

ORIGINAL ARTICLE

Predictors of Intraoperative Frozen Plasma Transfusion in Liver Transplantation

Rongrong Liu, Xiaofei Li

Department of Blood Transfusion, Capital Medical University Affiliated Beijing Friendship Hospital, Beijing, China

SUMMARY

Background: Liver transplantation (LT) is often accompanied by large intraoperative transfusions of blood products and worsens the patient's prognosis. The aim of our study was to identify the predictors of intraoperative frozen plasma (FP) transfusion in LT. At the same time, the effect of intraoperative plasma transfusion on clinical outcomes was evaluated as well.

Methods: Our retrospective study included 114 adult patients undergoing LT between January 1, 2020 and November 30, 2021. Patient demographics, including age, gender, and weight, were acquired. Patients were classified into one of two cohorts, FP transfusion and no FP transfusion, according to intraoperative FP transfusion or not. We used non-parametric Mann-Whitney U test and chi-squared test to compare the differences between the two groups. Variables significantly associated with intraoperative FP transfusion were included in multivariate logistic analysis. The multivariate logistic analysis was used to analyze the independent risk factors of intraoperative FP transfusion.

Results: Preoperative Fg (OR = 2.441, CI: 1.169 - 5.096, $p = 0.017$) and packed red blood cell transfusion (OR = 0.595, CI: 0.447 - 0.791, $p < 0.001$) were found to be predictive of FP transfusion. Intraoperative FP transfusions were significantly associated with worse clinical outcomes of postoperative PLT count, Fg, inpatient days, and length of ICU stay. There were statistically significant differences between the FP transfusion group and the non-FP transfusion group.

Conclusions: Preoperative Fg and intraoperative packed red blood cell transfusion were predictive of intraoperative FP transfusion. Intraoperative FP transfusion can reduce postoperative platelet and fibrinogen, prolong the hospital stay of patients, and increase the length of ICU stay.

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Correspondence:

Xiaofei Li
Department of Blood Transfusion
Capital Medical University
Affiliated Beijing Friendship Hospital
No. 95 Yong-An Road, Xi-Cheng District
Beijing, 100050
China
Phone: +86 17701390997
Email: lixiaofei@ccmu.edu.cn

KEYWORDS

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INTRODUCTION

LT is an effective method for patients with advanced liver disease. The management of coagulation and hemostasis is very challenging for those undergoing LT. Although the rate of intraoperative blood transfusion has decreased with the optimization of liver transplantation protocols, the selection of donor quality, and a better understanding of the pathophysiology of coagulation [1,2], massive blood product transfusion is still

often required for LT [3,4]. Previously, the first recorded death of a liver transplant patient was due to excessive intraoperative bleeding [5]. However, previous studies have shown that blood transfusion during LT increases mortality and decreases graft survivors [6,7]. At present, there is no clear consensus on the threshold of blood transfusion in LT [8,9]. For decades, FP transfusion has been the primary treatment of bleeding and coagulation abnormalities during LT. The risks of excessive FP transfusion are TRALI and thrombotic complications, which could have devastating consequences [4]. The Liver Intensive Care Group of Europe (LICAGE) has emphasized that unnecessary FP transfusions may be harmful [10].

Given the complexity and amount of blood loss involved in a liver transplant, appropriate preoperative and intraoperative interventions for high-risk LT patients to improve coagulation dysfunction remain an urgent task. The aim of this study was to assess the predictors of intraoperative plasma transfusion in LT. At the same time, the effect of intraoperative plasma transfusion on clinical outcome was also evaluated. The purpose of this research was to provide reference for preoperative blood management of LT patients.

MATERIALS AND METHODS

This is a retrospective cohort analysis of adult LT recipients performed at a single academic center from January 1, 2020, through November 30, 2021. Analysis was limited to transplant recipients aged 18 years and older. Patients with incomplete data records were excluded from the analysis. In terms of whether FP transfusion was used during LT, patients were divided into a FP transfusion group ($n = 77$) and a non-FP transfusion group ($n = 37$).

