12
Surgery history (%)	0.043	0.29		
HBG (g/L)	-0.006	0.88		
WBC (× 10^9/L)	-0.096	0.02	-0.066	0.46
Neutrophil count (× 10^9/L)	-0.089	0.02	-0.003	0.97
PLT count (× 10^9/L)	-0.03	0.45		
PCT (%)	-0.023	0.55		
PT (sec)	0.08	0.04	0.05	0.24
APTT (sec)	0.082	0.04	0.058	0.16

HGB: Hemoglobin; WBC: White Blood Cell; PLT: Platelet; PCT: Plateletcrit; PT: Prothrombin Time; APTT: Activated Partial Thromboplastin Time

Table 5: Linear regression analysis for LOS.

	Simple linear regression		Multiple linear regression	
LOS (d)	**B**	**P Value**	**B**	**P Value**
Fibrinogen (g/L)	0.082	0.01	0.073	0.04
Men (%)	-0.016	0.62		
Hypertension (%)	-0.005	0.88		
Hyperlipidemia (%)	-0.096	<0.01	-0.012	0.74
Diabetes (%)	0.007	0.83		
Surgery history (%)	0.023	0.47		
HBG (g/L)	-0.138	<0.01	-0.14	<0.001
WBC (× 10^9/L)	-0.006	0.85		
Neutrophil count (× 10^9/L)	0.033	0.31		
PLT count (× 10^9/L)	-0.018	0.58		
PCT (%)	-0.023	0.48		
PT (sec)	0.051	0.12		
APTT (sec)	0.08	0.02	0.063	0.08

LOS: Hospital Length of Stay; HGB: Hemoglobin; WBC: White Blood Cell; PLT: Platelet; PCT: Plateletcrit; PT: Prothrombin Time; APTT: Activated Partial Thromboplastin Time

Age has previously been shown to be an independent risk factor for ICU stay yet sex was a significant predictor for ICU stay in this study. This may be related to the higher frequency of complications and death after myocardial infarction in women [33]. Further, the prognosis of women is worse than that of men after acute coronary ischemia and coronary revascularization [34].

Despite our best efforts, there are still several limitations. First, as a retrospective study, we could only collect postoperative data, so we did not accurately evaluate perioperative fluid management. However, due to the skilled operation of heart surgery in Fuwai

Hospital, the bias may be minimal. Second, our study was conducted in a single center of ethnic Chinese patients which may not reflect worldwide.

In summary, this study illustrated preoperative bleeding volume and LOS correlated with fibrinogen. Fibrinogen may be able to be considered as an indicator to predict postoperative bleeding volume and LOS. Therefore, we strongly recommended taking fibrinogen levels into account in preoperative evaluation to provide a more accurate preoperative prediction of CABG outcomes and to achieve better economic benefits.

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