The data of recipients include age, gender, weight (kg), preoperative characteristics including Model for End Stage Liver Disease (MELD) score, international normalized ratio (INR), platelet (PLT) count, activated partial thromboplastin time (aPTT), prothrombin time (PT), and fibrinogen (Fg), intraoperative characteristics including EBL, plasma transfusion volume (1 mL), and packed red blood cell transfusion units, postoperative characteristics including PLT, INR, aPTT, PT, Fg, in-hospital mortality, inpatient days, and length of intensive care unit (ICU) stay. Demographic data and MELD score were taken from the electronic database of our liver transplant center. All preoperative characteristics data were obtained from the hospital laboratory information (LIS) system; the last laboratory results before surgery were used. All intraoperative characteristics data were obtained from the electronic medical records. All postoperative characteristics data were obtained from LIS system and electronic medical records; the first laboratory results after surgery were used.

Statistical analysis

All statistics were performed using SPSS version 23.0. Continuous variables were expressed as median (Q1 to Q3), and categorical variables were presented as percentages. For group comparison, non-parametric Mann-Whitney U test was used for continuous variables and chi-squared test was used for categorical variables. Multivariate logistic analysis was used to analyze the independent risk factors of intraoperative FP transfusion. Variables that showed a significant association with FP transfusion in the univariate logistic analysis were included in the multivariate logistic analysis. All tests of significance were two-sided, and a p -value < 0.05 was considered significant.

RESULTS

A total of 114 unique LT patients were included in this study (Figure 1). Out of those, 37 patients were not transfused FP, and 77 patients received intraoperative FP transfusion. Demographic data, clinical data, and laboratory data of the LT patients are displayed in Table 1.

The median age of the patients was 54 (45, 60) years, and 65 (57%) patients were male. The median weight of the patients was 67 (60, 75) kg. In univariate analysis, preoperative characteristics, including the median MELD score, of the FP transfusion group was 22 (15, 31), which was higher than of the non-FP transfusion group; the median INR of the FP transfusion group was 1.69 (1.42, 2.30), which was lower than of the other group; the median PLT of the FP transfusion group was 53 (37, 82), which was lower than of the other group; the median aPTT of the FP transfusion group was 38.9 (35.3, 45.2), which was higher than of the other group; the median PT of the FP transfusion group was 17.7 (15.6, 22.2), which was higher than of the other group; and the median Fg of the FP transfusion group was 1.20 (1.60, 1.88), which was lower than of the other group. Intraoperative EBL of the FP transfusion group was 1,000 (600, 1,300) mL. The median FP transfusion volume was 800 (600, 1,000) mL. The median number of the FP transfusion group transfused packed red blood cell was 4 (3, 8) units. All preoperative and intraoperative data were statistically significant between the two groups.

Despite MELD score, INR, PLT, aPTT, PT, Fg, EBL, and packed red blood cell transfusion between the FP transfusion group and the non-FP transfusion group were statistically significant, and we found preoperative Fg (OR = 2.441, CI: 1.169 - 5.096, $p = 0.017$) and packed red blood cell transfusion (OR = 0.595, CI: 0.447 - 0.791, $p < 0.001$) to be predictive of FP transfusion in multivariate analysis (Table 2). Intraoperative FP transfusions were also significantly associated with worse clinical outcomes, with lower PLT count of 52 (36, 72), higher INR of 1.94 (1.69, 2.30), higher aPTT of 44.7 (37.8, 50.7), higher PT of 21.1 (18.3, 25.1), low-

Table 1. Demographic and clinical characteristics of LT patients (n = 114).

Variable	Plasma transfusion (n = 77)	No plasma transfusion (n = 37)	Total (n = 114)	p-value
Demographics				
Age (years)	53 (42, 61)	56 (47, 60)	54 (45, 60)	0.449
Gender (male)	44 (57%)	21 (57%)	65 (57%)	0.969
Weight (kg)	67 (60, 75)	66 (59, 76)	67 (60, 75)	0.748
Preoperative characteristics				
MELD score	22 (15, 31)	16 (10, 25)	20 (13, 28)	0.026
INR	1.69 (1.42, 2.30)	1.20 (1.12, 1.33)	1.46 (1.23, 2.06)	< 0.001
PLT	53 (37, 82)	78 (58, 147)	62 (40, 103)	< 0.001
APTT	38.9 (35.3, 45.2)	38.8 (30.9, 37.2)	37.0 (33.7, 43.3)	< 0.001
PT	17.7 (15.6, 22.2)	13.0 (12.1, 14.4)	16.1 (13.3, 20.0)	< 0.001
Fg	1.20 (1.60, 1.88)	2.40 (1.95, 3.03)	1.77 (1.28, 2.39)	< 0.001
Intraoperative characteristics				
EBL (1 mL)	1,000 (600, 1,300)	600 (475, 800)	775 (538, 1,125)	0.001
Plasma transfusion volume (1 mL)	800 (600, 1,000)	-	-	-
Packed red blood cell transfusion units	4 (3, 8)	0	4 (0, 6)	< 0.001
Postoperative characteristics				
PLT	52 (36, 72)	84 (46, 103)	57 (40, 84)	0.001
INR	1.94 (1.69, 2.30)	1.81 (1.65, 2.17)	1.89 (1.69, 2.28)	0.255
aPTT	44.7 (37.8, 50.7)	39.1 (35.5, 46.7)	47.5 (47.2, 47.8)	0.051
PT	21.1 (18.3, 25.1)	19.6 (17.9, 23.1)	18.6 (18.4, 29.6)	0.248
Fg	1.31 (1.06, 1.67)	1.72 (1.23, 2.38)	1.69 (1.40, 1.85)	0.003
In-hospital mortality	8 (10.4%)	2 (5.4%)	10 (0.1%)	0.378
Inpatient days	29 (23, 40)	21 (17, 28)	26 (20, 37)	0.002
Length of ICU stay	4 (3, 4)	3 (2, 4)	3 (3, 4)	0.028

Table 2. Predictors of intraoperative plasma transfusion in LT patients.

	OR	95% CI	P
Preoperative Fg	2.441	1.169 - 5.096	0.017
Intraoperative EBL	0.999	0.997 - 1.000	0.058
Preoperative INR	0.211	0.018 - 2.409	0.210
Preoperative PLT count	1.003	0.993 - 1.014	0.549
Preoperative APTT	1.048	0.927 - 1.185	0.457
Preoperative PT	1.055	0.816 - 1.364	0.682
MELD score	0.972	0.921 - 1.027	0.311
Packed red blood cell transfusion units	0.595	0.447 - 0.791	< 0.001

er Fg of 1.31 (1.06, 1.67), higher in-hospital mortality of 8 (10.4%), more inpatient days of 29 (23, 40), and more length of ICU stay of 4 (3, 4). The clinical outcomes of postoperative PLT count, Fg, inpatient days,

and length of ICU stay were statistically significant between the FP transfusion group and the non-FP transfusion group.

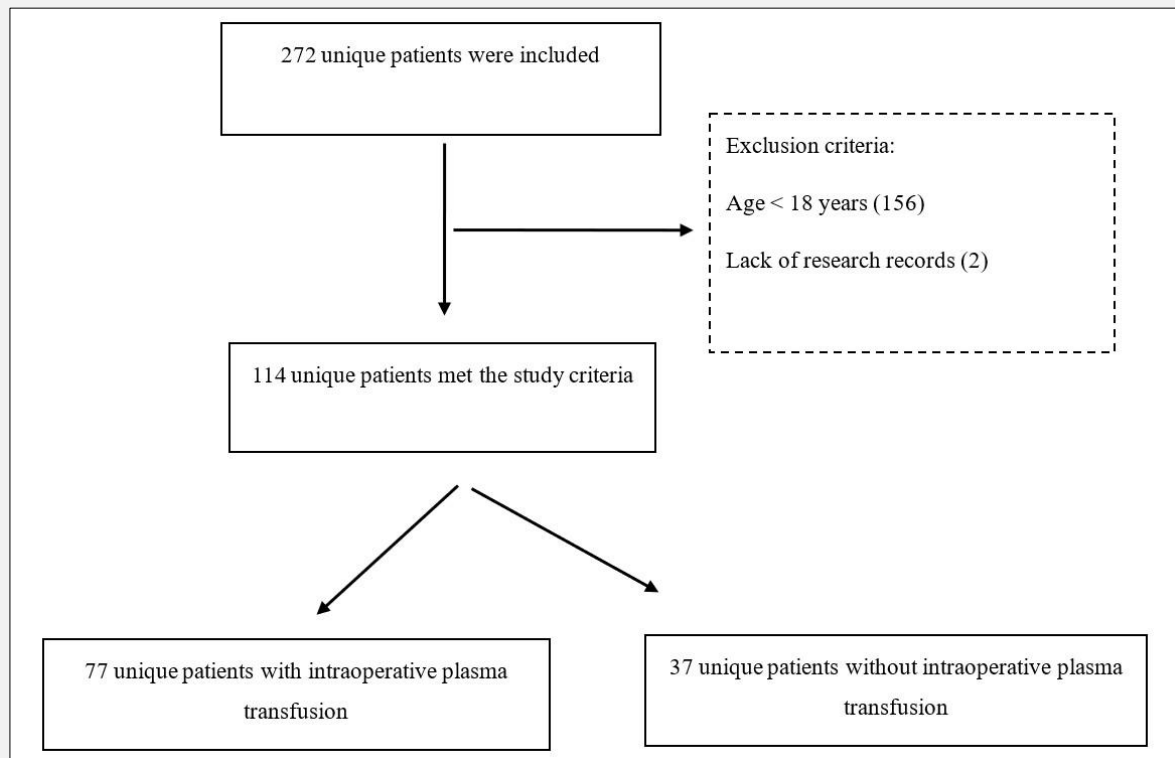


Figure 1. Flowchart.

DISCUSSION

The primary aim of this study was to evaluate the predictors of intraoperative FP transfusion in patients undergoing LT. In our study cohort, the median age of the patients was 54 (45, 60) years, and 65 (57%) patients were male. FPs were transfused intraoperatively to 77 (67.5%) patients, with a median of 800 milliliters. By using logistic regression analysis, we showed that Fg and packed red blood cell transfusion were predictive of intraoperative FP transfusion. We also noticed that intraoperative FP transfusions were associated with inferior clinical outcomes. Specifically, intraoperative FP transfusion significantly decreased the postoperative value of PLT count and Fg and increased inpatient days and length of ICU stay. Higher INR, aPTT, and PT values and higher in-hospital mortality can be observed in patients who received FP transfusions, even though there was no significant difference between the groups in terms of postoperative outcomes.

Although LT has made great progress, operative blood loss during LT remains a concern, associated with increased morbidity and reduced patient and graft survival [11,12]. For decades, FP transfusions have been a mainstay for the prevention and treatment of bleeding and coagulation disorders arising during LT. Although plas-

ma transfusion is safer today than it had been in the past, zero risk cannot be achieved, and clinicians must be aware of the potential dangers of plasma transfusion. Adverse effects of plasma transfusion include pathogen transmission, transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), and allergic reactions [13,14]. In LT patients, it has been proven that massive transfusion is associated with worse long-term outcomes, i.e., higher mortality, prolonged length of stay, and increased rate of infectious complications [15-18], but limited information is available regarding the intraoperative plasma transfusion. Predicting intraoperative plasma transfusion is of major interest for the individualization of perioperative management. Recent reviews have shown that overuse of fresh frozen plasma only exacerbates portal hypertension, leading to a vicious cycle of bleeding [19,20]. Therefore, identification of high-risk patients and early monitoring of clotting disorders to improve outcomes remain urgently needed [21,22]. Although plasma-based coagulation tests have been highly doubtful in assessing coagulation function in LT patients, they remain the most commonly used tests in monitoring hemostatic competence during LT [12,23]. Moreover, patients with cirrhosis often transfused in response to abnormal parameters of hemostasis [24]. Recent studies have shown

that INR and aPTT do not predict plasma transfusion in LT [25]. Our study also found that INR, PT, and aPTT are not suitable for predicting plasma transfusion during LT. Our research showed that the significant predictors for FP transfusion were preoperative Fg and packed red blood cell transfusion.

Fg is a large hexameric glycoprotein produced in the liver that plays a crucial role in hemostasis and is a precursor to fibrin [26,27]. Our study showed that Fg was a predictor of intraoperative FP transfusion. This conclusion has been endorsed by previous reports [28], which showed that a low baseline Fg level predicts intraoperative blood transfusion. Similarly, in the recent literature, Thibeault et al. [29] showed that higher preoperative Fg level is associated with fewer intraoperative RBC and other blood products' transfusion. Our study showed that preoperative FP transfusion in patients with low Fg was 2.441 times higher than that in patients with high Fg. The previous reports showed that the use of Fg concentrate reduces transfusion requirements, making it one of the most important indicators guiding intraoperative blood and blood product transfusion [30-32]. Bolliger et al. [33] proved that a Fg concentration above 2 g/L is the minimum concentration at which clot formation normalizes. Noval-Padillo et al. [34] showed that transfusion of platelet concentrates decreased by 50%, fresh frozen plasma was reduced by 65%, and RBCs was reduced by 53% after the patients received Haemocomplettan. In addition, the blood transfusion volume of patients who received blood transfusion also decreased. This is an indication that preoperative Fg management is beneficial to reducing the utilization of plasma during operation.

Several studies suggest a significant association between RBC transfusion volume and short- or middle-term mortality after LT [29,35]. Our study observed that intraoperative red blood cell transfusion was a predictor of FP transfusion. Modanlou et al. [36] showed that there was a direct correlation between the number of red blood cells transfused and the plasma ($r = 0.93$) and platelets ($r = 0.74$) transfused. Massicotte et al. [8] showed that transfusion of plasma increased the rate of packed red blood cell transfusion. It can be seen that intraoperative transfusions of different blood products may affect each other. In addition, the triggers for blood transfusion vary between institutions and individuals, which can lead to unnecessary blood transfusions. Hence, reducing intraoperative red blood cell transfusion is not only beneficial to the prognosis of patients but can also reduce intraoperative FP transfusion. Moreover, when blood resources are scarce, preoperative management can reduce intraoperative blood use and improve the prognosis of patients, as well as reduce the pressure of blood use caused by the shortage of blood resources.

Consistent with previous reports, our study confirms that intraoperative plasma transfusion can lead to worse clinical outcomes. Benson et al. [36] showed that plasma-related blood product transfusion is associated with

TRALI and that red blood cell transfusion is associated with postoperative infection in a dose-dependent manner.

This study had some limitations. First, many patients could not be included in the study group due to incomplete data, resulting in a small sample size of patients. We should increase the sample size in future studies and consider more factors to be included in the multivariate logistic analysis to predict the risk factors of plasma transfusion. Second, the data for this study came from a single center; the results of this study are only indicative of the intraoperative plasma transfusions in this institution and may not be applicable to other institutions. In the future, we will establish a multi-center retrospective analysis to make the research data more reliable. Third, preoperative blood transfusion was not recorded in this study, and the effect of preoperative blood transfusion on coagulation status during the operation was not evaluated. Finally, the factor of individual physician practice preferences was not included in the center's confounding variables, which can also affect initiating plasma transfusion during surgery.

In conclusion, this study provides evidence for clinicians. We analyzed the predictors of intraoperative plasma infusion and the effects of intraoperative FP transfusion on clinical outcomes. Preoperative management of Fg levels and intraoperative reduction of red blood cell infusion may be beneficial for liver transplant patients.

Declaration of Interest:

The authors declare that they have no conflict of interest.

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